Physical Activity Influences on Cancer Risk and Survival

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Physical activity across the cancer continuum:
- Prevention
- Treatment
- Rehabilitation
- Survival

Review of evidence from:
- Observational studies
- Randomized controlled exercise intervention trials

Biologic mechanisms in physical activity and cancer control:
- RCT evidence for cancer prevention, rehabilitation and survival

Future research directions
Physical Activity in Cancer Control Framework

Physical Activity and Cancer
Courneya and Friedenreich, editors

Topics:

- Physical Activity and Cancer Prevention
- Physical Activity and Cancer Survivorship
- Physical Activity and Cancer Special Topics

Recent Results in Cancer Research, Springer-Verlag, 2011
## Level of Evidence on Physical Activity and Cancer Risk Reduction

<table>
<thead>
<tr>
<th>Convincing or Probable</th>
<th>Insufficient or Null</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Rectal *</td>
</tr>
<tr>
<td>Breast</td>
<td>Pancreatic</td>
</tr>
<tr>
<td>Endometrial</td>
<td>Gastric</td>
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<td></td>
<td>Bladder</td>
</tr>
<tr>
<td><strong>Weaker evidence</strong></td>
<td><strong>Testicular</strong></td>
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<tr>
<td>Lung</td>
<td>Kidney</td>
</tr>
<tr>
<td>Prostate</td>
<td>Hematologic cancers (non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, multiple myeloma)</td>
</tr>
<tr>
<td>Ovarian</td>
<td></td>
</tr>
</tbody>
</table>

* No association

Friedenreich et al. *EJC*, 2010; 46:2593-2604
Physical Activity and Cancer Research: State of the Science

1. Identifying relations between physical activity and cancer risk
2. Identifying relations between physical activity and cancer survival
3. Examining the biologic mechanisms involved in physical activity and cancer risk in intervention trials
4. Characterizing prevalence of and determinants of physical activity in cancer survivors
5. Testing interventions to increase physical activity for cancer prevention and survival
6. Using the relevant evidence to inform programs and policy

Physical Activity and Breast Cancer Risk

Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention.

Summary of Evidence on Physical Activity and Breast Cancer Risk

- **Consistent evidence** *(66 out of 88 observed decreased risk)*:
  - 19 studies show no effect
  - 66 studies show decreased risk
  - 3 studies find increased risks

- **Fairly strong** risk reductions *(25% decrease for highest vs. lowest activity levels, on average)*:
  - 31% average risk reduction in case-control studies
  - 19% average risk reduction in cohort studies

- **Clear dose-response** with increasing activity and decreasing risk *(40 of 50 studies)*

- **Biologic plausibility exists** *(several possible mechanisms)*

- **Temporality exists**

Lynch et al. in Courneya and Friedenreich, Physical Activity and Cancer. Heidelberg: Springer-Verlag, 2011
Physical Activity and Breast Cancer Risk: Cohort Studies

Statistically significant reduction in 16 of 42 cohort studies (38%)
Statistically significant reduction in 22 of 47 case-control studies (46%)
Breast Cancer Risk Reduction by Type, Dose and Timing of Activity

![Graph showing breast cancer risk reduction by type, dose, and timing of activity.]
Population Subgroup Effects for Physical Activity and Breast Cancer

BMI

Family History

Parity

Race
Physical Activity and Risk of Colon Cancer
Summary of Evidence on Physical Activity and Colon Cancer Risk

- **Consistent evidence** *(72 of 86 studies)*
  - 15 show no effect and no studies find increased risk

- **Fairly strong risk reductions** *(~30% decreases for highest vs. lowest activity levels)*
  - 27% average risk reduction in case-control studies
  - 20% average risk reduction in cohort studies

- **Clear dose-response** *(41 of 47 studies)*

- Biologic plausibility exists

- Temporality exists
Physical Activity and Colon Cancer Risk: Cohort Studies

Statistically significant risk reductions in 16 of 41 studies (39%)
Physical Activity and Colon Cancer Risk: Case-control Studies

