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RESEARCH

Effectiveness of mat pilates on fatigue in women with breast cancer submitted to adjuvant radiotherapy: randomized controlled clinical trial

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Abstract

Purpose This clinical trial aimed to evaluate the influence of Mat Pilates and time on the change in fatigue scores in women with breast cancer undergoing adjuvant radiotherapy (RT). Additionally, assess the adherence and adverse effects of Mat Pilates sessions and the association of the level of physical activity with severe fatigue symptoms.

Methods One hundred fifty-six patients with non-metastatic breast cancer were randomized to usual care or supervised Mat Pilates exercise. Fatigue and physical activity level were measured at baseline, end of RT, 30 days, 3 and 6 months after RT. The generalized estimating equation (GEE) with intention to treat was applied.

Results A significant difference in the fatigue mean between the end of RT and the baseline was found in patients of both groups. There was no adverse effect with the practice of Mat Pilates, and it was analyzed the reduction of the symptom pain after the end of RT in women of intervention group compared to the control. There was no significant effect on fatigue between the groups. Patients with severe fatigue after 3 and 6 months of RT reported a significantly lower level of physical activity in the last periods.

Conclusion Fatigue levels increased at the end of RT but returned to baseline values after 6 months. A lower level of physical activity was associated with severe fatigue symptoms. Mat Pilates was safe for these women and reduced the symptom pain after treatment, but it did not successfully reduce fatigue during adjuvant RT.

Registration NCT03333993. November 7, 2017. https://clinicaltrials.gov/ct2/show/NCT03333993?term=breast+cancer&cond=pilates&draw=2&rank=1.

Keywords Breast Cancer · Radiotherapy · Fatigue · Exercise · Pilates Based Exercises

Background

Radiotherapy (RT) is an essential component of breast cancer treatment [1], which reduces locoregional recurrence by this neoplasm [2, 3]. Adjuvant RT can be adopted after breast-conserving surgery in ductal carcinoma in situ (DCIS) [4], in stage I and II invasive breast cancer [5] and after mastectomy in locally advanced breast cancer [6].

One of the main short-term side effects of RT in breast cancer is cancer-related fatigue (CRF) [7], among cancer survivors on active treatment, the prevalence of fatigue ranges from 62% to 85% [8]. As RT treatment weeks progress, the severity of fatigue significant worsening [9], in the last week of treatment it reaches maximum levels [10] and between 1 to 3 months of the end of RT treatment, fatigue levels can revert to pre-treatment level [11].

It is believed that reduced physical activity may play an important role in the development and/or persistence of CRF [12, 13]. In this sense, the American College of Sports Medicine (ACSM) guidelines recommend that cancer patients and survivors should be encouraged to "avoid inactivity" and be as physically active as possible [14]. During adjuvant

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treatment for breast cancer, a systematic review revealed a reduction in fatigue (-0.46, 95% CI: -0.66 to -0.27) in groups of physical exercise (resistance and/or aerobic supervised training, self-directed aerobic training, and supervised mind-body exercises) [15]. However, so far, only two clinical trials have analyzed the effects of the Pilates method, using Mat Pilates, on fatigue in women with breast cancer after the end of the treatments (surgical, radiotherapy and/or chemotherapy), and there was no significant reduction of this symptom in favor intervention groups [16, 17].

There is growing interest in the safety and effectiveness of exercise types that fall outside the traditional aerobic and resistance training modes [18]. Thus, the objective of this study is to evaluate the influence of Mat Pilates and time on the change in fatigue scores in women with breast cancer undergoing adjuvant radiotherapy. Additionally, assess the adherence and Mat Pilates adverse effects and the association of the level of physical activity with severe fatigue symptoms.

Methods

Study design

Randomized clinical trial conducted in Cancer Hospital III of the National Cancer Institute (HCIII/INCA) between May 2017 and October 2019. It was registered in ClinicalTrials.gov (NCT03333993) and approved by the Institutional Review Board of INCA (CAAE: 64099717.7.0000.5274) and of the National Public Health School (CAAE: 64099717.7.3001.5240).

Study population

Women over 18 years old, stage 0 to IIIC of breast cancer, with indication for adjuvant RT treatment at HCIII/INCA were eligible for the study. Exclusion criteria were previous cancer diagnosis, physical exercises at least twice a week for 40 mins or more a day, unable to respond to the questionnaires or to practice the Mat Pilates program for any reason (immediate breast reconstructions, acute infections, orthopedic, neurological, cardiorespiratory decompensated disorders, and severe renal dysfunctions).

Randomization and blinding

Before starting the RT treatment, a batch of 8 patients were randomized at a 1:1 ratio to either one of the two groups, intervention or control. Due to the nature of the intervention, patients, physical therapists supervising the exercises, and reviewers of outcome were not blinded to group allocation.

