Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women worldwide [1]. Improvements in screening programs and treatments have increased 5-year survival rates by about 85% [2]. However, cancer therapies are still associated with various side effects, many of which can persist after treatment has ended. One of the most common and distressing symptoms in BC survivors is cancer-related fatigue, which negatively affects health-related quality of life (HRQoL) [3]. Although the etiology of this condition is likely multifactorial, low physical activity (PA) levels together with decreased muscle mass and impaired physical fitness have been identified as potential contributors [4–6]. Systemic inflammation, genetic factors, metabolic disorders, and neuroendocrine factors (including dysfunction of the hypothalamic-pituitary-adrenal axis) might also increase the perception of fatigue [7–11].

Concurrent Exercise Interventions in Breast Cancer Survivors with Cancer-related Fatigue

Authors

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Key words

exercise is medicine, physical activity, high-intensity training, quality of life, body composition, physical fitness

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ABSTRACT

This study compared the effects of two supervised concurrent training interventions in breast cancer survivors with cancer-related fatigue at baseline. Twenty-three female breast cancer survivors (50 ± 8 years) were randomized to a high- (n = 13) or a moderate-intensity (n = 10) training program. Both interventions lasted 16 weeks and included the same resistance exercises, but the aerobic component was supervised and more intense in the former (i.e., rating of perceived exertion of 7–8 vs. 6 on a 1–10 scale for the high and moderate-intensity intervention, respectively). The primary endpoint was fatigue perception. Endpoints were assessed at baseline and after 16 weeks. The p-value for statistical significance was set at 0.004 after Bonferroni correction for multiple comparisons. The high-intensity training program increased lower-limb muscle strength significantly (p = 0.002) and tended to improve fatigue perception (p = 0.006), waist circumference (p = 0.013), neutrophil-to-lymphocyte ratio (p = 0.028) and some quality of life items (p = 0.011). Although the moderate-intensity training program did not provide such benefits in general (i.e., higher p-values for pre vs post-intervention comparisons), no significant differences were found between interventions (all p > 0.004). Further research is needed to elucidate if the benefits provided by high-intensity concurrent training are superior to those elicited by moderate-intensity training in breast cancer survivors.
Impaired cardiorespiratory fitness (CRF) is a common finding among cancer survivors. We previously reported that CRF was lower than 8 metabolic equivalents (MET) in nearly one-half of a cohort of cancer survivors (46% with BC) [12]. In this respect, CRF below the 8 MET threshold is associated with more than a 3-fold higher risk of BC-related mortality [13]. Lower levels of muscle strength have also been found in BC survivors as compared with the general population [14], with sarcopenia or decreased muscle mass affecting more than one-third of newly diagnosed BC patients [15]. Further, a higher cancer-specific and all-cause mortality risk has been reported in cancer patients with muscle dysfunction [16], and there is meta-analytical evidence that low levels of muscle mass are associated with worse overall, cancer-specific and disease-free survival in adults with solid tumors [17].

Aerobic and resistance exercise likely have an important role in the management of physical function, mental health, general well-being and HRQoL in cancer survivors [18]. Moreover, the inclusion of resistance training has proven to improve body composition in cancer patients, maintaining lean body mass (LBM) and reducing body fat [19], and exercise benefits seem to be maximized when interventions are supervised [20]. Along this line, a recent systematic review concluded that high-intensity exercise could provide greater benefits on CRF and muscle strength of cancer survivors than a less intense program (i.e. of moderate intensity) [21]. To the best of our knowledge, however, no study has specifically assessed the effects of a high-intensity exercise intervention in cancer survivors who have in all cases a perception of fatigue.

The present study aimed to compare, using a randomized controlled trial (RCT) design, the effects of two supervised concurrent training interventions (of high- and moderate-intensity, respectively) in BC survivors with cancer-related fatigue at baseline (i.e. score ≤ 45 in the PERFORM questionnaire of fatigue). The endpoints were fatigue (primary) and objectively-assessed PA levels, anthropometry/body composition, CRF, muscle strength, HRQoL, and blood biomarkers of inflammation (secondary).

