Exercise Oncology: implications for Recurrence and Survival

Daniel A. Galvão, PhD
Co-Director, Exercise Medicine Research Institute
Cancer Council Western Australia Research Fellow
Pooled data from 12 prospective US and European cohorts with self-reported PA
Looked at 26 types of cancer in 1.44 million adults, followed for median of 11 years
186,932 cancers

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal adenocarcinoma</td>
<td>0.58 (0.37-0.89)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.73 (0.55-0.98)</td>
</tr>
<tr>
<td>Lung</td>
<td>0.74 (0.71-0.77)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.77 (0.70-0.85)</td>
</tr>
<tr>
<td>Gastric cardia</td>
<td>0.78 (0.64-0.95)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>0.79 (0.68-0.92)</td>
</tr>
<tr>
<td>Myeloid leukemia</td>
<td>0.80 (0.70-0.92)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>0.83 (0.72-0.95)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.84 (0.77-0.91)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>0.85 (0.78-0.93)</td>
</tr>
<tr>
<td>Rectal</td>
<td>0.87 (0.80-0.95)</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.87 (0.82-0.92)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.90 (0.87-0.93)</td>
</tr>
</tbody>
</table>

“PA has far reaching value for cancer prevention”
Prospective observational study n=2987 female registered nurses in the Nurses’ Health Study

Protective association between increased PA after diagnosis and recurrence, cancer-related mortality, and overall mortality (stage I-III breast cancer)

BCa deaths
Adj. RR 0.80 (0.60 – 1.06) 3-8.9 M-h/wk
Adj. RR 0.50 (0.31 – 0.82) 9-14.9 M-h/wk

Holmes et al. JAMA 293:2479-2486, 2005
Impact of Physical Activity on Cancer Recurrence and Survival in Patients With Stage III Colon Cancer: Findings From CALGB 89803

Prospective observational study
N= 832 patients
PA 6 months after completing adjuvant chemotherapy
Median follow-up 2.7 years

Adj. HR 0.51 (0.26 – 0.97) 18-26.9 M-h/wk
Adj. HR 0.55 (0.33 – 0.91) ≥ 27 M-h/wk

Improvement in DFS
~ 6 or more hours walking/week
Prospective observational study of 573 women (stage I-III)

Cancer-specific mortality: HR 0.39 (0.18 – 0.82) ≥ 18 M-h/wk
Overall mortality: HR 0.43 (0.25 – 0.74) ≥ 18 M-h/wk

Fig 3. Impact of change of physical activity before and after colorectal cancer diagnosis. *Compared with no change. Adjusted for body mass index, stage of disease (I, II, III), grade of tumor differentiation, colon or rectal primary, age at diagnosis, year of diagnosis, receipt of chemotherapy (yes, no, unknown), time from diagnosis to physical activity measurement, change in body mass index, smoking status (current, past, never).
Data from these three observational studies suggest a reduced risk of recurrence of 50% to 60%. Such an effect parallels that of trastuzumab (herceptin) for HER-2–positive breast cancer patients, an agent heralded by the oncologic care community and by the Director of the National Cancer Institute, Andrew C. von Eschenbach, MD, as “a major advance and turning point in eliminating suffering and death from cancer.”
Exercise and Prostate Cancer Survival

Physical Activity and Survival After Prostate Cancer Diagnosis in the Health Professionals Follow-Up Study
Stacey A. Kenfield, Meir J. Stampfer, Edward Giovannucci, and June M. Chan

N = 2,705, activity after diagnosis from 1990-2008 548 deaths, 112 result of PCa

≥3 hours per week of **vigorous** activity (biking, tennis, jogging, swimming) after diagnosis:

- 49% lower risk of all-cause mortality [HR, 0.51 (0.36 – 0.72)]
- 61% lower risk of prostate cancer mortality [HR, 0.39 (0.18 – 0.84)]

