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ORIGINAL RESEARCH

Does a Resistance Training Program Affect Between-arms Volume Difference and Shoulder-arm Disabilities in Female Breast Cancer Survivors? The Role of Surgery Type and Treatments. Secondary Outcomes of the EFICAN Trial

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Abstract

Objective: The aims were (i) to assess the effects of a 12-week resistance training program on between-arms volume difference and shoulder-arm disabilities in breast cancer survivors and (ii) to evaluate whether the main risk factors for developing cancer-related lymphedema and shoulder-arm disabilities were associated with the effects of the training program.

Design: Randomized controlled trial.

Setting: University facilities.

Participants: 60 female breast cancer survivors participated. Eligibility criteria: to be a breast cancer survivor, and to have completed surgery, chemotherapy, and/or radiotherapy up to 10 years before recruitment. Exclusion criteria: metastatic breast cancer, a breast reconstruction intervention planned within 6 months, any absolute contraindication for exercise, to perform more than 300 minutes/week of structured exercise.

Interventions: Participants were randomized to an exercise group (12-week resistance training program) or a control group.

Main Outcome Measures: Between-arms volume difference, shoulder-arm disabilities, and upper-limb muscular strength were evaluated at baseline and at week 12. Treatment-related information was registered from medical history.

Results: No between-group differences were observed on between-arms volume difference (1.207; 95% CI -0.964, 3.377; *P*=.270) or shoulder-arm disabilities (2.070; 95% CI -4.362, 8.501; *P*=.521) after the training program. Likewise, there was no association of surgery type, presence of lymph node resection, chemotherapy, radiotherapy, and hormone therapy with the changes in between-arms volume and perceived shoulder-arm

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Clinical trial registration number: The study protocol was prospectively registered (ISRCTN14601208).

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disabilities after the intervention. However, a higher increase in upper limb muscular strength was associated with a reduced shoulder-arm disabilities (-0.429; *P*=.020) in the exercise group.

Conclusions: The findings suggest that resistance training does not affect between-arms volume difference and shoulder-arm disabilities in female breast cancer survivors. The main risk factors for developing lymphedema were not associated with the effects of the intervention, although a higher increase in upper-limb muscular strength was associated with reduced shoulder-arm disabilities.

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Upper limb disabilities and lymphedema are 2 of the most common side effects after breast cancer treatments that may affect the quality of life of breast cancer survivors.[1-6] Up to 70% of breast cancer survivors experience pain, discomfort, and/or decreased physical function in the affected shoulder, arm, and hand, depending on the surgery type, rehabilitation programs, or assessment tools, among other factors.[4,6-10] Percentage of women experiencing lymphedema after breast cancer surgery is very heterogeneous, ranging from 4% to more than 60% across studies.[11-16]

The consequences of upper-limb disabilities include a decreased ability to perform daily life activities,[11] which is of major clinical and public health concern. Additionally, the increase in arm volume and lymphedema may imply a considerable danger for life.[11,16,17] For instance, the presence of lymphedema is related to a higher risk of developing cellulitis, which is associated with a higher mortality risk.[17] Therefore, understanding the rationale behind upper-limb disability and lymphedema and potential treatment strategies is of wide interest.

The American Cancer Society and the National Cancer Institute recommend exercise, led by a specialist, as it is a safe and feasible method to reduce the risk of developing lymphedema.[18,19] Furthermore, many studies have observed that resistance training and concurrent training are useful in preventing short- and long-term upper limb impairments.[20,21] Resistance training and other forms of physical activity are proposed to be among the most effective therapies to regain shoulder joint mobility, reduce pain, and discomfort and increase quality of life in breast cancer patients.[21-23] Moreover, some studies suggest that resistance exercise could reduce lymphedema.[20,22] Nevertheless, there is still a lack of information for patients and a lack of application of these recommendations in clinical practice because of medical advice to restricting the affected arm,[24] which leads to a higher fear of using the affected arm, lower physical activity, lower muscular strength, and a higher perceived weakness.[24]