Materials and Methods

Participants and study design

Analysis and reporting of this RCT (ClinicalTrials.gov ID: NCT02647398) was in accordance with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement [22, 23]. The study protocol was conducted ethically according to international as well as journal standards [24] and was approved by the Institutional Research Ethics Committee. All participants gave their written informed consent. The RCT was conducted from March 2016 to June 2017. Inclusion criteria for eligibility were the following: i) woman aged 18–65 years; ii) diagnosed with BC; iii) no evidence of tumor recurrence or metastasis; iv) ≤ 5 years after last anti-cancer treatment (chemotherapy or radiotherapy); (v) score < 45 in the PERFORM questionnaire of fatigue; and (vi) signing the written informed consent. Subjects were excluded if they presented one or more of the following conditions: i) unable to perform the exercise sessions due to mobility limitations; ii) treated with beta-blockers; iii) presenting any exclusion criteria to perform the maximal exercise test (cardiovascular disease or neuromuscular disorders). Of note, in the original protocol (NCT02647398 - blinded for peer-review) we also aimed to include colon cancer survivors with cancer-related fatigue such as to recruit a total sample size of 32 patients with BC or colon cancer (for improving the perception of fatigue score from an anticipated initial 38 to a post-intervention 48 [with power = 80% and α = 0.05, enrollment ratio 1:1]). Yet, to avoid heterogeneity and due to the low number of eligible participants with colon cancer (n = 9), for the present study we decided to focus on BC only (n = 23, as described below).

Participants were randomly assigned (using a computer-generated list of random numbers) to a high- or moderate-intensity training group, with the latter being used as the control group. In this respect, based on the reported benefits of aerobic and resistance exercise for BC survivors [18], we considered it unethical not to prescribe at least a minimal dose of exercise to all participants. Both groups performed the same supervised resistance exercises, but the ‘intense’ training group also performed supervised high-intensity aerobic exercises while the moderate-intensity group was instructed to follow (without supervision) international recommendations for moderate-vigorous physical activity (MVPA i.e. ≥ 150 minutes/week) [25]. Both interventions lasted 16 weeks, and included two weekly training sessions. Endpoints were assessed in the week before (baseline) and after the intervention. The researchers responsible for assessing eligibility and study endpoints were blinded to group allocation.

Exercise intervention

In the high-intensity training group, each session lasted 75 minutes, and included a dynamic warm-up followed by high-intensity aerobic and resistance exercises, respectively. Training sessions started with a 10-minute warm-up consisting of respiratory and mobility exercises. The aerobic component of the session lasted approximately 35 minutes and was divided into three consecutive periods of 10–15 minutes, in which patients could choose to perform individually-supervised cycle-ergometer pedaling, aerobic games, treadmill running, or elliptical ergometer exercise at an intensity level of 7–8 (i.e. very hard) on the 1 to 10 Borg’s rating of perceived exertion (RPE) scale [26]. Resistance training was also individually-supervised and included the following: exercises with elastic bands, dumbbells or Fit Balls; and suspension training and bodyweight exercises that involved the major muscle groups (i.e. biceps, triceps, chest, deltoid, back and abdominal muscles, quadriceps, hamstrings, buttocks, calf, and adductor/abductor muscles). Participants performed 8–10 exercises per session depending on their perceived fatigue, with 2–3 sets per exercise (2 sets of 12 repetitions during weeks 1–4, 3 series of 12 repetitions during weeks 5–8, 2 series of 8 repetitions during weeks 9–12, and 3 series of 8 repetitions during weeks 13–16) and a rest period of 2 minutes between sets and 30 seconds between exercises. An intensity score of 6–7 (i.e. severe to very severe) on the Borg RPE scale was required. Thus, each participant progressed in training intensity such as to maintain the aforementioned RPE score throughout the 16-week intervention period. To determine adherence to training,
we considered a session to be completed when \( \geq 90\% \) of the prescribed exercises were successfully performed [27].

