RBFEx
ISSN Online: 2675-1372

Revista Brasileira de Fisiologia do Exercício

Literature review

Exercise as an adjuvant therapy for breast cancer: a review of current exercise oncology evidence and perspectives

Exercício físico como terapia adjuvante para o câncer de mama: Uma revisão sobre as evidências atuais e perspectivas do exercício em oncologia

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ABSTRACT

Objective: To describe the effects and moderators of exercise on fatigue and cardiorespiratory fitness in women with breast cancer as well as the relationship between exercise and survival in this group of patients. **Methods:** We undertook a narrative review describing and discussing studies examining the effects of exercise on fatigue and cardiorespiratory fitness in breast cancer patients. Also, relevant information regarding the relationship between exercise and survival in cancer patients was examined. **Results:** Exercise resulted in significant effects on cancer-related fatigue, with greater reductions observed in patients undertaking supervised exercise sessions or with higher fatigue levels. For cardiorespiratory fitness, exercise provides significant increases following aerobic-based exercise programs. Effects derived from exercise on cardiorespiratory fitness were more pronounced in younger patients, patients undertaking supervised aerobic-based exercise programs, or undertaking non-linear aerobic exercise prescriptions. Although epidemiological studies indicate associations between higher physical activity levels and overall survival, randomised controlled trials are necessary to confirm such a relationship for exercise in cancer patients. **Conclusion:** Sufficient evidence indicates that exercise promotes significant effects on fatigue and cardiorespiratory fitness in women with breast cancer. In addition, specific subgroups of patients based on age and baseline levels appear to respond more favourably than others.

Keywords: breast cancer; exercise; fatigue; cardiorespiratory fitness.

RESUMO

Objetivo: Descrever os efeitos e os moderadores do exercício físico na fadiga e capacidade cardiorrespiratória de pacientes com câncer de mama em tratamento primário, bem como a relação entre o exercício físico e sobrevida nessa população. **Métodos:** Foi realizada uma revisão narrativa de estudos que examinaram os efeitos do exercício na fadiga e capacidade cardiorrespiratória em mulheres com câncer de mama. Além disso, examinamos informações relevantes sobre a relação entre exercício e sobrevivência em pacientes com câncer. **Resultados:** O exercício reduziu significativamente a fadiga relacionada ao câncer com maiores reduções observadas em pacientes que realizaram exercício de forma supervisionada ou apresentaram maiores queixas de fadiga. Na capacidade cardiorrespiratória, aumentos significativos foram observados após a realização de programas baseados em treinamento aeróbio. Pacientes mais jovens, que realizaram programas supervisionados, ou que participaram de prescrição não-lineares de treinamento aeróbio apresentaram maiores efeitos. Apesar de estudos epidemiológicos indicarem associações entre maiores níveis de atividade física e sobrevivência, ensaios clínicos randomizados são necessários para confirmar tal relação em pacientes com câncer. **Conclusão:** Sugerimos a promoção do exercício na redução da fadiga e aumento da capacidade cardiorrespiratória em mulheres com câncer de mama. Além disso, grupos específicos de pacientes baseados na idade e níveis iniciais parecem responder melhor ao exercício que outros.

Palavras-chave: neoplasias da mama; exercício físico; fadiga; aptidão cardiorrespiratória.

Received: May, 27, 2021; Accepted: August, 2, 2021

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Introduction

Cancer is one of the leading causes of death in 6 out of the 13 countries of South America [1]. Specifically, breast cancer is the most prevalent cancer and the main cause of death in women in Brazil [2].

During the primary treatment, both systemic (e.g., chemotherapy, hormonal, and biological therapies) and local therapies (e.g., surgery and radiotherapy) are used to eliminate tumoral cells and reduce the risk of cancer recurrence; or reduce disease progression as observed in patients with advanced cancer. However, despite the efficacy and success of these treatments for cancer control, most patients have their quality of life affected by some treatment-related side effects [3]. Among them, fatigue and reductions in cardiorespiratory fitness are commonly observed in response to treatment toxicities during and even following primary treatment [4-6]. To date, exercise has been considered an effective intervention to counteract these side effects [7-15].

In the past few years, guidelines from the *American Cancer Society* [7,8], *American College of Sports Medicine* [9-12], *Exercise and Sport Science Australia* [13,14] and the Spanish Society of Medical Oncology [15] were published highlighting the importance of being physically active and exercise to prevent [16], during [17] and following breast cancer treatment [18]. However, even with numerous studies demonstrating that exercise is effective for counteracting fatigue and reductions in cardiorespiratory fitness in patients undergoing chemotherapy [7-15], the relationship between its prescription variables and effects on these outcomes is unclear. Consequently, it is of great interest to understand the effects of different exercise modalities (e.g., resistance training, aerobic exercise or combined resistance and aerobic exercise) and their effects on fatigue and cardiorespiratory fitness. In addition, whether exercise effects on these outcomes differ due to patients' characteristics is unclear (i.e., moderators of exercise effects).

Therefore, the present study aimed to describe the exercise effects and moderators on fatigue and cardiorespiratory fitness in women with breast cancer undergoing primary treatment and the relationship between exercise and overall survival in this population. This information will support the promotion of exercise during the primary treatment and adequate prescription of exercise medicine to women with breast cancer.