Most studies addressing the role of exercise on lymphedema used exercises aimed to improve lymphedema, but it remains unclear whether a resistance training program aimed at increasing muscular strength might result in a higher risk of lymphedema or lymphedema-related disability. The *Ejercicio FÍsico para supervivientes de CÁNcer de mama* (EFICAN) randomized controlled trial (RCT) revealed that a 12-week resistance training program combined with home-based physical activity produced a large increase in muscular strength compared with home-based physical activity alone, with no effects on health-related quality of life or symptoms of depression.[25] Understanding whether the EFICAN RCT, a generic resistance training program designed to increase muscular strength, produced a detrimental effect on arms volume difference or shoulder-arm disabilities is of clinical and public health interest, as it includes 4 strength exercises representing major movement patterns that comprise muscle groups involved in everyday tasks and that are commonly used in resistance training programs. These exercises were selected as breast cancer survivors could practice at any sports center with or without supervision.In addition, it is well known that several factors might influence the development of shoulder-arm disabilities and lymphedema,[1,26] such as the surgery type, axillary lymph node resection, chemotherapy, or radiotherapy, among others. However, it remains unknown to what extent these risk factors might influence the effects of a resistance training program on the between-arms volume difference and perceived shoulder-arm disabilities.

Therefore, the aim of these secondary analyses of the EFICAN RCT was to evaluate the effects of a 12-week supervised resistance training program combined with home-based physical activity, compared with home-based physical activity alone, on between-arms volume difference and shoulder-arm disabilities in female breast cancer survivors. Additionally, an exploratory aim of this study was to assess the association of the surgery type, the presence of axillary lymph node resection, chemotherapy, radiotherapy, and hormone therapy with between-arms volume difference and shoulder-arm disabilities. Furthermore, we explored the association of the changes in upper-limb muscular strength with the between-arms volume difference and shoulder-arm disabilities.

List of abbreviations:

CG	**control group**
EFICAN study	***Ejercicio FÍsico para supervivientes de CÁNcer de mama* study**
EG	**exercise group**
RCT	**randomized controlled trial**

Methods

Study design and registration

A parallel-group, RCT was conducted. The study protocol was prospectively registered (ISRCTN14601208) on August 1, 2019, before the beginning of the participants enrolment. An in-depth description of the methodology was published elsewhere.[27]

Participants

Sixty volunteer female breast cancer survivors participated. They were recruited through regional cancer-related associations, local radio and press advertisements, social networks announcements, and referral from oncologists of the Torrecárdenas University Hospital. Eligibility criteria were to be a breast cancer survivor, and to have completed surgery, chemotherapy, and/or radiotherapy (ie, core treatments) up to 10 years prior to recruitment.

Exclusion criteria were to have a metastatic breast cancer, to have a breast reconstruction intervention planned within the following 6 months, to have any absolute contraindication for exercise, or to perform more than 300 minutes per week of structured exercise. The study protocol was approved by the Almería Provincial Research Ethics Committee, Almería, Spain, (ref: Ejercicio-CáncerUAL[98/2019]) on 31/07/2019.

Protocol

Volunteer women filled out an online questionnaire including basic information about themselves and their disease and treatments. Those women who were potentially eligible were scheduled for a medical screening to assess the compliance of inclusion and exclusion criteria and to obtain the written informed consent. Subsequently, participants attended the baseline assessments at the exercise laboratory of the University of Almería. The present study follows the CONSORT guidelines.[28]

Sample size, blinding, and randomization

The sample size was calculated for the primary outcome of the EFICAN trial, muscular strength, using Stata v.13[a] as described elsewhere.[27] Participants were randomized to either an exercise or control group using a computer-generated simple randomization sequence. During the trial, the primary outcome assessors and the data analysts were blinded. A detailed description of this procedure is reported elsewhere.[27]

Outcomes

Between-arms volume difference

Presence of lymphedema was assessed as the estimation of between-arms volume difference (%). Lymphedema is considered when the between-arms volume differs 3%-10%.[29,30] Arms volume was estimated using the truncated cone formula.[31] Arms circumference (perimeter) was measured using the protocol by Sander et al,[31] which demonstrated statistically significant correlation (r=0.97, P<.01) with the water displacement method (considered as the criterion standard method). Thus, perimeters were assessed at 6 different points (separated by 6 cm), depending on each participant's arm length. After that, the difference between arms volume was computed.

