Exercise as Synergistic Medicine for Prostate Cancer

Daniel A. Galvão, PhD
Co-Director, Exercise Medicine Research Institute
Edith Cowan University
Cancer Council WA Research Fellow
Cardiorespiratory Capacity and Mortality Among Men

- 6213 men
- 6.2 years of follow-up
- 1256 deaths during follow-up
- peak exercise capacity strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease
- Each 1-MET increase in exercise capacity conferred a 12 percent improvement in survival

Muscle Strength and Mortality in Men

Association between muscular strength and mortality in men: prospective cohort study

- Aerobics centre longitudinal study
- 8762 men aged 20-80
- follow-up of 18.9 years
- 503 deaths occurred (145 cardiovascular disease, 199 cancer)
- Muscular strength is inversely and independently associated with death from all causes and cancer in men, even after adjusting for cardiorespiratory fitness and other potential confounders

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

**Review of Exercise Intervention Studies in Cancer Patients**

Daniel A. Galvão and Robert U. Newton

---

**Purpose:** Androgen deprivation therapy is a common treatment in men with prostate cancer that may cause fatigue, functional decline, increased body fatness, and loss of lean body tissue. These physical changes can negatively affect health-related quality of life. Resistance exercise may help to counter some of these side effects by reducing fatigue, elevating mood, building muscle mass, and reducing body fat.

**Methods:** In a two-site study, 155 men with prostate cancer who were scheduled to receive androgen deprivation therapy for at least 3 months after recruitment were randomly assigned to an intervention group that participated in a resistance exercise program three times per week for 12 weeks (82 men) or to a waiting list control group (73 men). The primary outcomes were fatigue and disease-specific quality of life as assessed by self-reported questionnaires after 12 weeks. Secondary outcomes were muscular fitness and body composition.

**Results:** Men assigned to resistance exercise had less interference from fatigue on activities of daily living \( (P = .002) \) and higher quality of life \( (P = .001) \) than men in the control group. Men in the intervention group demonstrated higher levels of upper body \( (P = .009) \) and lower body \( (P < .001) \) muscular fitness than men in the control group. The 12-week resistance exercise intervention did not improve body composition as measured by changes in body weight, body mass index, waist circumference, or subcutaneous skinfolds.

**Conclusion:** Resistance exercise reduces fatigue and improves quality of life and muscular fitness in men with prostate cancer receiving androgen deprivation therapy. This form of exercise can be an important component of supportive care for these patients.

National/International Position Stands Exercise and Cancer

American Cancer Society

Exercise & Sports Science Australia

American College of Sports Medicine

Headline:

Exercise and Sport Science position stand: Optimising cancer outcomes through exercise

Author:

Sandra C. Hayes,1,2, Rosalind R. Spence3, Daniel A. Galvão,1, Robert U. Newton2

Affiliation:

1 Australian Institute of Sport, Canberra, Australia; 2 Exercise Medicine Research Institute, Edith Cowan University, Australia; 3 Exercise and Sports Science Australia

Abstract:

Cancer represents a major public health concern in Australia. Cancer of the breast and the prostate are the two most common cancers in men and women. The Australian Cancer Society, the Exercise & Sports Science Australia, and the American College of Sports Medicine have joined forces to issue a joint statement on the importance of exercise and physical activity in the prevention and management of cancer. This statement is based on a review of the available scientific literature and is intended to guide health professionals in the development of programs and policies to promote exercise and physical activity among individuals at risk for, or diagnosed with, cancer.

1. Exercise and cancer prevention

One in three Australian men and one in four women will be directly affected by cancer before the age of 75, while menopause, prostate, colorectal, breast, and lung cancers are the most common cancers among men and women, respectively. The Australian Cancer Society, the Exercise & Sports Science Australia, and the American College of Sports Medicine have joined forces to issue a joint statement on the importance of exercise and physical activity in the prevention and management of cancer. This statement is based on a review of the available scientific literature and is intended to guide health professionals in the development of programs and policies to promote exercise and physical activity among individuals at risk for, or diagnosed with, cancer.