The moderate exercise-training group also performed the aforementioned resistance training exercises (after the warm-up session). With regard to the aerobic component, participants were instructed to complete \( \geq 150 \text{ minutes/week of MVPA} \) \((-6 \text{ on the } 1–10 \text{ Borg’s RPE scale [26]}\) without supervision.

**Fatigue**

Fatigue perception was assessed using the PERFORM questionnaire, which includes 12 items rated on a five-point ordinal scale, distributed in three dimensions: “Physical Limitations”, “Activities of Daily Living,” and “Beliefs and Attitudes” [28]. An overall score is obtained, with lower scores indicating a more severe fatigue, and with a score of 3.5 considered the “minimal important difference” [28]. The PERFORM questionnaire has proven feasible, reliable (including both internal consistency and test-retest), valid and sensitive to change [28].

**Physical activity**

MVPA levels were objectively monitored using a triaxial accelerometer (GT3X monitor, Actigraph; Pensacola, FL). Prior research has confirmed the validity of this device [29]. Participants were instructed to wear the accelerometer (near the right iliac crest) for a minimum of seven and a maximum of ten consecutive days while awake, and to remove it only for water activities or during bicycling. A minimum of five-day monitoring including two weekend days, and a minimum of ten hours of complete accelerometer data per day, was considered necessary for MVPA assessment to be considered valid. When participants provided more than seven consecutive days, was considered necessary for MVPA assessment to be considered valid. When participants provided more than seven consecutive days of recordings, only the data for the last seven days including two weekend days were used. Data were analyzed with ActiLife5 LITE software (Actigraph).

**Anthropometry and body composition**

Body mass index (BMI) was determined as body mass/height squared \((\text{kg/m}^2)\). Body composition (whole body fat percentage, LBM, and bone mineral density \([\text{BMD}]\)) and waist circumference were evaluated by dual energy X-ray absorptiometry (Hologic QDR series Discovery; Bedford, MA).

**Cardiorespiratory fitness**

CRF (peak oxygen uptake, VO2peak) was determined using “breath-by-breath” analysis with a metabolic cart \((V_{\text{max}} \text{ 29C; SensorMedics Corp., Yorba Linda, CA})\) during a maximal incremental cycle ergometer test (Ergometrics Ergoline 800, Jaeger, Bitz, Germany). The test started at 20 watts and the load was increased by 10 watts/minute while cadence was kept constant at 60–70 rpm. Participants were verbally encouraged to continue pedaling until volitional exhaustion, and were continuously monitored electrocardiographically. VO2peak was defined as the highest value (mean of 20 seconds) reached during the test. The ventilatory threshold (VT) was determined as explained elsewhere [30].

**Muscle strength**

Handgrip strength was measured using a dynamometer \((\text{TKK 5001 Grip-D; Takei, Tokyo, Japan})\), and scores were recorded in kilograms (to the nearest 0.1 kg) [31].

The sit-to-stand (STS) test, which measures the time (seconds) required to perform five consecutive repetitions of sitting down and rising up from a chair, was used for the assessment of lower-limb strength. Participants began the test with their arms crossed on their chest and sitting with their back against the chair. They were instructed to perform the task “as fast as possible,” starting and finishing in the sitting position.

**Health-related quality of life**

HRQoL was evaluated with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23). The QLQ-C30 is a multidimensional cancer HRQoL questionnaire that contains 30 items assessing six functional and nine symptom scales. This questionnaire has been validated in Spanish patients with cancer [32]. The QLQ-BR23 is a special HRQoL scale for BC patients that includes 23 items and two sub-scales: functional and symptom. This questionnaire has also been validated in Spanish patients with BC [33]. Results from this questionnaire are transformed into scores ranging from 0 to 100 according to EORTC scoring, with higher scores in the functioning scales indicating a better functional status and global HRQoL, and higher scores on the symptoms’ scales indicating more symptoms.

**Blood analyses**

Blood samples were drawn from the antecubital vein after an overnight fast to measure the concentration of neutrophils and lymphocytes with an automated system (model XN-10 and XN-20, Sysmex; Kobe, Japan). The neutrophil-to-lymphocyte ratio (NLR) was also calculated.