Intervention

The patients in the intervention group underwent the Mat Pilates program with sessions performed in the gym of HCIII/INCA physiotherapy from the beginning to the end of the adjuvant RT treatment, that varies from 7 to 12 visits, for a period of 3 to 6 weeks. The exercises were supervised by physiotherapists, in groups of four patients at the most.

The duration of the Mat Pilates program was 60-min sessions twice a week consisted in 5 mins warm-up exercises, 50 mins of strengthening exercises with flexibilization of the muscle fibers, where the concentric phase of the movement was performed during the expiration, followed by 5 mins of relaxation, and stretching, increasing the difficulty over the weeks. The program was based on the Classic Pilates Exercises [19]. Patients were instructed to perform the movements slowly and with a maximum of 10 repetitions. Mats, Swiss balls, of the brand Liveup with diameters of 65 and 55 cm and elastic bands of the brand Thera Band of light and moderate intensity were used in the exercises. The intensity was controlled using the adapted Borg Scale (0-10), in which the perceived exertion ranges from 2 (very light) to 7 (moderate-intense).

Women in the intervention and in the control groups were instructed to perform specific home exercises for the upper limbs (ULs) from the first postoperative day and regular physical activities.

Outcomes

Fatigue and level of physical activity were collected in individual interviews at baseline, after completion of radiotherapy, 30 days, 3 months, and 6 months after the end of RT. A physical examination was performed at every assessment to verify the presence of symptoms of pain, intercostobrachial nerve paresthesia, subjective lymphedema (report of feelings of heaviness and swelling in the upper limb (UL) ipsilateral to surgery), lymphedema by ULs circumference and transformation to volume using the truncated cone formula [20] and range of motion (ROM) of ULs. Information was collected on the practice of home exercises for the upper limbs and possible physical exercise co-interventions in the assessment after the end of the RT.

Fatigue was assessed using the 4^{th} version of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire. The score ranges from 0 to 52 and higher scores represent lower level of fatigue. In this study, a severe symptom of fatigue was determined when the score was < 37 [12, 21].

The level of physical activity (PA) was assessed using the long version of the International Physical Activity

Questionnaire (IPAQ). Energy expenditure is calculated for each activity performed and estimated in METS/minute per week (metabolic equivalent), representing the number of times the resting metabolism was multiplied in a given activity.

In order to follow-up the adherence to the program, the number of Mat Pilates sessions was distributed by percentage ranges according to the radiotherapy scheme received. Seven sessions for patients undergoing 17 fractions of RT, 10 sessions for patients undergoing 25 fractions of RT and 9 or 12 sessions for patients submitted to 22 or 30 fractions of RT due to booster doses were considered 100.0% of the program. Complete adherence success was established for patients who attended at least 90.0% of the Mat Pilates program [22]. At each exercise session, participants who reported to the physical therapists any adverse events were logged on the participant assessment sheets.

Statistical analysis

The sample calculation suggests that 156 patients (78 per group) have a power of 80% to detect difference of 0.9 points for fatigue between the groups, with an estimated standard deviation of 2 points, considering a significance level of 5% in a one-tailed hypothesis test.

Statistical was conducted following intention-to-treat analysis, using the Statistical Package for Social Sciences (SPSS) version 20.0. The association between Mat Pilates and time (after the end, 30 days, 3 months, and 6 months after RT) and fatigue differences was evaluated using the generalized estimating equation (GEE), as well as the interaction between groups and times, and their confidence intervals of 95% (95%CI). The model chosen was the dependent variable with gamma distribution (since it was the distribution that presented the best explanation by the adherence index - QIC), independent matrix (all covariance matrices were tested to assess the goodness of fit) and identity link function. The Bonferroni method was used to adjust the multiple comparisons of means. Estimates of differences between groups were adjusted for baseline data (fatigue, age, time from completion of chemotherapy to RT and physical activity level). The constant variation of the residuals was evaluated, and the quality of the model attested.

The level of physical activity was assessed using the mean of METS/minute per week and was compared between the fatigue groups, that is, patients with or without severe fatigue by the Mann-Whitney U Test in the same evaluation period and subsequent periods.

Results

Of a total of 181 patients who were at HCIII/INCA for their first adjuvant radiotherapy consultation and agreed to participate in the study, 164 were considered eligible. The reasons for ineligibility and exclusions are presented in Fig. 1.

