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The Impact of Multimodal Exercise Program on Physical and Functional Outcomes in Breast Cancer Survivors: A Randomized Controlled Trial

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1. Abstract

1.1. Objectives: Cancer, a leading cause of death and morbidity in Western countries, often results in reduced cardiorespiratory fitness (CRF), altered body composition, and increased fatigue, impacting their quality of life. This study aimed to evaluate the impact of a multimodal oncological exercise program on these parameters in breast cancer patients.

1.2. Design: Randomized controlled trial.

1.3. Methods: Patients were allocated to either an intervention group, which underwent a 16-week at least two times per week multimodal exercise program (N=40), or a control group, (N=34). CRF was used as the main outcome measure; measurements were completed at baseline and and after the 16-week intervention period.

1.4. Results: The program was available both in-person and online. Key outcomes measured included CRF, body composition, functional capacity, fatigue, and quality of life. The intervention's efficacy was compared between the in-person and online modalities. The intervention group showed a significant 22.4% increase in CRF, 10% reduce in fat mass and 5.24% increase in lean mass. Interestingly, no significant differences were observed between the in-person and online modalities of the exercise program, indicating the potential effectiveness of remote interventions.

1.5. Conclusion: A structured, multimodal exercise program significantly improves CRF, body composition, and functional capacity in breast cancer patients. The comparable effectiveness of in-person and online modalities suggests that remote exercise interventions could be a viable option for patients unable to attend in-person sessions. These findings support the integration of exercise programs into the treatment plan for breast cancer patients, potentially improving their survival and quality of life. Future research should explore the long-term sustainability of these benefits and the applicability to a broader range of cancer patients.

2. Introduction

Cancer is one of the most frequent causes of death and morbidity in Western countries, with more than 300,000 new cases expected by 2035, according to the annual report of the Spanish Society of Medical Oncology. Thanks to advances in treatment and screening techniques, the survival rate has increased across all types of cancer, but especially in breast, colon and lung cancer [1]. However, these patients often experience various comorbidities that impact their health and quality of life, such as reduced levels of cardiorespiratory fitness (CRF), alterations in body composition, and increased fatigue [2–4].

The evidence has demonstrated the effectiveness of physical exercise in reducing many of the side effects of cancer and its treatments, primarily by addressing alterations in body composition, CRF, and fatigue, all of which are associated with quality of life

and survival [5–7]. Despite a considerable number and variety of physical exercise programs having demonstrated benefits in these patients 8, the greatest effectiveness is achieved by combining high-intensity cardiovascular exercises with resistance and balance training (multimodal training program), as they are also capable of reducing cardiotoxicity and neuromuscular injuries [2,9–11].

Despite these benefits, it is estimated that only 36% of breast cancer survivors adhere to the exercise recommendations for cancer survivors set by the World Health Organization (WHO) [12]. This is due, among other factors, to the lack of awareness and difficulty in accessing oncology exercise programs by patients and the scarcity of qualified professionals in this field. A systematic review has shown that certain factors improve patient adherence to oncology exercise programs, including group exercise sessions, tailoring the intensity and type of exercise to CRF and functional level, and proximity to the training center [13]. On the other hand, the potential of online training remains largely unknown due to the scarcity of studies in this area [14,15].

In this randomized controlled trial (RCT), we examined the impact of a multimodal oncological exercise program on body composition, CRF, fatigue, and quality of life in patients with breast cancer in stage IA to IIIB.

3. Methods

3.1. Trial design

We conducted a RCT with two groups: intervention group and control group. The randomization was done in a 1:1 ratio at an oncology exercise center. This research has been approved by the Ethical Committee of the Universidad Autónoma de Madrid and it has been registered in ClinicalTrials.gov (NCT05882578). All patients willing to participate signed an informed consent before being randomized. The clinical trial protocol was designed and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, ensuring the welfare and rights of the participants involved in the study.

3.2. Participants

Patients were informed of the project by their oncologist, the media or social networks. Patients then contacted the research team to schedule baseline assessments at the Madrid Exercise-Oncology Center.