Shoulder-arm disabilities

Shoulder-arm disabilities were assessed using the Spanish version[32] of the Disabilities of the Arm, Shoulder, and Hand questionnaire, which demonstrated statistically significant construct validity (t=-5.81, P<.0001).[33] The score ranges from 0 to 100. A higher score indicated higher difficulties or disability.

Upper-limb muscular strength

Peak isometric muscular strength (N) was evaluated using an electromechanical dynamometer[b] (bias<13.9 N; random error<52.1 N; r=1.00)[34] and it was assessed for 2 different exercises: unilateral isometric seated bench press (fig 1A) and unilateral isometric seated row (fig 1B). Upper-limb muscular strength was defined as the sum of right and left arms values in each exercise, as the resistance training protocol included bilateral exercises. Changes from baseline to week 12 were calculated for these sums as the average of the standardized score (z score=[value-mean]/standard deviation) of the change from baseline to week 12 of the above-mentioned exercises.

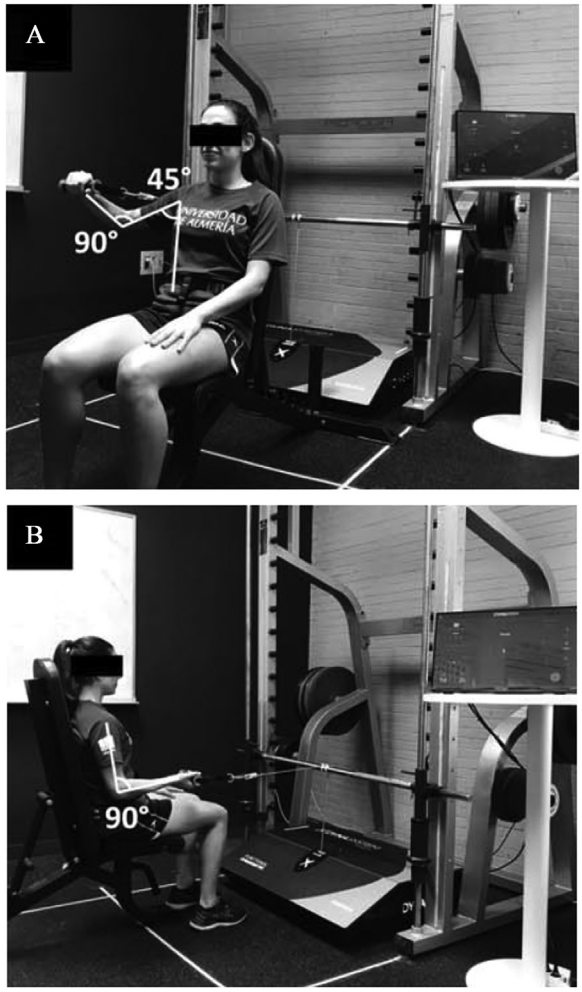

Fig 1 **(A)** Unilateral isometric seated bench press. **(B)** Unilateral isometric seated row.

Intervention

Participants were encouraged to continue their lifestyle during de intervention period. They were also all requested to undertake≥10,000 steps per day.[35,36] Steps per day were monitored using an activity bracelet,[37,c] which has been reported to show nearly perfect validity (ICC>0.99) with respect to the criterion (that is, a validated time-motion tracking system).