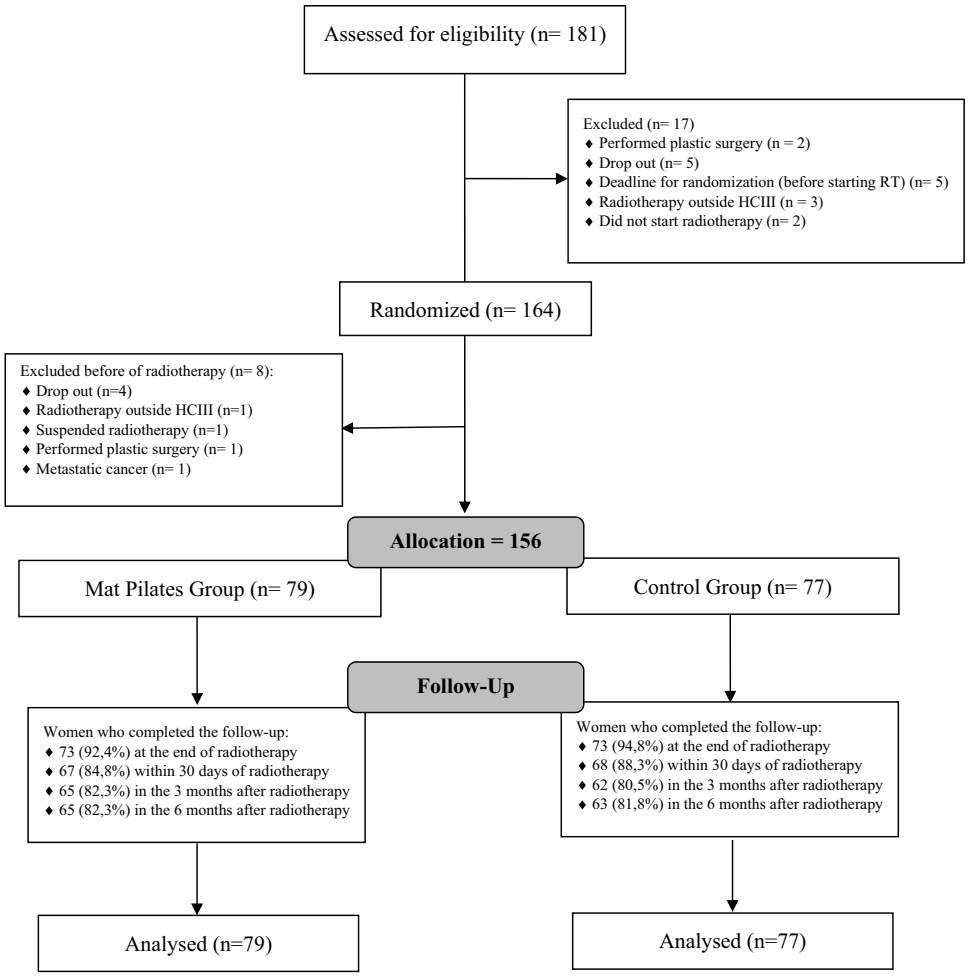
The baseline characteristics of the study, sociodemographic, clinical, lifestyle, physical examination, histological characteristics of the tumor and cancer treatments of the patients were similar in both groups and are described in Table 1. Mean age of patients in the intervention group was 52.91 years and in the control group 54.08 years. Most of the patients were not White (60.0%), housewives (74.3%), overweight (44.2%) and in 61.0% of them the clinical stage was considered advanced (IIB to IIIC).

Adherence to the Mat Pilates exercise program can be seen in Table 2. Seventeen patients (21.5%) attended less than 50.0% of the Mat Pilates sessions, 21 patients (26.6%) attended from 50.0% to 70.0% of the sessions and 41 patients (51.9%) performed more than 70.0% to 100.0% of the sessions. Complete adherence success with at least 90.0% of visits was seen in 19 patients (24.1%) (data not shown). Patients who underwent Mat Pilates did not interrupt the therapy due to major adverse effects, such as cardiac and blood pressure decompensation, oxygen saturation below 90.0% and opening of the surgical wound at the time of the intervention. However, two patients, after performing 4 and 5 sessions, needed to suspend Mat Pilates due to discomfort at the surgical site caused by radiodermatitis. After 8 Mat Pilates sessions, one patient had radiotherapy suspended due to severe radiodermatitis opening surgical wound. Two patients suspended Mat Pilates after 5 and 6 sessions because of joint discomfort and one patient had a fractured foot (outside of Mat Pilates) after 5 sessions and was unable to continue the program. None of the patients withdrew from the study because of these complications.

The practice of home exercises for the upper limbs during the RT treatment was present in 66.7% of the patients in the intervention group and in 72.6% of the patients in the control group. It was observed co-interventions in 3 patients in the intervention group and in 2 patients in the control group, through the practice of walking, and in 1 patient in the control group, through running and fighting activity (Table 2).

