Journal of Physiotherapy 62 (2016) 68–82

Journal of PHYSIOTHERAPY

journal homepage: www.elsevier.com/locate/jphys

Research

Moderate-intensity exercise reduces fatigue and improves mobility in cancer survivors: a systematic review and meta-regression

Amy M Dennett [a], Casey L Peiris [b], Nora Shields [b], Luke A Prendergast [c], Nicholas F Taylor [a]

[a] School of Allied Health, La Trobe University and Allied Health Clinical Research Office, Eastern Health; [b] School of Allied Health, La Trobe University and Northern Health; [c] Department of Mathematics and Statistics, La Trobe University, Melbourne, Australia

KEY WORDS

Exercise therapy
Cancer
Fatigue
Mobility
Physical therapy (specialty)

ABSTRACT

Question: Is there a dose-response effect of exercise on inflammation, fatigue and activity in cancer survivors? **Design:** Systematic review with meta-regression analysis of randomised trials. **Participants:** Adults diagnosed with cancer, regardless of specific diagnosis or treatment. **Intervention:** Exercise interventions including aerobic and/or resistance as a key component. **Outcome measures:** The primary outcome measures were markers of inflammation (including C-reactive protein and interleukins) and various measures of fatigue. The secondary outcomes were: measures of activity, as defined by the World Health Organization's International Classification of Functioning, Disability and Health, including activities of daily living and measures of functional mobility (eg, 6-minute walk test, timed sit-to-stand and stair-climb tests). Risk of bias was evaluated using the PEDro scale, and overall quality of evidence was assessed using the Grades of Research, Assessment, Development and Evaluation (GRADE) approach. **Results:** Forty-two trials involving 3816 participants were included. There was very low-quality to moderate-quality evidence that exercise results in significant reductions in fatigue (SMD 0.32, 95% CI 0.13 to 0.52) and increased walking endurance (SMD 0.77, 95% CI 0.26 to 1.28). A significant negative association was found between aerobic exercise intensity and fatigue reduction. A peak effect was found for moderate-intensity aerobic exercise for improving walking endurance. No dose-response relationship was found between exercise and markers of inflammation or exercise duration and outcomes. Rates of adherence were typically high and few adverse events were reported. **Conclusions:** Exercise is safe, reduces fatigue and increases endurance in cancer survivors. The results support the recommendation of prescribing moderate-intensity aerobic exercise to reduce fatigue and improve activity in people with cancer. **Review registration:** PROSPERO CRD42015019164. **[Dennett AM, Peiris CL, Shields N, Prendergast LA, Taylor NF (2016) Moderate-intensity exercise reduces fatigue and improves mobility in cancer survivors: a systematic review and meta-regression. *Journal of Physiotherapy* 62: 68–82]**

Introduction

Cancer is a leading cause of burden of disease globally[1] and is responsible for approximately three in 10 deaths.[2] However, with improved screening and advancing treatment options, survival rates are improving. As a result, cancer is now recognised as a chronic disease.[3,4] While treatment may improve survival, the side-effects on physical and psychological function often reduce quality of life. There is an increasing need for rehabilitation to address these issues.

Exercise is an effective treatment for many chronic diseases. Recent systematic reviews have demonstrated that exercise used as part of cancer care reduces cancer-related fatigue and improves cardiovascular function, strength and quality of life.[5–9] There is also emerging evidence that exercise can reduce recurrence and mortality in some cancer populations.[10–16]

Despite these benefits of exercise, there is a lack of evidence on the safety and efficacy of exercise in relation to dose.[6,17] The ideal mode and intensity of exercise for people with cancer is unclear, and exercise guidelines are based largely on expert clinical opinion and adaptations of guidelines for healthy people. Current recommendations suggest that cancer survivors complete at least 150 minutes of moderate-intensity physical activity per week.[6] However, these recommendations may not recognise the specific health needs of cancer survivors. Recent reviews have reported a low number of adverse events in relation to exercise trials,[6,7,18–20] suggesting that exercise is generally safe for cancer survivors. However, in these reviews, there has been variable reporting of the dose of prescribed exercise.

The association between inflammation and cancer is well documented.[21–23] Chronic inflammation plays a role in the pathogenesis of insulin resistance and tumour growth, and has been linked to cancer risk and mortality.[23–26] Inflammatory cytokines have also been implicated in the development of cancer-related fatigue.[27–29] Exercise plays a role in mediating the effects of chronic inflammation, reducing inflammatory

http://dx.doi.org/10.1016/j.jphys.2016.02.012

markers such as C-reactive protein (CRP), tumour necrosis factor-alpha, and various types of interleukin (IL), including IL6, in people with and without cancer.[30–32] Furthermore, the protective effects of exercise have been attributed to the creation of an anti-inflammatory environment through increasing anti-inflammatory cytokines such as ILRa and IL10 in healthy people.[26,33,34] The relationship between exercise dose and inflammatory markers in people with cancer needs to be considered because strenuous exercise can induce pro-inflammatory cytokines in healthy people.[35] Therefore, it is important to know how much exercise can be safely tolerated in this immune-compromised population of people with cancer.