Inclusion criteria for participation were: women diagnosed with primary breast cancer, cancer stages IA to IIIB; aged 18 years or older; no more than 10 years since cancer diagnosis; and without other comorbidities that would limit their capacity to engage in exercise, such as recent surgery or functional limitations. Patients undergoing chemotherapy and radiotherapy, as well as those with metastatic disease, were excluded from the study.

3.3. Intervention

After completing the baseline assessments, the participants included in the study were randomly allocated to one of the two groups. Subjects assigned to the “control group” were provided with explanations regarding activity recommendations for cancer survivors published by the WHO. After 16 weeks, they were scheduled for the final assessment.

Patients assigned to the “intervention group” underwent a multimodal exercise program intervention for 16 weeks. This intervention was conducted both in-person at the training center and online to enhance participant adherence. The online and in-person interventions were identical in terms of structure, types of exercises, intensity, duration, and frequency.

The intervention comprised a multimodal program that included endurance, resistance, balance, and proprioception exercises, with an intensity ranging from 55% to 95% of heart rate reserve (HRR). Each session lasted 75 minutes and was structured as follows: 10 minutes of warm-up involving joint mobilities, balance and proprioceptive exercises, and aerobic exercise at an intensity ranging from 55% to 75% HRR. This was followed by two 20-minute bouts of combined activities (endurance activities combined with resistance exercises) at an average intensity of 70-75% HRR with 30-second to 60-second bouts of high-intensity activity of 85% to 100% HRR. The resistance exercises were developed with free weights in circuits of 6 to 8 exercises of 3x10 or 3x15, combined with endurance activities of 60% HRR. Intensity perception in resistance exercises was assessed using Borg Scale, and endurance exercise intensity was assessed by HRR. Finally, full body stretching was performed, holding each exercise for 30 to 45 seconds.

3.4. Outcomes

The outcomes were evaluated at baseline and after the 16-week intervention period. The main variable was the CRF, assessed by the Bruce test and controlled by heart rate monitors. To estimate VO2max, the Mackenzie equation (4.38 x T - 3.9) was used. A minimum change of 3.5 ml x kg-1 x min-1 was settled as minimum significant difference [16]. Body composition was assessed by bioimpedance (Tanita 601F), collecting data on body fat percentage and mass, lean percentage and mass, body water percentage, and visceral fat score [17]. All patients were required to follow a homogenized diet, hydration and instructions to monitor bioimpedance. After this, the functional capacity or participants was assessed through 3 tests: Sit & Stand test during 30 seconds, 6 minutes-walking test (6MWT) walking as fast as possible; and 1 km as fast as they could (35524144). Additionally, information on physical activity was obtained using the International Physical Activity Questionnaire (IPAQ) [18]; and specific questionnaires for Fatigue and Breast Cancer patients’ Quality of Life questionnaire (FACT-F and FACT-B) from the FACIT.org [19,20]. All questionnaires were online and self-reported before the in-person assessments.

3.5. Sample size

To ascertain various parameters and enable the extrapolation of

their values to the studied population, the anticipated sample size will consist of a minimum of 38 participants per group. The necessary sample size has been estimated by accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, to detect a difference equal to or greater than 3.49 mil x kg-1 x min-1 of cardiovascular capacity. For this purpose, the common standard deviation is assumed to be 5.1 with an estimated loss-to-follow-up rate of 10%.

3.6. Data analysis

The collected data were analyzed with the Stata 15 program. Homogeneity was analyzed by Saphiro-Wilk test showing a normal distribution of the sample p=0.31. Demographic data were analyzed by descriptive methods and were presented by mean and standard deviation and by frequencies. Baseline analysis comparison between groups were developed by t test for independent samples. Final group comparisons were developed with ANCOVA test, adjusting results by baselines assessments in each variable. Cohen's d was performed to find the effect size in the final group comparison results.

4. Results

4.1. Recruitment

Eighty-three patients were evaluated for eligibility. Three patients were excluded and finally 83 patients were randomized: 42 to the intervention group and 41 to the control group. During follow-up, 2 patients were lost in the intervention group and 7 in the control group. Finally, 40 patients in the intervention group and 34 in the control group were analysed (Figure 2).

4.2. Baseline characteristics of the subjects

The mean age in the intervention group (N=40) was 50.2±1.05 years old, and in the control group (N=34), it was 49.48±1.88 years old, showing no significant differences (p=0.73). The level of adherence was also similar between the intervention group (95.23%) and the control group (82.93%) (p=0.10).