2. Exercise and cancer treatment

Exercise and physical activity during and after cancer treatment: An American Cancer Society guide for informed choices

Colette Doyle, Lawrence H. Kushi, Tim Bross, Kerry L. Caan, Wendy Demark-Wahnefried, Barbara Grant, Anne McTiernan, Cheryl L. Rock, Cynthia Thompson, Tod Gansler, Kimberly S. Andrews and for the 2006 Nutrition, Physical Activity and Cancer Survivorship Advisory Committee

CA Cancer J Clin. 2006;56:323-35

DOI: 10.3323/canjclin.56.4.325

This information is current as of May 30, 2011

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.cancer.org/.../596/532

To subscribe to the print issue of CA: A Cancer Journal for Clinicians, go to (US individuals only):
http://www.cancer.org/caonline/subscriptions/CAonline

About the Authors:

Colette Doyle, PhD, is a registered dietitian and an associate professor at the University of California, San Francisco (UCSF). She is also a member of the UCSF Cancer Prevention and Control Research Program. Dr. Doyle’s research focuses on nutrient-environment interactions and the role of diet in the prevention and management of cancer. She is also a member of the American Society for Nutrition and the American Society for Clinical Nutrition. Dr. Doyle received her PhD in nutrition from the University of Vermont.

Lawrence H. Kushi, MD, is a professor of medicine, nutrition, and population health at the Feinberg School of Medicine at Northwestern University. He is also the director of the Institute for Health Research and Education and the director of the Comprehensive Cancer Centers at Northwestern Memorial Hospital. Dr. Kushi’s research focuses on diet and lifestyle factors and their impact on the prevention and management of cancer. He is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. Kushi received his MD from the University of Chicago.

Tim Bross, MD, is a professor of medicine and the associate dean for clinical and translational science at the University of California, San Francisco (UCSF). He is also the director of the Cancer Prevention and Control Research Program at UCSF. Dr. Bross’s research focuses on the role of diet and lifestyle factors in the prevention and management of cancer. He is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. Bross received his MD from the University of California, San Francisco.

Barbara Grant, MD, is a professor of medicine at the University of California, San Francisco (UCSF) and the director of the Cancer Prevention and Control Research Program at UCSF. She is also the director of the Cancer Prevention and Control Research Program at UCSF. Dr. Grant’s research focuses on the role of diet and lifestyle factors in the prevention and management of cancer. She is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. Grant received her MD from the University of California, San Francisco.

Anne McTiernan, MD, is a professor of medicine at the University of Texas MD Anderson Cancer Center and the director of the Cancer Prevention and Control Research Program at UCSF. She is also the director of the Cancer Prevention and Control Research Program at UCSF. Dr. McTiernan’s research focuses on the role of diet and lifestyle factors in the prevention and management of cancer. She is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. McTiernan received her MD from the University of Texas MD Anderson Cancer Center.

Cheryl L. Rock, MD, is a professor of medicine at the University of California, San Francisco (UCSF) and the director of the Cancer Prevention and Control Research Program at UCSF. She is also the director of the Cancer Prevention and Control Research Program at UCSF. Dr. Rock’s research focuses on the role of diet and lifestyle factors in the prevention and management of cancer. She is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. Rock received her MD from the University of California, San Francisco.

Cynthia Thompson, MD, is a professor of medicine at the University of California, San Francisco (UCSF) and the director of the Cancer Prevention and Control Research Program at UCSF. She is also the director of the Cancer Prevention and Control Research Program at UCSF. Dr. Thompson’s research focuses on the role of diet and lifestyle factors in the prevention and management of cancer. She is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. Thompson received her MD from the University of California, San Francisco.

Tod Gansler, MD, is a professor of medicine at the University of California, San Francisco (UCSF) and the director of the Cancer Prevention and Control Research Program at UCSF. He is also the director of the Cancer Prevention and Control Research Program at UCSF. Dr. Gansler’s research focuses on the role of diet and lifestyle factors in the prevention and management of cancer. He is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. Gansler received his MD from the University of California, San Francisco.

Kimberly S. Andrews, MD, is a professor of medicine at the University of California, San Francisco (UCSF) and the director of the Cancer Prevention and Control Research Program at UCSF. She is also the director of the Cancer Prevention and Control Research Program at UCSF. Dr. Andrews’s research focuses on the role of diet and lifestyle factors in the prevention and management of cancer. She is also a member of the American Society for Clinical Nutrition and the American Society for Nutrition. Dr. Andrews received her MD from the University of California, San Francisco.

Note:

1 Corresponding author.

2 E-mail address: kushi@medERIC.org.

3 Presented at U.S. National Cancer Institute Scientific Workshops on Risk Factors for Cancer Prevention, Bethesda MD, 2000; and at the American College of Sports Medicine annual meeting, Atlanta, GA, 2000. (Received for publication December 15, 2005; revised March 22, 2006; accepted for publication March 28, 2006.) (Published online March 15, 2006.) (American Cancer Society, Inc. 2006. All rights reserved. 0005-8579/06/2006-0023/04 $0.00 + .00) (System error)
Evidence for Prostate Cancer

During and after treatment - Effects of exercise on key endpoints
Results from 12 trials
During or following ADT/Radiation