Prospective study in 243 patients with KPS ≥ 70

Aged 20-77 years
68% men
Godin Leisure-Time Exercise Questionnaire

Median survival:
13 months < 9 MET-h/wk
22 months ≥ 9 MET-h/wk

HR: 0.64 (0.46 – 0.91)
Exercise and Prostate Cancer Survival

Physical Activity and Survival among Men Diagnosed with Prostate Cancer

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

4,623 men with localised PCa 1997-2002 followed-up until 2012
Post-diagnosis activity, 561 deaths with 194 from PCa

HR, 0.63 (0.52 – 0.77)

HR, 0.70 (0.57 – 0.86)
HR, 0.61 (0.43 – 0.87)

HR, 0.68 (0.48 – 0.94)
Exercise and Prostate Cancer Survival

Physical Activity and Survival After Prostate Cancer

Christine M. Friedenreich\textsuperscript{a,b,c,*}, Qinggang Wang\textsuperscript{a}, Heather K. Neilson\textsuperscript{a}, Karen A. Kopciuk\textsuperscript{a,b,d}, S. Elizabeth McGregor\textsuperscript{b,c,e}, Kerry S. Courneya\textsuperscript{f}

- 830 men with stage II-IV PCa between 1997-2000 with follow-up to 2014 (458 deaths, 170 PCa-specific)
- post-diagnosis recreational activity was associated with a significantly lower PCSM risk [HR 0.56 (0.35 – 0.90)]
- sustained physical activity (pre and post) was associated with overall survival [HR 0.66 (0.49 – 0.88)]

Exercise and Breast Cancer Survival

HR from breast cancer-specific death, 95% CI

- Holick et al. (n=4,482)
- Irwin et al. 2011 (n=4,643)
- Irwin et al. 2008 (n=933)
- Borugian et al. 2004 (n=602)
- Sternfeld et al. 2009 (n=1,970)
- Bradshaw et al. 2014 (n=1,423)
- Holmes et al. 2005 (n=2,987)
- Total (n=17,040)

Exercise and cancer outcomes: Impact of ER status

HR from cancer-specific death, 95% CI

Holmes et al. *JAMA* (≥9 MET-hrs·wk)
- ER negative (HR: 0.91)
- ER positive (HR: 0.50)

Irwin et al. *JCO* (>0 MET-hrs·wk)
- ER negative (HR: 1.26)
- ER positive (HR: 0.20)

Sternfeld et al. *BCRT* (≥18 MET-hrs·wk)
- ER negative (HR: 0.75)
- ER positive (HR: 0.59)
Physical activity and survival among long-term cancer survivor and non-cancer cohorts

Anthony Gunnell¹, ², Sarah Joyce³, Stephania Tomlin³, Dennis R. Taaffe¹, ⁴, ⁵, Prue Cormie⁶, Robert U. Newton¹, ⁷, ⁴, David Joseph¹, ⁸, Nigel Spry¹, ⁹, Kristjana Einarsdottir¹⁰, Daniel A. Galvão¹, ⁴*  

N=1589 Western Australian Cancer Survivors; 8.8 years follow-up  
Cox proportional hazards regression

<table>
<thead>
<tr>
<th></th>
<th>Cancer Specific Death</th>
<th>All-Cause Death</th>
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<tbody>
<tr>
<td>&lt;150 minutes</td>
<td>HR 0.62 (0.36-1.06)</td>
<td>HR 0.70 (0.46-1.08)</td>
</tr>
<tr>
<td>150-359 minutes</td>
<td>HR 0.55 (0.28-1.08)</td>
<td>HR 0.55 (0.31-0.97)</td>
</tr>
<tr>
<td>360+ minutes</td>
<td>HR 0.30 (0.13-0.70)</td>
<td>HR 0.30 (0.21-0.79)</td>
</tr>
</tbody>
</table>

Gunnell et al. Frontiers Public Health 2017
Resistance Exercise and Cancer Survival

The Effect of Resistance Exercise on All-Cause Mortality in Cancer Survivors

Justin P. Hardee, MS; Ryan R. Porter, MS; Xuemei Sui, MD, MPH, PhD; Edward Archer, PhD; I-Min Lee, MD, ScD; Carl J. Lavie, MD; and Steven N. Blair, PED

- 2863 cancer survivors enrolled in the Aerobics Center Longitudinal Study
- RE was associated with a 33% lower risk of all-cause mortality (95% CI, 0.45-0.99) after adjusting for potential confounders, including PA

PA, physical activity; RE, resistance exercise.