At baseline, participants in both groups exhibited similar demographic characteristics (p>0.05) regarding marital status, place of residence, employment status (active or inactive), work status (worker, retired, homemaker, on work leave, unemployed, others), and hospital of origin. However, the educational level was higher in the intervention group than in the control group (p=0.02) (Supplementary Table 1).

At baseline, both groups showed similar clinical characteristics (p>0.05) in terms of time since diagnosis, time since treatment, tumor subtype (Hormonal +, Triple Positive (Hormonal + & Her 2+), HER2 Positive, Hormonal negative, or Triple Negative), BRCA Mutated status, whether they were undergoing treatment, and the type of treatment (Tamoxifen, Exemestane, LHRH Analogues, Aromatase Inhibitor, Monoclonal Antibody, Cyclin Inhibitors), as well as received treatments (surgery, breast reconstruction, lymphadenectomy, radiotherapy, chemotherapy, or other treatments), and comorbidities. It should be noted that 88% of the women were undergoing hormonal therapy at the time of the study, with the majority of them taking aromatase inhibitors (52%) and tamoxifen (25%). Approximately 60% of the women had undergone lumpectomy, and 45% of them had undergone lymphadenectomy. Around 70% had received chemotherapy, and 72% had received radiotherapy. The mean time elapsed since the completion of treatments was 3.54 years, and the mean time since diagnosis was 4.35 years (Supplementary Table 2).

The baseline level of CRF, measured using the Bruce test, was similar between the intervention group (25.66±5.86 mil x kg-1 x min-1) and the control group (25.19±4.58 mil x kg-1 x min-1) (p=0.71). No significant differences were found in body composition variables (weight, mass, body fat percentage, lean mass percentage and mass, water, and Visceral Fat Score) (p>0.05). Quality of life and functional characteristics, assessed using the Sit & Stand test, 6MWT, and the 1 km test, were similar between the groups (p>0.05). Likewise, the total amount of physical activity and physical activity of high, moderate, and low intensity were similar between both groups (p>0.05). However, the baseline level of fatigue was higher in the control group than in the intervention group (92.44 ± 14.94 and 30.82 ± 8.24, $p < 0.001$) (Supplementary Table 3).

4.3. Adherence to the exercise program

The women assigned to the intervention group had an attendance rate of 85.13%. In the intervention group, 14 (35.9%) patients participated in the online program, while 25 (64.1%) attended the in-person sessions. Participants who opted for the online program cited reasons such as incompatible schedules, challenges in maintaining work-life balance, travel constraints, or residing outside Madrid. The attendance rates for the intervention group were 89.5% in both instances. Specifically, for the online intervention, 84.02% of the sessions were conducted online, while 15.98% of the attendance occurred in-person. Conversely, for the in-person intervention, 76.64% of the sessions were face-to-face, and 23.35% of the attendance was through online classes. The results of the effect of both exercise interventions, in-person or online, on the analyzed variables are shown in "Table 1".

Supplementary Table 1: Baseline sociodemographic characteristics (n=74).