Exercise group (EG)

Participants in the EG completed a 12-week (2 sessions per week) resistance training protocol, divided into: 2 weeks of individual training sessions and 10 weeks of small-group training sessions. Training sessions consisted of 3 parts: preparatory part (aerobic activity, thoracic mobility exercises, core stability exercises, scapulohumeral joint stability exercises, and dynamic stability exercises); resistance training part (circuit-based strength exercises); and cool-down part (dynamic/static stretching of major muscle groups). Supplemental table S1 shows the main exercises and adaptations to be performed during the training sessions and

supplemental table S2 describe the periodization protocol of the training program. A complete description of equipment, in-session assessments (including downloadable supplementary materials with a video recording of the intervention), as well as strategies to maximize adherence and motivation are comprehensively described elsewhere.[25]

Control group (CG)

Participants in the waiting-list CG were required to undertake home-based physical activity by completing ≥10,000 steps per day.[35,36] A member of the stuff who was not involved in outcomes assessments contacted participants in the CG twice per month during the intervention period to collect steps data.

Statistical analysis

Descriptive characteristics of the participants are presented by the mean and standard deviation (or number and frequency for categorical variables). The distribution of the variables was analyzed using histograms, the Kolmogorov-Smirnov test, and Q-Q plots. Comparability of the groups was checked after the baseline assessments. Linear regressions were computed to assess the between groups differences in the change from baseline in between-arms volume difference and shoulder-arm disabilities, including baseline outcomes values as covariates. The association between the type of surgery, the presence of lymph node resection, chemotherapy, radiotherapy, and hormone therapy with the changes in between-arms volume difference and shoulder-arm disabilities was assessed through linear regression analyses. Additionally, the association of the changes in upper limb muscular strength and the changes in between-arms volume difference and shoulder-arm disabilities was assessed using correlation analyses. The statistical analyses were carried out with SPSS (IBM SPSS Statistics for Windows, Version 28.0, IBM Corp, Armonk, New York, NY, USA). Statistical significance was set at $P<.05$.

Results

Figure 2 presents the CONSORT flowchart of the participants during the study. Sixty female breast cancer survivors participated and were randomly allocated to EG (n=32) and CG (n=28). In EG, 2 participants discontinued the intervention and were lost to follow-up. In CG, all the participants completed the trial. Two adverse events occurred in the EG: 1 participant presented a muscular overload in session 15 and 1 participant experienced