At the end of adjuvant RT, the presence of pain symptoms was significantly lower in patients undergoing the Mat Pilates program than in patients in the control group (38.1% versus 61.9%, p=0.015), with no significant difference in the other follow-ups (data not shown). The remainder of the signs and symptoms were similar in both groups (Table 2). Additionally, it was verified that there was no difference between the groups according to differences in ULs volume [Median (interquartile range)] before and after RT, respectively [Intervention group: 10.45 (113.42)

Fig. 1 Consort Flow Diagram



and 8.73 (109.62). Control group: 9.01 (87.19) and 5.36 (99.45)].

Fatigue means from baseline to 6 months after adjuvant RT for the intervention group and for the control group are shown in Table 3. For both groups, this symptom worsened after the end of treatment of RT [Intervention group: 43.34 (SD: 7.61) to 40.21 (SD: 10.07), control group: 44.65 (SD: 5.15) to 42.12 (SD: 7.13), initial and end of RT, respectively]. After 6 months of RT, the fatigue means in both groups returned to values closer to the baseline of the study [Intervention group: 43.08 (SD: 7.48); control group: 44.03 (SD: 5.91)].

In the GEE analysis, a significant effect was found over time on repeated fatigue measures. Patients who underwent Mat Pilates had lower fatigue mean (more symptoms of fatigue) than the control group, but without statistical significance (Mean Change 1.31, 95%CI: -3.33, 0.72). Another observation is the significant difference in the mean between the end of RT and the baseline for fatigue (β: -2.53; 95%CI: -3.71, -1.35), which meant stronger symptom of fatigue in patients in both groups at the end of adjuvant RT when compared to symptoms prior to beginning the treatment.

Figure 2 shows the group versus time interaction. Over time, patients who practiced Mat Pilates and those who did not had homogeneous fatigue results, this can be seen by the crossed confidence intervals.

Finally, it was observed that in the 3 months after adjuvant RT, the presence of severe fatigue (score < 37) was associated (p=0.018) with patients who reported lower level of physical activity (PA) in the last week (mean: 1,438.78; SD: 1,427.46) compared to patients with higher level of physical activity (mean: 2,499.84; SD: 2,643.73). For patients with severe fatigue at 6 months after adjuvant RT, this symptom was also associated (p=0.021) with lower level of physical activity in the 3 months after RT (mean: 1,242.53; SD: 1,076.82) compared to patients with higher level of physical activity (mean: 2,185.94; SD: 1,076.82). The two groups of patients, with or without severe fatigue, reported improvement in their physical activity levels 6 months after RT, with means, respectively, of 2,598.86 (SD: 6,078.86) and 2,463.35 (SD: 2,311.83), with the difference between groups being statistically significant (p=0.041) (Table 4).

Table 1 Distribution of Mat Pilates group ($n = 79$) and controls ($n = 77$) according to selected variables, Rio de Janeiro, Brazil, 2017-2019

	Variables	Pilates n (%)	Controls n (%)	*p*-value*
Age (years)	< 45	19 (52.8)	17 (47.2)	0.726
	45 – 55	26 (54.2)	22 (45.8)	
	> 55	34 (47.2)	38 (52.8)	
Skin color	White	28 (44.4)	35 (55.6)	0.203
	Others	51 (54.8)	42 (45.2)	
Marital status	With spouse	41 (51.2)	39 (48.8)	0.876
	Without partner	38 (50.0)	38 (50.0)	
Education level	≥ 8 years of study	61 (53.5)	53 (46.5)	0.238
	< 8 years of study	18 (42.9)	24 (57.1)	
Occupation	Work out	24 (60.0)	16 (40.0)	0.170
	Housewives	55 (47.4)	61 (52.6)	
Family income	> 1 minimum wage	55 (51.4)	52 (48.6)	0.779
	≤ 1 minimum wage	24 (49.0)	25 (51.0)	
Alcohol use	No	65 (52.0)	60 (48.0)	0.495
	Yes	14 (45.2)	17 (54.8)	
Smoking	No	56 (50.9)	54 (49.1)	0.918
	Ex or currently smoker	23 (50.0)	23 (50.0)	
Body Mass Index	Ideal	17 (54.8)	14 (45.2)	0.530
	Overweight	37 (53.6)	32 (46.4)	
	Obesity	25 (44.6)	31 (55.4)	
Arterial hypertension	No	41 (51.2)	39 (48.8)	0.876
	Yes	38 (50.0)	38 (50.0)	
Clinical staging	0/I/IIA	27 (44.3)	34 (55.7)	0.282
	IIB/IIIA	34 (58.6)	24 (41.4)	
	IIIB/IIIC	18 (48.6)	19 (51.4)	
Histological type	IDC	73 (52.1)	67 (47.9)	0.267
	Others	6 (37.5)	10 (62.5)	
Histological grade	Grade 1	13 (56.5)	10 (43.5)	0.828
	Grade 2	44 (49.4)	45 (50.6)	
	Grade 3	22 (50.0)	22 (50.0)	
Molecular subtype	Luminal A	19 (57.6)	14 (42.4)	0.253
	Luminal B	48 (45.7)	57 (54.3)	
	HER2 positive	2 (50.0)	2 (50.0)	
	Triple negative	10 (71.4)	4 (28.6)	
Chemotherapy	No	14 (58.3)	10 (41.7)	0.212
	Neoadjuvant	49 (54.4)	41 (45.6)	
	Adjuvant	16 (39.0)	25 (61.0)	
	Neoadjuvant and adjuvant	0 (0.0)	1 (100.0)	
Herceptin (Target therapy)	No	68 (50.7)	66 (49.3)	0.948
	Yes	11 (55.0)	11 (50.0)	
Hormone therapy	No	13 (61.9)	8 (38.1)	0.267
	Yes	66 (48.9)	69 (51.1)	
Breast surgery	Segmentectomy	37 (50.0)	37 (50.0)	0.879
	Mastectomy	42 (51.2)	40 (48.8)	
Axillary emptying	No	37 (50.0)	37 (50.0)	0.879
	Yes	42 (51.2)	40 (48.8)	
Sentinel lymph node biopsy	No	34 (56.7)	26 (43.3)	0.234
	Yes	45 (46.9)	51 (53.1)	
Histopathological staging	0/I/IIA	52 (50.5)	51 (49.5)	0.381
	IIB/IIIA	23 (56.1)	18 (43.9)	
	IIIB/IIIC	4 (33.3)	8 (66.7)	

