Exercise Rehabilitation Following a Cancer Diagnosis: Cardiorespiratory Fitness to Prognosis Outcomes

Lee W. Jones, PhD
Duke Cancer Institute
Introduction

- Therapeutic properties of exercise been recognized since ancient Greeks and Chinese


- Exercise is the cornerstone of numerous disease pathologies; many conditions are qualifying dx for exercise rehabilitation

- Comparably less attention in the role of exercise following a cancer diagnosis, until recently....
Rapid emergence of cancer survivorship

<table>
<thead>
<tr>
<th>Site</th>
<th>1975 (%)</th>
<th>2009 (%)</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>50</td>
<td>67</td>
<td>17</td>
</tr>
<tr>
<td>Childhood</td>
<td>30</td>
<td>79</td>
<td>49</td>
</tr>
<tr>
<td>Prostate</td>
<td>67</td>
<td>99</td>
<td>32</td>
</tr>
<tr>
<td>Breast</td>
<td>75</td>
<td>91</td>
<td>16</td>
</tr>
<tr>
<td>Colon</td>
<td>49</td>
<td>66</td>
<td>17</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>16</td>
<td>4</td>
</tr>
</tbody>
</table>

- ~13m cancer survivors in the US (~25m worldwide)
- Projected to explode with further improvements & aging population
- Increased risk of the late-effects of cancer therapy

Jones, AICR, 2011
CVD – impt competing cause of mortality

- Early-stage breast cancer pts x2 as likely to die from competing causes compared with breast cancer
- CVD – leading cause of death


Jones, AICR, 2011
The ‘Multiple-Hit’ hypothesis

Jones et al. Lancet Oncol, 2009
Jones, AICR, 2011
What is cardiovascular reserve / exercise tolerance?

Pulmonary function ($O_2$ diffusion) +
Cardiac function ($Q$, Hb concn, $SpO_2$) +
Vascular compliance +
Skeletal muscle function (oxidative capacity, fiber type distribution) II

CV reserve / aerobic capacity

Jones, AICR, 2011
Measurement of cardiovascular reserve

- Symptom-limited cardiopulmonary exercise test (CPET)
- Peak oxygen consumption ($\text{VO}_{2\text{peak}}$ - mL.kg.$^{-1}$min.$^{-1}$)

Endurance trained

Active

Sedentary

Risk of Death

1.0 – 5.9
6.0 – 7.9
8.0 – 9.9
10 – 12.9
≥13.0

Increasing Fitness

Impaired fitness across breast cancer continuum

Mean VO$_{2\text{peak}}$ = 5.7 METs (Q1)!!

Jones et al. *J Clin Oncol* submitted

Jones, AICR, 2011
## VO$_{2peak}$ & all-cause mortality in operable NSCLC (n=398)

<table>
<thead>
<tr>
<th>VO$_{2peak}$ (mL·kg$^{-1}$·min$^{-1}$)</th>
<th>&lt;13.9 (4 METS)</th>
<th>14.0 – 17.3 (&gt;4 – 5 METS)</th>
<th>&gt;17.3 (&gt; 5 METS)</th>
<th>$P$ for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, Mths</td>
<td>30.5</td>
<td>42.7</td>
<td>39.1</td>
<td></td>
</tr>
<tr>
<td>5-year survival, %</td>
<td>30</td>
<td>34</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>Referent</td>
<td>0.79</td>
<td>0.76</td>
<td>0.0403</td>
</tr>
</tbody>
</table>

*adjusted for age, gender, performance status, and FEV$_1$

Jones et al. *Cancer*, 2010

Jones, AICR, 2011
**VO₂peak & all-cause mortality in metastatic breast cancer (n=52)**

<table>
<thead>
<tr>
<th>VO₂peak (L·min⁻¹)</th>
<th>≤1.09</th>
<th>&gt;1.09</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, Mths</td>
<td>16 (7 to 27)</td>
<td>36 (24 to 57)</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>Referent</td>
<td>0.32</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*adjusted for number of metastatic sites, age, and performance status

<table>
<thead>
<tr>
<th>VO₂peak (mL·Kg⁻¹·min⁻¹)</th>
<th>≤15.4 (4.4 METS)</th>
<th>&gt;15.4 (&gt;4.4 METS)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, Mths</td>
<td>22 (12 to 40)</td>
<td>29 (18 to 42)</td>
<td></td>
</tr>
<tr>
<td>Adjusted*</td>
<td>Referent</td>
<td>0.59</td>
<td>0.141</td>
</tr>
</tbody>
</table>

*adjusted for number of metastatic sites, age, and performance status

Jones et al. *J Clin Oncol*, submitted

Jones, AICR, 2011
Treatment vs. prevention of injury?