<table>
<thead>
<tr>
<th>Population-based</th>
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<tbody>
<tr>
<td>Juarranz et al, 2002</td>
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<td>Longnecker et al, 1995</td>
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<td>Marcus et al, 1994</td>
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<td>Parent et al, 2011</td>
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<td>Boyle et al, 2011</td>
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<td>Proximal colon</td>
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<td>Orebrant et al, 1994</td>
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<td>Whitemore et al, 1990</td>
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<td>Le Marchand et al, 1997</td>
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<td>Slattery et al, 1997</td>
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<td>Hou et al, 2004</td>
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<td>White et al, 1996</td>
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<tr>
<td>Male</td>
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<td>Izomura et al, 2006 Female</td>
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<td>Khoury-Shakour et al, 2009</td>
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<td>Fraser et al, 1993</td>
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<td>Peters et al, 1989</td>
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<td>Kune et al, 1990</td>
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<td>La Vecchia et al, 1999</td>
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<td>Veneil et al, 1993 Male</td>
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<td>Fernandes et al, 2004</td>
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<td>Yeh et al, 2003 Col. Female</td>
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<td>Brownson et al, 1991</td>
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<td>Kotake et al, 1995 Col.</td>
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<td>Yeh et al, 2003 Col. Male</td>
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<td>Boutron-Ruault et al, 2001</td>
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<td>Arberman et al, 1993</td>
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<th>Case-cohort design</th>
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<td>Hughes et al, 2011 CIMP-</td>
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<td>Hughes et al, 2011 CIMP+</td>
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<tr>
<th>Nested case-control study (within a cohort)</th>
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<tr>
<td>Thun et al, 1992</td>
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</table>

Statistically significant risk reductions in 18 of 44 studies (41%)
Type, Dose and Timing of Activity: Colon Cancer

- **Type of Activity**
  - All types may be effective for lowering risk
    - e.g., occupational activity (22% decrease in risk), recreational (23%)
  - Sedentary behaviour may increase risk

- **Intensity**
  - Vigorous or moderate activity decrease risk

- **Timing of activity**
  - Inconsistent findings

- **Population Sub-groups**
  - Relatively constant effects across BMI categories
  - Association may vary by tumour sub-site
    - i.e., proximal or distal
  - Benefit for men and women
  - Unclear effects of race/ethnicity, dietary intake, HRT use
Physical Activity and Risk of Gynecologic Cancer
Summary of Evidence on Physical Activity and Endometrial Cancer Risk

- **Consistent evidence** *(23 of 28 studies)*
  - Nearly all of studies show risk reductions
- **Fairly strong** risk reductions *(30-35% decreases for highest vs. lowest activity levels)*
  - 25% average risk reduction in cohort studies
  - 37% average risk reduction in case-control studies
- **Evidence of dose-response** *(12 of 19 studies)*
- **Biologic** plausibility exists
- Sedentary behaviour emerging as possibly important
Physical Activity and Endometrial Cancer Risk

Statistically significant risk reduction in 14 of 28 studies (50%)
Summary of Evidence on Physical Activity and Ovarian Cancer Risk

- **Moderately consistent evidence** *(12 of 24 studies)*
  - 12 studies show risk reductions
  - 3 studies show increased risk (1 is statistically significant)

- **Weak risk reductions** *(<10% average decreases for highest vs. lowest activity levels)*
  - Average 10% increased risk in cohort studies
  - Average 25% decreased risk from case-control studies

- **Some evidence of dose-response** *(9 of 11 studies)*
Physical Activity and Ovarian Cancer Studies

Cohort Studies

- Prospective
  - Schnohr et al, 2005
  - Hannan et al, 2005
  - Biesma et al, 2006
  - Patel et al, 2006
  - Bertone et al, 2001
  - Weiderpass, 2006
  - Weiderpass et al, 2012
  - Leitzmann et al, 2009
  - Lahmann et al, 2009
  - Anderson et al, 2004
  - Chionh et al, 2010

Case-control Studies

- Population-based case-control
  - Riman et al, 2004
  - Carnide et al, 2009
  - Cottreau et al, 2000
  - Pan et al, 2005
  - Olsen et al, 2007
  - Moorman et al, 2011
  - Rossing et al, 2010
  - Bertone et al, 2002
  - Zheng et al, 1993

- Hospital-based case-control
  - Dosemeci et al, 1993
  - Zhang et al, 2003
  - Tavani et al, 2001
Physical Activity and Risk of Prostate Cancer
Summary of Evidence on Physical Activity and Prostate Cancer Risk