Table 1 (continued)

	Variables	Pilates n (%)	Controls n (%)	*p*-value*
Radiotherapy site	Breast/Plastron	19 (47.5)	21 (52.5)	0.540
	Breast/Plastron and SCF	50 (54.3)	42 (45.7)	
	Breast/Plastron and armpit	0 (0.0)	1 (100.0)	
	Breast/Plastron/SCF and armpit	10 (43.5)	13 (56.0)	
Radiotherapy mode	Hypofractionated	11 (44.0)	14 (56.0)	0.511
	Conventional	58 (50.4)	57 (49.6)	
	Boost	10 (62.5)	6 (37.5)	
Technique of radiotherapy***	Two-dimensional (2D)	62 (49.2)	64 (50.8)	0.560
	Three-dimensional (3D)	14 (53.8)	12 (46.2)	
End of CT to RT	No	14 (58.3)	10 (41.7)	0.330
	1 to 3 months	10 (35.7)	18 (64.3)	
	4 to 5 months	13 (56.5)	10 (43.5)	
	≥ 6 months	42 (51.9)	39 (48.1)	
Pain	No	47 (47.0)	53 (53.0)	0.224
	Yes	32 (57.1)	24 (42.9)	
Paresthesia	No	22 (51.2)	21 (48.8)	0.936
	Yes	57 (50.4)	56 (49.6)	
ROM of ULs	Functional	78 (50.3)	77 (49.7)	0.506**
	Incomplete	1 (100.0)	0 (0.0)	
Subjective lymphedema	No	62 (48.1)	67 (51.9)	0.159
	Yes	17 (63.0)	10 (37.0)	

* Chi-square test; ** Fisher's exact test; *** Total variations due to missing in each variable. *CT* chemotherapy, *HER2* Human epidermal growth factor receptor 2, *IDC* invasive ductal carcinoma, *ROM* range of motion, *ULs* upper limbs, *RT* radiotherapy, *SCF* supraclavicular fossa

Discussion

This is the first randomized clinical trial to evaluate the effect of the Pilates method, already widespread in the general population and in rehabilitation, on the symptom of fatigue during adjuvant RT in women with breast cancer. This intervention proved to be safe, with no serious adverse effects occurring during the exercise program. However, the results show that this intervention had no effect on the reduction of fatigue symptoms compared to usual care.

Significant worsening of fatigue at the end of adjuvant RT was observed in both groups, with improvement after 30 days and 3 months after RT, with fatigue returning to close to baseline levels after 6 months of treatment. This reduction after 6 months was also verified in another clinical trial with women with breast cancer, who were evaluated according to the National Cancer Institute Common Toxicity Criteria v4.0, where acute fatigue was observed in 84% (n=126) of women undergoing radiotherapy by conventional fractionation (CF) (50Gy in 25 fractions with boost) and in 79% (n=109) of women undergoing moderate hypofractionated (HF) radiotherapy (42.56 Gy in 16 fractions with boost), up to 42 days after RT. Six months after the end of RT, the presence of fatigue was detected in 37% (n=53) of the women who underwent CF and in 27% (n=35) of the women who underwent moderate HF [23].

