Exercise for primary prevention among patients receiving Lung Cancer Screening

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Overview

- What do we know about exercise and prevention of CVD, Pulmonary Disease, Cancer.... Including lung cancer?
  - Mechanisms

- What would happen if we exercised patients screened for lung cancer?

- Muscle matters to these patients in overcoming COPD problems.
  - Review musculature in COPD as seen on Thoracic CT
    - Can exercise change this?

- Implementation issues
  - How do we mobilize exercise as a drug of presymptomatic COPD, Heart Disease, Lung Cancer?
  - CT scans happen annually, could this be an opportunity to prescribe exercise?
  - We know exercise works, how do we make it happen?
Source for this section...

2018 Physical Activity Guidelines Advisory Committee Scientific Report
Exercise and Prevention of CVD Mortality

30% reduced CVD mortality for walkers

Figure F6-4. The Association Between Walking and Cardiovascular Mortality Risk in Men and Women

<table>
<thead>
<tr>
<th>Authors/year</th>
<th>Exposure</th>
<th>Sample size</th>
<th>Hazard ratio (95% CI)</th>
<th>0.0</th>
<th>Hazard ratio (95% CI)</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Hakim et al (1998)</td>
<td>Walking &gt; 2.2 km/day</td>
<td>707</td>
<td>0.39</td>
<td>0.10 to 1.46</td>
<td>0.0</td>
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</tr>
<tr>
<td>2 Hakim et al (1999)</td>
<td>Walking &gt; 2.5 km/day</td>
<td>2678</td>
<td>0.43</td>
<td>0.24 to 0.77</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>3 Blijlen et al (1998)</td>
<td>Walking &gt; 3 hours/day</td>
<td>982</td>
<td>0.69</td>
<td>0.45 to 1.05</td>
<td>0.0</td>
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</tr>
<tr>
<td>4 Sesso et al (2000)</td>
<td>Walking &gt; 10 km/day</td>
<td>12516</td>
<td>0.68</td>
<td>0.38 to 1.20</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>5 Davey Smith et al (2000)</td>
<td>Brisk walking</td>
<td>6702</td>
<td>0.47</td>
<td>0.26 to 0.87</td>
<td>0.0</td>
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<tr>
<td>6a Tainasou et al (2002)</td>
<td>Walking &gt; 3.5 hours/week</td>
<td>44452</td>
<td>0.90</td>
<td>0.73 to 1.11</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>6b Tainasou et al (2002)</td>
<td>Brisk walking</td>
<td>44452</td>
<td>0.51</td>
<td>0.31 to 0.84</td>
<td>0.0</td>
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</tr>
<tr>
<td>7 Node et al (2005)</td>
<td>Walking &gt; 1 hour/day</td>
<td>31023</td>
<td>0.85</td>
<td>0.72 to 1.00</td>
<td>0.0</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>1a Manson et al (1999)</td>
<td>Walking &gt; 3 hours/week</td>
<td>72486</td>
<td>0.65</td>
<td>0.47 to 0.91</td>
<td>0.0</td>
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<tr>
<td>1b Manson et al (1999)</td>
<td>Brisk walking</td>
<td>72486</td>
<td>0.64</td>
<td>0.47 to 0.98</td>
<td>0.0</td>
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<tr>
<td>1c Sesso et al (1999)</td>
<td>Walking &gt; 10 km/day</td>
<td>1956</td>
<td>0.67</td>
<td>0.46 to 1.01</td>
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<tr>
<td>2a Lee et al (2001)</td>
<td>Walking &gt; 2 hours/week</td>
<td>39372</td>
<td>0.48</td>
<td>0.29 to 0.78</td>
<td>0.0</td>
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<tr>
<td>2b Lee et al (2001)</td>
<td>Brisk walking</td>
<td>39372</td>
<td>0.52</td>
<td>0.30 to 0.90</td>
<td>0.0</td>
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<tr>
<td>3a Manson et al (2002)</td>
<td>Walking &gt; 3 hours/week</td>
<td>73743</td>
<td>0.68</td>
<td>0.56 to 0.82</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>3b Gregg et al (2003)</td>
<td>Walking &gt; 806 loca/week</td>
<td>9518</td>
<td>0.62</td>
<td>0.49 to 0.78</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>4a Node et al (2005)</td>
<td>Walking &gt; 1 hour/day</td>
<td>42242</td>
<td>0.64</td>
<td>0.58 to 1.02</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>4b Matthew et al (2007)</td>
<td>Walking &gt; 1 MET-hour/day</td>
<td>417390</td>
<td>0.11</td>
<td>0.04 to 0.27</td>
<td>0.0</td>
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</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Male and female</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Lacero et al (1998)</td>
<td>Walking &gt; 4 hours/week</td>
<td>16245</td>
<td>0.58</td>
<td>0.52 to 0.60</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Note: Walking is favored, with a shift of the estimate to the left. Notice the similarity of these estimates to the effects on all-cause mortality in Question 1, Figure F6-1.