Cancer-related fatigue affects 80 to 100% of patients.[36] Fatigue is a complex multi-dimensional construct related to reduced physical function and reduced health-related quality of life.[27,37] Recent reviews have concluded that exercise reduces cancer-related fatigue,[19,38–40] but the optimal dose to achieve this has not been established. It has been suggested that patients undergoing treatment may need to exercise at a lower intensity or for a shorter duration than those who have completed primary treatment.[41] However, others have suggested that higher-intensity exercise may be better.[42,43] For example, Brown et al[40] found that moderate-intensity resistance exercise may be more effective than low-intensity exercise for reducing cancer-related fatigue. The most effective duration and intensity of exercise remain unclear.

Therefore, the research questions that we sought to answer with this systematic review were:

1. Is there a dose-response effect of exercise on inflammation and fatigue in adult cancer survivors?
2. Is there a dose-response effect of exercise for improving functional activity in this population?

Method

This systematic review was reported in accordance with PRISMA guidelines.[44,45]

Search strategy

The Medline, EMBASE and CINAHL databases were searched from the earliest records to April 2015. PubMed was also searched from 2010 for more recent publications. The search strategy was based around synonyms and MeSH subject headings of the key concepts of *exercise* and *cancer* combined with the primary outcomes of *fatigue* and *inflammation*. These terms were combined with relevant filters to identify randomised, controlled trials.[46] The detailed search strategy is presented in Appendix 1 (see eAddenda). The database searches were supplemented by citation tracking of included articles using Google Scholar and checking the reference lists of included studies.

Eligibility criteria

The eligibility of papers identified by the searches was assessed by two reviewers who independently considered information from the titles and abstracts against predetermined eligibility criteria (Box 1). Disagreements were resolved by discussion, with a third reviewer consulted when necessary. Where eligibility was unclear from the title and abstract, the full-text version was obtained and examined by both reviewers.

To be included, studies had to be randomised, controlled trials that: examined the effect of exercise in adults who had been diagnosed with cancer, reported at least one of the primary outcomes (fatigue or inflammation) and were published in English. The exercise intervention had to meet the definition 'physical activity that is planned, structured and repetitive and has a final or intermediate objective of the improvement or maintenance of physical fitness'[47] with aerobic or resistance training as a key component, because these modes of exercise are expected to result in significant physiological changes that may affect inflammation and fatigue, and are quantifiable. Furthermore, the intensity (eg, percentage of maximum heart rate, repetition maximum, etc) or duration of completed exercise needed to be reported. For studies using a combined exercise intervention (ie, aerobic and resistance training), the intensity or total duration for both components must have been specified. Studies were excluded if only a single bout of exercise was used or if it was combined with a co-intervention such as diet or education.

Box 1. Inclusion criteria.

Design
- Randomised trial
- Published in English

Participants
- Adults with cancer

Intervention
- Exercise intervention with aerobic or resistance exercise as a key component
- Sufficient reporting of dose (ie, the intensity or duration must be reported). For combined modalities, the intensity or total duration for both components must be specified.

Outcome measures
- Must report at least one measure of fatigue or inflammation

Comparisons
- Exercise versus control
- Exercise plus usual care versus usual care only
- One exercise dose compared to another (eg, high versus low intensity)

Quality assessment

The studies were assessed by two reviewers, who independently rated the 11 criteria on the PEDro scale as yes or no. One criterion relates to external validity; the remaining 10 criteria contribute 1 point each, if met, to give a score out of 10. The PEDro score is a valid measure of internal validity and completeness of reporting. It has undergone Rasch analysis and has moderate levels of inter-rater reliability (ICC 0.68, 95% CI 0.57 to 0.76).[48,49] Trials scoring < 6 were deemed to be of low quality.[50]

Synthesis of results

A standardised mean difference (SMD) was calculated for each outcome from post-intervention means and SDs to compare the control and treatment groups and to account for different scales of measurement between studies. Where only change scores were reported, the post-intervention mean was estimated in reference to the baseline mean and the SD based on baseline data. If only a range was given, the SD was calculated.[51] Authors were contacted if there was insufficient published data for analysis. Data from outcome measures were classified into three categories to address the primary and secondary aims of the review: inflammation, fatigue and activity. Activity was defined according to the World Health Organization International Classification of Functioning as 'the execution of a task or action by an individual', which included measures of activities of daily living and functional mobility.[52]

Meta-analysis was completed using the R statistics package 'metafor'[53] to provide evidence of the pooled effect size of the exercise intervention. Data were combined if clinically homogenous for more than two trials. Random effects models and a restricted maximum likelihood estimator for the random effect variance parameter were used.[54] A meta-analysis of the ratio of sample variances[55] provided evidence of unequal variances