Methods

The present study is a narrative literature review concerning the exercise effects and moderators of exercise response on fatigue, cardiorespiratory fitness, and overall survival in women with breast cancer. The search was undertaken in Pubmed using the following terms: 'cancer' AND 'exercise' AND ('fatigue' OR 'cardiorespiratory fitness' OR 'overall survival') in January 2021. Given the specificity of the topic and outcomes of interest, we selected 7 systematic reviews with meta-analysis to describe the exercise effects and moderators of exercise response on fatigue and cardiorespiratory fitness in breast cancer patients [19-25]. For overall survival, only a single randomized controlled trial involving exercise was found [26]. Furthermore, figures were utilized to present the main results.

Results and discussion

Cancer-related fatigue

Fatigue is one of the most prevalent symptoms in women with breast cancer undergoing primary treatment. About 80% of patients present this symptom during treatment [27,28], with 30% with persistent fatigue even following treatment [29]. In addition, cancer-related fatigue is often associated with psychological distress symptoms such as pain, anxiety, depression and sleep disorders [30].

Although the mechanisms underlying fatigue such as central (e.g., dysregulation of cytokines, hypothalamic-pituitary-adrenal axis, circadian rhythm and serotonin, and afferent vagal nerve alterations) or peripheral mechanisms (e.g., interference on the muscle metabolism, ATP dysregulation, and muscle properties) are still speculative [31], exercise is considered one of the main interventions for reducing fatigue in cancer patients [10,18], recommended by the clinical practice guidelines from National Comprehensive Cancer Network [32] and other professional organisations [7,9,13].

Considering the high prevalence of fatigue and its impact on quality of life, therapies targeting fatigue in breast cancer patients were always of great clinical interest. Over the past few years, non-pharmacological interventions such as exercise are on the list of potential therapies to control cancer-related fatigue [33]. Nevertheless, the clinical relevance of exercise is still debatable despite numerous studies indicating its significant fatigue reductions in patients with breast cancer.

In a previous systematic review [20], for example, Cramp et al. combined the results of 18 studies investigating the exercise effects in patients with breast cancer (n = 4,068 participants) and found a significant reduction in fatigue (effect size (ES) = -0.35, 95% confidence interval (95% CI): -0.51 to -0.19; Figure 1). However, these effect sizes were considered modest in this group of patients [20]. The exercise programs included in this study were resistance training (ES = -0.18, 95% CI: -0.39 to 0.02; Figure 1) and aerobic exercise (ES = -0.22, 95% CI: -0.34 to 0.10; Figure 1). In addition, as previously reported [20,25,33], these effects appear to be smaller than studies undertaking massage, relaxation, yoga, or other psychosocial interventions. Thus, although a significant reduction in cancer-related fatigue following exercise, explained by reductions in proinflammatory cytokines (e.g., interleukin 6) [34], it is important to question how much patients will benefit from this type of intervention.

The reasons for such attenuated exercise effect may be associated with studies design and methodology. For example, women with breast cancer present with different demographic and clinical characteristics, and are submitted to different chemotherapy regimens and exercise programs. Also, the assessing methods of cancer-related fatigue, involving different questionnaires and scales, may increase the imprecision around the results of exercise interventions [19,25]. Therefore, these methodological characteristics are associated with the high heterogeneity of studies in women with breast cancer.

Consequently, it is of great importance for health professionals that promotes or prescribe exercise to understand for whom (i.e., demographic and clinical characteristics) and how exercise will achieve its aims (i.e., exercise prescription variables), since it is premature the assumption that a given treatment/intervention/prescription will promote benefits to all patients (i.e., one-size-does-not-fit-all [35-37]). In this way, we presented below some information that could assist the prescription of exercise for reducing or attenuate fatigue during the primary treatment for breast cancer.

Previous studies investigated the association between demographic and clinical characteristics with exercise effects on fatigue in women with breast cancer [19,25,38]; these studies did not find significant associations between age, cancer stage and chemotherapy regime with exercise effects on this outcome. Therefore, it is reasonable to suggest that patients with different ages, cancer stages and treatments may similarly respond and benefit from exercise [19,25].

However, the delivery of exercise interventions seems to affect the exercise effects on fatigue. Supervised exercise programs present greater effects than unsupervised programs on fatigue in women with breast cancer (supervised exercise, ES= -0.23, 95% CI: -0.29 to -0.17 vs. unsupervised exercise, ES= -0.04, 95% CI: -0.13 to 0.04; Figure 1) [25]. These results were regardless of exercise modality (e.g., resistance training, aerobic exercise, and combined resistance and aerobic exercise) or exercise intensity (e.g., low, moderate, or high intensity) [25]. Although the reasons for that are still unknown, it could be related to the motivation and engagement of patients undertaking supervised exercise programs [25]. Thus, if feasible and realistic, the design of supervised exercise programs could result in greater fatigue reductions in breast cancer patients during treatment.

The baseline levels of fatigue seem to be another important aspect in this population. Before commencing exercise, the fatigue levels are an important factor that can predict how much benefit patients could derive from exercise [19]. Patients presenting with higher fatigue levels present greater reductions following exercise programs (> 1 standard deviation above average, ES = -0.22, 95% CI: -0.37 to -0.07; average to > 1 standard deviation above average, ES = -0.20, 95% CI: -0.30 to -0.11; average to < 1 standard deviation below average, ES = -0.17, 95% CI: -0.25 to -0.19; < 1 standard deviation below average, ES = -0.03, 95% CI: -0.13 to -0.08; Figure 1) [19]. The reasons for this finding may be associated with the larger window for adaptations in patients presenting with higher fatigue levels as well as the exercise benefits in quality of life and cardiorespiratory fitness. In contrast, patients with lower baseline levels of fatigue do not present such improvement [19]. Additionally, this result is of great importance as it can indicate that exercise effectively reduces fatigue in patients most in need and, therefore, could be considered an effective intervention to counteract fatigue in women with breast cancer presenting with exacerbated symptoms.