Dose Response Relationships PA and Breast Cancer, Colon Cancer, Diabetes, Ischemic Heart Disease, and Ischemic Stroke

MET-hours/week = time walking
- 8.5 MET-hrs/week = 2 hrs, 15 min
- 17 MET-hrs/week = 4 hrs, 30 min
- 35 MET-hrs/week = 9 hrs, 15 min
Figure 3—This is theoretical dose-response curve demonstrating that the magnitude of the benefit for any given increase in activity is greater for less active persons.
Life-Long Physical Activity Involvement Reduces the Risk of Chronic Obstructive Pulmonary Disease: A Case-Control Study in Japan

Fumi Hirayama, Andy H. Lee, and Tetsuo Hiramatsu

Table 3  Life-Long Physical Activity and Risk of COPD and Breathlessness

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Life-long physical activity</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inactive</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>0.73 (0.51, 1.06)</td>
<td>0.59</td>
<td>(0.36, 0.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inactive</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>active</td>
<td>0.65 (0.44, 0.97)</td>
<td>0.56</td>
<td>(0.36, 0.88)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Logistic regression models adjusting for age, gender, BMI (5 years ago), education level, marital status, residential location, alcohol drinking, cigarette smoking, smoking pack-years, daily intake of red meat, chicken, fish, vegetables, and fruits (in grams).
Fig. 1. Forest plot of the study-specific associations between physical activity and lung cancer risk with combined estimates for case-control and cohort studies provided separately.
Among the mechanisms: Exercise Reduces Chronic Inflammation
Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby*, Robert J Glynn*, on behalf of the CANTOS Trial Group

Summary

Background Inflammation in the tumour microenvironment mediated by interleukin 1β is hypothesised to have a

HR  (95% CI)  p
---  ------  ----
Placebo 1.0 (ref) (ref)
Canakinumab 50 mg 0.74 (0.47–1.17) 0.20
Canakinumab 150 mg 0.61 (0.39–0.97) 0.034
Canakinumab 300 mg 0.33 (0.18–0.59) <0.0001

p trend across groups <0.0001

Cumulative incidence (%)

Number at risk

Placebo 3344 3241 3142 2835 1401 251
Canakinumab 50 mg 2170 2110 2047 1825 827 53
Canakinumab 150 mg 2284 2207 2148 1950 982 233
Canakinumab 300 mg 2663 2201 2128 1928 1002 222
What would happen if we started to exercise patients screened for lung cancer?

- Improved use of oxygen
- Energy levels
- Anxiety, depression
- Sleep
- Self-esteem
- Cardiovascular Fitness
- Muscular Strength
- Improved shortness of breath
Muscle Matters

- Altered body composition is predictive of increasing mortality among COPD patients

- Thoracic CT scans allow for measurement of
  - Pectoralis Muscle Area
  - Erector Spinae muscles
  - Intercostal muscles
  - Subcutaneous Adipose Tissue

![Survival Curve](image)

**Figure 3.** Kaplan–Meier survival curves stratified by the cross-sectional area of the erector spinae muscles ($ESM_{CSA}$) ($n = 130$). The cutoff values correspond to the mean, mean −1 SD, and mean −2 SD determined in the smoking control subjects (39, 32, and 25 cm$^2$, respectively). The patients with COPD with lower $ESM_{CSA}$ values exhibited significantly worse survival rates ($P < 0.0001$ by log-rank test).
Intercostal Muscles, Pectoral Muscles

Intercostal muscles and breathlessness

**Figure 6** Cross-sectional area (CSA) of the intercostal muscles by extent of breathlessness (mMRC grade) in patients with COPD

Ju Clin Respir J 2018

Pectoral Muscle Quartiles and Mortality

**Figure 2** Kaplan-Meier curves for all-cause mortality by sex-specific quartiles of pectoralis muscle area (PMA) in ex-smokers. The survival probabilities decrease with decreasing PMA quartiles.