In a prospective study assessing fatigue in breast cancer women using the same questionnaire adopted in this study (FACIT-F), it was possible to detect the presence of severe fatigue in 33% (n=141) before adjuvant RT, 53% after the end of RT and 40% after 4 months of RT. For the latter, fatigue persisted for up to 1 year after the end of treatment [24], while in a recent multicenter cohort study (n=1098), using the Multidimensional Fatigue Inventory (MFI-20), one-third of breast cancer patients still reported moderate to severe fatigue at 2 years after adjuvant radiotherapy [25]. The percentage of severe fatigue in this study was 14.1% at baseline, with an increase to 20.5% at the end of RT, followed by a decrease to 18.1% within 3 months and 14.8% within 6 months (data not shown in the tables).

There are few clinical trials in the literature addressing the effectiveness of mind-body exercises in fatigue during adjuvant RT for breast cancer. A trial used the Qigong method as intervention and assessed the mean fatigue using the Brief Fatigue Inventory (BFI) questionnaire. Similar to this study, at the end of RT treatment mean fatigue was

Table 2 Adherence to Mat Pilates, practice of exercises at home, co-intervention, and physical examination, at the end of radiotherapy (n = 145)

Variables	Pilates n (%)	Controls n (%)	p-value*
Adherence to Mat Pilates		-	-
< 50%	17 (21.5)		
≥ 50% - 70%	21 (26.6)		
> 70% - 100%	41 (51.9)		
Home Exercises***			0.672
Does not perform	23 (53.5)	20 (46.5)	
Performs every day	34 (47.9)	37 (52.1)	
Performs occasionally	12 (42.9)	16 (57.1)	
Co-intervention			0.653**
No	70 (50.4)	69 (49.6)	
Yes	3 (50.0)	3 (50.0)	
Pain			**0.015**
No	48 (58.5)	34 (41.5)	
Yes	24 (38.1)	39 (61.9%)	
Paresthesia			0.672
No	21 (52.5)	19 (47.5)	
Yes	51 (48.6)	54 (51.4)	
ROM of ULs			0.685**
Functional	70 (49.6)	71 (50.4)	
Incomplete	2 (50.0)	2 (50.0)	
Subjective lymphedema***			0.255
No	56 (47.5)	62 (52.5)	
Yes	15 (60.0)	10 (40.0)	

* Chi-square test **; Fisher's exact test ***; Total variations due to missing in each variable. *ROM* range of motion, *ULs* upper limbs

The p-value < 0.05 are in bold

similar in the groups [3.1 (SD: 2.0)]; in the 49 breast cancer women in the intervention group and 2.7 (SD: 2.1) in the 47 breast cancer women in the control group, both considered mild fatigue (1-3) [26], in another recent trial with Yoga performed twice a week, also did not occur the significant change in fatigue assessed by BFI in 12 women intervention group when compared to 12 in control group [27]. Two other trials evaluated Yoga during adjuvant RT for breast cancer. The first, with 44 women in the intervention group and 44 women in the control group, assessed fatigue using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core (EORTC-QLQ-C30) and showed that after the end of this treatment, women who practiced Yoga had lower mean of fatigue when compared to the control group (mean difference: -17.26 ±4.89; p=0.001) [28]. In the second trial, with 53 women in the Yoga group and 54 women in the control group, fatigue was assessed by the BFI questionnaire with significant reduction in the Yoga group (initial mean: 3.2, final mean: 2.9) compared to the

Table 3 Unadjusted means and standard deviation (SD) and adjusted mean difference and 95% confidence interval (CI) for fatigue (n = 156)

Time	Fatigue Mean (SD)		Unadjusted Mean Change						Adjusted Mean Change*					
			Between-group difference			Within-group difference (Time)			Between-group difference			Within-group difference (Time)		
	Pilates	Controls	Mean Change	95% CI	p-value	Mean Change	95% CI	p-value	Mean Change	95% CI	p-value	Mean Change	95% CI	p-value
Baseline	43.34 (7.61)	44.65 (5.15)	-1.308	(-3.33, 0.72)	0.205	Ref.	.	.	-0.774	(-2.30, 0.78)	0.329	Ref.	.	.
End of RT	40.21 (10.07)	42.12 (7.13)	.	.	.	-2.526	(-3.71, -1.35)	**<0.001**	.	.	.	-2.756	(-4.06, -1.45)	**<0.001**
30 days after RT	42.15 (7.86)	43.71 (6.91)	.	.	.	-0.943	(-2.39, 0.50)	0.201	.	.	.	-0.951	(-2.57, 0.66)	0.249
3 months after RT	42.97 (7.79)	43.16 (7.51)	.	.	.	-1.488	(-3.18, 0.20)	0.084	.	.	.	-1.408	(-3.29, 0.48)	0.143
6 months after RT	43.08 (7.48)	44.03 (5.91)	.	.	.	-0.618	(-1.89, 0.66)	0.342	.	.	.	-0.376	(-1.68, 0.93)	0.572