- **Less consistent evidence (26 of 56 studies)**
  - 25 studies find no effect
  - 26 studies find decreased risk
  - 5 studies find increased risk

- **Weak risk reductions (10% decreases for highest vs. lowest activity levels)**

- **Evidence of dose-response (12 of 18 studies)**
  - about half of the studies that examined these trends

- **Some biologic plausibility exists**
Physical Activity and Prostate Cancer: Cohort Studies

Statistically significant risk reductions in 7 of 30 studies (23%)
Physical Activity and Prostate Cancer: Case-control Studies

Statistically significant risk reductions in 8 of 26 studies (30%)
Physical Activity and Risk of Lung Cancer
Summary of Evidence on Physical Activity and Lung Cancer Risk

- Consistent evidence *(20 of 28 studies)*
  - 7 show no effect
  - 20 show decreased risks

- Fairly strong risk reductions *(25% decreases for highest vs. lowest activity levels)*

- Evidence of dose-response *(9 of 11 studies)*
  - About half of the studies that examined these trends

- Weaker evidence for biologic plausibility exists

- Effect of smoking needs to be considered
Physical Activity and Lung Cancer: Cohort Studies

Statistically significant risk reduction in 7 of 19 studies (37%)
Physical Activity and Lung Cancer: Case-Control Studies

Statistically significant risk reduction in 6 of 8 studies (75%)
## Summary of Evidence on Physical Activity and Cancer Risk by Site

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number of Studies</th>
<th>Studies found reduced risk</th>
<th>Consistency of evidence</th>
<th>Magnitude of risk reduction</th>
<th>Dose-response effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>86</td>
<td>72</td>
<td>Yes</td>
<td>30%</td>
<td>Yes</td>
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<tr>
<td>Breast</td>
<td>88</td>
<td>66</td>
<td>Yes</td>
<td>25%</td>
<td>Yes</td>
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<tr>
<td>Endometrial</td>
<td>28</td>
<td>23</td>
<td>Yes</td>
<td>30-35%</td>
<td>Yes</td>
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<tr>
<td>Lung</td>
<td>28</td>
<td>20</td>
<td>Some</td>
<td>25%</td>
<td>Some</td>
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<tr>
<td>Prostate</td>
<td>56</td>
<td>26</td>
<td>No</td>
<td>10%</td>
<td>Limited</td>
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<tr>
<td>Ovarian</td>
<td>24</td>
<td>12</td>
<td>No</td>
<td>&lt;10%</td>
<td>Limited</td>
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<tr>
<td>All Others</td>
<td></td>
<td></td>
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<td>Insufficient or Null</td>
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</table>
Physical Activity During Cancer Treatment
Supervised Trial of Aerobic vs Resistance Training (START Trial)

Histologically confirmed operable disease

Scheduled to initiate chemotherapy

n=242
3 centres in Canada

Supervised aerobic training (n=78) (3x/wk @60%-75% VO$_{2\text{peak}}$,)

Progressive resistance training (n=82) (3x/wk @60%-75% RM)

Usual Care (no intervention) (n=82)

~17 weeks

Aerobic capacity

Fatigue

Self-esteem

QOL

VO₂peak (mL.kg⁻¹.min⁻¹)

Control  Aerobic Tx  Resistance Tx

Aerobic capacity

Fatigue

Self-esteem

QOL

Control  Aerobic Tx  Resistance Tx

Adapted from Jones, AICR, 2011

Main Results from START Trial

- **Aerobic exercise (AET)** was better than usual care (UC) for:
  - Self-esteem
  - Aerobic fitness
  - Percent body fat
  - Fat mass

- **Resistance exercise (RET)** was better than usual care for:
  - Self-esteem
  - Lower body strength
  - Upper body strength
  - Lean body mass
  - Chemotherapy completion rate

- Improved quality of life, fatigue, depression and anxiety in exercise groups as compared to usual care (*non-statistically significant improvements*)

Courneya et al. JCO, 2007; 25:4396-4404
**Combined Aerobic and Resistance Exercise Trial (CARE Trial)**

- **Histologically confirmed operable disease**
- **Scheduled to initiate chemotherapy**
- **n=300 in three Canadian cities**