DIAGNOSIS

MULTIPLE HIT
Direct + indirect effects of therapy

CV reserve

Late-occurring CVD risk

Premature death

Adjuvant Therapy

Post Adjuvant Therapy (Recovery / Survivorship)

Jones, AICR, 2011
Treatment of injury

MULTIPLE HIT
Direct + indirect effects of therapy

CV reserve

Late-occurring CVD risk

Normal lifespan

Adjuvant Therapy

Jones, AICR, 2011

Stage I-III
Completed therapy
Post-menopausal

n=53

Wait-List Control
(n=28)

Supervised Aerobic Training
(n=25)

Provided with exercise program >study

Cycle ergometry, @ 75%
VO$_2$peak 20-45 mins/session, 3x/wk for 15 wks


Jones, AICR, 2011
**VO₂peak (mL.kg⁻¹ min⁻¹)**

- **CON**
  - p<0.001

- **AT**
  - p<0.05

**Anaerobic Threshold (L.min⁻¹)**

- **CON**
  - p<0.05

- **AT**
  - p<0.05

**Fatigue (FACT-F)**

- **CON**
  - p=0.030

- **AT**
  - p<0.001
  - p<0.05

**Courneya et al. J Clin Oncol, 2003**

**Jones, AICR, 2011**
Efficacy of aerobic training post therapy: Summary

• ~17 studies

• Majority tested aerobic-based interventions
  • Cycle ergometry/treadmill walking
  • 3d.wk for 6-24 weeks, moderate intensity

• Adherence: 88 ± 12; Loss-to-follow-up: 11 ± 14

• Few SAEs (few studies monitor / report SAEs)

• ↑VO$_{2\text{peak}}$, ↑QOL & ↓fatigue

• Strong preliminary evidence

• 2$^{nd}$ generation trials underway (optimal exercise px)

Jones et al. C Med Assoc J, submitted
<table>
<thead>
<tr>
<th>Trial</th>
<th>Funding Source</th>
<th>Population</th>
<th>Design</th>
<th>Intervention</th>
<th>Length</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LUNGEVITY</td>
<td>NIH (R01)</td>
<td>160 Early NSCLC post therapy</td>
<td>4 Arm RCT</td>
<td>1. AT</td>
<td>16 weeks</td>
<td>50 patients randomized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. AT + RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. Att. Con</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. EXCITE</td>
<td>NIH (R01)</td>
<td>174 Early breast cancer post therapy</td>
<td>3 Arm RCT</td>
<td>1. Moderate AT</td>
<td>16 weeks</td>
<td>42 patients randomized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. High AT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Att. Con</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Exercise -</td>
<td>NIH (R21)</td>
<td>50 Post-Sx prostate cancer</td>
<td>2 Arm RCT</td>
<td>1. High - moderate AT</td>
<td>24 weeks</td>
<td>32 patients randomized</td>
</tr>
<tr>
<td>ED</td>
<td></td>
<td></td>
<td></td>
<td>2. Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Exercise -</td>
<td>NIH (U54)</td>
<td>120 Post-Tx CRC</td>
<td>4 Arm RCT</td>
<td>1. AT</td>
<td>24 weeks</td>
<td>Nov, 2011</td>
</tr>
<tr>
<td>CRC</td>
<td></td>
<td></td>
<td></td>
<td>2. Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. AT + Metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. Control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Jones, AICR, 2011
Prevention of injury?