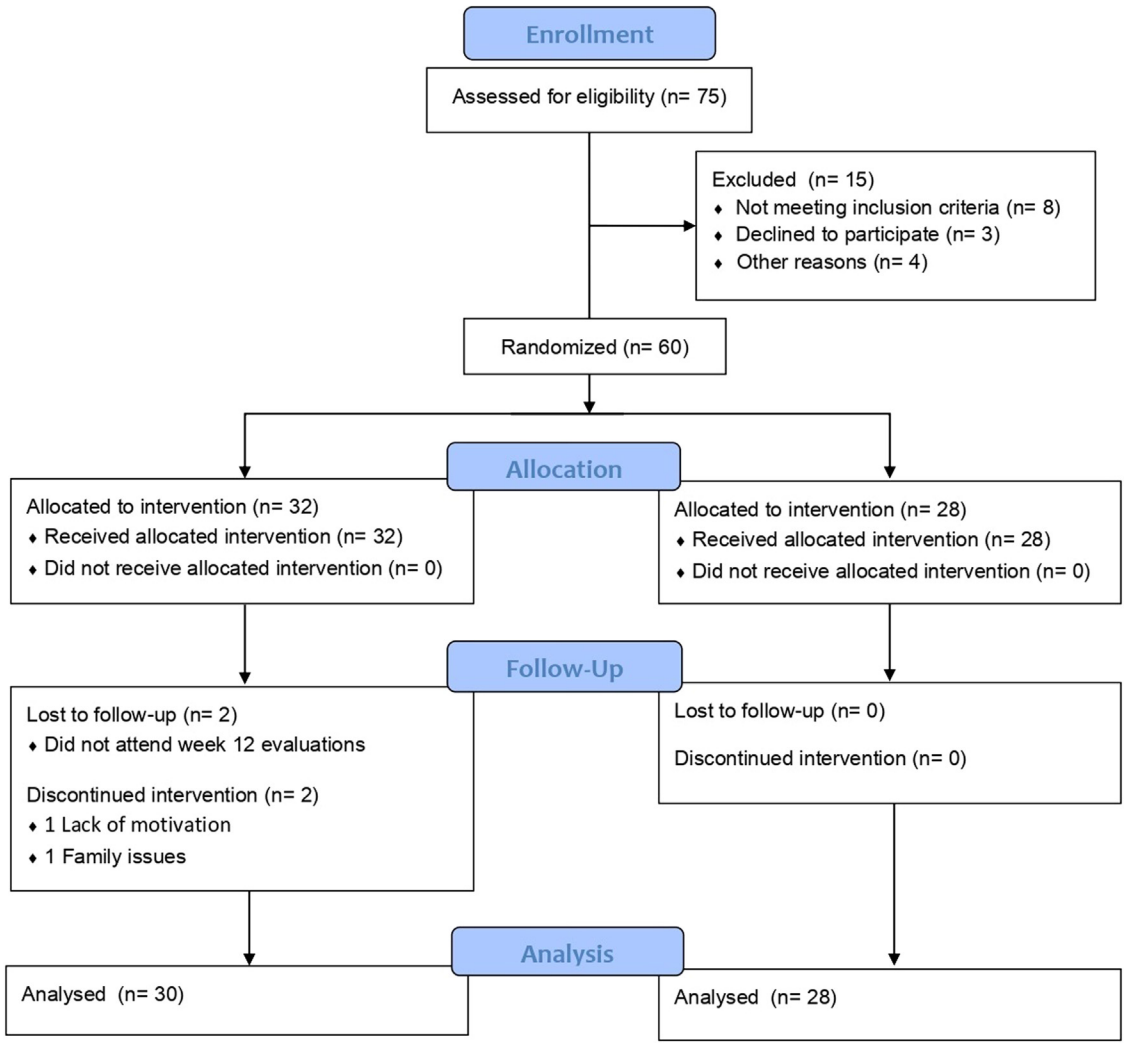

Fig 2 CONSORT flowchart of the study participants throughout the EFICAN randomized controlled trial.

Table 1 Descriptive characteristics of the study participants overall and by intervention group

	Exercise (n=32) Mean ± SD	Control (n=28) Mean ± SD
Age, years	52.6 (8.8)	52.0 (9.4)
Occupational status, n (working/housewife/not working; %)	20 (62.5)/4 (12.5)/8 (25.0)	21 (65.0)/1 (3.6)/6 (21.3)
BMI, kg/m^2	27.4 (4.2)	26.3 (5.3)
Current smoking, n (%)	3 (9.4)	3 (10.7)
Menopause, n (%)	20 (62.5)	19 (67.9)
Medical Information	**Mean ± SD**	**Mean ± SD**
Time since core treatments ended, years*	3.5 (1−6.75)	4.5 (2−7)
Tumor type, HR+HER2-/HR+HER2+/HR-HER2+/HR-HER2-, (%)	59.4/18.8/6.3/15.6	71.4/17.9/0.0/10.7
Surgical procedure (tumorectomy/mastectomy), n (%)	22 (69)/10 (31)	19 (68)/9 (32)
Lymph node resection, n (%)	15 (46.9)	10 (35.7)
Endocrine therapy, n (%)	27 (84.4)	25 (89.3)
Diagnosed lymphedema, n (%)	1 (3%)	5 (18%)
Outcomes-related Information	**Pre/Post-intervention Mean ± SD**	**Pre/Post-intervention Mean ± SD**
Between-arms volume difference (%)†	1.4 (4.9)/0.5 (5.5)	2.2 (7.9)/2.3 (7.4)
DASH (total score, 0-100)	16.2 (13.9)/13.1 (16.2)	20 (18.9)/18.9 (19.7)
Peak isometric muscular strength		
Affected arm seated BP, N	101.1 (26.5)/117.4 (30.9)	95.8 (29.5)/100.5 (34.1)
Unaffected arm seated BP, N	107.9 (20.9)/131.1 (26.6)	108.6 (26.5)/112.6 (31.0)
Affected arm seated row, N	127.8 (39.5)/163.0 (37.6)	127.5 (37.7)/144.2 (39.8)
Unaffected arm seated row, N	145.3 (27.6)/171.5 (29.9)	141.9 (35.1)/148.0 (36.2)
Steps per day (mean)	12,918.3 (2784.1)	12,925.3 (3950.8)

