Exercise as Synergistic Medicine for Cancer

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Co-Director, Exercise Medicine Research Institute
Cancer Council Western Australia Research Fellow

NHMRC Centre for Research Excellence
PROSTATE CANCER SURVIVORSHIP

Exercise Medicine Research Institute
vario health clinic
Overview

- Developments in *Exercise Oncology*
- Clinical questions in *Exercise Oncology*
- Implications for disease outcome
- Pre-clinical studies/ biological mechanisms
- Exercise guideline/recommendations
"Historically clinicians advised cancer patients to rest and avoid activity given the rigors of undertaking treatment."

"Three decades of research is showing that exercise plays a vital role in cancer prevention and control."
Physical Activity & Cancer Control Framework

Specific phases along the cancer continuum

**DIAGNOSIS**

- Prediagnosis

**CANCER CONTROL CATEGORIES**

- Treatment preparation/effectiveness
- Recovery/rehabilitation
- Disease prevention/health promotion
- Palliation
- Survival

**postdiagnosis**
Exercise Oncology in *Journal of Clinical Oncology* - 2001-2016

First RCTs in *Journal of Clinical Oncology* (JCO)

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Meyerhardt et al.</td>
<td>Segal et al.</td>
</tr>
<tr>
<td>2005</td>
<td>Courneya et al.</td>
<td>Galvão and Newton</td>
</tr>
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<td>2009</td>
<td>Courneya et al.</td>
<td>Segal et al.</td>
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<td>2013</td>
<td>Rudden et al.</td>
<td>Kenfield et al.</td>
</tr>
<tr>
<td>2016</td>
<td>Irwin et al.</td>
<td>ASCO - Obesity</td>
</tr>
<tr>
<td></td>
<td>Waart et al.</td>
<td>ASCO - PCa</td>
</tr>
<tr>
<td></td>
<td>Jones</td>
<td>ASCO - Breast</td>
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</tbody>
</table>

*Vol 2, No 1 - June - July 2010*
EX can blunt reduced physical functioning
EX improved aerobic capacity (3.5 mL/kg/min; P = .01) - not receiving chemotherapy
EX reduced body weight (24.8 kg; P < .05) - participants not receiving chemotherapy
No major adverse events
Peak oxygen consumption increased EX vs CON (0.29 L/min; 95% CI, 0.18 to 0.40; P < .001)
Overall QOL increased EX vs CON (8.8 points; 95% CI, 3.6 to 14.0; P=.001)
Change in peak oxygen consumption correlated with change in QOL (r =0.45; P < .01)
No major adverse events
EX had less interference from fatigue on activities of daily living \((P=0.002)\) than CON.

Ex had higher quality of life \((P=0.001)\) than CON.
As clinicians, we are often asked: “what more can I do to improve my overall health”?

“They respond directly to concerns identified by patients and families and do so in the context of randomized controlled trials…importance of studies of this type will only increase.”
Review of Exercise Intervention Studies in Cancer Patients

Daniel A. Galvão and Robert U. Newton

By June 2004 – 20+ studies; majority of studies with breast cancer using cardiovascular exercise

“Evidence underlines the preliminary positive physiological and psychological benefits from exercise when undertaken during or after cancer treatment.”

Table 3. Guidelines and Possible Physiological Outcomes from Exercise in Cancer Patients

<table>
<thead>
<tr>
<th>Exercise Modality</th>
<th>Intensity</th>
<th>Frequency (/week)</th>
<th>Volume</th>
<th>Dosage</th>
<th>Cancer Relevant Expected Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular exercises</td>
<td>55-90% MHR, 40-85% MHRR</td>
<td>3-5</td>
<td>20-60 minutes</td>
<td>Continuous or intermittent</td>
<td>Carbonipulmonary function, Insulin sensitivity*, HDL*, LDL*, Fat mass, Fatigue</td>
</tr>
<tr>
<td>Anabolic/resistance exercises</td>
<td>50-80% 1-RM, 6-12 RM</td>
<td>1-3</td>
<td>1-4 sets per muscle group</td>
<td></td>
<td>Muscle mass*, Muscle strength, Muscle power*, Muscle endurance, BMD*, FP, Fatigue, Resting metabolic rate*, Fat mass*</td>
</tr>
<tr>
<td>Flexibility exercises</td>
<td>?</td>
<td>2-3</td>
<td>2-4 sets per muscle group</td>
<td>10-30 seconds</td>
<td>Range of motion</td>
</tr>
</tbody>
</table>

Abbreviations: ↑, increase; ↓, decrease; ↔, no change; MHR, maximum heart rate; MHRR, maximum heart rate reserve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMD, bone mineral density; FP, functional performance; RM, repetition maximum.