**DIAGNOSIS**

- **MULTIPLE HIT**
  - Direct + indirect effects of therapy

- Adjuvant Therapy

**Post Adjuvant Therapy**

- Late-occurring CVD risk

**OR**

- CV reserve

**Normal lifespan**

Jones, AICR, 2011

Histologically confirmed operable disease

Scheduled to initiate chemotherapy

n=242

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

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

Usual Care (no intervention) (n=82)

~17 weeks
Aerobic capacity

\[ \text{VO}_{2\text{peak}} \text{ (mL.kg}^{-1}\text{.min}^{-1}) \]

\[ \begin{array}{c}
\text{Control} \\
\text{Aerobic Tx} \\
\text{Resistance Tx}
\end{array} \]

\[ p=0.004 \]

Fatigue

\[ p=0.338 \]

QOL

\[ \begin{array}{c}
\text{Control} \\
\text{Aerobic Tx} \\
\text{Resistance Tx}
\end{array} \]

\[ p=0.286 \]

Self-esteem

\[ \begin{array}{c}
\text{Control} \\
\text{Aerobic Tx} \\
\text{Resistance Tx}
\end{array} \]

\[ p=0.025 \]


Jones, AICR, 2011
Breast cancer neoadjuvant trial

- Tumors >1.5 cm
- LVEF >50%
- KPS >70%
- n=20

Chemotherapy Alone

4 x AC
60/600 mg/m²

Chemotherapy + Aerobic Training

4 x AC + AT
60/600 mg/m² / cycle ergometry (3x.wk, 60% - 100% VO₂peak for 12 wks)

- Aerobic capacity (CPET; VO₂peak)
- LV Function (2-D echo)
- Endothelial function (flow-mediated dilatation)
- Patient-reported outcomes

Jones et al. *in prep*
Aerobic capacity

Cardiac function (ejection fraction)

Endothelial function

Jones et al. *in prep*
Efficacy of aerobic training during therapy: Summary

- ~20 studies (breast Ca, small sample sizes)
- Majority tested aerobic-based interventions
  - Cycle ergometry/treadmill walking
  - 3d.wk for 6-24 weeks, moderate intensity
- Adherence: 84 ± 15; Loss-to-follow-up: 13 ± 13
- Few SAEs (few studies monitor / report SAEs)
- \( \uparrow \text{VO}_{2\text{peak}}, \text{QOL} \& \downarrow \text{fatigue} \) (more equivocal)
- Promising evidence
- Larger, more diverse RCTs (other Ca’s; novel tx)

Jones et al. *C Med Assoc J*, submitted

Jones, AICR, 2011
Timing of exercise rehab: during vs. after therapy?

- **Aerobic Tx During Therapy**
  - Continuous Aerobic Training
  - Attention Control

- **Aerobic Tx After Therapy**
  - Control

- **End of Therapy**
  - Control
  - Aerobic Tx

- **End of Study**
  - Control
  - Aerobic Tx

Timeline:
- **T0**: Randomization
- **T1**: 6 months
- **T2**: 6 months

Jones, AICR, 2011
Exercise / physical activity and cancer-specific mortality in cancer survivors
Women engaging in $\geq 9$ MET (hrs.wk) (30 mins walking, 5d/wk) $\sim 50\% \downarrow$ in BC-mortality & $\sim 30\% \downarrow$ all-cause vs. inactive women

Holmes et al. JAMA 2005;293:2479-86

Individuals engaging in $\geq 18$ MET (hrs.wk) (60 mins walking, 5d/wk) $\sim 50\% \downarrow$ in CRC-mortality & $\sim 30\% \downarrow$ all-cause vs. inactive individuals

Physical activity and prognosis: Summary

• No RCTs of exercise on disease outcomes following a cancer diagnosis

• 13 observational studies self-reported exercise and cancer-specific and all-cause mortality

• 85% reported significant inverse relationship with risk reduction of 15% to 61% (cancer-specific) and 18% to 67% (all-cause mortality)

• ‘Dose-response’ reported in 6 studies

• Exercise volume from >2 hrs.wk\(^{-1}\) to >7.5 hrs.wk\(^{-1}\) of moderate-intensity exercise
**CHALLENGE Trial** (Courneya et al. *Curr Oncol*, 2008)

- **Randomization**
  - Histologically confirmed operable colon cancer
  - >60 - <180 d post adjuvant tx
  - Baseline Assessment
  - N=962

- **Randomization Process**
  - Physical activity program + general health materials (supervised PA + counseling)
  - General health materials (usual care)

- **End of Study**
  - Progressive Disease or Unacceptable toxicity or withdrawal of consent

- **Primary**: disease-free survival
- **Secondary**: PROs, functional capacity, etc.