	Total	Intervention group	Control group	P value
	N / %	N / %	N / %	
Marital Status				0.86
With partner, single	11 / 14.86	4 / 10.00	7 / 20.59	
With partner, married	46/ 62.16	29 / 72.50	17 / 50.00	
With partner, widowed	0	0	0	
With partner, divorced	0	0	0	
Without partner, single	8/10.81	3 / 7.50	5 / 14.71	
Unmarried, divorced	3 / 4.05	2 / 5.00	1 / 2.94	
Without partner, widowed	6/8.11	2 / 5.00	4 /11.76	
Education Level				0.02
Primary School	3/ 4.05	2/ 5.00	1 / 2.94	
High School	2/1.35	0	1 / 2.94	
Professional qualification	5/6.76	1 / 2.5	4 / 11.76	
Bachelor's degree	40/54.05	19 / 47.50	21 / 61.76	
Post-Graduate	25/33.78	18 / 45.00	7 / 20.59	
Place of residence				0.35
Madrid	66/89.19	37 / 92.50	29 / 85.29	
Other Spanish cities	7/9.46	2 / 5.00	5 / 14.71	
Other cities abroad	1/1.35	1 / 2.50	0 / 0	
Working at this moment				0.18
Yes	35/47.30	24 / 60.00	15 / 44.12	
Not	39/52.70	16 / 40.00	19 / 55.88	
Laboral Status				0.19
Worker	38/51.35	24 /60.00	14 / 41.18	
Retired	8 / 10.85	2 / 5.00	6 /17.65	
Homemaker	1/1.35	0 / 0	1 /2.94	
Work leave	21/28.38	12 / 30.00	9 /26.47	
Unemployed	4/5.41	2 / 5.00	2 / 5.88	
Other	2/2.70	0 / 0	2 / 5.88	
Hospital				0.07
HGUGM	18 / 24.32	11/ 27.50	7 20.59	
FJD	17 / 22.97	11/ 27.50	6 / 17.65	
HM Sanchinarro	8/10.81	2/ 5.00	6 / 17.65	
MD Anderson	6/8.11	2 / 5.00	4 / 11.77	
Hospital Universitario Ramón y Cajal	5/6.76	3 / 7.50	2 / 5.88	
Hospital Universitario Clínico San Carlos	4/5.41	1 / 2.50	3 / 8.82	
Others	16 / 21.62	10/ 25.00	6 / 17.65	

Abbreviations: FJD = Fundación Jiménez Díaz; HGUGM = hospital General Universitario Gregorio Marañón; HM Sanchinarro: Hospitales Madrid Sanchinarro.

Supplementary Table 2: Baseline clinical characteristics (n=74).

	Total	Intervention group	Control group	P value
	Mean (SD)	Mean (SD)	Mean (SD)	
	N / %	N / %	N / %	
Time from diagnosis (in months)	4.35 (2.48)	4.27 (2.40)	4.47 (2.61)	0.74
Time from treatments (in months)	3.54 (2.47)	3.61 (2.40)	3.65 (2.61)	0.75
Tumoral Subtype				
Hormonal +	48/61.54	25 / 60.98	23 / 62.16	
Triple Positive (Hormonal + & Her 2+)	19/24.36	9 / 21.95	10 / 27.03	
HER2 Positive, Hormonal negative	9 / 11.54	5 / 12.20	4 / 10.81	
Triple Negative	2/2.56	2 / 4.88	0 / 0	
BRCA Mutated	2 / 2.56	1 / 2.44	1 / 2.70	
Under treatment	69/ 88.46	38 / 92.68	31 / 83.78	0.22
Type of treatment				
Tamoxifen	20 / 25.64	13 /31.71	7 / 18.92	
Exemestane	4 / 5.13	0 / 0	4 / 10.81	
LHRH Analogues	14 / 17.95	5 / 12.20	9 / 24.32	
Aromatase Inhibitor	41/52.56	21 / 51.22	20 / 54.05	
Monoclonal Antibody	8 / 10.26	8 / 19.51	0 / 0	
Cyclin Inhibitors	8 / 10.26	2 / 4.88	6 / 16.22	
Received Treatments				
Surgery				0.26
Tumerectomy	48/61.54	23 / 56.10	25 /67.57	
Mastectomy	24/30.77	3/ 7.32	3 / 8.11	
Bilateral Mastectomy	6/7.69	15/ 36.59	9 / 24.32	
Other surgeries	8/10.26	7/17.07	1 / 2.70	
Breast Reconstruction	15/19.23	11 / 26.83	4 / 10.81	0.08
Lymphadenectomy	34/45.33	19 / 46.34	15 / 44.12	0.85
Radiotherapy	54/72.00	30 / 73.17	24 / 70.59	0.81
35 sessions	1	1 / 2.44	0 / 0	
33 sessions	3	3 / 7.32	0 / 0	
25 sessions	19	9 / 21.95	10 / 29.41	
15 sessions	28	15 / 36.59	13 / 38.24	
5 seasons	3	2 / 4.88	1 / 2.94	
Chemotherapy	52/69.33	30 / 73.17	22 / 64.71	0.43
Taxol + cyclophosphamide	11/15.07	7 / 17.07	4 / 12.50	
Antracycline and cyclophosphamide + Taxol	32/43.84	18 / 43.90	14 / 43.75	
Taxol + Carboplatin	8/10.96	5 / 12.21	3 / 9.38	
FEC	1/1.37	0 / 0	1 / 3.12	
Other treatment received	27 / 36.00	17 / 41.46	10 / 29.41	0.28
Trastuzumab	10/13.33	4 / 9.76	6 / 17.65	
Trastuzumab+pertuzumab	8/10.67	8 /19.51	0 / 0	
Cyclin Inhibitors	3 / 4.00	1 / 2.44	2 / 5.88	
Combabilities				0.46
0	40 / 53.33	21 / 51.22	19 / 55.88	
1	18/24.00	9 / 21.95	9 / 26.47	
2	11/14.67	6 / 14.63	5 / 14.71	
3	3/ 4.00	3 / 7.32	0 / 0	
>3	3 / 4.00	2 / 4.88	1 / 2.94	