*Adjusted for baseline value of the outcome, age, end of CT (chemotherapy) to RT (radiotherapy) and physical activity level

The p-value < 0.05 are in bold

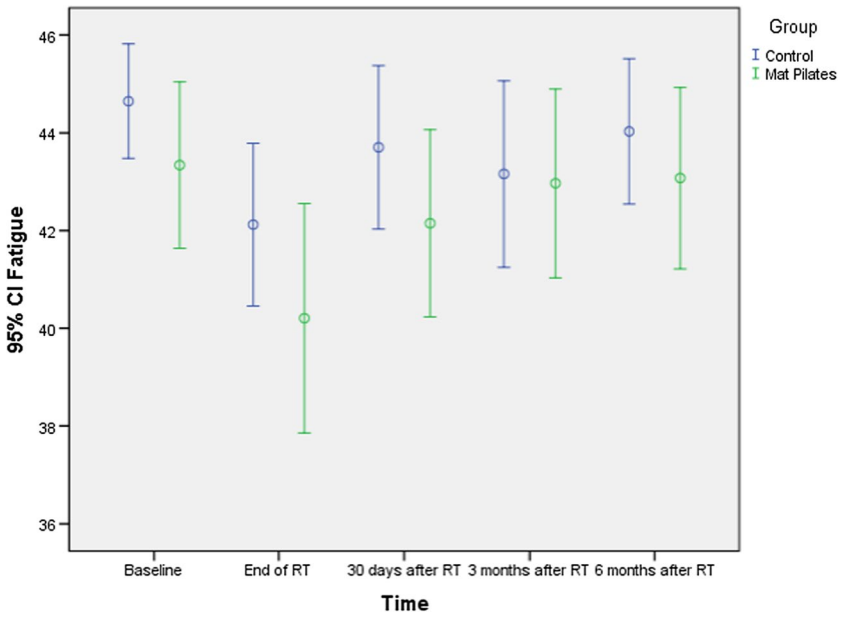


Fig. 2 Interaction groups versus time. CI = Confidence Interval, RT = radiotherapy

control group (initial mean: 2.6, final mean: 3.2) at the end of the RT treatment (p=0.04) [29].

In addition to the different questionnaires used to measure fatigue, these trials have other methodological differences, as the frequency of supervised classes. In both trials that had a reduction in fatigue, using Yoga, the sessions were offered 3 times a week, in this study, two weekly Mat Pilates sessions were offered, while for Qigong only one weekly session. There is still a gap in scientific evidence about the most effective components of physical activity – frequency, type, intensity, and duration – in cancer populations [18].

Few clinical trials had analyzed the effects of the Pilates Method on fatigue in women with breast cancer applied after the completion of surgery and adjuvant treatments (radiotherapy and/or chemotherapy), unlike this study where the intervention was applied during adjuvant RT. The frist, for the intervention group (n=27), Mat Pilates exercises were supervised by a physiotherapist and performed for 1 h, 3 times a week, for 8 weeks. Pilates and control (n=15) groups were instructed to walk 3 times a week for 8 weeks. Comparison of means, before and after the intervention, showed a non-significant reduction in fatigue assessed by the BFI in both groups [Pilates initial mean: 6.63 (SD: 4.14), final mean: 5.58 (SD: 4.67); p=0.14. Control initial mean: 7.75 (SD: 5.68); final mean: 6.55 (SD: 4.42); p=0.82], furthermore, there was no significant difference between the groups [16]. The second, breast cancer survivors were randomly into mat Pilates (n = 25), belly dance (n = 25) or control group (educational sessions) (n = 24). Mat Pilates and belly dance groups received a 16-week intervention, 3 days a week, for 1 h and and no difference was observed in mean fatigue between groups [17].

Despite the known prevalence of cancer-related fatigue, the specific mechanisms of its pathophysiology are still not well elucidated. The dysregulation of pro-inflammatory cytokines is the mechanism that has garnered rising evidence at the most [30]. Exercise-based interventions can be the most promising as a first-line treatment for CRF [31], while meta-analyses have already shown that these can reduce serum concentrations of some pro-inflammatory markers, such as IL-6, C-reactive protein and tumor necrosis factor in women during and after breast cancer treatment [32–34].