Figure 1. Kaplan-Meier survival curves for all-cause mortality according to RE performed at least 1 day/week in cancer survivors enrolled in the Aerobics Center Longitudinal Study, Dallas, Texas, 1987 to 2003.
Observational Studies: Exercise and Cancer Survival?

**Limitations:**
- Self-report of physical activity/exercise
- Reverse causation bias
- Association vs. cause and effect

**Causal criteria of Hill:**
- Strength
- Consistency (replicated)
- Biological gradient
- Plausibility

Hill BA. Proceedings of the Royal Society of Medicine, 58 (1965), 295-300.
Effects of Aerobic and Resistance Exercise 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 survivors initiating chemotherapy (median 17 weeks)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Assigned</th>
<th>Completed ≥ 66% of Supervised Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic</td>
<td>78 (71)</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22 did not complete</td>
</tr>
<tr>
<td>Resistance</td>
<td>82 (73)</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26 did not complete ≥ 66% of supervised exercise</td>
</tr>
<tr>
<td>Usual Care</td>
<td>82 (75)</td>
<td>82</td>
</tr>
</tbody>
</table>

Courneya et al. JCO 2007;25:4396-4404
Disease-Free Survival
8-year DFS was 82.7% for EX vs. 75.6% for UC

HR 0.68 (95% CI 0.37-1.24; log-rank p=0.205)

Courneya et al. MSSE 2014;46:1744-51
Overall Survival

8-year OS was 91.2% for EX vs. 82.7% for UC

Courneya et al. MSSE 2014;46:1744-51
Physical Activity and Cancer Outcomes: A Precision Medicine Approach

Exercise

Body composition

- Sex hormones
- Insulin sensitivity
- Chronic low-level inflammation

Other mechanisms (modifiable and nonmodifiable)

Biologic mechanisms

Biomarkers

- Insulin
- IGF-1
- CRP
- Gene expression
- Others

Patient subgroups
- ER (breast)
- HER2 (breast)
- CTNNB1 (colon)
- P21 (colon)
- P27 (colon)
- PTGS2 (colon)
- IRS1 (colon)
- Gleason score (prostate)
- Others

Cancer recurrence, survival

Protective association between exercise and survival
- May be exercise responsive

No protective association between exercise and survival
- May be exercise resistant

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Definitive Trials

The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group

K.S. Courneya PhD, * C.M. Booth MD, † S. Gill MD, ‡ P. O’Brien MSc, † J. Vardy MD PhD, § C.M. Friedenreich PhD, † H.J. Au MD, # M.D. Brundage MD, † D. Tu PhD, † H. Dhillon MA, § and R.M. Meyer MD †

Accumulating Evidence for Physical Activity and Prostate Cancer Survival: Time for a Definitive Trial of Exercise Medicine?

Robert U. Newton *, Daniel A. Galvão
Exercise Medicine Research Institute, Edith Cowan University, Joondalup, WA, Australia