*Data not available with cancer population, recommendation based from studies undertaken with noncancer population.
American Cancer Society

Exercise & Sports Science Australia

American College of Sports Medicine

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Major Developments ACSM 2010

1. Exercise and cancer prevention

One in three Australians are now one in four women will be directly affected by cancer before the age of 75, with melanoma, prostate, colorectal, breast and lung cancers comprising the most common types. There are an estimated 100,000 new cancer cases and 42,000 replacements cancer deaths each year in Australia, and consequently cancer represents a major public health concern. While the causes for many cancers remain unknown, lifestyle factors including physical activity levels are considered contributory and attributable for some. 

Exercise has been linked to improved cancer survival rates through enhanced anti-cancer effects including reduced risk of some cancers, improved survival rate for cancer patients, and improved quality of life. The benefits of exercise on cancer patients can be long-term and can extend to cancer survivors. 

Exercise and cancer survivors have been shown to experience improved physical fitness, reduced fatigue, improved quality of life, and improved mood and psychological well-being. 

However, the benefits of exercise for cancer prevention and management cannot be overstated. Exercise has been shown to reduce the risk of cancer recurrence and improved cancer survival rates. 

2. Exercise and cancer treatment

Exercise has been shown to improve overall quality of life for cancer patients undergoing treatment. Exercise can improve mood, reduce fatigue, and improve sleep quality. Exercise can also improve physical function and reduce the risk of complications associated with cancer treatment. 

Exercise can also improve immune function and reduce the risk of infections associated with cancer treatment. Exercise has been shown to improve survival rates for cancer patients undergoing treatment. 

However, the benefits of exercise for cancer patients undergoing treatment cannot be overstated. Exercise has been shown to improve overall quality of life, reduce the risk of cancer recurrence, and improve cancer survival rates. 

3. Exercise and cancer prognosis

Exercise has been shown to improve overall quality of life for cancer patients with advanced disease. Exercise can improve mood, reduce fatigue, and improve sleep quality. Exercise can also improve physical function and reduce the risk of complications associated with cancer treatment. 

Exercise has been shown to improve cancer survival rates for cancer patients with advanced disease. 

However, the benefits of exercise for cancer patients with advanced disease cannot be overstated. Exercise has been shown to improve overall quality of life, reduce the risk of cancer recurrence, and improve cancer survival rates.
American College of Sports Medicine
Roundtable on Exercise Guidelines for Cancer Survivors

EXPERT PANEL
Kathryn H. Schmitz, PhD, MPH, FACSM
Kerry S. Courneya, PhD
Charles Matthews, PhD, FACSM
Wendy Demark-Wahnefried, PhD
Daniel A. Galvão, PhD
Bernardine M. Pinto, PhD
Melinda L. Irwin, PhD, FACSM
Kathleen Y. Wolin, ScD, FACSM
Roanne J. Segal, MD, FRCP
Alejandro Lucia, MD, PhD
Carole M. Schneider, PhD, FACSM
Vivian E. von Gruenigen, MD
Anna L. Schwartz, PhD, FAAN

Focus on adult cancers and sites with the most evidence
Evaluation of Evidence A-D
Breast, Prostate, Colon, Hematological, Gynecological
85 studies

A - overwhelming data from RCTs
B - few RCTs exist
C - uncontrolled, nonrandomized and/or observational studies
D - insufficient for categories A-C
Breast Cancer
During chemotherapy or radiation
Results from 22 RCTs

- Evidence category A – Safety
- Evidence category A – Aerobic Fitness
- Evidence category A – Muscle Strength
- Evidence category A – Fatigue
- Evidence category B – Body Size/Composition
- Evidence category B – Quality of Life
- Evidence category B – Physical Function
- Evidence category B – Anxiety

Prostate Cancer
During and after treatment
Effects of exercise on key endpoints

Results from 12 RCTs

- Evidence category A – Safety
- Evidence category A – Aerobic Fitness
- Evidence category A – Muscle Strength
- Evidence category A – Fatigue
- Evidence category B – Body Size/Composition
- Evidence category B – Quality of Life
- Evidence category B – Physical Function

• can exercise help manage treatment side effects/reduce treatment toxicities (e.g. muscle loss, fatigue)?
• will exercise interfere with treatment or response?
• can exercise lower the risk of cancer recurrence, delay progression and improve survival?
• what are the potential biological mechanisms?
• what is the optimal exercise program for benefit?
Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer

Daniel A. Galvão\textsuperscript{1,2}, Nigel A. Spry\textsuperscript{3,4}, Dennis R. Taaffe\textsuperscript{5}, Robert U. Newton\textsuperscript{1,2}, John Stanley\textsuperscript{6}, Tom Shannon\textsuperscript{6}, Chris Rowling\textsuperscript{7} and Richard Prince\textsuperscript{3,4}