**Randomization**

1. **Moderate supervised aerobic training (n=100)**
   - (150 mins/wk, @60%-75% VO$_{2\text{max}}$)

2. **High supervised aerobic training (n=100)**
   - (300 mins/wk, @60%-75% VO$_{2\text{max}}$)

3. **Moderate aerobic and progressive resistance exercise training (n=100)**
   - (300 mins/wk, @60%-75% VO$_{2\text{max}}$ and RM)

**Follow-up**

- 6, 12, 24 months
- ~17 weeks
Randomized Controlled Trials of Physical Activity in Cancer Survivors
### Summary of Effects of Exercise on Physical Characteristics By Cancer Phase

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment</th>
<th></th>
<th>Survivorship</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect</td>
<td>$P$-value</td>
<td>Effect</td>
</tr>
<tr>
<td>PA level</td>
<td>↑</td>
<td>0.70</td>
<td>↑↑</td>
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<tr>
<td>Aerobic fitness</td>
<td>↑</td>
<td>0.03</td>
<td>↑</td>
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<tr>
<td>Upper body strength</td>
<td>↑↑</td>
<td>0.006</td>
<td>↑↑</td>
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<tr>
<td>Lower body strength</td>
<td>↑↑</td>
<td>0.006</td>
<td>↑</td>
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<tr>
<td>Body weight</td>
<td>↓</td>
<td>0.05</td>
<td>↓↓</td>
</tr>
<tr>
<td>% body fat</td>
<td>↓</td>
<td>0.04</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

*Speck et al., J Cancer Survivorship 2010;4:87-100*
### Summary of Effects of Exercise on Patient Reported Outcomes By Cancer Phase

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment</th>
<th>Survivorship</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effect</td>
<td>$P$-value</td>
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<tr>
<td>Fatigue</td>
<td>↓</td>
<td>0.75</td>
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<tr>
<td>Quality of life</td>
<td>↑</td>
<td>0.11</td>
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<tr>
<td>Physical function</td>
<td>↑↑</td>
<td>0.04</td>
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<tr>
<td>Depression</td>
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<td>0.70</td>
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<tr>
<td>Anxiety</td>
<td>↓</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Speck et al., *J Cancer Survivorship* 2010;4:87-100
Observational Studies on Physical Activity and Breast Cancer Survival

Ballard-Barbash et al. JNCI 2012; 104: 815-840
Physical Activity and Breast Cancer Mortality: Observational Studies

Average risk reduction is 25% ranging from 0-50% for active vs least active
Physical Activity and Breast Cancer
Observational Studies: All Cause Mortality

Average risk reduction is 29% ranging from 0-67% for active vs least active
Risk of Breast Cancer Recurrence and Mortality by Physical Activity Level

Holmes et al. JAMA 2005; 293:2479-86
Alberta Cohort Study of Lifetime PA and Breast Cancer Survival

Friedenreich et al., *Int J Ca* 2009; 124:1954-62
Alberta Cohort Study of Lifetime PA and Breast Cancer Survival

Friedenreich et al., *Int J Ca* 2009; 124:1954-62
Alberta Cohort Study of Lifetime PA and Breast Cancer Survival

Friedenreich et al., *Int J Ca* 2009; 124:1954-62
Observational Studies on Physical Activity and Colon Cancer Cancer Survival
Physical Activity and Colon Cancer Mortality and All Cause Mortality: Observational Studies

Average risk reduction is 48% (27-67%) for colon cancer mortality and 44% (23-63%) for all cause mortality for most vs. least active.
Nurses Health Study: Survival After Colorectal Cancer by Level of Post-diagnosis Physical Activity

Fig 1. Cumulative incidence curve of colorectal cancer–specific deaths by level of postdiagnosis physical activity. MET, metabolic equivalent task.

Fig 2. Kaplan and Meier curve of overall survival by level of postdiagnosis physical activity. MET, metabolic equivalent task.

Cumulative incidence and Kaplan-Meier survival curves

Meyerhardt et al. JCO 2006; 24:3527-34
Multivariate-Adjusted Hazard Ratios of CRC Specific and Overall Mortality (n=554)

- Hazard Ratios for CRC deaths and all deaths.
- Physical Activity (MET-hrs/week) categories: <3, 3 to 9, 9 to 18, >18.
- Multivariate-adjusted hazard ratios with P-trend values: 0.008 for CRC deaths and 0.003 for overall deaths.