Supplementary Table 3: Baseline characteristics of participants in terms of fitness capacity, body composition, functionality, physical activity, fatigue, and quality of life (n=74).

	Total	Intervention group	Control group	P value
	Mean (SD)	(n=40)	(n=34)	
		Mean (SD)	Mean (SD)	
Fitness Capacity	25.46 (5.29)	25.66 (5.86)	25.19 (4.58)	0.71
Body Composition				
Weight	64.86 (14.62)	64.21 (11.77)	65.63 (17.55)	0.67
Fat Mass (%)	33.21 (8.28)	33.64 (7.35)	32.71 (9.35)	0.62
Fat Mass (kg)	22.61 (9.49)	22.31 (8.72)	22.94 (10.43)	0.78
Lean Mass (%)	63.49 (7.15)	63.47 (6.97)	63.51 (7.46)	0.61
Lean Mass (kg)	40.45 (6.36)	40.10 (4.20)	40.85 (8.25)	0.98
Body Water (%)	44.43 (9.83)	43.83 (9.37)	45.09 (10.44)	0.59
Visceral Fat Score	7 (03)	7 (3)	7 (3)	0.98
Functional Variables				
Sit & Stand (nº)	22 (7)	23 (7)	21 (8)	0.35
Time in 1 Km (min)	7.62 (2.75)	7.41 (2.20)	7.86 (3.31)	0.49
Six MWT (m)	584.68 (161.42)	614.51 (81.25)	549.75 (217.68)	0.081
Patients Reported Outcomes				
Total METS (min/wk)	1034.72 (1251.43)	1182.99 (1289.46)	855.93 (1198.39)	0.26
METS High intensity (min/wk)	209.60 (538.50)	222.43 (632.89)	194.12 (407.22)	0.82
METS moderate intensity (min/wk)	255.60 (455.81)	327.07 (537.27)	169.41 (319.36)	0.14
METS light intensity (min/wk)	654.72 (756.27)	742 (726)	548.87 (788.84)	0.27
Leve lof Fatigue	33.56 (8.21)	30.82 (8.24)	36.85 (6.95)	0.001
Quality of Life	93.19 (14.50)	93.80 (14.31)	92.44 (14.94)	0.69

Table 1: Differences between type of intervention in cardiorespiratory fitness, body composition, functional variables, and patient-reported outcomes (n=74).

	In person exercise intervention	Online exercise intervention	Mean Difference	p
	Mean (SD)	Mean (SD)		
VO2Max	32.84 (4.81)	30.67 (3.50)	2.16	0.35
Body composition				
Weight (kg)	64.11(11.55)	62.64 (12.35)	1.47	0.71
Fat mass (%)	31.30 (6.40)	30.23 (8.65)	1.02	0.67
Fat mass (kg)	20.65 (7.60)	19.81 (9.26)	0.85	0.76
Lean mass (%)	66.11 (6.41)	65.97 (2.80)	0.13	<0.001
Lean mass (kg)	41.76 (0.85)	40.36 (1.14)	1.39	0.33
Body water (%)	49.95 (4.59)	50.11 (5.91)	-0.16	0.92
Visceral Fat Score	6 (2)	6 (3)	-0.19	0.212
Functional variables				
Sit & Stand (nº)	27 (6)	27 (5)	-0.39	0.83
Time in 1 Km (min)	6.72 (1.85)	6.58 1.97)	0.14	0.82
Six MWT (m)	680.4 (60.38)	670 (94.54)	10.4	0.68
Patient-reported outcomes				
TOTAL METS (min/wk)	1983.48 (1541.56)	1480.18 (1445.88)	503.3	0.32
METS High intensity (min/wk)	796.8 (834.90)	702.86 (875.33)	93.94	0.74
METS moderate intensity (min/wk)	435.6 (712.31)	237.86 (306.95)	197.74	0.33
METS light intensity (min/wk)	896.28 (737.70)	618.75 (692.11)	277.53	0.26
Level of fatigue	34.40 (7.12)	37.71 (2.95)	-3.31	0.11
Quality of life	95.56 (10.29)	96.57 (10.50)	-1.01	0.77