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>36 weeks</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>22.6 (3.1)</td>
<td>0.23 (0.05)</td>
<td>-98.2 (0.5)*</td>
</tr>
<tr>
<td>Testosterone</td>
<td>15.1 (0.6)</td>
<td>0.80 (0.03)</td>
<td>-93.3 (0.3)*</td>
</tr>
<tr>
<td>Whole body LM (kg)</td>
<td>55.8 (0.8)</td>
<td>54.4 (0.8)</td>
<td>-2.4 (0.4)*</td>
</tr>
<tr>
<td>ASM (kg)</td>
<td>23.4 (0.3)</td>
<td>22.4 (0.3)</td>
<td>-4.2 (0.5)*</td>
</tr>
<tr>
<td>Whole body FM (kg)</td>
<td>20.8 (0.7)</td>
<td>23.1 (0.7)</td>
<td>+13.8 (2.3)*</td>
</tr>
<tr>
<td>Trunk FM (kg)</td>
<td>12.1 (0.4)</td>
<td>13.1 (0.4)</td>
<td>+12.0 (2.5)*</td>
</tr>
</tbody>
</table>

Galvão et al. BJU International 2008;102:44-47
Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive cross-sectional investigation

DA Galvão¹, DR Taaffe², N Spry³,⁴, D Joseph³,⁴, D Turner¹ and RU Newton¹

<table>
<thead>
<tr>
<th>Variable</th>
<th>AST (n = 48)</th>
<th>Controls (n = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-m usual walk (s)</td>
<td>4.8 ± 0.6</td>
<td>4.5 ± 0.6</td>
<td>0.042</td>
</tr>
<tr>
<td>6-m fast walk (s)</td>
<td>3.7 ± 0.5</td>
<td>3.5 ± 0.3</td>
<td>0.013</td>
</tr>
<tr>
<td>400-m walk (s)</td>
<td>274.3 ± 32.7</td>
<td>256.1 ± 34.0</td>
<td>0.005</td>
</tr>
<tr>
<td>6 m backward walk (s)</td>
<td>23.8 ± 13.8</td>
<td>19.9 ± 6.3</td>
<td>0.035</td>
</tr>
<tr>
<td>Chair rise (s)</td>
<td>13.5 ± 2.8</td>
<td>12.0 ± 2.6</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Muscle strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest press (kg)</td>
<td>32.4 ± 10.5</td>
<td>37.5 ± 9.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Seated row (kg)</td>
<td>38.7 ± 6.6</td>
<td>42.4 ± 8.4</td>
<td>0.014</td>
</tr>
<tr>
<td>Leg press (kg)</td>
<td>91.0 ± 41.4</td>
<td>86.8 ± 37.4</td>
<td>0.567</td>
</tr>
<tr>
<td>Leg extension (kg)</td>
<td>36.3 ± 13.0</td>
<td>44.9 ± 12.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Muscle endurance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest press (rep)</td>
<td>11.6 ± 4.1</td>
<td>11.4 ± 5.0</td>
<td>0.819</td>
</tr>
<tr>
<td>Leg press (rep)</td>
<td>18.0 ± 6.7</td>
<td>17.7 ± 7.5</td>
<td>0.867</td>
</tr>
</tbody>
</table>

Abbreviations: AST, androgen suppression therapy; rep, repetitions performed at 70% of 1 repetition maximum (1-RM).
Muscle Strength and Function

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Diagnosis (d)</th>
<th>ADT (d)</th>
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<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>336</td>
<td>65*</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>92</td>
<td>88*</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>184</td>
<td>120*</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>363</td>
<td>210*</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>365</td>
<td>300*</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>732</td>
<td>420†</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>2520</td>
<td>720†</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>1821</td>
<td>1622†</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>3605</td>
<td>3240†</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>3960</td>
<td>3955†</td>
</tr>
</tbody>
</table>

Min: 59  92  65
Max: 82  3960  3955
Mean: 70.3  1397.8  1135.6
SD: 8.3  1481.8  1360.4

Percent Change (%)