Meyerhardt et al. JCO 2006; 24:3527-34
Colon Health and Life-Long Exercise Change (CHALLENGE) Trial

Histologically confirmed operable colon cancer

>60 - <180 d post adjuvant tx

Baseline Assessment

N=962

Physical activity program + general health materials (supervised PA + counseling)

General health materials (usual care)

3 years

Primary: disease-free survival

Secondary: PROs, functional capacity, etc.

Progressive Disease or Unacceptable toxicity or withdrawal of consent

Courneya et al. Curr Oncol, 2008;15:262-70
Physical Activity and Prostate Cancer Survival
Risk of Prostate Cancer Mortality by Post-diagnosis PA

Risk

Prostate Cancer

All Cause Mortality

Physical Activity Level (MET-Hours/Week)

Kenfield et al. *JCO* 2011;29:726-32
Risk of Prostate Cancer and All Cause Mortality by Vigorous Post-diagnosis Physical Activity

Kenfield et al. JCO 2011; 29:726-32.
## Summary of Evidence on Physical Activity and Cancer Mortality by Site

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number of studies</th>
<th>Magnitude of reduction in cancer specific mortality</th>
<th>Magnitude of reduction in all cause mortality</th>
<th>Dose-response effect</th>
</tr>
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<tbody>
<tr>
<td>Breast</td>
<td>17</td>
<td>25%</td>
<td>30%</td>
<td>Some</td>
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<tr>
<td>Colon</td>
<td>6</td>
<td>45-50%</td>
<td>40-45%</td>
<td>Some</td>
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<td>Prostate</td>
<td>1</td>
<td>60%</td>
<td>45%</td>
<td>NA</td>
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<td>Ovarian</td>
<td>2</td>
<td>10%*</td>
<td>10%</td>
<td>NA</td>
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<td>Glioma</td>
<td>1</td>
<td>NR</td>
<td>55%</td>
<td>NA</td>
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</table>

* Increased risk
Physical Activity and Cancer Risk: Biologic Mechanisms
How physical activity could interact with carcinogenesis

Physical Activity → DNA Damage

Metabolism/ Detoxification

Chemical Carcinogens

DNA Damage → Initiation

DNA Repair

Endogenous Oxidative Stress

Reactive Oxygen Species

Physical Activity → Promotion and Progression

Growth Factors

Promotion and Progression → Clinical Disease

Hormone Levels

Immune Function

Physical Activity

Positive Association

Negative Association

Adapted from Rundle A. CEBP 2005;14:227-36
Hypothesized Biologic Mechanisms Between Physical Inactivity, Sedentary Behaviour and Cancer Risk

↓ Physical Activity  
↑ Adiposity  
↑ Sedentary Behavior 

Sex Hormones  
Adipokines  
Inflammation  
Insulin Resistance  

↑ Cancer risk 
Lung  
Ovarian  
Prostate  
Breast & Endometrial  
Colon

Friedenreich CM, Lynch BM, Langley A. in press
## Biologic Mechanisms: Emerging Evidence of Effect of PA

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Possible effect of Physical Activity</th>
<th>Cancer Sites</th>
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</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>• Associated with higher 25-hydroxyvitamin D blood levels</td>
<td>Colon, Breast</td>
</tr>
<tr>
<td>Insulin-like growth factors</td>
<td>• Might ↓ IGF-1 and ↑ IGFBP-3</td>
<td>Colon, Premenopausal breast, Endometrium, Ovaries, Prostate, Lung</td>
</tr>
<tr>
<td>Immune function</td>
<td>• May improve innate and acquired immune responses to recognize and eliminate cancer cells</td>
<td>Most cancers</td>
</tr>
<tr>
<td></td>
<td>• Effects of long-term, moderate intensity PA on humans at risk not well understood</td>
<td></td>
</tr>
<tr>
<td>Oxidative stress, anti-oxidant defense and DNA repair</td>
<td>• May reduce oxidative stress, increase anti-oxidant enzymes (e.g. superoxide dismutase), and/or enhance DNA repair</td>
<td>Most cancers</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>• May inhibit synthesis of prostaglandins</td>
<td>Colon</td>
</tr>
<tr>
<td>Gastrointestinal transit time</td>
<td>• ↑ Gut motility and may ↓ transit time → less interaction between mucosa and carcinogens but changes may not be large enough to alter risk</td>
<td>Colon</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>• ↓ Concentration of carcinogens in lung and ↓ exposure time of carcinogens to lung tissue</td>
<td>Lung</td>
</tr>
</tbody>
</table>
Randomized Controlled Exercise Intervention Trials for Breast Cancer Prevention

