Physical exercise interventions in cancer survivors

Effects and methodological issues

Anne May, PhD
I have no disclosures.
<table>
<thead>
<tr>
<th>History of exercise- oncology</th>
<th>Exercise interventions</th>
<th>Effects of exercise</th>
<th>POLARIS project</th>
<th>UMBRELLA FIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advice to rest and avoid exercise</td>
<td>Late 1980s First (small) exercise study (n=24)</td>
<td>1990s Few studies, clinical practice unchanged</td>
<td>2000 onwards: Increase in # of studies and attention in clinical practice</td>
<td>2003: cancer exercise recommendations (American Cancer Society)</td>
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</tbody>
</table>

- Beneficial effects on fitness, body composition, nausea

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**Content exercise interventions:**
- Divers and no consensus about optimal intervention

- **Types of interventions:**
  - **Supervised** interventions (2-3/week):
    - Aerobic exercise
      (30-45 mins/session, moderate-to-high intensity)
    - Resistance exercise
      (about 10 exercises, 60-70% of 1RM)
    - Combined aerobic and resistance exercise
  - **Home-based** interventions:
    - Walking
      (e.g. 5 d/week for 20-30 mins, low-to-moderate intensity)
    - Resistance exercises
      (body weight or elastic bands)
Effects of exercise after cancer diagnosis

• **Aim:**
  – During treatment: Prevention of side effects (e.g., fatigue, ↓ fitness)
  – After treatment: Improvement of fitness, fatigue, QoL
  – Mechanistic studies: e.g., effects on bloodmarkers (immune system, etc)

• **Beneficial effects on disease and treatment related side effects**
  – Cardiorespiratory fitness and muscle strength ↑
  – Fatigue, sleep disturbances and depression ↓
    → Quality of life ↑

  – Body composition ↑
  – Inflammation ↓
  – Chemotherapy completion rate ↑

(Courneya et al. (2007); van Waart et al. (2015))

• Although conclusion of meta-analyses are positive, future research needed for:

  – Patients with rarer type of cancer
    e.g. ongoing PERFECT study (oesophageal cancer, abstract #17)
  – Patients with advanced disease
  – Specific side effects (cognitive complaints (PAM study), osteoporosis, side-effects from novel targeted therapies)
  – Focus on cancer outcomes (progression and survival)
    e.g. ongoing CHALLENGE RCT (colon cancer, Courneya et al. CEBP 2016)
  – Focus on optimal frequency, intensity, type, timing of exercise

  BUT:
  One size does not fit all
Predicting OptimaL cAncer Rehablitation and Supportive care

- Internationally shared database for individual patient data (IPD) meta-analyses

- Aim:
  - evaluate the effect of exercise interventions on quality of life
  - identify important demographic, clinical, personal, or intervention-related moderators of the effect;
  - build and validate clinical prediction models identifying the most relevant predictors of intervention success.

→ Personalised programs

Buffart et al. Cancer Treat Rev 2014
1,779 RCTs identified through database searching (medline, Embase, PsychINFO, CINAHL)

397 duplicates removed

1,423 RCTs screened on title and abstract

957 records excluded

337 full-text RCTs excluded with reasons:
- No usual care, wait-list or attention control group (91)
- No physical activity/exercise or psychosocial intervention (64):
  (multimedal lifestyle intervention (9), diet/diet education (9), pain management (8), yoga (6), mindfulness (6), medical qigong (5), polarity therapy (4), reflexology (3), physiotherapy (sholder / pelvic rehabilitation) (3), healing touch (2), dignity therapy (1), hypnosis (1), keif therapy (1), massage therapy (1), meditation (1), music therapy (1), reiki therapy (1), sexuality training and information (1), video game intervention (1)).
- No quality of life (46)
- No RCT (42)
- No English, German or Dutch written article (9)
- No adult, cancer patients (6)
- Multiple articles on the same dataset (72)
- Preliminary results (7)

466 full-text RCTs screened for eligibility

129 RCTs for which IPD were sought:
- Result papers for which IPD were sought: 105
- Protocol papers for which IPD were sought: 24

Final number of RCTs for which IPD were sought: 136
- PSI (58)
- Mixed (12) (including additional PSI (2) and PA arm (3))
- PA (66)

PA:
- 31 RCTs for which IPD were provided

Mixed:
- 6 RCTs for which IPD were provided
  - Additional physical activity arm (3)
  - Additional psychosocial arm (1)

PSI:
- 20 RCTs for which IPD were provided
  - 140 patients from 1 RCT excluded who received nutritional support

Available data

PA:
- 34 RCTs in database (n = 4,519)

Mixed:
- 6 RCTs in database (n = 1,075)

PSI:
- 21 RCTs in database (n = 4,060)