**Statistical analysis**

Data are shown as mean \( \pm \) standard deviation \((\text{SD})\) and were analyzed using non-parametric tests due to the small sample size. Between-group differences at baseline were evaluated using the Mann-Whitney U test (for continuous variables) and Fisher’s exact test (for proportions). Within-group differences (post-intervention vs. baseline) were assessed with the Wilcoxon signed-rank test, whereas between-group differences in exercise training effects (i.e., differences in mean values of post-intervention minus baseline results by group) were assessed with the Mann-Whitney U test. Effect sizes (ES, Hedges’ g) were also computed to examine the magnitude of the changes within groups. All statistical analyses were conducted using a statistical software package (SPSS 23.0, IBM statistics; Chicago, IL). To minimize the risk of type I error, all the analyses were corrected for multiple comparisons using the stringent Bonferroni method, that is, dividing 0.05 by the number of comparisons. Thus, the threshold p-value for statistical significance was set at 0.004 \((\sim 0.05/12)\).
Results
A flow diagram of study participants is shown in ▶ Fig. 1. A final sample of 23 female BC survivors (50 ± 8 years) participated in the study, of which 13 and 10 were randomized to the high-intensity and moderate exercise-training group, respectively. No significant differences were found between groups at baseline (▶ Table 1).

A high adherence to supervised training sessions was observed in both high-intensity and moderate training groups (83 ± 12 % and 83 ± 11 % of the total number of planned sessions, respectively) and no major adverse effect was noted in any of the exercise sessions.

Primary endpoint
Both training programs tended to attenuate fatigue perception (i.e. higher value in the PERFORM questionnaire score at post-intervention compared with baseline, with a large ES (> 1 in both cases), especially the high-intensity intervention (p = 0.006, slightly above the corrected threshold p-value of 0.004 with p = 0.020 for the moderate-intensity intervention) (▶ Table 2). On the other hand, the magnitude of improvement did not differ between groups (p = 0.384).