- Three year-long RCTs conducted to date on aerobic exercise and breast cancer biomarkers among postmenopausal, inactive, 50-75 yr old healthy women:
  - McTiernan et al. *(Physical Activity for Total Health Trial)* (N=173)
  - Monninkhof et al. *(Sex Hormones and Physical Exercise Trial)* (N=189)
  - Friedenreich et al. *(Alberta Physical Activity and Breast Cancer Prevention Trial)* (N=320)
ALPHA Trial: Design

- **Study design:** Two-armed, two-centered RCT
- **Intervention:** Year-long, 5 days/week, 45 mins/session (3 supervised, 2 unsupervised), aerobic exercise only, no change in diet
- **Eligibility criteria:** Postmenopausal, 50-74 yrs, no previous cancer, healthy, BMI=22-40, no HRT use, non-smoker, non-excessive alcohol, inactive
- **Control:** No change in exercise or diet
- **Sample size:** 320
- **Outcomes:** Sex hormones, adiposity, insulin resistance, inflammation, mammographic density
Hypothesized Biologic Mechanisms Between Physical Activity and Breast Cancer

Friedenreich CM, Neilson HK, Lynch BM. *Eur J Cancer*. 2010; 46:2593-2604
ALPHA Trial: Flow Chart

Assessed for eligibility (n=3454)

Did not meet inclusion criteria (n=1840) Refused (n=798) Other reasons (n=274)

Attend information session and remain eligible and interested (n=542)

Randomized (n=320)

Exercise Group (n=160) Control Group (n=160)

12 month blood samples (n=154) 12 month blood samples (n=156)
Impact of Exercise Intervention on Endogenous Estrogens: Estradiol

Mean Change in log(Estradiol) During 12 Months Follow-up by Groups

P=0.001

Friedenreich et al., JCO, 2010; 28:1458-66
Impact of Exercise Intervention on Sex Hormone Binding Globulin

Mean Change in log(SHBG) During 12 Months Follow-up by Groups

Exercisers: Mean 95%CI
Controls: Mean 95%CI

P=0.002

Friedenreich et al., JCO, 2010; 28:1458-66
# Impact of Exercise Intervention on Adiposity Outcomes

<table>
<thead>
<tr>
<th>Change from Baseline</th>
<th>Exercisers</th>
<th>Controls</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-2.3</td>
<td>-0.5</td>
<td>-1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>-0.9</td>
<td>-0.2</td>
<td>-0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>-2.2</td>
<td>0.1</td>
<td>-2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abdominal fat area (cm²)</td>
<td>-48.5</td>
<td>-9.6</td>
<td>-38.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intra-abdominal fat area (cm²)</td>
<td>-16.5</td>
<td>-1.6</td>
<td>-14.9</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Friedenreich et al., *Int J Obes* 2010; 35:427-35
## Impact of Exercise Intervention on Adiposity Outcomes

<table>
<thead>
<tr>
<th>Change from Baseline</th>
<th>Exercisers</th>
<th>Controls</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous fat area (cm²)</td>
<td>-32.0</td>
<td>-7.9</td>
<td>-24.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>-2.0</td>
<td>-0.2</td>
<td>-1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>-2.4</td>
<td>-0.4</td>
<td>-2.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lean muscle mass (kg)</td>
<td>-0.0</td>
<td>-0.1</td>
<td>0.1</td>
<td>0.564</td>
</tr>
</tbody>
</table>

Friedenreich et al., *Int J Obes* 2010; 35:427-35
Percent Change of Total Body Fat and Intra-abdominal Fat Change by Average Weekly Duration of Exercise

<table>
<thead>
<tr>
<th>Total Body Fat</th>
<th>Intra-abdominal Fat Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Percentage (%)</td>
<td>Change in Percentage (%)</td>
</tr>
<tr>
<td>Control</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Control</td>
<td>&lt;150</td>
</tr>
<tr>
<td>-1.3</td>
<td>-2.5</td>
</tr>
<tr>
<td>-1.6</td>
<td>-10.4</td>
</tr>
</tbody>
</table>

- * Significant difference compared with control group (P<0.05).
- † Significant difference compared with low-active group (P<0.05).