The Effect of Resistance Exercise on Physical Function/Muscle Thickness

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 10</th>
<th>Week 20</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng·mL⁻¹)</td>
<td>3.09 ± 6.58</td>
<td>1.28 ± 1.58</td>
<td>0.90 ± 1.13</td>
<td>0.374</td>
</tr>
<tr>
<td>Free testosterone (pg·mL⁻¹)</td>
<td>2.13 ± 3.64</td>
<td>2.15 ± 3.61</td>
<td>1.56 ± 3.68</td>
<td>0.532</td>
</tr>
<tr>
<td>GH (ng·mL⁻¹)</td>
<td>0.72 ± 0.75</td>
<td>0.83 ± 0.78</td>
<td>0.48 ± 0.37</td>
<td>0.239</td>
</tr>
<tr>
<td>Cortisol (ng·mL⁻¹)</td>
<td>10.63 ± 3.54</td>
<td>10.35 ± 3.32</td>
<td>10.42 ± 3.67</td>
<td>0.979</td>
</tr>
<tr>
<td>Hemoglobin (g·L⁻¹)</td>
<td>141.3 ± 13.1</td>
<td>142.3 ± 14.4</td>
<td>141.2 ± 13.5</td>
<td>0.913</td>
</tr>
</tbody>
</table>

- Quadriceps Muscle Thickness Increase by 15% \( P=0.050 \) B-Mode Ultrasound

Combined Resistance and Aerobic Exercise Program Reverses Muscle Loss in Men Undergoing Androgen Suppression Therapy for Prostate Cancer Without Bone Metastases: A Randomized Controlled Trial

Daniel A. Galvão, Dennis R. Taaffe, Nigel Spry, David Joseph, and Robert U. Newton

<table>
<thead>
<tr>
<th>Design</th>
<th>RCT</th>
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<tr>
<td>Sample</td>
<td>57</td>
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<tr>
<td>Intervention</td>
<td>12-week (2x) resistance &amp; aerobic</td>
</tr>
<tr>
<td>Protocol</td>
<td>2-4 sets 6-12 RM 15-20 min 60%-85% HRmax 10-13 RPE</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Lean mass</td>
</tr>
</tbody>
</table>

RPE, repetitions per event
Combined Resistance and Aerobic Exercise Program Reverses Muscle Loss in Men Undergoing Androgen Suppression Therapy for Prostate Cancer Without Bone Metastases: A Randomized Controlled Trial

Daniel A. Galvão, Dennis R. Taaffe, Nigel Spry, David Joseph, and Robert U. Newton

Table 2. Total and Regional Body Composition Absolute Values and Change Over 12 Weeks Exercise Training

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>Adjusted Group Difference in Mean Change Over 12 Weeks</th>
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<tbody>
<tr>
<td></td>
<td>Exercise</td>
<td>Control</td>
<td>Exercise</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body</td>
<td>56.1</td>
<td>6.7</td>
<td>57.8</td>
</tr>
<tr>
<td>Upper limb</td>
<td>6.3</td>
<td>0.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Lower limb</td>
<td>17.2</td>
<td>2.5</td>
<td>18.0</td>
</tr>
<tr>
<td>ASM</td>
<td>23.5</td>
<td>3.4</td>
<td>24.6</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body</td>
<td>22.5</td>
<td>5.6</td>
<td>23.2</td>
</tr>
<tr>
<td>Trunk</td>
<td>12.2</td>
<td>3.3</td>
<td>12.4</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>27.5</td>
<td>4.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Whole body mass, kg</td>
<td>80.7</td>
<td>10.3</td>
<td>89.2</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; ASM, appendicular skeletal muscle.
*Between group change by analysis of covariance (adjusted for baseline, androgen suppression treatment time, use of antiandrogen, number of medications, and education).

Combined Resistance and Aerobic Exercise Program Reverses Muscle Loss in Men Undergoing Androgen Suppression Therapy for Prostate Cancer Without Bone Metastases: A Randomized Controlled Trial

Daniel A. Galvão, Dennis R. Taaffe, Nigel Spry, David Joseph, and Robert U. Newton

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>EX&gt;CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean Mass</td>
<td>~1 kg</td>
<td></td>
</tr>
<tr>
<td>Muscle Strength</td>
<td>3-31 kg</td>
<td>EX&gt;CO</td>
</tr>
<tr>
<td>Aerobic Capacity</td>
<td>-7 sec</td>
<td>EX&gt;CO</td>
</tr>
<tr>
<td>Dynamic Balance</td>
<td>-4 sec</td>
<td>EX&gt;CO</td>
</tr>
<tr>
<td>Vitality</td>
<td>+13</td>
<td>EX&gt;CO</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-11</td>
<td>EX&gt;CO</td>
</tr>
<tr>
<td>CRP</td>
<td>-3.5 mg/L</td>
<td>EX&gt;CO</td>
</tr>
</tbody>
</table>

CO, usual care control; CRP, C-reactive protein; EX, exercise.

