Why Cardiac Rehabilitation is Important for Cancer Patients

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Outline

• Exercise and health: historical perspective

• Importance of Exercise and Fitness
  – Cardiovascular outcomes
  – Metabolic control
  – Cardiovascular risk in cancer patients

• MD Anderson Healthy Heart Program

• Cardiac Rehabilitation for Cancer Patients
Coronary Heart Disease Events Among Sedentary vs. Active Workers men 35-64, in London 1949-1952

Morris, JN. Lancet. 1953;265:1111-1120
Vigorous Activity and Reduction in CVD Mortality in European and North American Men

Leon (1991)  n = 12138
Lindsted (1991)  n = 9484
Mensink (1996)  n = 954
Morgan (1997)  n = 635
Rosengren (1997)  n = 7142
Bijnen (1998)  n = 802
Hakim (1998)  n = 707
Sherman (1999)  n = 962
Andersen (2000)  n = 17265
Yu (2003)  n = 1975
Barengo (2004)  n = 15852
Meta-Analysis

*Adjusted RR

Vigorous Activity and Reduction in CVD Mortality in European and North American Women

Physical Activity Estimated Using Questionnaires

• **Strengths**
  – Inexpensive
  – Noninvasive

• **Weaknesses**
  – Self-report bias
  – Accuracy and reliability
Cardiorespiratory Fitness

• Index of functional capacity of hearts & lungs

• Reflects efficiency of $O_2$ uptake, transport, and utilization in muscles

• Excellent surrogate of exercise dose and reproducible measurement
Cardiorespiratory Fitness: Global Assessment of Health

Diet
Physical Activity
Smoking/Alcohol Consumption
Stress Management

Morphologic Components
Muscular Component
Cardiorespiratory Component
Motor Component
Metabolic Component

Behavior
Fitness
Outcome

Genetic/Social/Environmental Factors

Low Fitness and Cardiovascular Risk
Fitness and Mortality in Caucasian Men (n= 6213 referred for exercise testing)

Relative Risk of Death

Fitness Quintiles

- Normal
- Known Cardiovascular Disease

Myers, J. *NEJM.* 2002;346:798-801.
Lifetime Risk of CVD Death According to Baseline Fitness Levels at age 55

Fitness and 30-Year Survival in “Low-Risk Adults”

1-MET increase = 18% reduction in CVD Mortality

Does Fitness Lower CV Risk by Metabolic Control?
Fitness - Metabolic Control – CV Risk

Dose of PA and Metabolic Parameters: Dallas Heart Study

1 = <150 min·wk⁻¹ of moderate activity, 2 = ≥150 min·wk⁻¹, 3 = ≥60 min·wk⁻¹ of vigorous activity in ≥10-minute bouts

**Fitness and Risk of Diabetes in Men**
(n=16,745 white men 20-79 years, 2 visits)

**HR for Diabetes**

- **Unfit (Q1)**: 12.4**
- **Q2**: 5.6
- **Q3**: 4.5
- **Q4**: 3.5
- **Fit (Q5)**: 2.4

**P<0.001**

*Adjusted: age, BMI, year, parental history, smoking, alcohol, blood pressure, cholesterol, diabetes*

Relationship between Change in Visceral Adiposity and VO2 max

Fitness and Reduction in Liver Fat %
Independent of Visceral Adiposity
n=190 whites, Germany

Summary

• Fitness prevents weight gain and excess visceral adiposity.

• Fitness may prevent diabetes and CVD risk, in part, through alteration in visceral adiposity.

• Fitness may mitigate CVD in other populations (i.e. cancer) through similar mechanisms.
Loss of Fitness and Metabolic Dysregulation in CVD and Cancer

Competing CVD Risk After a Cancer Diagnosis

Global Cardiovascular Reserve in Oncology Setting

- Pulmonary function (Systemic therapy, RT)
- Cardiac function (DOX, Herceptin, RT, TKIs)
- Vascular compliance (DOX, RT, TKIs)
- Skeletal muscle function (decadron, ADT, chemotherapy)

$\downarrow\downarrow\downarrow CV \text{ reserve}$

Fitness Following Breast Cancer Treatment with nL LVEF

VO_{2peak} \text{ (mL.kg}^{-1}.\text{min}^{-1})

\begin{array}{|c|c|c|c|}
\hline
\text{Cohort} & 40\text{yrs} & 50\text{yrs} & 60\text{yrs} & 70\text{yrs} \\
\hline
\text{Patients After Therapy (n=140)} & 21.05 & 19.51 & 17.97 & 16.44 \\
\hline
\text{Healthy controls (n=107)} & 29.82 & 26.32 & 22.82 & 19.32 \\
\hline
\end{array}