Friedenreich et al., *Int J Obes* 2010; 35:427-35
Insulin Resistance Outcomes

Friedenreich et al., Endocrine-Related Cancer, 2011;18:357-69
Impact of Exercise Intervention on Insulin

Mean Change in log(Insulin) During 12 Months Follow-up by Groups

Exercisers: Mean 95%CI
Controls: Mean 95%CI

P<0.001

Friedenreich et al., Endocrine Related Cancer 2011;18:357-69
Impact of Exercise Intervention on Leptin

Mean Change in log(Leptin) During 12 Months Follow-up by Groups

Exercisers: Mean 95%CI
Controls: Mean 95%CI

P<0.001

Friedenreich et al., *Endocrine Related Cancer* 2011;18:357-69
Impact of Exercise Intervention on Insulin Resistance (HOMA)

Mean Change in HOMA Score During 12 Months Follow-up by Groups

<table>
<thead>
<tr>
<th>Follow-up Time</th>
<th>Exercisers: Mean</th>
<th>Controls: Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Month</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001
Percent Change in Insulin Biomarkers by Adherence Levels

Friedenreich et al., *Endocrine Related Cancer* 2011;18:357-69
Inflammatory Marker Outcomes

Friedenreich et al., Cancer Prev Research 2011;4 (epub)
Impact of Exercise Intervention on C-reactive Protein

Mean Change in CRP During 12 Months Follow-up by Groups

P = 0.005

Percent Change of C-reactive Protein by Average Weekly Duration of Exercise

Ratio of 12 months: baseline of CRP, by controls and three exercise adherence groups

- Controls
- <150 min/wk
- 150-225 min/wk
- >225 min/wk

P for trend = 0.021

Friedenreich CM et al. Cancer Prev Research 2011;4
## Main Findings on Exercise and Breast Cancer Biomarkers

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PATH Trial</th>
<th>SHAPE Trial</th>
<th>ALPHA Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex hormones</strong></td>
<td>↓estrone and estradiol restricted to women who lost &gt;2% body fat</td>
<td>No effect on estrogens or androgens</td>
<td>↓estradiol and ↑SHBG</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>↓ all adiposity measures</td>
<td>↓ body fat but no effect on weight, BMI or hip circumference</td>
<td>↓all adiposity measures</td>
</tr>
<tr>
<td><strong>Insulin resistance</strong></td>
<td>↓insulin, leptin, HOMA score</td>
<td>Not reported</td>
<td>↓insulin, HOMA-IR, leptin, adiponectin/leptin ratio</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>↓C-reactive protein</td>
<td>Not reported</td>
<td>↓ C-reactive protein</td>
</tr>
<tr>
<td><strong>Publications</strong></td>
<td>Irwin 2003; McTiernan 2004; Frank 2005; Campbell 2009</td>
<td>Monninkhof 2009; Velthuis, 2009</td>
<td>Friedenreich 2010a; Friedenreich 2010b, Friedenreich 2011</td>
</tr>
</tbody>
</table>
Breast Cancer and Exercise Trial in Alberta: Study Design

Recruit 400 postmenopausal healthy women 50-74 years

Randomize

High volume exercise group
(5 days/wk x 60 mins/session @ 70-80% max HRR)

Moderate volume exercise group
(5 days/wk x 30 mins/session @ 70-80% max HRR)

Compare high vs. moderate exercise groups on endogenous sex hormones, obesity and inflammatory markers, insulin, glucose

Follow-up at 24 months: examine exercise maintenance and long term effect on biomarkers

Funded by ACF and CCSRI
Alberta Moving Beyond Breast Cancer (AMBER) Cohort Study
**Alberta Moving Beyond Breast Cancer Cohort (AMBER) Study**

**Study Time Line and Design**

- **2012-2017**
  - Enroll 1500 incident Stage I-IIIb breast cancer cases
  - Measure physical activity, health-related fitness, determinants of PA, patient-related outcomes, biomarkers, lymphedema
  - Repeat baseline measurements at 1, 3 and 5 years post-diagnosis

- **2017-2022**
  - Follow-up for mortality outcomes (disease-specific and all cause)

How can physical activity and health related fitness be used to inform clinical recommendations for improving patient-related outcomes and survival in breast cancer survivors?
Figure 6. Hypothesized biologic model relating proposed biomarkers to long-term physical activity, health-related fitness, breast cancer therapies and breast cancer mortality and recurrence.