Abbreviations: BMI, body mass index; BP, bench press; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.
* Median and interquartile range.
† Difference between the volume of the affected and non-affected arm (expressed in %).

discomfort in her shoulder in session 17. Both events lasted to the end of the trial; however, they did not compromise the completion of the other exercises. The details on attendance, and adherence to original protocol related to the intervention and the follow-up were detailed in a previous paper.[25] Table 1 shows the descriptive characteristics of the participants. Regarding the surgical procedure, 41 participants underwent a tumorectomy, 19 had unilateral mastectomy, and no participant had bilateral mastectomy. Additionally, 25 participants had lymph node resection during surgery.

The effects of the training program on between-arms volume difference (%) and shoulder-arm disabilities are shown in table 2. No difference between-groups was observed in between-arms volume difference (1.207, *P*=.270) or shoulder-arm disabilities (2.070, *P*=.521).

Exploratory analyses were conducted to assess the association of the surgery type, the presence of lymph node resection during surgery, chemotherapy, radiotherapy, and hormone therapy with changes in between-arms volume difference and perceived shoulder-arm disabilities. As shown in table 3, the surgery type, lymph node resection, and having received chemotherapy, radiotherapy, or hormone therapy were not associated with the changes in between-arms volume difference or in the shoulder-arm disabilities as a result of the intervention.

However, an inverse association (-0.429, *P*=.020) between the changes in upper limb muscular strength and changes in perceived shoulder-arm disabilities was observed in the EG (table 4). In fact, the inverse association between the changes in muscular strength and perceived shoulder-arm disabilitites observed in the EG, was

Table 2 Effects of the EFICAN exercise program on between-arms volume difference and shoulder-arm disabilities in women breast cancer survivors

	Intervention				
Change From Baseline at Week 12	Exercise (n=30) Mean Change (SE)	Control (n=28) Mean Change (SE)	Mean Difference in the Change From Baseline to Week 12 (95% CI)	Effect Size (Cohen's d)	*P*
Δ Between-arms volume difference*	−1.065 (0.752)	0.142 (0.778)	1.207 (−0.964, 3.377)	0.293	.270
Δ DASH	−2.211 (2.174)	−0.141 (2.337)	2.070 (−4.362, 8.501)	0.175	.521

Abbreviations: DASH, disabilities of the arm, shoulder and hand questionnaire; SE, standard error; CI, confidence interval; P, p-value.
* Difference between the volume of the affected and non-affected arm (expressed in %).

Table 3 Linear regression analysis assessing the association of the surgery type (tumorectomy/mastectomy), the presence of lymph node resection, chemotherapy, radiotherapy, and hormone therapy with changes in between-arms volume difference and perceived shoulder-arm disabilities after the EFICAN intervention