Football training improves lean body mass in men with prostate cancer undergoing androgen deprivation therapy

J. Uth¹, T. Hornstrup², J. F. Schmidt², J. F. Christensen¹, C. Frandsen¹, K. B. Christensen³, E. W. Helge², K. Brasso¹, M. Rørth¹, J. Midtgaard¹,², P. Krstrup¹,²,⁷

doi: 10.1111/sms.12260
**Study protocol**

**A phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer**

Robert U Newton*1, Dennis R Taaffe2, Nigel Spry3,4, Robert A Gardiner5, Gregory Levin1, Bradley Wall1, David Joseph3,4, Suzanne K Chambers6 and Daniel A Galvão1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ADT (~5 months)</th>
<th>Design</th>
<th>RCT (3-arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>12 months</td>
<td>Sample</td>
<td>164</td>
</tr>
<tr>
<td>Protocol</td>
<td>(1) Supervised resistance/impact vs. (2) Supervised resistance/aerobic vs. (3) Usual care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Bone mass (lumbar spine &amp; hip BMD); lean mass; VO2, fatigue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wall et al. in review MSSE.
Taaffe et al. European Urology 10 Feb 2017
Quartiles of Fatigue and Vitality

Fatigue

- EORTC QLQ-C30 – fatigue is a 3-item subscale
- Vitality scale of the SF-36 – a 4-item domain with scores from 0-100

Vitality

P < 0.001

Taffee, Newton et al. European Urology 2017
# Exercise After Treatment

A Multicentre Year-long Randomised Controlled Trial of Exercise Training Targeting Physical Functioning in Men with Prostate Cancer Previously Treated with Androgen Suppression and Radiation from TROG 03.04 RADAR


<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>(&gt;5 yr post diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>RCT (2-arm)</td>
</tr>
<tr>
<td>Sample</td>
<td>100</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>Resistance &amp; aerobic exercise (6 months supervised + 6 months home based) vs. physical activity education material</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Cardiorespiratory fitness</td>
</tr>
</tbody>
</table>

**Exercise vs Physical Activity Recommendations After Treatment**

**Graph A**
- 400-m walk time/sec
- **P=.028**
- Baseline: 288.0 (7.6)
- 6 Months: 279.4 (8.4)
- 12 Months: 270.4 (7.3)

**Graph B**
- Chair rise time/sec
- **P=.001**
- Baseline: 12.8 (0.4)
- 6 Months: 11.9 (0.5)
- 12 Months: 11.7 (0.4)

**Graph C**
- 1-RM Chest Press kg
- **P=.004**
- Baseline: 38.6 (1.8)
- 6 Months: 40.4 (1.8)
- 12 Months: 39.5 (2.1)

**Graph D**
- 1-RM Leg Extension kg
- **P=.011**
- Baseline: 51.0 (2.9)
- 6 Months: 50.7 (3.0)
- 12 Months: 50.2 (2.8)

PA, physical activity.
Exercise After Treatment

A Multicentre Year-long Randomised Controlled Trial of Exercise Training Targeting Physical Functioning in Men with Prostate Cancer Previously Treated with Androgen Suppression and Radiation from TROG 03.04 RADAR

Daniel A. Galvão a,*, Nigel Spry a,b,c, James Denham d,e, Dennis R. Taaffe a,f, Prue Cormie a, David Joseph a,b,c, David S. Lamb g, Suzanne K. Chambers a,h,i, Robert U. Newton a

Adjusted Group Difference in Mean Change Over 6- and 12-Months*

Exercise Oncology
Research/clinical questions

- can exercise help manage treatment side effects/reduce treatment toxicities (e.g. muscle loss, fatigue)?
- **will exercise interfere with treatment or response?**
- can exercise lower the risk of cancer recurrence, delay progression and improve survival?
- what are the potential biological mechanisms?
- what is the optimal exercise program for benefit?
Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial

Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, and Donald C. McKenzie

START trial - Multicenter RCT 24 weeks exercise intervention (different modes) n=242 breast cancer patients initiating chemotherapy (median 17 weeks)

78 (71) assigned to aerobic exercise
56 received intervention
22 did not complete ≥ 66% of supervised exercise

82 (73) assigned to resistance exercise
56 received intervention
26 did not complete ≥ 66% of supervised exercise

82 (75) assigned to usual care
82 received intervention
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Change in VO2max

Change in Muscle Strength

Courneya et al. JCO 2007;25:4396-4404
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Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, and Donald C. McKenzie

Percentage of participants who received 85\% of their planned RDI was:

- 65.9\% UC group
- 78.0\% RET group
- 74.4\% AET group

Chemotherapy Received (RDI)

P=.033

P=.266

Courneya et al. JCO 2007;25:4396-4404
Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients

Kerry S. Courneya, Christopher M. Sellar, Clare Stevinson, Margaret L. McNeely, Carolyn J. Peddle, Christine M. Friedenreich, Keith Tankel, Sanraj Basi, Neil Chua, Alex Mazurek, and Tony Reiman