▶ Table 1 Main demographic and clinical characteristics at baseline by group

<table>
<thead>
<tr>
<th></th>
<th>Moderate-intensity training group (n = 10)</th>
<th>High-intensity training group (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 ± 6</td>
<td>47 ± 7</td>
<td>0.162</td>
</tr>
<tr>
<td>Time since diagnosis (median IQR, in years)</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>0.446</td>
</tr>
<tr>
<td>Time since treatment ended (median IQR, in years)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0.648</td>
</tr>
<tr>
<td>Radiotherapy (%)</td>
<td>40 %</td>
<td>23 %</td>
<td>0.102</td>
</tr>
<tr>
<td>Hormonotherapy (%)</td>
<td>100 %</td>
<td>92 %</td>
<td>1.000</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td>100 %</td>
<td>100 %</td>
<td>1.000</td>
</tr>
<tr>
<td>Chemotherapy (%)</td>
<td>87 %</td>
<td>50 %</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
### Table 2  Effects of the exercise interventions on the study endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>N with complete data</th>
<th>Group</th>
<th>Baseline</th>
<th>Post</th>
<th>Change post minus baseline within groups (95 % CI)</th>
<th>ES (Hedges’ d)</th>
<th>p-value within-groups</th>
<th>Between-group (high vs. moderate-intensity) difference in change post minus baseline (95 % CI)</th>
<th>p-value between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (PERFORM questionnaire score)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>28 ± 13</td>
<td>42 ± 12</td>
<td>14 (4, 23)</td>
<td>1.07</td>
<td>0.020</td>
<td>5 (−8, 18)</td>
<td>0.384</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>High-intensity</td>
<td>31 ± 8</td>
<td>50 ± 9</td>
<td>19 (9, 29)</td>
<td>1.36</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STS test (seconds)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>6.7 ± 1.0</td>
<td>5.1 ± 0.9</td>
<td>−1.6 (−2.1, −1.2)</td>
<td>2.05</td>
<td>0.005</td>
<td>0.1 (−0.7, 1.0)</td>
<td>0.278</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>High-intensity</td>
<td>6.3 ± 1.3</td>
<td>4.8 ± 0.8</td>
<td>−1.5 (−2.2, −0.7)</td>
<td>1.35</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handgrip (kg)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>32 ± 3</td>
<td>32 ± 5</td>
<td>0 (−3, 3)</td>
<td>0</td>
<td>0.721</td>
<td>0 (−3, 5)</td>
<td>0.577</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>High-intensity</td>
<td>32 ± 4</td>
<td>32 ± 4</td>
<td>0 (−3, 2)</td>
<td>0</td>
<td>0.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRF (MET)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>6.3 ± 1.4</td>
<td>6.8 ± 1.4</td>
<td>0.5 (0, 1.4)</td>
<td>0.55</td>
<td>0.041</td>
<td>0 (−3, 4, 3.8)</td>
<td>0.402</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>High-intensity</td>
<td>6.6 ± 1.4</td>
<td>7.1 ± 1.4</td>
<td>0.5 (−0, 1.4)</td>
<td>0.35</td>
<td>0.152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPA (min/week)</td>
<td>8</td>
<td>Moderate-intensity</td>
<td>361 ± 28.8</td>
<td>319 ± 213</td>
<td>−42 (−119, 36)</td>
<td>0.16</td>
<td>0.109</td>
<td>31 (−110, 184)</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>High-intensity</td>
<td>332 ± 131</td>
<td>340 ± 111</td>
<td>−8 (−17, −153)</td>
<td>0.06</td>
<td>0.686</td>
<td></td>
<td></td>
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<tr>
<td>Body mass (kg)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>68.8 ± 9.0</td>
<td>69.1 ± 9.7</td>
<td>0.3 (−1.0, 1.6)</td>
<td>0.1</td>
<td>0.407</td>
<td>−0.9 (−2.6, 0.7)</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>High-intensity</td>
<td>68.2 ± 14.4</td>
<td>67.6 ± 13.7</td>
<td>−0.6 (−1.8, 0.5)</td>
<td>0.04</td>
<td>0.262</td>
<td></td>
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<tr>
<td>BMI (kg·m⁻²)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>27.3 ± 3.7</td>
<td>27.3 ± 3.9</td>
<td>0.0 (−0.5, 0.6)</td>
<td>0</td>
<td>0.646</td>
<td>−0.7 (−4.0, 2.0)</td>
<td>0.203</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>High-intensity</td>
<td>25.8 ± 5.8</td>
<td>25.1 ± 4.3</td>
<td>−0.7 (−1.8, 0.3)</td>
<td>0.13</td>
<td>0.091</td>
<td></td>
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<tr>
<td>Waist circumference (cm)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>96 ± 8</td>
<td>96 ± 10</td>
<td>0 (−2, 3)</td>
<td>0.18</td>
<td>0.445</td>
<td>−2 (−5, 0)</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>High-intensity</td>
<td>96 ± 14</td>
<td>94 ± 13</td>
<td>−2 (−4, −1)</td>
<td>0.14</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat mass (% of total body mass)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>43 ± 4</td>
<td>43 ± 4</td>
<td>0 (−2, 1)</td>
<td>0</td>
<td>0.575</td>
<td>−1 (−3, 1)</td>
<td>0.218</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>High-intensity</td>
<td>42 ± 6</td>
<td>41 ± 6</td>
<td>−1 (−3, −1)</td>
<td>0.16</td>
<td>0.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBM (% of total body mass)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>54 ± 3</td>
<td>54 ± 3</td>
<td>0 (−1, 2)</td>
<td>0.4</td>
<td>0.575</td>
<td>1 (−1.2)</td>
<td>0.260</td>
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<tr>
<td></td>
<td>11</td>
<td>High-intensity</td>
<td>55 ± 6</td>
<td>56 ± 6</td>
<td>1 (0, 3)</td>
<td>0.15</td>
<td>0.075</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD (g·cm⁻²)</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.0 (−1.0, 1.0)</td>
<td>0.96</td>
<td>0.055</td>
<td>0.0 (0.0, 0.1)</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>High-intensity</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.0 (−0.1, 0.0)</td>
<td>0</td>
<td>0.389</td>
<td></td>
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</tr>
<tr>
<td>NLR</td>
<td>10</td>
<td>Moderate-intensity</td>
<td>2.3 ± 0.6</td>
<td>2.2 ± 1.3</td>
<td>−0.1 (−0.9, 0.7)</td>
<td>1.11</td>
<td>0.646</td>
<td>−0.3 (−1.1, 0.7)</td>
<td>0.595</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>High-intensity</td>
<td>2.0 ± 0.8</td>
<td>1.6 ± 0.6</td>
<td>−0.4 (−0.7, −0.1)</td>
<td>0.54</td>
<td>0.028</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD and significant p-value is in bold. We corrected all the analyses for multiple comparisons using the stringent Bonferroni method, that is, dividing 0.05 by the number of comparisons. Thus, the threshold p-value for statistical significance was set at 0.004 ( = 0.05/12). Because not all outcomes could be assessed in all subjects, the number of subjects assessed for each outcome is specified in the column ‘N with data’. Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CRF, cardiorespiratory fitness; ES, effect size (Hedges’ d); LBM, lean body mass; MET, metabolic equivalent; MVPA, moderate-vigorous physical activity; NLR, neutrophil-to-lymphocyte ratio; STS, sit-to-stand.
Secondary endpoints