	All Participants					Exercise Group (n=30)				
	β	B	SE	95% CI	*P*	β	B	SE	95% CI	*P*
Surgery type (tumorectomy/mastectomy)										
Δ Between-arms volume difference* (n=58)	0.033	0.309	1.265	−2.225, 2.842	.808	0.021	0.225	2.013	−3.898, 4.348	.912
Δ DASH (n=56)	0.037	0.950	3.471	−6.009, 7.910	.785	−0.071	−2.320	6.148	−14.914, 10.274	.709
Lymph node resection										
Δ Between-arms volume difference* (n=57)	−0.049	−0.427	1.182	−2.795, 2.943	.720	0.028	0.267	1.838	−3.505, 4.039	.885
Δ DASH (n=55)	0.044	1.045	3.274	−5.522, 7.612	.751	0.142	4.171	5.583	−7.285, 15.626	.462
Treatment										
Chemotherapy										
Δ Between-arms volume difference* (n=58)	−0.052	−0.539	1.379	−3.302, 2.225	.698	−0.084	−0.938	2.098	−5.235, 3.358	.658
Δ DASH (n=56)	0.059	1.679	3.886	−6.111, 9.470	.667	0.144	4.917	6.377	−8.146, 17.980	.447
Radiotherapy										
Δ Between-arms volume difference* (n=58)	0.089	1.179	1.761	−2.349, 4.707	.506	0.146	2.756	3.531	−4.477, 9.989	.442
Δ DASH (n=56)	−0.066	−2.489	5.153	−12.819, 7.842	.631	0.103	5.952	10.869	−16.312, 28.217	.588
Hormone therapy										
Δ Between-arms volume difference* (n=56)	−0.181	−2.775	2.050	−6.886, 1.336	.182	−0.162	−3.061	3.649	−10.561, 4.440	.409
Δ DASH (n=54)	−0.047	−1.901	5.643	−13.224, 9.421	.737	0.030	1.699	11.165	−21.250, 24.648	.880

Abbreviations: β, standardized regression coefficient; B, non-standardized regression coefficient; SE, standard error; P, p-value; CI, confidence interval; DASH, disabilities of the arm, shoulder and hand questionnaire.
* Difference between the volume of the affected and non-affected arm (expressed in %).

Table 4 Correlation assessing the association between the change in upper limb muscular strength (*z* score) and the changes in between-arms volume difference and perceived shoulder-arm disabilities

	All Participants		Exercise Group (N=29)	
Variable	r/ρ	*P*	r/ρ	*P*
Δ Between-arms volume difference* (n=57)	−0.113	.402	−0.115	.552
Δ DASH (n=55)	−0.216	.112	−0.429	.020

Abbreviations: ρ, Spearman's correlation coefficient; DASH, disabilities of the arm, shoulder and hand questionnaire; *r*, correlation coefficient.
* Difference between the volume of the affected and non-affected arm (expressed in %).

consistent for both the changes in muscular strength of the unaffected (r= -0.385, P=.039) and the affected (r= -0.367, P=.050) arms.

Discussion

The main findings of the present study suggest that a generic resistance training program aimed to increase muscular strength and improve quality of life does not increase between-arms volume difference and upper limb impairments in female breast cancer survivors. Additionally, the surgery type, lymph node resection during surgery, or having received chemotherapy, radiotherapy, or hormone therapy were not associated with the effects of the intervention on between-arms volume difference and shoulder-arm disabilities. Interestingly, the exploratory analyses revealed that a higher increase in muscular strength as a result of the intervention was associated with a more favorable perceived shoulder-arm disability in the EG, which should be confirmed or contrasted in a trial specifically designed for this purpose.

The resistance training program showed no effect on between-arms volume difference or perceived shoulder-arm disabilities. This result contrasts with the systematic review and meta-analysis presented by Hasenoehrl et al,[20] whose results showed a reduction in breast cancer-related lymphedema after a resistance exercise intervention. This difference may be explained by the exercises comprised in the intervention. In the present study, the exercises involving the upper limbs were mainly performed in sitting position in the sagittal plane, in contrast to the studies included in the paper by Hasenoehrl et al,[20] which included a wider variety of exercises. Therefore, the findings that the intervention produced no harm are of wide clinical relevance and support that resistance training is safe regarding shoulder-arm disabilities and lymphedema, although suggesting that the selected exercises might influence the effects of the training program.