In summary, the design of supervised exercise programs could benefit women with breast cancer. In addition, exercise could result in greater effects in patients presenting with higher levels of fatigue when compared to those who do not present this symptom. These results are presented in Figure 1. The reader can find some examples of supervised exercise programs in studies from the Supervised Trial of Aerobic Versus Resistance Training (START [17]), Combined Aerobic and Resistance Exercise (CARE [39]) and Optimal Training Women with Breast Cancer trials (OptiTrain [40]). These studies prescribed resistance training, aerobic exercise and combined resistance and aerobic exercise, 2 to 3 exercise sessions per week, 1-3 sets of 8-12 repetitions at 60-70% of one-repetition maximum (1RM) per resistance exercise, and 20 to 30 min of continuous or high-intensity interval aerobic exercise at 13-15 of the rated perceived exertion (RPE) scale.

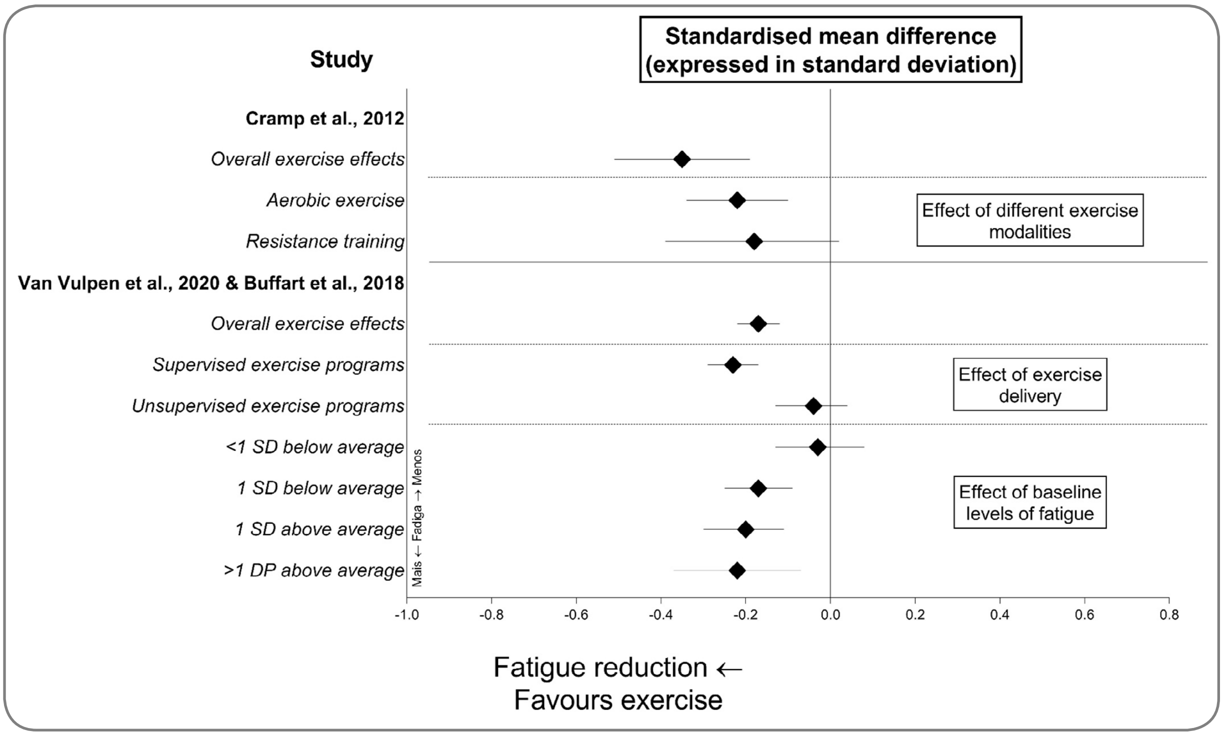

Figure 1 - Systematic reviews with meta-analysis examining the exercise effects on cancer-related fatigue in women with breast cancer; DP = standard deviation; diamond represents the standardized mean difference and its respective 95% confidence interval

Cardiorespiratory fitness

Despite the effects of aging and physical inactivity, breast cancer patients can present substantial reductions in the peak rate of oxygen consumption (VO2peak) following primary treatment [41,42]. During treatment, sedentary patients with breast cancer present mean VO2peak values 30% smaller than sedentary healthy women [43]. In addition, these lower values are maintained even following treatment, with patients presenting VO2peak values below 25 ml.kg.min-1 [43] and a higher risk of cardiovascular disease (multiple hits hypothesis [44]) and all-cause mortality [45-48].