American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors

- 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

### DXA fat and lean changes

Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer

Daniel A. Galvão¹,², Nigel A. Spry³,⁴, Dennis R. Taaffe⁵, Robert U. Newton¹,², John Stanley⁶, Tom Shannon⁶, Chris Rowling⁷ and Richard Prince³,⁴

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>36 weeks</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<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>
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

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

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

NO change in PSA or testosterone in either group

CRP = C-reactive protein; EX= exercise; CO= usual care control
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,d, Prue Cormie a, David Joseph a,b,c, David S. Lamb, Suzanne K. Chambers a,d, Robert U. Newton a

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>(&gt;5 yr post diagnosis – post ADT/radiation)</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>12 months</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 After Treatment

**A**
- **400-m walk time/sec**
- Baseline: 288.0 (7.6)
- 6 Months: 279.4 (8.4)
- 12 Months: 276.5 (7.6)
- *P=.029**

**B**
- **Chair rise time/sec**
- Baseline: 12.8 (0.4)
- 6 Months: 11.9 (0.5)
- 12 Months: 11.5 (0.4)
- *P=.006**

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

**D**
- **1-RM Leg Extension kg**
- Baseline: 51.0 (2.9)
- 6 Months: 59.3 (3.0)
- 12 Months: 56.6 (2.8)
- *P<.001**

PA, physical activity.
Exercise in PCa with Bone Mets

Efficacy and safety of a modular multi-modal exercise program in prostate cancer patients with bone metastases: a randomized controlled trial

Daniel A Galvão1, Dennis R Taaffe2, Prue Cormie1, Nigel Spry1, Suzanne K Chambers1,6, Carolyn Peddle-McIntyre1, Michael Baker1, James Denham1,8, David Joseph3,4, Geoff Groom9 and Robert U Newton1

- 103 patients with PCa bone metastatic disease were screened in WA
- 57 patients were randomized to exercise (n=28) or usual care (n=29) group
- no major adverse events or bone pain were reported in relation to the intervention

Exercise improved self-reported physical function compared to controls - adjusted mean difference at 12 weeks between groups of 3.5 points (95% confidence interval; 0.70 to 6.3; p=.015)

Galvão et al. BMC Cancer 2011; unpublished data
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*
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.
Exercise and Prostate Cancer Survival

≥3 hours per week of **vigorous** activity after prostate cancer diagnosis:

- 49% lower risk of all-cause mortality ($P<.001$)
- 61% lower risk of prostate cancer mortality ($P=.030$)

Exercise and Prostate Cancer Survival

Physical Activity and Survival among Men Diagnosed with Prostate Cancer

Stephanie E. Bonn, Arvid Sjölander, Ylva Tolle Lagerros, Fredrik Wiklund, Pär Stattin, Erik Holmberg, Henrik Grönberg, and Katarina Bälter

Published OnlineFirst December 19, 2014; DOI: 10.1158/1055-9965.EPI-14-0707

Kaplan–Meier survival estimates
- Total recreational MET-hours and overall mortality
- Walking/bicycling and overall mortality

Exercise and Prostate Cancer Survival

Physical Activity and Survival After Prostate Cancer

Christine M. Friedenreich, Qinggang Wang, Heather K. Neilson, Karen A. Kopciuk, S. Elizabeth McGregor, Kerry S. Courneya

- 830 men with stage II-IV prostate cancer
- post-diagnosis recreational activity was associated with a significantly lower PCSM risk (HR 0.56, 95% CI 0.35–0.90; p = 0.01)
- more vigorous physical activity was associated with overall survival
- congruent with previous research
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.
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
INTense Exercise for survival among men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL – mCRPC)

Multicentre, randomised, controlled phase III trial evaluating highly specific anabolic and aerobic exercise prescription tailored for men with metastatic castrate-resistant prostate cancer with the primary outcome being overall survival

866 men with mCRPC, 24 month intervention

Elucidate mechanisms by which exercise delays cancer progression

Jointly led by ECU and UCSF

Protocol presented at ASCO 2016 Saad et al.
Considerations

- Evidence of exercise in the setting of ADT/Radiation *****
- Evidence of exercise post-treatment ***
- Preliminary evidence of exercise during advanced disease **
- Preliminary evidence of lifestyle (exercise) during AS *
- Evidence of exercise on prostate cancer survival *
- Several potential mechanisms of exercise should be investigated
- GAP-4 INTERVAL – mCRPC currently recruiting
Research Support

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)
Akhliil Hamid (PRH, ECU)
Evan Ng (RPH, Genesis)
Raphael Chee (Genesis, UWA)
Jerard Ghossein (JHC)
Siobhan Ng (SCGH, SJG)
Yvonne Zissiadis (Genesis, ECU)