The current study found significant association of severe fatigue symptom with low level of physical activity within 3 and 6 months after adjuvant RT, and other studies have also reported this finding, where 72% (n=321) of breast and prostate cancer patients who experienced fatigue during radiotherapy performed less physical activity, including daily activity (mean difference (MD)): 0.48 (0.17-0.78); p=0.003), moderate (MD: 0.65 (0.24-1.06); p=0.002) and vigorous (MD: 0.50 (0.18-0.83); p=0.003) in comparison with patients without fatigue [35], and in women after 1 to 6 months of adjuvant chemotherapy treatment, where 70% of the patients underwent radiotherapy. It was also found that lower levels of pro-inflammatory cytokines IL-6 and IL-8 were connected to physically active lifestyle [36].

Another effect seen in this study was the reduction of pain symptoms after the end of adjuvant RT in women who practiced Mat Pilates when compared to the control group. In a systematic review with meta-analysis, including interventions studies in surgical breast cancer women with or without adjuvant treatment, Pilates was shown to be statistically more effective in reducing upper limb pain by the Visual Analogue Scale (VAS) when compared to other interventions (n=97 of 2 studies, summary measure: -0.48; 95%CI:

Table 4 Means and standard deviation (SD) of total MET-min/week (metabolic equivalent- minute per week) by severe fatigue status (n = 156)

Time of measure of MET-min/week	Means MET-min/week (SD) Without Fatigue at baseline	Fatigue at baseline	p-value	Without Fatigue at end of RT	Fatigue at end of RT	p-value	Without Fatigue at 30 days of RT	Fatigue at 30 days of RT	p-value	Without Fatigue at 3 months of RT	Fatigue at 3 months of RT	p-value	Without Fatigue at 6 months of RT	Fatigue at 6 months of RT	p-value
Baseline	1762.59 (2160.36)	1579.61 (1634.77)	0.905	1679.86 (2057.84)	1906.85 (2401.25)	0.965	1683.05 (1965.45)	1846.84 (2613.82)	0.960	1687.11 (1843.51)	1803.10 (2571.17)	0.332	1628.58 (1961.99)	1136.61 (1211.98)	0.282
End of RT*	-	-	-	1828.08 (1871.12)	1857.21 (1478.21)	0.345	1691.84 (1757.99)	2132.74 (1815.23)	0.152	1825.01 (1891.84)	1997.22 (1782.28)	0,487	1616.89 (1638.94)	2171.11 (2129.42)	0.251
30 days of RT	-	-	-	-	-	-	2442.22 (6807.02)	2663.00 (5689.19)	0.544	2490.44 (7485.21)	2484.05 (5293.91)	0.746	2349.78 (7285.89)	1757.27 (944.39)	0.351
3 months of RT	-	-	-	-	-	-	-	-	-	2499.84 (2643.73)	1438.78 (1427.46)	**0.018**	2185.94 (2250.71)	1242.53 (1076.82)	**0.021**
6 months of RT	-	-	-	-	-	-	-	-	-	-	-	-	2463.35 (2311.83)	2598.03 (6078.86)	**0.041**

* Mat Pilates was one of the activities computed by IPAC (International Physical Activity Questionnaire) at the end of the radiotherapy (RT)

The p-value < 0.05 are in bold

-0.88, -0.07) [37]. However, cautious is required when analyzing the response of the symptom pain in this study since as it was performed through a generic assessment of the presence or absence of pain, without continuous assessment of the pain analogue scale along the follow up after RT.

Among the limitations of this study, there is the small sample, the absence of a control group with a minimum of intervention, the 14.1% of losses during follow-ups and the fact that women who developed radiodermatitis during RT were not screened, making it difficult the understanding of adherence to the exercise program.

We conclude that fatigue levels in women with breast cancer increased at the end of the therapy and returned to baseline after 6 months of RT. Furthermore, lower level of physical activity was associated with severe fatigue symptoms after 3 and 6 months of radiotherapy. Mat Pilates was not successful in reducing fatigue during adjuvant RT; however, it was possible to verify a reduction in the symptom of pain after the end of this treatment in women who practiced Mat Pilates when compared to the control group and there was no occurrence of adverse effects during the exercise program.

It was also found less severe symptoms of fatigue among patients who had high level of physical activity, so the practice of PA during adjuvant RT should be encouraged, and this is one of the clinical impacts of the results of this trial, in addition to showing the safety of Mat Pilates for women with breast cancer, which makes it an alternative for improving the level of PA in these patients and preventing the severity of symptoms such as fatigue. Future clinical trials to understand the benefits of different types of exercise to improve cancer-related fatigue are necessary.

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Declarations

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Registered and approved by the Institutional Review Board of INCA (CAAE: 64099717.7.0000.5274) and of the National Public Health School (CAAE: 64099717.7.3001.5240) and was registered in ClinicalTrials.gov (NCT03333993).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish Not applicable.

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