Among the main factors related to reductions in cardiorespiratory fitness, chemotherapy regimens comprising anthracycline drugs such as doxorubicin, epirubicin [49-51] or trastuzumab [52] are associated with short- (e.g., left ventricular dysfunction, arrhythmias, pericarditis/myocarditis, cardiomyopathy, and reduced ejection fraction) and long-term cardiac dysfunction (e.g., progressive decrease in left ventricular function, and heart failure), consequently reducing the oxygen supply [44]. Therefore, exercise and specifically interventions comprising aerobic exercise (specific for this outcome) could be an important strategy to attenuate the side effect derived from primary treatment [9,10].

Several studies have been demonstrating the aerobic exercise effects, either prescribed by High Intensity Interval Training (HIIT), continuous aerobic exercise or combined resistance and aerobic exercise on cardiorespiratory fitness in different types of cancer [21-23,53].

In studies prescribing aerobic exercise, effects ranging from 2.1 to 3.4 ml.kg.min-1 (or ES = 0.28 to 1.19; Figure 2) are found favouring exercise compared to control groups (or usual care) [22,23]. These results can be explained by the cardioprotective effects from exercise [54], reducing the toxicities from breast cancer treatment as well as increasing the cardiorespiratory capacity during exercise [23]. Also, it is quite expected that the exercise dosage prescribed achieves the threshold for cardiorespiratory adaptations due to the clinical status and sedentary behaviour of this group of patients [23]. However, the exercise effects on cardiorespiratory fitness can vary across demographic and clinical characteristics and exercise prescription in this population [19,21,23]. So, it is necessary to clarify the circumstances that exercise achieves its aims in women with breast cancer.

Regarding the demographic and clinical characteristics, age seems to be an important factor that can modulate the effects of exercise on cardiorespiratory fitness in breast cancer patients [19,24,38]. Although the non-significant relationship between clinical characteristics such as cancer stage or chemotherapy regimen [24,38], younger patients ($\leq$ 50 yrs) presented better cardiorespiratory results following exercise than older patients (> 50 yrs) ($\leq$ 50 yrs, ES = 0.41, 95% CI: 0.31 to 0.52; 50 to $\leq$ 70 yrs, ES = 0.22, 95% CI: 0.15 to 0.29; > 70 yrs, ES = 0.23, 95% CI: 0.07 to 0.40; Figure 2) [24,38]. Among the explanations, less treatment-related side effects [24,38] or higher VO2peak baseline values [19] presented by younger patients could be associated with better results since lower fitness levels are associated with poorer cardiorespiratory fitness response following exercise [19].

These results could be counterintuitive, but also can indicate some limitations regarding exercise prescription for this population. For example, the underestimation or overestimation of exercise intensity could preclude patients receive the necessary exercise stimulus to improve this outcome. This may be associated with a conservative prescription or unfamiliarity with breast cancer comorbidities [55].

Furthermore, lower cardiorespiratory fitness values are associated with a higher risk of treatment comorbidities and toxicities and fatigue [38,56] and limited exercise history [57], resulting in a lower exercise program adherence.

Regarding the exercise program prescription, supervised, high-intensity or non-linear schedule aerobic exercise are also associated with greater effects on cardiorespiratory fitness [21,23,24]. The fact that supervised exercise results in greater benefits in cardiorespiratory fitness compared to unsupervised programs (supervised exercise, ES = 0.34, 95% CI: 0.28 to 0.40; unsupervised exercise, ES = 0.19, 95% CI: 0.07 to 0.32; Figure 2) is an important information [24]. The main reason seems to be related to more exercise sessions attended by patients when supervised by a health professional, which could result in greater cardiorespiratory fitness adaptations.

Furthermore, studies that prescribed high-intensity aerobic exercise (defined as 64-90% of VO2peak by Maginador et al. [21]) resulted in greater cardiorespiratory fitness improvements when compared to low intensity aerobic exercise prescriptions (high intensity, ES = 1.47, 95% CI: 0.60 to 2.34; low intensity, ES = 0.20, 95% CI: -1.44 to 1.85; Figure 2) [21]. Nevertheless, when comparing HIIT vs. continuous aerobic exercise, both were effective for improving VO2peak (HIIT, ES = 1.79, 95% CI: 0.28 to 3.29; continuous aerobic exercise, ES = 1.01, 95% CI: 0.19 to 1.83; Figure 2) [21]. Therefore, undertaking supervised and high-intensity aerobic exercise prescribed by either HIIT or continuous aerobic exercise is viable for women with breast cancer undergoing primary treatment [21,24]

Finally, the utilization of non-linear schedule aerobic exercise is another interesting strategy [23,58]. Considering the variation in fitness and fatigue during chemotherapy, patients may not adhere to or achieve the necessary performance throughout exercise sessions using progressive loads [58]. In this way, a non-linear aerobic exercise prescription (i.e., varying volume and intensity according to the chemotherapy regimen) could be an effective strategy to increase adherence and respect patients' characteristics and limitations during breast cancer primary treatment [14,58,59]. The results of each study abovementioned are shown in Figure 2.

Regarding contraindications, the exercise prescription should occur accordingly to and with the clearance of the oncologist and the medical team, respecting patients' individualities, the feasible period for exercise, symptoms, and treatment course [12,14]. Specifically, exercise should be avoided when patients present with compromised levels of haemoglobin or platelets during chemotherapy.