Impaired Fitness 7 years after Breast Cancer Treatment

1 MET loss = 18% higher CVD mortality risk**

Fitness and Survival After Breast Cancer

Exercise and Risk of Major CVD Events in Adult Survivors of Hodgkin Lymphoma

### All-Cause, Cancer, and CVD-Specific Mortality Among Men with Cancer by Pre-Diagnosis Cardiorespiratory Fitness

<table>
<thead>
<tr>
<th></th>
<th>Cardiorespiratory Fitness Levels</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1-MET Δ</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td></td>
</tr>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>769</td>
<td>207</td>
<td>189</td>
<td>141</td>
<td>138</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>*Adjusted HR</td>
<td>0.85 (.81-.88)</td>
<td>1</td>
<td>0.80</td>
<td>0.50</td>
<td>0.52</td>
<td>0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cancer Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>347</td>
<td>96</td>
<td>82</td>
<td>62</td>
<td>69</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>*Adjusted HR</td>
<td>0.86 (.81-.91)</td>
<td>1</td>
<td>0.83</td>
<td>0.51</td>
<td>0.59</td>
<td>0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CVD Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>151</td>
<td>49</td>
<td>36</td>
<td>28</td>
<td>21</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>*Adjusted HR</td>
<td>0.77 (.69-.85)</td>
<td>1</td>
<td>0.61</td>
<td>0.44</td>
<td>0.34</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, smoking, total cholesterol, systolic blood pressure, diabetes, physical activity, time between baseline examination and cancer diagnosis

Exercise Training to Mitigate Loss of Fitness in Cancer Patients
## Effects of Exercise Training on Fitness Across the Cancer Continuum (2005-2015)

Table 1: Systematic Reviews on the Effect of Exercise Training on VO2 in Cancer Patients (2005-2015)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer Type</th>
<th>Studies Reviewed (studies measuring Δ VO2)</th>
<th>Timepoint of Intervention (studies measuring Δ VO2)</th>
<th>Effect of ET on VO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh et al., 2013[66]</td>
<td>lung (61%), colorectal, prostate, colon, pancreatic, liver, colon, rectum, sarcoma, esophagus</td>
<td>Systematic review of 18 clinical trials. (6)</td>
<td>Pre-surgical.</td>
<td>↑</td>
</tr>
<tr>
<td>Schmitz et al., 2005[68]</td>
<td>Breast (72%), colon, lung, ovarian, leukemia, lymphoma, testicular, sarcoma, stomach, prostate, other</td>
<td>Systematic review of 22 high-quality studies. (9)</td>
<td>During (5) and after (4) cancer treatment.</td>
<td>↑ (weak evidence, during) ↑(strong evidence, after)</td>
</tr>
<tr>
<td>Jones et al., 2011[102]</td>
<td>Breast (67%), lymphoma, prostate, colon</td>
<td>Meta-analysis of 6 clinical trials. (6)</td>
<td>During (2) and after (4) cancer treatment.</td>
<td>↑</td>
</tr>
<tr>
<td>Wolin et al., 2010[103]</td>
<td>Hematologic cancer (100%)</td>
<td>Review of 23 high-quality intervention studies in adults and pediatric population. Adults (1) Children (6)</td>
<td>Receiving and not receiving hematopoietic stem cell transplantation.</td>
<td>↑ (weak evidence, adults) ↑(strong evidence, children)</td>
</tr>
</tbody>
</table>
Exercise Training (Aerobic/Resistance) to Reduce Body Fat Gained During Chemotherapy

Integrating Exercise Training Into Care of Cancer Patients
MD Anderson Healthy Heart Program

• The Healthy Heart Program helps patients improve their overall fitness and heart health.

• Healthy Heart Program staff will provides patients with a personalized exercise routine.

• Patients also receive information regarding risk of heart disease and ways to modify risk factors.
Cumulative Risk Factors and Risk of Cardiac Events in Breast Cancer

Hershman DL. JCO. 2018.
CV Risk Factors and Major CVD Events in Adult Survivors of Childhood Cancer

2+ CV risk factors (RR, 2.4; 95% CI, 1.2 to 4.9)

Armstrong GT et al. JCO. 2013; 31:3673-3680.
MD Anderson Healthy Heart Program: How it Works

• MDA Referral: type: CARDIO FIT in EPIC facility list
• The patient’s evaluation will include a heart risk screening exam and a treadmill exercise test.
  • Impact of prior cancer treatment on heart health
  • Fitness level
  • Cholesterol levels
  • Risk of hypertension or high blood pressure
  • Risk of Diabetes
  • Body weight and waist measurements
  • Impact of family history on heart health
  • Smoking cessation information, if needed
Measuring Fitness in Oncology Setting

1. Assess Cardiopulmonary Safety
2. Determine Exercise Dose
3. Compare Fitness Level to Healthy Age-Sex Matched Individuals
### Table 4 | Exercise prescription guidelines for cancer patients