Jones, AICR, 2011
Mechanisms of action

Changes in the host environment

- Metabolic steroid hormones
- Cytokines / angiogenic factors
- Immunity
- Sex steroid hormones
- Oxidative damage

Modulation of the tumor microenvironment (seed) and microenvironment of distant organs (soil)

Hallmarks of cancer progression and metastatic dissemination / therapeutic outcome

Jones, AICR, 2011
Preliminary data (breast cancer)

4T1 (ER positive)

PyMT (ER positive; transgenic)

E0771 (ER positive)

↓ 30% - 50% tumor growth rate

Jones, AICR, 2011
Preliminary data: prostate cancer

Primary tumor weight

![Graph showing primary tumor weight comparison between control and exercise groups at different days.]

Distant metastasis

![Graph showing weight of metastases and total number of metastases comparison between control and exercise groups.]

Preliminary data: prostate cancer

Control

Exercise

T2WI         Perfusion Map

Heterogeneous blood flow

tumor implant

T2WI         Perfusion Map

Uniformly increased blood flow

tumor implant

Preliminary data: prostate cancer

- Endurance exercise increases tumor vascularization but leads to ‘productive’ tumor angiogenesis & less aggressive phenotype

- Next steps
  - Implications to the adjuvant setting / other solid malignancies?
  - Mechanisms of action?
  - Therapeutic response / efficacy?
Aerobic training during chemotherapy

- ‘Proof-of-concept’ pilot study of aerobic training on plasma cytokines, bone marrow stem cells, and tumor gene expression in breast cancer pts undergoing neoadjuvant chemotherapy

- Tumors >1.5 cm
- LVEF >50%
- KPS >70%
- n=20

Chemotherapy Alone

4 x AC
60/600 mg/m²

Chemotherapy + Aerobic Training

4 x AC + ET
60/600 mg/m² / cycle ergometry (3x.wk, 60% - 100% VO₂peak for 12 wks)

Jones et al. *in prep*
Preliminary results

- Changes in VO$_{2peak}$ and endothelial function (NO-bioavailability)
- Changes in circulating cytokines and angiogenic factors (e.g., IL’s, PDGF)
- ↑ circulating bone marrow-derived ‘stem cells’ implicated in injury response / tumor angiogenesis
- Significant ↓ in tumor perfusion
- Significant changes in tumor gene expression favoring ↓ pro-migration and proliferation (less aggressive phenotype)

Jones et al. *J Natl Cancer Inst*, submitted
Metastatic feasibility trial (3-yr, R21)

- VO₂peak, PROs, AEs; serial bio-banking (q.3wk)
- 18 patients ‘on trial’

Histologically confirmed metastatic disease

Baseline Assessment

Randomization

Standard therapy + supervised aerobic training (3x/wk @60%-100% VO₂peak)

Standard therapy + progressive stretching (attention control)

Progressive Disease or Unacceptable toxicity or withdrawal of consent

END OF THERAPY

3 months

Jones, AICR, 2011
Conclusion

- Growing research and clinical interest in exercise training (rehabilitation) following a cancer diagnosis
- Cancer not a qualifying dx for exercise rehabilitation
- Exercise training impt adjunct to prevent &/or treat cardiovascular impairment
- Exercise may be associated with prolonged survival
- Direct and correlative mechanistic data is lacking; initial results ‘proof-of-concept’ modulate host–tumor interaction
- Tip of the iceberg......
Acknowledgements

• Collaborators

• Duke Exercise-Oncology Team
  Miranda West, Whitney Hornsby, Amy Lane, Beth Fowler, Caroline Bishop, Wendy Chase, Aarti Kenjale, Lauren Valera, Emily Schwitzer, Kaitlin Ray, Allison Betof, Erik Nelson

• Funding Agencies

• Participating Patients