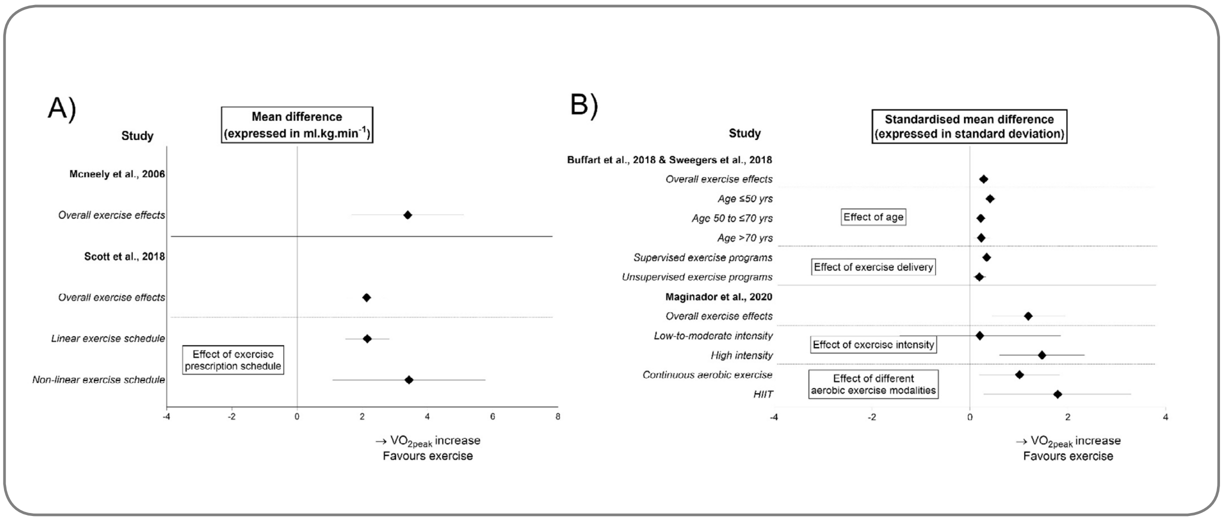

Figure 2 - Systematic reviews with meta-analysis examining the exercise effects on cardiorespiratory fitness expressed as A) ml.kg.min-1 and B) standardised mean difference in women with breast cancer; HIIT, high intensity interval training; diamond represents the effect size and its respective 95% confidence interval

Survival

Despite the relevance of investigating the exercise effects on fatigue and cardiorespiratory fitness, and several others not approached in this study (e.g., physical function and body composition), one of the most important questions is "Exercise can improve overall survival in cancer patients?".

The assumption that exercise can increase overall survival in patients with breast cancer comes from series of evidence indicating that physically active patients (i.e., those that undertake ≥ 150 min of physical activity per week) present ~40% improved overall survival compared to sedentary patients [16,60-63]. Although the mechanisms for such effect remain to be determined, they can be related to reductions and exposition to estrogen [64,65] and insulin-related factors [66,67], both perhaps associated with improved body composition and reductions in body weight [68,69]. However, this information should be viewed with caution due to imprecisions of studies design such as self-reported physical activity (e.g., overestimation of physical activity quantity and intensity) as well as the statistical and conceptual difference between association and causality [70].

Furthermore, the assumption that exercise can improve overall survival in breast cancer patients derives from an exploratory randomized clinical trial [17]. Follow-up analyses from the START trial [17], involving 242 breast cancer patients (average age: 49.2 yrs) randomized to aerobic exercise (n = 78), resistance training (n = 82) and usual care (n = 82), indicates a trend for improved survival in patients undertaking exercise, although the lack of statistical significance [26]. However, these results derived from the START trial are only exploratory [17,26] and should be viewed with caution given methodological limitations. Thus, specific randomized clinical trials should be designed to test this hypothesis.

Randomized clinical trials were designed to investigate the relationship between exercise and overall survival in patients with different cancer types [71-73]. These studies are 1) the Colon Health and Life-Long Exercise Change (CHALLENGE [71]) trial, 2) the Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation (PETRA [72]) trial, and 3) the Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4 [73]). Although these trials were not designed for breast cancer patients, they will be of great importance for the field and, maybe, to support exercise as adjuvant therapy for cancer, including breast cancer.

Conclusion

This study aimed to revise the effects of exercise for reducing cancer-related fatigue improving cardiorespiratory fitness in breast cancer patients undergoing primary treatment. From the information provided, it was possible to observe that there is a relatively consistent level of evidence indicating that exercise promotes improvements in the outcomes of fatigue and cardiorespiratory capacity, in addition to evidence of certain subgroups of patients who respond better to the exercise program, and suggestions how to enhance the effect of exercise through its prescription in women with breast cancer. Also, there is some suggestion that exercise could improve overall survival in breast cancer patients, although additional studies are required to confirm such a hypothesis. Therefore, we suggest promoting exercise for this population of cancer patients due to the significant reductions in common treatment adverse effects such as fatigue and cardiorespiratory fitness reductions during primary treatment.

Conflict of interest
No potential conflicts of interest relevant to this article have been reported.

Financing source
Pedro Lopez is a doctoral student funded by National Health and Medical Research Council (NHMRC) Centre of Research Excellence (CRE) in Prostate Cancer Survivorship Scholarship. Alice A. R. F. Francisco is director of the non-governmental organization Maple Tree Cancer Alliance® Brasil.