- **BODY FAT**
  - HT affects bone mineral density; CT, HT may ↑ fat mass
  - ↑ BMI, ↑ body weight
  - ↑ androgens, ↓ SHBG
  - ↓ leptin, ↓ adiponectin
  - ↑ TNF-α, ↑ IL-6, ↑ C-reactive protein

- **Ovaries premenopause**
  - Oophorectomy, ovarian ablation, CT can induce menopause
  - ↑ estrogens, ↓ SHBG
  - ↑ insulin
  - ↑ IGF-1, ↓ IGFBP-3

- **HT**

- **Increased breast cancer mortality and recurrence**

- **CT**

- **HRF**

- **PA**

CT - chemotherapy; HRF - health-related fitness; HT - hormone therapy; PA - physical activity
Lifestyle and Breast Cancer Risk: Current State of the Scientific Inquiry

- NCI Workshop on Feasibility of Physical Activity and Weight Control Trial to Prevent Breast Cancer, March, 2006

**Background:**
- Diabetes Prevention Program (DPP)
- Dietary Approaches to Prevent Hypertension (DASH)
- Look Action for Health in Diabetes (Look AHEAD)

**Recommended study design:**
- **Primary endpoint:** breast cancer
- **Inclusion criteria:** age 45-75, postmenopausal, Gail score > 1.7
- **Exclusion criteria:** invasive breast cancer, DCIS, use of SERMs
- **Intervention:** calorie-controlled diet and 150-225 mins/wk of moderate intensity activity, 5 days or more per week
- **Trial goal:** 10% weight loss if BMI > 25 kg/m², overall 5-7% avg wt loss
- **Sample size:** Estimated breast cancer risk reduction with increased physical activity would be 18% and for weight control 12% with an additive effect with the two components for a 30% reduction in risk
Sample Size for RCT of PA and Weight Control for Primary Prevention of Breast Cancer

For a 20% risk reduction, power of 85-90% and 5 year follow-up would need 26,000-30,000 women

No trial currently planned
Future Research Directions

- Investigate sedentary behaviour and light intensity activity as risk factors for cancers
- Improve PA measurements including objective assessments
- More precision on type, dose, timing of activity in relation to risk and survival
- Examine effect modification by other factors
- Conduct prospective observational studies of new biomarkers
- Need more mechanistic RCTs that evaluate different doses and types of PA
- Need more research on PA and survival at other cancer sites
- **Ultimate objective:** provide more quantitative data to enhance public health recommendations regarding PA type, dose, timing for cancer risk reduction and improved survival
Conclusion

- Strong, consistent evidence worldwide that PA reduces colon, breast, endometrial cancer risks and possibly also prostate, lung and ovarian cancers by 10-30% with a dose-response effect and some sub-group effects.

  - Several plausible biologic mechanisms exist
  - RCTs are finding support for these mechanisms

- PA also improves survival after breast, colon and prostate cancers by 30% or more.
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  - CIHR
  - AI-HS

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  - Alberta Cancer Foundation
  - CIHR
  - Canadian Breast Cancer Research Alliance

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- **Others:** Drs. Rollin Brant, Yutaka Yasui, Anne McTiernan, Rachel Ballard-Barbash, Tim Terry, Charlotte Jones, Melinda Irwin, Martin Yaffe, Norman Boyd, Frank Stanczyk, Robert Millikan, David Lau, John Mackey, Jeff Vallance, Nicole Culos-Reed, Margaret McNeely, Kristin Campbell, Kristina Karvinen

- **Trainees:** Dr. Christy Woolcott, Ame-Lia Tamburrini, Rita Biel, Dr. Brigid Lynch, Dr. Fabiola Aparicio-Ting, Dr. Shannon Conroy

- **Staff:** Department of Population Health Research, Alberta Health Services-Cancer Care