Patients stratified by disease type (HL v NHL aggressive v NHL indolent) and treatment status (receiving chemotherapy v no treatment) randomly assigned (n = 122)

- Patients assigned to usual care (n = 62)
  - Reported no regular vigorous exercise during intervention (n = 49; 79%)
  - Reported regular vigorous exercise during intervention (n = 13; 21%)
  - Mean change in vigorous exercise from baseline: -4 minutes

- Patients assigned to supervised aerobic exercise (n = 60)
  - Attended ≥ 66% of sessions (n = 45; 75%)
  - Attended ≥ 80% of sessions (n = 39; 65%)
  - Attended 100% of sessions (n = 21; 35%)
Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients

Patients stratified by disease type (HL v NHL aggressive v NHL indolent) and treatment status (receiving chemotherapy v no treatment) randomly assigned (n = 122)
Exercise Oncology
Research/clinical questions

• can exercise help manage treatment side effects/reduce treatment toxicities (e.g. muscle loss, fatigue)?
• will exercise interfere with treatment or response?
• can exercise lower the risk of cancer recurrence, delay progression and improve survival?
• what are the potential biological mechanisms?
• what is the optimal exercise program for benefit?
Prospective Cohort Studies of Post Diagnosis Exercise and Cancer-Specific Mortality

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. Events/Cases</th>
<th>Effect Estimate</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Breast</td>
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<tr>
<td>Bradshaw, 2014 (10)</td>
<td>195/1,033</td>
<td>0.27</td>
<td>0.17-0.42</td>
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<tr>
<td>Holick, 2008 (26)</td>
<td>109/4,482</td>
<td>0.49</td>
<td>0.27-0.89</td>
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<tr>
<td>Colorectal</td>
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<tr>
<td>Kuiper, 2014 (10)</td>
<td>337/1,021</td>
<td>0.62</td>
<td>0.44-0.87</td>
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<tr>
<td>Inoue-Choi, 2013 (21)</td>
<td>184/2,017</td>
<td>0.72</td>
<td>0.47-1.10</td>
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<tr>
<td>Overall</td>
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<tr>
<td>Pooled Estimate (I²=47.9%)</td>
<td>3,307/38,580</td>
<td>0.63</td>
<td>0.54-0.73</td>
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Across 24 studies (n=38,580) of breast, colorectal, prostate, and mixed cancer patients, there was a 37% reduction in risk of cancer-specific mortality, comparing the most versus the least active patients (pooled relative risk=0.63, 95% CI: 0.54-0.73)
Prospective Cohort Studies of Post Diagnosis Exercise and Cancer Recurrence and Progression

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<tr>
<td>Overall</td>
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Risks of recurrence or progression were also reduced (pooled relative risk=0.65, 95% CI: 0.56-0.75)

## Physical activity and survival among long-term cancer survivor and non-cancer cohorts

Anthony Gunnell\(^1,2\), Sarah Joyce\(^3\), Stephanie Tomlin\(^3\), Dennis R. Taaffe\(^1,4,5\), Prue Cormie\(^6\), Robert U. Newton\(^1,7,4\), David Joseph\(^1,8\), Nigel Spry\(^1,9\), Kristjana Einarsdottir\(^10\), Daniel A. Galvão\(^1,4\)

<table>
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<tr>
<th></th>
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<th>Cancer Specific Death</th>
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<th>All-Cause Death</th>
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<tr>
<td></td>
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<td>HR 0.62 (0.36-1.06)</td>
<td>150-359 minutes</td>
<td>HR 0.30 (0.13-0.70)</td>
<td>HR 0.70 (0.46-1.08)</td>
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<tr>
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<td>HR 0.55 (0.28-1.08)</td>
<td>150-359 minutes</td>
<td>HR 0.55 (0.31-0.97)</td>
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<td>HR 0.30 (0.13-0.70)</td>
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<td>HR 0.30 (0.21-0.79)</td>
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N=1589 Western Australian Cancer Survivors; 8.8 years follow-up Cox proportional hazards regression

Gunnell et al. Frontiers Public Health 2017
No established recommendations exist for delaying (or preventing) the progression of low-risk PCa cancer

*Preliminary* evidence suggests that lifestyle and/or exercise interventions might have therapeutic potential:

*Delay disease progression*

*Transition to active therapy*

Lifestyle interventions during active surveillance

- PSA decreased 4% in the experimental group but increased 6% in the control group (p=0.016)
- n=6 controls undertook active treatment before 12 months (3x prostatectomy; 1 external beam radiation; 1 brachytherapy; 1 ADT) due to increased PSA (n=4) and MRI (n=2)
- The growth of LNCaP prostate cancer cells was inhibited ~8 times more by the serum from the experimental than control group (70% vs 9%, p<0.001)
Clinical Events in Prostate Cancer Lifestyle Trial: Results From Two Years of Follow-Up