Both groups followed international MVPA guidelines, and no significant between- or within-group differences were observed after the intervention (Table 2). The high-intensity training program induced a significant improvement in leg muscle strength (determined by performance in the STS test, \( p = 0.002, \text{ES} = 1.35 \)), with a quasi-significant trend (\( p = 0.005 \)) and a very large ES (\( -2.05 \)) for the other group, and with no between-group differences in the magnitude of the improvement (\( p = 0.278 \)). The high-intensity exercise intervention tended to decrease waist circumference (\( p = 0.013 \)), whereas no such trend was observed in the moderate exercise-training group (\( p = 0.445 \)). Only the high-intensity exercise program led to a tendency towards a lower NLR after the intervention (\( p = 0.028 \)), with no between-group differences (\( p = 0.595 \)). On the other hand, no significant within-group differences was found for the VT with the moderate (\( p = 0.285 \); baseline, 3.9 ± 0.7 MET; post-intervention 4.2 ± 0.9 MET) or high-intensity program (\( p = 0.421 \); baseline, 4.0 ± 0.9 MET; post-intervention 4.3 ± 0.9 MET). Likewise, no between-group difference was identified (\( p = 0.976 \)).

Regarding HRQoL, no significant improvements were found in either group, with a trend towards an increase in physical function for the high-intensity training group only (\( p = 0.011 \), above the threshold \( p \)-value of 0.003). No differences were found between groups (all \( p > 0.1 \)) (Supplementary Material).

Discussion

The results of this RCT show that a 16-week training program for short-term BC survivors who already reported cancer-related fatigue at baseline (as reflected by a PERFORM score <45), including high-intensity aerobic and resistance exercises, significantly increased lower-limb muscle strength and tended to induce improvements in fatigue perception (in both cases with large ES), some HRQoL items, a marker of central adiposity (waist circumference), and systemic inflammation (as reflected by NLR). However, none of the between-group differences reached the corrected threshold \( p \)-value for significance. A previous study analyzed the effects of a moderate-intensity concurrent training program in BC survivors with fatigue [34]. However, to our knowledge, this is the first RCT to assess the effects of a high-intensity exercise intervention in BC survivors, with all of them having cancer-related fatigue at baseline.