Considering that some of the risk factors that may influence the development of lymphedema or shoulder-arm disabilities are surgery type, treatment type, and lymph node resection,[1,26] it is interesting to determine if these factors might also influence the effects of a resistance training program on between-arms volume difference and shoulder-arm disabilities. According to our results, there were no significant different effects on between-arms volume difference and perceived shoulder-arm disabilities depending on surgery type, treatment type, or lymph node resection after a resistance training program not specifically designed for the management of these side effects. To our knowledge, this is the first study to assess the association of surgery type, treatment type and lymph node resection, with the effects of a training program on

between-arms volume difference and shoulder-arm disabilities, so further investigations are needed to confirm or contrast our findings. We could expect to observe some differences in the effects of the training program; however, because of the lack of information, we did not control the potential confounding effect of the rehabilitation program that the participant took after surgery, because, as Yuan et al[23] and Bruce et al,[26] explain, the effects of a resistance training program might be influenced by rehabilitation.

Agreeing with Campbell et al,[21] exercise prescription needs to move forward to a higher personalization considering the specific characteristics of each patient. Thus, when designing a training program for breast cancer survivors, exercise specialists might wonder if surgery issues or the treatment type could influence the training program effects as these are risk factors for developing lymphedema and upper limb impairments. Our results suggest that, in the case of a generic resistance training program (based on multi-joint exercises involving the basic movement patterns), surgery type, lymph node resection and having received chemotherapy, radiotherapy or hormone therapy, did not influence the effects of the program, so it could be safely conducted. In this line, clinicians could feel confident when recommending resistance training to their patients (considering all the potential benefits of resistance training), even when recommending exercises not specifically designed to manage lymphedema or upper limb impairments.

Attending to EG, a higher increase in upper limb muscular strength was associated with lower levels of perceived shoulder-arm disabilities, agreeing with Bruce et al,[38,39] who explained that resistance training is one of the most effective therapies for upper limb rehabilitation after breast cancer, as well as a cheaper strategy than usual care. For this reason, it should be a first-line recommendation for the management of shoulder-arm disabilities after breast cancer.

Study limitations

The present study has limitations that must be underlined. The sample size was relatively small and larger studies are needed to confirm our findings. Also, potential confounding factors that may influence the effects of the exercise intervention (that is, rehabilitation program) were not included in analyses because of the lack of information. It is important to acknowledge that few participants were diagnosed with lymphedema before the beginning of the study, consequently, results might not be generalized to patients with a worse lymphedema status. Further research including diagnosis of lymphedema are needed to confirm our findings. The resistance training program was not designed for the management of between-arms volume difference, lymphedema, or shoulder-arm disabilities. However, the results demonstrated that the generic resistance training program used in this study, aimed to increase muscular strength, is not harmful, and might be safely undertaken by breast cancer survivors. Nevertheless, further research is needed to determine the most efficient resistance training program in order to manage lymphedema and shoulder-arm disabilities through exercise.

Conclusions

The main findings of the present study suggest that a generic resistance training program aimed to increase muscular strength and improve quality of life does not increase between-arms volume difference and upper limb impairments in female breast cancer survivors. Additionally, the surgery type, the presence of lymph node resection during surgery, or treatment type were not associated with the effects of the EFICAN training program on between-arms volume difference and shoulder-arm disabilities. Finally, no association was found between changes in upper-limb muscular strength and between-arms volume difference, whereas a higher increase in upper-limb muscular strength was associated with a reduced shoulder-arm disabilities in the exercise group, which warrants further research.

Suppliers

a. Stata v.13; StataCorp LP.
b. Dynasystem Research; Symotech.
c. Xiaomi MiBand3; Xiaomi Inc.

Keywords

Breast cancer-related lymphedema; Muscular strength; Rehabilitation; Resistance training; Shoulder-arm disabilities

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