Author's contributions
Conception and design of the research: Lopez P, Francisco AARF; **Data collection:** Lopez P, Francisco AARF; **Data analysis and interpretation:** Lopez P, Francisco AARF; **Writing of the manuscript:** Lopez P, Francisco AARF; **Critical review of the manuscript:** Lopez P, Francisco AARF

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-49. doi: 10.3322/caac.21660

2. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). [Internet]. 2019 [cited 2021 Aug 3]. Estimativa 2020: incidência de câncer no Brasil. https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020-incidencia-de-cancer-no-brasil.pdf

3. Kayl AE, Meyers CA. Side-effects of chemotherapy and quality of life in ovarian and breast cancer patients. Curr Opin Obstet Gynecol 2006;18(1):24-8. doi: 10.1097/01.gco.0000192996.20040.24

4. Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, *et al.* Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5(5):353-60. doi: 10.1634/theoncologist.5-5-353

5. Freedman RJ, Aziz N, Albanes D, Hartman T, Danforth D, Hill S, *et al.* Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. J Clin Endocrinol Metab 2004;89(5):2248-53. doi: 10.1210/jc.2003-031874

6. Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, *et al.* Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. J Clin Oncol 2004;22(18):3700-4. doi: 10.1200/jco.2004.03.516

7. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, *et al.* Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62(4):243-74. doi: 10.3322/caac.21142

8. Rock CL, Thomson C, Gansler T, Gapstur SM, McCullough ML, Patel AV, *et al.* American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin 2020;70(4):245-71. doi: 10.3322/caac.21591

9. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, *et al.* American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42(7):1409-26. doi: 10.1249/MSS.0b013e3181e0c112

10. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, *et al.* Exercise guidelines for cancer survivors: Consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc 2019;51(11):2375-90. doi: 10.1249/MSS.0000000000002116

11. Patel AV, Friedenreich CM, Moore SC, Hayes SC, Silver JK, Campbell KL, *et al.* American College of Sports Medicine Roundtable Report on Physical Activity, Sedentary Behavior, and Cancer Prevention and Control. Med Sci Sports Exerc 2019;51(11):2391-402. doi: 10.1249/Mss.0000000000002117

12. Schmitz KH, Campbell AM, Stuiver MM, Pinto BM, Schwartz AL, Morris GS, *et al.* Exercise is medicine in oncology: Engaging clinicians to help patients move through cancer. CA Cancer J Clin 2019;69(6):468-84. doi: 10.3322/caac.21579

13. Hayes SC, Spence RR, Galvao DA, Newton RU. Australian Association for Exercise and Sport Science position stand: Optimising cancer outcomes through exercise. J Sci Med Sport 2009;12(4):428-34. doi: 10.1016/j.jsams.2009.03.002

14. Hayes SC, Newton RU, Spence RR, Galvao DA. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. J Sci Med Sport 2019;22(11):1175-99. doi: 10.1016/j.jsams.2019.05.003

15. Pollan M, Casla-Barrio S, Alfaro J, Esteban C, Segui-Palmer MA, Lucia A, *et al.* Exercise and cancer: a position statement from the Spanish Society of Medical Oncology. Clin Transl Oncol 2020;22(10):1710-29. doi: 10.1007/s12094-020-02312-y

16. Friedenreich CM, Stone CR, Cheung WY, Hayes SC. Physical activity and mortality in cancer survivors: a systematic review and meta-analysis. JNCI Cancer Spectr 2020;4(1):pkz080. doi: 10.1093/jncics/pkz080

17. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, *et al.* Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol 2007;25(28):4396-404. doi: 10.1200/jco.2006.08.2024

18. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, *et al.* Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med 2009;361(7):664-73. doi: 10.1056/NEJMoa0810118

19. Buffart LM, Sweegers MG, May AM, Chinapaw MJ, van Vulpen JK, Newton RU, *et al.* Targeting exercise interventions to patients with cancer in need: an individual patient data meta-analysis. J Natl Cancer Inst 2018;110(11):1190-200. doi: 10.1093/jnci/djy161

20. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev 2012;11:Cd006145. doi: 10.1002/14651858.CD006145.pub3

21. Maginador G, Lixandrão ME, Bortolozo HI, Vechin FC, Sarian LO, Derchain S, *et al.* Aerobic exercise-induced changes in cardiorespiratory fitness in breast cancer patients receiving chemotherapy: a systematic review and meta-analysis. Cancers (Basel) 2020;12(8). doi: 10.3390/cancers12082240

22. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. Cmaj 2006;175(1):34-41. doi: 10.1503/cmaj.051073

23. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, *et al.* Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. J Clin Oncol 2018;36(22):2297-305. doi: 10.1200/jco.2017.77.5809

24. Sweegers MG, Altenburg TM, Brug J, May AM, van Vulpen JK, Aaronson NK, *et al.* Effects and moderators of exercise on muscle strength, muscle function and aerobic fitness in patients with cancer: a meta-analysis of individual patient data. Br J Sports Med 2019;53(13):812. doi: 10.1136/bjsports-2018-099191

25. Van Vulpen JK, Sweegers MG, Peeters PHM, Courneya KS, Newton RU, Aaronson NK, *et al.* Moderators of exercise effects on cancer-related fatigue: a meta-analysis of individual patient data. Med Sci Sports Exerc 2020;52(2):303-14. doi: 10.1249/mss.0000000000002154

26. Courneya KS, Segal RJ, McKenzie DC, Dong H, Gelmon K, Friedenreich CM, *et al.* Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. Med Sci Sports Exerc 2014;46(9):1744-51. doi: 10.1249/mss.0000000000000297