Joanne Frattaroli, Gerdi Weidner, Ann M. Dnistrian, Colleen Kemp, Jennifer J. Daubenmier, Ruth O. Marlin, Lila Crutchfield, Loren Yglecias, Peter R. Carroll, and Dean Ornish


- Prostate Cancer Lifestyle Trial (PCLT)
- 2 years of follow-up, 13 of 49 (27%) control patients and 2 of 43 (5%) experimental patients had undergone conventional prostate cancer treatment (radical prostatectomy, radiotherapy, or ADT, P<0.05)
  - 4 due to PSA increase; 4 due to PSA increase + unfavorable biopsy; 5 due to MRI compared with earlier findings (controls)
  - 1 due to PSA increase; 1 due to cancer-related anxiety (intervention)
- No differences were found between the untreated experimental and untreated control patients in PSA change or velocity at the end of 2 years
Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study

Dean Ornish, Jue Lin, June M Chan, Elissa Epel, Colleen Kemp, Gerdi Weidner, Ruth Marlin, Steven J Frenda, Mark Jesus M Magbanua, Jennifer Daubenmier, Ivette Estay, Nancy K Hills, Nita Chainani-Wu, Peter R Carroll, Elizabeth H Blackburn

Telomere shortness in humans is a prognostic marker of ageing, disease, and premature morbidity

- Intervention associated with increases in relative telomere length after 5 years.

*Figure 1:* Mean change in relative telomere length over 5 years with lifestyle intervention compared with control
Vertical lines represent 1 SEM. T/S = telomere to single-copy gene ratio units.

*Figure 2:* Changes in telomere length for individual participants in the lifestyle intervention and control groups
T/S = telomere to single-copy gene ratio units.
Exercise Oncology
Research/clinical questions

- Can exercise help manage treatment side effects/reduce treatment toxicities (e.g. muscle loss, fatigue)?
- Will exercise interfere with treatment or response?
- Can exercise lower the risk of cancer recurrence, delay progression and improve survival?
- What are the potential biological mechanisms?
- What is the optimal exercise program for benefit?
Potential Mechanisms

Research in *Exercise Oncology* still lacks a mechanistic understanding of how exercise directly influences tumor biology and growth.

During a bout of exercise, circulation of immune cells increase.

Increase in NK cells frequency is more pronounced than the increase in T and B cells.

Catecholamine levels, which also rise during exercise, are thought to drive the mobilization of immune cells into circulation.

At exercise cessation, the induced levels of myokines are proposed to affect immune cells redistribution and activation.
Exercise-Dependent Regulation of NK Cells in Cancer Protection

Manja Idom\textsuperscript{1} and Pernille Hojman\textsuperscript{2,*}

- Mobilization of NK cells are affected by:
  - muscle derived myokines
  - exercise-dependent hyperthermia
  - intratumoral vascularization and perfusion
- subsequently inducing the regulation, redistribution, and activation of mobilized NK cells
Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

Line Pedersen, Manja Idorn, Gitte H. Olofsson, Britt Lauenborg, Intawat Nookaew, Rasmus Hvass Hansen, Helle Hjorth Johannesen, Jürgen C. Becker, Katrine S. Pedersen, Christine Dethlefsen, Jens Nielsen, Julie Gehl, Bente K. Pedersen, Per thor Straten, and Pernille Hojman

C

D

E

CON

EX

Pedersen et al. Cell Metabolism 2016
Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

Line Pedersen,1 Manja Idorn,2 Gitte H. Olofsson,2 Britt Lauenborg,1 Intawat Nookaew,3,4 Rasmus Hvass Hansen,5 Helle Hjorth Johannesen,5 Jürgen C. Becker,6 Katrine S. Pedersen,1 Christine Dethlefsen,1 Jens Nielsen,3 Julie Gehl,7 Bente K. Pedersen,1 Per thor Straten,2,8 and Pernille Hojman1,7,*

- Exercise reduces tumor incidence and growth in several mouse models
- Exercise increases NK cell infiltration, thereby controlling tumor growth
- Epinephrine mobilizes NK cells and β-blockade blunts the tumor suppression
- Exercise-induced muscle-derived IL-6 is involved in NK cell redistribution

Pedersen et al. Cell Metabolism 2016
Hypoxia and poor blood supply promote an aggressive phenotype
Can exercise increase blood perfusion and sensitivity to chemotherapy?
Modulation of Murine Breast Tumor Vascularity, Hypoxia and Chemotherapeutic Response by Exercise