Reasons for not providing IPD:
- IPD not available at the moment, but willing to share in the future (20, n = 3,142)
  - 7 PSI (n = 1,168), 1 Mixed (n = 256), 12 PA (n = 1,217)
  - 13 PSI (n = 963), 0 Mixed (n = 0), 4 PA (n = 390)
  - No reaction after initial response (11, n = 945)
  - No approval (7, n = 983)
  - 1 PSI (n = 390), 4 Mixed (n = 391), 2 PA (n = 390)
- Not willing to share IPD at the moment (7, n = 670)
  - 4 PSI (n = 453), 0 Mixed (n = 0), 3 PA (n = 215)
## Characteristics

<table>
<thead>
<tr>
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<th>Intervention (n= 2,514)</th>
<th>Control (n=2,005)</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (SD) years</td>
<td>54.6 (11.5)</td>
<td>54.5 (11.2)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1961 (78.0)</td>
<td>1567 (78.2)</td>
</tr>
<tr>
<td>Cancer Type, n (%)</td>
<td></td>
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</tr>
<tr>
<td>Breast</td>
<td>1757 (69.9)</td>
<td>1406 (70.1)</td>
</tr>
<tr>
<td>Male genitourinary</td>
<td>326 (13.0)</td>
<td>248 (12.4)</td>
</tr>
<tr>
<td>Haematological</td>
<td>199 (7.9)</td>
<td>195 (9.7)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>146 (5.8)</td>
<td>87 (4.3)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>44 (1.8)</td>
<td>33 (1.6)</td>
</tr>
<tr>
<td>Respiratory track</td>
<td>28 (1.1)</td>
<td>29 (1.4)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (0.6)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>Timing of intervention, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Pre-during-post treatment</td>
<td>80 (1.8)</td>
<td></td>
</tr>
<tr>
<td>During treatment</td>
<td>2122 (47.0)</td>
<td></td>
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<tr>
<td>Post-treatment</td>
<td>2314 (51.2)</td>
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</table>
Effects on QoL using individual patient data

• Positive effects on QoL and physical functioning

• No demographic & clinical & intervention –related moderators were found
  → PA is equally effective across subgroups

• Effect of supervised exercise intervention larger when compared to unsupervised exercise (p for interaction < 0.05)
Next steps:

• Cancer specific analyses

• (Moderating) effects on fatigue, physical fitness, other psychosocial and clinical outcomes
PART 2: Methodological challenges in exercise oncology research:

Blinding not possible:

- Difficult accrual
- Drop-out after randomization to control
- Contamination between study arms (mainly non-compliance in the control group)
UMBRELLA Fit study

cohort randomized controlled trial (cmRCT) on effects of exercise on quality of life of patients with breast cancer

Anne May, Roxanne Gal, Evelyn Monninkhof, Petra Peeters, Carla van Gils, Lenny Verkooijen, Desirée van den Bongard, Marco van Vulpen
**Informed consent UMBRELLA cohort**

1. Collection of clinical data and patient reported outcomes

Optional:
2. Randomization to future interventions

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**UMBRELLA Fit trial**

*cmRCT design*  
*(Relton et al. BMJ 2010)*

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**Prospective cohort**  
*(UMBRELLA breast cancer cohort)*

- Diagnosis 3-m 6-m (Radiotherapy)
- 12-m 18-m 24-m 36-m etc.

**Random selection**

- *Exercise group* (12 wks)
- *Control group*

**Subpopulation**

**Repeated measurements**
cmRCT design

Possible benefits

- Control group unaware of the trial
  - Less drop-out after randomisation
  - Less contamination (non-compliance)
  - Better reflection of the real world (pragmatic)

- Study within UMBRELLA cohort
  - Faster recruitment
  - Long-term effects

- Less selective population

Possible disadvantages

- Higher drop-out rate intervention group
  - Non-compliance (decline intervention)
  - Drop-out during intervention

- Restricted to data from cohort
  - Definition of subpopulation
  - Outcome measurements
Present state of research (Aug 2016)

Randomized ($N = 106$ of 166)

Age: 58.0 ± 9.2 | PA*: 16.7 ± 36.6 min/wk

Intervention group ($N = 53$)
Age: 58.4 ± 8.7

“Maybe later” ($N = 6$; 11%)
Age: 60.7 ± 7.7

“No” ($N = 17$; 32%)
Age: 58.5 ± 8.3

Control group ($N = 53$)
Age: 57.6 ± 9.6

Results expected in 2017

* Physical activity = cycle to work and during leisure time (moderate/fast), walking during leisure time (fast) & sports (> MET 4.0)
Conclusion

• Overall exercise interventions are beneficial

• Research should focus on targeted interventions, intervention characteristics, special side-effects, specific types of cancer, mechanisms, cancer prognosis

• If feasible, cmRCT design might facilitate exercise research
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Students
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