Diaz Respiratory Research 2018
Exercise improves musculature relevant to COPD

**Pectoralis Major Muscles**

![Graph showing changes in muscle size after training]

Bernard Am J Respir Crit Care Med 1999

**Intercostal muscles**

<table>
<thead>
<tr>
<th></th>
<th>Sham Training Group</th>
<th>Inspiratory Training Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Global fiber size</td>
<td>47 ± 9</td>
<td>51 ± 10</td>
</tr>
<tr>
<td>Least diameter, μm</td>
<td>3.08 ± 1.25</td>
<td>3.27 ± 1.28</td>
</tr>
<tr>
<td>Type I fibers</td>
<td>50 ± 14</td>
<td>47 ± 16</td>
</tr>
<tr>
<td>CSA, μm²</td>
<td>2.60 ± 0.94</td>
<td>2.94 ± 1.24</td>
</tr>
<tr>
<td>Least diameter, μm</td>
<td>44 ± 7</td>
<td>49 ± 9</td>
</tr>
<tr>
<td>SD, μm</td>
<td>6 ± 1</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Type II fibers</td>
<td>50 ± 14</td>
<td>53 ± 16</td>
</tr>
<tr>
<td>CSA, μm²</td>
<td>3.67 ± 1.47</td>
<td>3.58 ± 1.32</td>
</tr>
<tr>
<td>Least diameter, μm</td>
<td>50 ± 12</td>
<td>53 ± 11</td>
</tr>
<tr>
<td>SD, μm</td>
<td>7 ± 2</td>
<td>8 ± 1</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CSA = cross sectional area; SD = standard deviation of mean least fiber diameters.

* p Value < 0.05 when compared with pretraining evaluation.

Ramirez-Sarmiento Am J Respir Crit Care Med 2002
So we know exercise helps...

How do we make it happen as standard of care?
Current State of Implementation

- Exercise is not standard of care in the setting of pulmonary screening for lung cancer
- A minority of patients are adequately active
- Multifactorial causes include:
  - Lack of awareness by patients and providers
  - Lack of programming
  - Lack of referral from clinicians
  - Lack of a well trained exercise workforce
  - Lack of payment for programming
Themes toward the goal of broad implementation of exercise in the lung cancer screening population

• Policy, funding
  • Federal
  • Organizational
  • Institutional

• Research

• Workforce development

• Program development

• Stakeholder engagement: changing culture
Policy, Funding: Federal Government level

• Exercise interventions require funding. Options:
  • Delivery by health care professionals (e.g.; PTs)
  • Change policy so that exercise professionals become HCP
  • Demonstrate that programs are effective in community settings, change policy to ‘cover’ costs of programs (e.g.; DPP model)

• Issues in determining how best to proceed
  • Workforce preparedness
  • Referrals to programs remain low
Policy relevant to exercise in lung cancer screening populations: Organizational level examples

- Accreditation bodies for lung cancer screening centers
  - Standards drive behavior (example: distress screening in cancer)
- American College of Sports Medicine
  - Preparticipation guidelines do not currently include pulmonary disease
Research

- Efficacy trials
  - Outcomes need to fit the policy needs
    - Treatment efficacy
    - Health services outcomes

- Evaluative trials
  - Comparison of the common implementation models
    - Counseling, individual training, group training
  - Cost evaluation
  - Health care utilization

- Implementation science trials
Patients screened for lung cancer with CT scans

Randomize by Clinic

Arm A (Standard Arm)
- Exercise advice as usual practice by providers
- Brochures about exercise interventions in waiting room

Arm B (Implement Exercise Is Medicine Approach)
- Implementation facilitation applied to adapt clinical work flow to enable patient assessment, advice, referral, and connection to an evidence based exercise intervention by providers and staff

Design: Cluster Randomized Trial
Implementing exercise interventions in community CT screening clinics

- Existing gap in testing effective implementation strategies for improving physician referrals and utilization of evidence-based exercise interventions in the setting of lung cancer screening clinics
  - Evidence base exists for SBIRT in primary care

- Community clinics are important in studying the real-world factors that influence implementation
Multilevel intervention

• Patient
  • Evidence based Exercise Intervention

• Treating Clinician
  • Clinical work flow: The Ask Advise Refer Connect Process

• Care Delivery Team / Level of the Practice
  • Implementation Facilitation
Specific Aims

• Aim 1: To assess whether implementation facilitation of the Ask, Advise, Refer, Connect (AARC) process results in increased proportion of patients with a completed referral to exercise. (IMPLEMENTATION OUTCOME)

• Aim 2: To examine mechanisms by which implementation facilitation of the AARC process results in increased proportion of patients with a completed referral. (IMPLEMENTATION AIM)

• Aim 3: To assess the effectiveness on patient level outcomes regarding symptom burden (breathlessness). (CLINICAL EFFECTIVENESS OUTCOME)
Workforce Development

• Exercise professionals are, in general, not currently being prepared to work with lung cancer screening patients
  • This needs to change
• Need to identify KSAs needed in exercise professionals to work with lung cancer screening patients
  • Credential re-tool at ACSM
• Creation of 101 module
Program Development

• Identify where programs already exist
• Map them
• Enlist national fitness chains to start pulmonary specific programs
• Help existing programs to spread
Implementation of exercise for patients receiving screening for lung cancer

- Policy
- Stakeholder awareness
- Program development
- Workforce development
- Research

Thank you!