**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.
# National/international Sites

**INTERVAL – mCRPC**

<table>
<thead>
<tr>
<th></th>
<th>Investigator Sites</th>
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<tbody>
<tr>
<td>1.</td>
<td>Edith Cowan University - WA, AUS. - Open for Recruitment</td>
</tr>
<tr>
<td>2.</td>
<td>Deakin University - VIC, AUS.</td>
</tr>
<tr>
<td>3.</td>
<td>Queensland Consortium - QLD, AUS.</td>
</tr>
<tr>
<td>4.</td>
<td>Orange Base Hospital - NSW, AUS.</td>
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<tr>
<td>6.</td>
<td>Auckland University of Technology - NZ.</td>
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<tr>
<td>7.</td>
<td>University of California, San Francisco - USA.</td>
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<td>8.</td>
<td>Ohio State Health University - USA.</td>
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<tr>
<td>9.</td>
<td>University of Washington - USA.</td>
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<tr>
<td>10.</td>
<td>Cedars-Sinai Medical Centre - USA.</td>
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<tr>
<td>11.</td>
<td>Fred Hutchison Cancer Centre - USA.</td>
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<tr>
<td>12.</td>
<td>University of Colorado, Denver – USA.</td>
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<tr>
<td>14.</td>
<td>University of Montreal Hospital Centre - Canada.</td>
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<tr>
<td>15.</td>
<td>Princess Margaret Cancer Center - Canada.</td>
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<td>17.</td>
<td>University of Surrey - UK.</td>
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<tr>
<td>18.</td>
<td>University of Bristol - UK.</td>
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<tr>
<td>20.</td>
<td>University of Glasgow - UK.</td>
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<tr>
<td>21.</td>
<td>Trinity College, Dublin - IRE.</td>
</tr>
<tr>
<td>22.</td>
<td>German Sports University - GER. Open for Recruitment</td>
</tr>
<tr>
<td>23.</td>
<td>Erasmus Medical Centre – ND.</td>
</tr>
</tbody>
</table>
Summary/Conclusions

• Self-reported PA/exercise behavior is associated with survival in several cancer groups (breast, colon, prostate)
• Phase II data suggestive of possible survival benefit of supervised exercise in breast cancer
• Phase III exercise trials ongoing in colon and prostate cancer
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)
Prospective Cohort Studies of Post Diagnosis Exercise and Cancer-Specific Mortality

Across 24 studies 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)

Risks of recurrence or progression were also reduced (pooled relative risk=0.65, 95% CI: 0.56-0.75)

Postdiagnostic walking duration, walking pace, and risk of PCa progression among 1,455 men diagnosed with clinically local PCa.
Colon Health and Life-Long Exercise Change (CHALLENGE) Trial

- RCT comparing 3 year PA intervention to CON on disease-free survival in colon cancer survivors 2-6 months after treatment.
- first exercise trial with survival outcome as primary endpoint.
- multinational trial with 962 planned participants.
- trial opened to accrual in May 2009.
- funded by NCIC-CTG and NHMRC in Australia.
What Are MET Hours?

- Each activity is assigned a MET score
- 1 MET is the energy expenditure for sitting quietly
- MET scores are the ratio of the metabolic rate for the activity / resting metabolic rate
- MET-hours/week for each activity calculated from the reported hours per week for that activity x assigned MET score
- Values from individual activities summed for a total of MET-hours/week

<table>
<thead>
<tr>
<th>Leisure-Time Activity</th>
<th>MET-Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal pace walking (2 to 2.9 mph)</td>
<td>3</td>
</tr>
<tr>
<td>Brisk pace walking (3 to 3.9 mph)</td>
<td>4</td>
</tr>
<tr>
<td>Very brisk pace walking (4+ mph)</td>
<td>4.5</td>
</tr>
<tr>
<td>Jogging (slower than 10 min/mile)</td>
<td>7</td>
</tr>
<tr>
<td>Running (faster than 10 min/mile)</td>
<td>12</td>
</tr>
<tr>
<td>Bicycling</td>
<td>7</td>
</tr>
<tr>
<td>Tennis, squash, racquetball</td>
<td>7</td>
</tr>
<tr>
<td>Lap swimming</td>
<td>7</td>
</tr>
<tr>
<td>Calisthenics, ski or stair machine, other aerobic exercise</td>
<td>6</td>
</tr>
<tr>
<td>Yoga, stretching, toning, lower intensity exercise</td>
<td>4</td>
</tr>
<tr>
<td>Other vigorous activities (lawn mowing)</td>
<td>6</td>
</tr>
</tbody>
</table>

Walking at Average Pace
- < 3 MET-h/wk = < 1 hr/wk
- 3-9 MET-h/wk = 1-3 hr/wk
- 9-18 MET-h/wk = 3-6 hr/wk

Abbreviations: MET, metabolic equivalent task; mph, miles per hour.