27. Smets EM, Garssen B, Schuster-Uitterhoeve AL, Haes JC. Fatigue in cancer patients. Br J Cancer 1993;68(2):220-4. doi: 10.1038/bjc.1993.319

28. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18(4):743-53. doi: 10.1200/jco.2000.18.4.743

29. Ganz PA, Bower JE. Cancer related fatigue: a focus on breast cancer and Hodgkin's disease survivors. Acta Oncol 2007;46(4):474-9. doi: 10.1080/02841860701367845

30. Bardwell WA, Ancoli-Israel S. Breast cancer and fatigue. Sleep Med Clin 2008;3(1):61-71. doi: 10.1016/j.jsmc.2007.10.011

31. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nat Rev Clin Oncol 2014;11(10):597-609. doi: 10.1038/nrclinonc.2014.127

32. Network NCC. NCCN guidelines for supportive care: Cancer-related fatigue. NCCN [Internet]. Version 1, January 17, 2018 [cited 2021 Aug 3]. Available from: https://www.nccn.org/guidelines/category_1#supportive

33. Hilfiker R, Meichtry A, Eicher M, Nilsson Balfe L, Knols RH, Verra ML, *et al.* Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. Br J Sports Med 2018;52(10):651-8. doi: 10.1136/bjsports-2016-096422

34. Hiensch AE, Mijwel S, Bargiela D, Wengström Y, May AM, Rundqvist H. Inflammation mediates exercise effects on fatigue in patients with breast cancer. Med Sci Sports Exerc 2021;53(3):496-504. doi: 10.1249/mss.0000000000002490

35. Adams SC, Iyengar NM, Scott JM, Jones LW. Exercise implementation in oncology: one size does not fit all. J Clin Oncol 2018;36(9):925-6. doi: 10.1200/jco.2017.76.2906

36. Newton RU, Taaffe DR, Chambers SK, Spry N, Galvão DA. Effective exercise interventions for patients and survivors of cancer should be supervised, targeted, and prescribed with referrals from oncologists and general physicians. J Clin Oncol 2018;36(9):927-8. doi: 10.1200/jco.2017.76.7400

37. Newton RU, Taaffe DR, Galvao DA. Clinical Oncology Society of Australia position statement on exercise in cancer care. Med J Aust 2019;210(1):54-.54.e1. doi: 10.5694/mja2.12043

38. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, *et al.* Moderators of the effects of exercise training in breast cancer patients receiving chemotherapy: a randomized controlled trial. Cancer 2008;112(8):1845-53. doi: 10.1002/cncr.23379

39. Courneya KS, McKenzie DC, Mackey JR, Gelmon K, Friedenreich CM, Yasui Y, *et al.* Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. J Natl Cancer Inst 2013;105(23):1821-32. doi: 10.1093/jnci/djt297

40. Mijwel S, Backman M, Bolam KA, Jervaeus A, Sundberg CJ, Margolin S, *et al.* Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial. Breast Cancer Res Treat 2018;168(1):79-93. doi: 10.1007/s10549-017-4571-3

41. Bender CM, Sereika SM, Gentry AL, Duquette JE, Casillo FE, Marsland A, *et al.* Physical activity, cardiorespiratory fitness, and cognitive function in postmenopausal women with breast cancer. Support

Care Cancer 2020;29(7):3743-52. doi: 10.1007/s00520-020-05865-4

42. Lakoski SG, Barlow CE, Koelwyn GJ, Hornsby WE, Hernandez J, Defina LF, *et al.* The influence of adjuvant therapy on cardiorespiratory fitness in early-stage breast cancer seven years after diagnosis: the Cooper Center Longitudinal Study. Breast Cancer Res Treat 2013;138(3):909-16. doi: 10.1007/s10549-013-2478-1

43. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, *et al.* Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol 2012;30(20):2530-7. doi: 10.1200/jco.2011.39.9014

44. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol 2007;50(15):1435-41. doi: 10.1016/j.jacc.2007.06.037

45. Erikssen G, Liestøl K, Bjørnholt J, Thaulow E, Sandvik L, Erikssen J. Changes in physical fitness and changes in mortality. Lancet 1998;352(9130):759-62. doi: 10.1016/s0140-6736(98)02268-5

46. Kavanagh T, Mertens DJ, Hamm LF, Beyene J, Kennedy J, Corey P, *et al.* Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. J Am Coll Cardiol 2003;42(12):2139-43. doi: 10.1016/j.jacc.2003.07.028

47. Jones LW, Watson D, Herndon JE, 2nd, Eves ND, Haithcock BE, Loewen G, *et al.* Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. Cancer 2010;116(20):4825-32. doi: 10.1002/cncr.25396

48. Groarke JD, Payne DL, Claggett B, Mehra MR, Gong J, Caron J, *et al.* Association of post-diagnosis cardiorespiratory fitness with cause-specific mortality in cancer. Eur Heart J Qual Care Clin Outcomes 2020;6(4):315-22. doi: 10.1093/ehjqcco/qcaa015

49. Von Hoff DD, Layard MW, Basa P, Davis HL, Jr., Von Hoff AL, Rozencweig M, *et al.* Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979;91(5):710-7. doi: 10.7326/0003-4819-91-5-710

50. Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. J Clin Oncol 2005;23(34):8597-605. doi: 10.1200/jco.2005.02.5841