Fatigue is a prevalent cancer-related side effect even years after having finished the treatment [35]. Our results show that a training program including supervised resistance exercises combined with aerobic training, whether or not the latter was supervised, tended to decrease fatigue perception with a large ES (i.e. post-training increase in scores of 19 and 14, respectively, well above the minimal important difference of 3.5) [28]. An additional important finding is that, on average, only the high-intensity intervention eliminated fatigue, that is, elicited a mean PERFORM score >45 upon completion of intervention (i.e. mean post-intervention scores of 50 vs. 42 in the high- and moderate-intensity training group, respectively, with 9 [69 % of the total group] and 5 participants [50 %] showing a score >45). Although the potential of combined aerobic and resistance training to ameliorate cancer-related fatigue in BC has been previously highlighted [36], no significant benefits with only resistance training neither with low-intensity (e.g. mind-body exercise) interventions on fatigue in BC survivors were found [36]. In our study, only high-intensity aerobic exercise tended to improve some HRQoL items, which is in agreement with previous studies in cancer survivors using resistance and high-intensity aerobic training [37, 38].

We observed significant (\( p = 0.002 \)) and large benefits (\( \text{ES} = 1.35 \)) for lower-limb muscle strength (as reflected by improved performance in the STS test) after the high-intensity intervention. Likewise, the benefits were quasi-significant (\( p = 0.005 \), just below the 0.004 threshold) and in fact with a very large ES (2.05) for the moderate-intensity intervention. These findings are important because lower-limb strength has been identified as a predictor of persistent fatigue in older BC survivors [4]. In turn, only the high-intensity intervention demonstrated benefits (albeit above the corrected \( p \)-threshold) on anthropometry, reflected by a tendency to decrease waist circumference (from 96 to 94 cm at post-intervention). This suggests the need to implement long-term, high-intensity aerobic interventions in this population, because the mean values of this variable remained, even after the high-intensity intervention, well above the 88 cm threshold value, which has been recently advocated as an independent predictor of mortality in BC (i.e. hazard ratio if waist circumference >88 cm = 1.32, 95 % confidence interval: 1.03, 1.70) [39]. Furthermore, our results are in overall agreement with those of a recent systematic review concluding that high-intensity exercise provides greater benefits than moderate-intensity exercise in cancer survivors [21]. Additionally, in the present study only the high-intensity intervention tended to decrease the NLR (from 2.0 to 1.6), which is an inflammation marker independently associated with a higher risk of short- and long-term BC mortality at NLR >3.3 [40]. In line with our results, Fu et al. [41] found that high- but not moderate-intensity training reduced plasma levels of inflammatory biomarkers in patients with heart failure. Additionally, previous research suggests that inflammation can negatively affect the benefits of exercise training on fatigue in BC survivors, which might potentially explain, at least partly, why the stringent threshold \( p \)-value was not reached for the effects of moderate-intensity training on fatigue [34]. Thus, although more research is needed, high-intensity aerobic exercise combined with resistance training might, at least partly, provide some important health benefits to BC survivors.

Our study has some limitations, including the small sample size and the lack of a non-exercise control group. However, there is meta-analytic evidence to support the benefits of exercise versus a non-exercised control group in cancer survivors [18, 42], and we thus considered it unethical not to prescribe at least a minimal dose of exercise to all participants. Another limitation is the lack of control on nutritional variables, which can largely influence body composition. On the other hand, a major strength of our study was the novelty of our approach, as this is the first study to assess the effects of an exercise intervention in patients with cancer-related fatigue (for all cases) at baseline, together with the analysis of several important outcomes and a stringent adjustment for multiple comparisons.
In conclusion, a 16-week training program including supervised resistance exercise and high-intensity aerobic exercise increased lower-limb strength in BC survivors diagnosed with cancer-related fatigue. The inclusion of high-intensity aerobic exercise also tended to induce additional benefits on fatigue perception, HRQoL, central adiposity (i.e. waist circumference), and systemic inflammation (i.e. NLR). These results should be considered in future efforts to prescribe effective, personalized exercise programs (i.e. achieving an optimal stimulus) in cancer survivors. Further research is warranted to determine whether applying a different training stimulus (i.e. varying type, intensity or volume of training program) might maximize responsiveness in these patients.

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Conflict of Interest
The author have no conflict of interest to declare.

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