<table>
<thead>
<tr>
<th>Patient characteristics (examples)</th>
<th>Goal of exercise</th>
<th>Initial prescription</th>
<th>Exercise progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>General (patients following the completion of adjuvant therapy for localised disease presenting with no overt underlying comorbid disease)</td>
<td>To improve all components of the oxygen cascade</td>
<td>Frequency: 3–5 days/week</td>
<td>Frequency: 4–6 days/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intensity:* light to moderate</td>
<td>Intensity:* light to vigorous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type: aerobic endurance</td>
<td>Type: aerobic endurance, interval training and resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time: 20–40 min/session</td>
<td>Time: ~30–60 min/session</td>
</tr>
<tr>
<td>Cardiovascular limitation (patients with chemotherapy-induced LV dysfunction and/or anaemia)</td>
<td>Improved LV filling and relaxation, enhanced LV compliance, improved in endothelial function, and decreased arterial stiffness</td>
<td>Frequency: 3 days/week</td>
<td>Frequency: 3–5 days/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intensity:* light to moderate</td>
<td>Intensity:* moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type: aerobic endurance</td>
<td>Type: aerobic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time: ~20–30 min/session</td>
<td>Time: ~20–60 min/session</td>
</tr>
<tr>
<td>Respiratory limitation (patients following pulmonary resection with concomitant COPD)</td>
<td>Reduced ventilatory demand and dyspnoea, with favourable skeletal muscle adaptations</td>
<td>Frequency: 3–4 days/week</td>
<td>Frequency: 4–5 days/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intensity:* light to moderate</td>
<td>Intensity:* moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type: aerobic endurance and resistance</td>
<td>Type: aerobic endanence and resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time: &gt;20 min/session</td>
<td>Time: ~20–60 min/session</td>
</tr>
<tr>
<td>Peripheral limitation (patients presenting with tumour and/or treatment-induced cachexia or muscle atrophy)</td>
<td>Increased muscle mass and aerobic enzymes, and improved fibre type transition and oxidative metabolism</td>
<td>Frequency: 3 days/week</td>
<td>Frequency: ~3 days/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intensity:* light to moderate</td>
<td>Intensity:* moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type: resistance</td>
<td>Type: resistance and aerobic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time: 20–30 min/session</td>
<td>Time: ~20–60 min/session</td>
</tr>
</tbody>
</table>

*Relative intensities guideline for aerobic endurance training: light (light effort, normal or slight breathing, 40–50% of measured heart rate maximum or VO₂peak); moderate (moderate effort, elevated breathing, 50–70% of measured heart rate maximum or VO₂peak); vigorous (hard effort, greater breathing, >70% of measured heart rate maximum or VO₂peak). Relative intensities guideline for resistance training: light (50–60% of measured one repetition maximum), moderate (60–80% of measured one repetition maximum), and hard (>80% of measured one repetition maximum).*  

Abbreviations: COPD, chronic obstructive pulmonary disease; LV, left ventricular; VO₂peak, peak oxygen consumption.

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Systemic Integration of Exercise And CV Risk Factor Modification for Cancer Patients
Components of Cardiac Rehabilitation

- First event Clinical Disease:
  - Angina, MI, CHF, PAD, stroke, sudden death
- Subclinical Disease:
  - Left ventricular dysfunction, carotid stenosis, coronary calcification, myocardial ischemia, more vulnerable plaque, potential for thrombosis
- Traditional Risk Factors:
  - Age, family history, hypertension, dyslipidemia, diabetes, obesity
- Nontraditional Risk Factors:
  - Psychosocial stressors, air pollution, inflammation, other (?)

- Lifestyle Modification and Pharmacotherapies (if appropriate)
- Secondary Prevention
- Core components of Cardiac Rehabilitation:
  - Exercise Training
  - Patient Assessment
  - Nutrition Counseling
  - Physical Activity Counseling
  - Psychosocial Management
  - Tobacco Cessation
  - Diabetes Management
  - Weight Management
  - Blood Pressure Management
  - Lipid Management

- Unhealthy Lifestyle Practices

Existing CVD

Impairment in Physical Functioning - Speech

Cardiac Symptoms

Hx MI or PCI/CABG, ↓LVEF, valvular dx

Low-dose anthracycline or trastuzumab + (≥2 RF or age ≥ 60 yrs)

Low-dose anthracycline + trastuzumab

Low-dose anthracycline + trastuzumab

None or other**

High-dose anthracycline/radiotherapy*

Oncology/Cancer rehabilitation

Cardio-Oncology REhabilitation (CORE)

Community-based programs for cancer patients

PT/OT/speech consult

CV consult

Cardiopulmonary exercise testing

After exposure, assess symptom/dx

No symptoms/dx

Repeat algorithm if complete program or change in exposure or symptom/dx

*High-dose anthracycline (eg, doxorubicin ≥ 250 mg/m²); High-dose radiotherapy (RT; ≥ 30 Gy) where the heart is in the treatment field; or lower-dose anthracycline + lower-dose RT (< 30 Gy)

** Other therapies should be reviewed by treating health care provider to determine appropriateness for community-based program versus need for consultation or other testing
Next Steps:
Cardio-Oncology Rehabilitation (CORE) Integration

• Continue to provide cutting edge services at MD Anderson and to regional centers

• Clinical Trial

• CMS Coverage discussions
Conclusion

• Cancer patients are at competing risk for CVD.

• The mechanism for this risk is likely mediated by overlapping metabolic pathways between CVD and cancer.

• Improving fitness is a key strategy to offset CVD risk.
Conclusion

• Healthy Heart is one programmatic example of introducing fitness and CVD risk modification for cancer patients.

• Dissemination to other hospitals and communities likely will require CMS coverage for Cardiac Rehab.