Allison S. Betof, Christopher D. Lascola, Douglas Weitzel, Chelsea Landon, Peter M. Scarbrough, Gayathri R. Devi, Gregory Palmer, Lee W. Jones*, Mark W. Dewhirst*

Tumor volume (mm$^3$)

N=12/group

Chemotherapy treatment

Cardio-Oncology Research Program
exercise stimulates “productive” or “physiologic” angiogenesis and vascular normalization, leading to a substantial reduction in intratumoral hypoxia
Effect of Acute Exercise on Prostate Cancer Cell Growth

Helene Rundqvist¹*, Martin Augsten¹, Anna Strömberg², Eric Rullman², Sara Mijwel¹, Pedram Kharaziha¹, Theocharis Panaretakis¹, Thomas Gustafsson², Arne Östman¹

Figure 1. Growth of prostate cancer cells is reduced when exposed to exercise serum from 9 out of 10 individuals. A) Effect on LNCaP cells incubated for 48 hours with resting (rest) and exercise serum (exercise) from 10 individuals separately. B) Effect of the 10 individual serums on NIH3T3 cells. Data show all individuals separately (left panel) and as mean ± SEM. au (arbitrary units). π denotes a significant (p≤0.05) difference between incubation with rest and exercise serum.
Can exercise impact cancer outcomes?

Phase III Definitive trials
Colon - CHALLENGE
Prostate INTERVAL GAP-4

Disease and Overall Survival
Exercise Oncology
Research/clinical questions

- can exercise help manage treatment side effects/reduce treatment toxicities (e.g. muscle loss, fatigue)?
- will exercise interfere with treatment or response?
- can exercise lower the risk of cancer recurrence, delay progression and improve survival?
- what are the potential biological mechanisms?
- what is the optimal exercise program for benefit?
ACS/ACSM/ASCO/ESSA/NCCN Recommendations

- Engage in regular physical activity
- Avoid inactivity and return to normal daily activities as soon as possible
- Aim to exercise at least 150 min per week (aerobic) or 75 min (HI)
- Include strength training exercises at least 2 days per week

Considerations

- Long way since early studies from Winninghan (followed by RCTs in JCO)
- Exercise improves recovery/QoL after cancer
- Exercise manages symptoms during therapy (especially for symptomatic patients)
- Potential effects of exercise beyond symptoms/toxicities (cancer outcomes)
- Phase III Definitive trials (impact on disease endpoints)
- Biological mechanism
Robert Newton (ECU)
Dennis Taaffe (ECU)
Nigel Spry (SCGH, Genesis)
Suzanne Chambers (GU)
David Joseph (SCGH, ECU)
Frank Gardiner (RBH, UQ, ECU)
Nicolas Hart (ECU)
Favil Singh (ECU)
Dickon Hayne (FH, UWA)
Thomas Shannon (HH)
James Denham (UNew, NMH)
David Lamb (UOtago)
Carolyn McIntyre (ECU)
Akhil Hamid (PRH, ECU)
Evan Ng (RPH, Genesis)
Raphael Chee (Genesis, UWA)
Jerard Ghossein (JHC)
Siobhan Ng (SCGH, SJG)
Yvonne Zissiadis (Genesis, ECU)
**KEY CHALLENGES**
Men are living longer with prostate cancer. They are not surviving well. PC survivorship research & translation under-represented & poorly co-ordinated.

**KNOWLEDGE GENERATION**

**PSYCHOSOCIAL & PSYCHOSEXUAL HEALTH**
- Stepped model of psychosocial care
- Model of psychosexual care
- Test models in RCT

**EXERCISE MEDICINE**
- RCTs of exercise interventions
- Lifestyle programs

**ECONOMIC MODELLING**
- Heath economics model
- Suite of cost-effectiveness analyses

**SOCIODEMOGRAPHIC & GEOGRAPHIC INEQUALITIES IN OUTCOMES**
- National atlas of outcomes
- Contextual model to describe why inequalities exist
- Community & awareness action campaign

**OUTCOMES**

**High level evidence**: Descriptive & implementation research, systematic reviews & meta-analyses.
**Translation**: Guidelines & tool kits, community partnerships, policy & practice, clinical pathways, evidence-based survivorship guidelines.
**Sustainability**: Training new research & translation leaders, building national & global action networks.
Vision

To make physical activity a standard component of chronic disease prevention and management
Resources


**Factsheet library** exercising safely for 30 health conditions including diabetes, cancer, heart disease, arthritis, depression

**Screening tools** identify patient risk levels and determine an appropriate action plan

**Action Guides** and referral templates for Healthcare Providers

**APNA approved workshops** to build confidence, knowledge and skills

**Practice Support** Medical Software, waiting room materials, on the spot resources

**Position Statements** Written in collaboration with leading medical researchers

**Education** RACGP, ACRRM and