51. Trudeau M, Charbonneau F, Gelmon K, Laing K, Latreille J, Mackey J, *et al.* Selection of adjuvant chemotherapy for treatment of node-positive breast cancer. Lancet Oncol 2005;6(11):886-98. doi: 10.1016/s1470-2045(05)70424-1

52. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, *et al.* Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365(14):1273-83. doi: 10.1056/NEJMoa0910383

53. Lavín-Pérez AM, Collado-Mateo D, Mayo X, Humphreys L, Liguori G, James Copeland R, *et al.* High--intensity exercise to improve cardiorespiratory fitness in cancer patients and survivors: A systematic review and meta-analysis. Scand J Med Sci Sports 2021;31(2):265-94. doi: 10.1111/sms.13861

54. Ansund J, Mijwel S, Bolam KA, Altena R, Wengström Y, Rullman E, *et al.* High intensity exercise during breast cancer chemotherapy - effects on long-term myocardial damage and physical capacity - data from the OptiTrain RCT. Cardiooncology 2021;7(1):7. doi: 10.1186/s40959-021-00091-1

55. Scharhag-Rosenberger F, Kuehl R, Klassen O, Schommer K, Schmidt ME, Ulrich CM, *et al.* Exercise training intensity prescription in breast cancer survivors: validity of current practice and specific recommendations. J Cancer Surviv 2015;9(4):612-9. doi: 10.1007/s11764-015-0437-z

56. van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM, *et al.* Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the paces randomized clinical trial. J Clin Oncol 2015;33(17):1918-27. doi: 10.1200/jco.2014.59.1081

57. Kampshoff CS, Jansen F, van Mechelen W, May AM, Brug J, Chinapaw MJ, *et al.* Determinants of exercise adherence and maintenance among cancer survivors: a systematic review. Int J Behav Nutr Phys Act 2014;11:80. doi: 10.1186/1479-5868-11-80

58. Kirkham AA, Bland KA, Zucker DS, Bovard J, Shenkier T, McKenzie DC, *et al.* "Chemotherapy-periodized" exercise to accommodate for cyclical variation in fatigue. Med Sci Sports Exerc 2020;52(2):278-86. doi: 10.1249/mss.0000000000002151

59. Scott JM, Iyengar NM, Nilsen TS, Michalski M, Thomas SM, Herndon J, 2nd, *et al.* Feasibility, safety, and efficacy of aerobic training in pretreated patients with metastatic breast cancer: A randomized controlled trial. Cancer 2018;124(12):2552-60. doi: 10.1002/cncr.31368

60. Borugian MJ, Sheps SB, Kim-Sing C, Van Patten C, Potter JD, Dunn B, *et al.* Insulin, macronutrient intake, and physical activity: are potential indicators of insulin resistance associated with mortality

from breast cancer? Cancer Epidemiol Biomarkers Prev 2004;13(7):1163-72.

61. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. Jama 2005;293(20):2479-86. doi: 10.1001/jama.293.20.2479

62. Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, *et al.* Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. J Clin Oncol 2008;26(24):3958-64. doi: 10.1200/jco.2007.15.9822

63. Friedenreich CM, Gregory J, Kopciuk KA, Mackey JR, Courneya KS. Prospective cohort study of lifetime physical activity and breast cancer survival. Int J Cancer 2009;124(8):1954-62. doi: 10.1002/ijc.24155

64. Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 1993;15(1):17-35. doi: 10.1093/oxfordjournals.epirev.a036102

65. Key TJ, Allen NE, Verkasalo PK, Banks E. Energy balance and cancer: the role of sex hormones. Proc Nutr Soc 2001;60(1):81-9. doi: 10.1079/pns200068

66. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor--I. Proc Nutr Soc 2001;60(1):91-106. doi: 10.1079/pns200070

67. Okumura M, Yamamoto M, Sakuma H, Kojima T, Maruyama T, Jamali M, *et al.* Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells: reciprocal involvement of PKC-alpha and PPAR expression. Biochim Biophys Acta 2002;1592(2):107-16. doi: 10.1016/s0167-4889(02)00276-8

68. Loucks AB. Energy availability, not body fatness, regulates reproductive function in women. Exerc Sport Sci Rev 2003;31(3):144-8. doi: 10.1097/00003677-200307000-00008

69. McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, *et al.* Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res 2004;64(8):2923-8. doi: 10.1158/0008-5472.can-03-3393

70. Altman N, Krzywinski M. Association, correlation and causation. Nat Methods 2015;12(10):899-900. doi: 10.1038/nmeth.3587

71. Courneya KS, Booth CM, Gill S, O'Brien P, Vardy J, Friedenreich CM, *et al.* The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. Curr Oncol 2008;15(6):279-85. doi: 10.3747/co.v15i6.378

72. Wiskemann J, Kuehl R, Dreger P, Huber G, Kleindienst N, Ulrich CM, *et al.* Physical Exercise Training versus Relaxation in Allogeneic stem cell transplantation (PETRA Study) - Rationale and design of a randomized trial to evaluate a yearlong exercise intervention on overall survival and side-effects after allogeneic stem cell transplantation. BMC Cancer 2015;15:619. doi: 10.1186/s12885-015-1631-0

73. Newton RU, Kenfield SA, Hart NH, Chan JM, Courneya KS, Catto J, *et al.* Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4): a multicentre, randomized, controlled phase III study protocol. BMJ Open. 2018;8(5):e022899. doi: 10.1136/bmjopen-2018-022899