Abbreviations: Kg = kilograms; MET= metabolic equivalent of task; m = meters; min/wk = minutes per week; MWT = minutes walking test; Nº = number; SD= standard deviation.

4.4. Cardiorespiratory fitness and physical function

CRF improved significantly by 22.4% in the intervention group, while in the control group CRF was reduced by 4.96%. Differences between group showed an effect size (cohens'd) of 1.16 and p<0.001. Significant better results in functional capacity were observed in group comparisons, in both the sit-to-stand test (p=0.002) and in the 6-minute walk test (p=0.001). In pre-post analysis, significant improvements were found in the intervention group, for sit-to stand test (p=0.0005) and for 6 minutes walking test (p=0,016). No significant differences were observed pre-post analysis in these variables in the control group (p>0.05 in both). In relation to the level of physical activity, total METs improved by almost 50% after the intervention in the intervention group (p=0.004), while METs remained unchanged in the control group (p=0.431). When comparing METs at high intensity, the intervention group nearly quadrupled their values from baseline to final ratios (p=0.0002). Significant differences between the groups were observed in all cases (p=0.032) (Table 2).

Table 2: Comparisons between intervention and control groups in cardiorespiratory fitness, body composition, functional variables, and patient-reported outcomes (n=74).

VARIABLE	Intervention Group	Control	Mean Difference	CI 95%	p
	Mean (SD)	Group			
		Mean (SD)			
VO2max	31.41 (7.94)	23.94 (3.50)	7.196	4.50 – 9.60	< 0.001
Body composition					
Weight (kg)	62.22(15.19)	61.56 (25.87)	2.23	-3.85 – 8.30	0.467
Fat mass (%)	30.20 (8.53)	31.58 (13.56)	-1.81	-3.32	0.033
Fat mass (kg)	19.94 (8.66)	22.71 (12.53)	-4.67	-7.98	0.022
Lean mass (%)	66.09 (7.87	60.57 (7.26)	5.24	3.74 – 6.74	<0.001
Lean mass (kg)	40.42 (7.77)	36.55 (13.93)	4.67	0.68 – 8.66	0.022
Body water (%)	48.72 (9.22)	42.08 (16.12)	7.12	1.42 – 12.81	0.015
Visceral Fat Score	6 (3)	7 (4)	-0.59	-0.35 – 0.21	0.212
Functional variables					
Sit & Stand (nº)	26 (7)	20 (8)	5.26	2.01 – 5.26	0.002
Time in 1 Km (min)	6.50 (2.10)	7.29 (4.36)	-0.452	-072 – 1.63	0.45
Six MWT (m)	659.76 (127.58)	512.08 (229.16)	89.58	36.78 – 142.37	0.001
Patient-reported outcomes					
TOTAL METS (min/wk)	1783.13 (1505.91)	836.27 (1534.11)	946.85	212.08 - 1681.64	0.012
METS High intensity (min/wk)	783.13 (1505.91)	306.21 (716.84)	419.65	37.93 - 801.36	0.032
METS moderate intensity (min/wk)	373.17 (599.89)	173.79 (389.29)	199.38	-506.96	0.12
METS light intensity (min/wk)	808.50 (745.87)	414.21 (695.26)	394.29	43.05 - 745.54	0.03
Level of fatigue	35.41 (6.28)	38.62 (4.39)	-3.2	-5.1	0.014
Quality of life	96.31(10.25)	94.32 (10.68)	1.99	-9.66	0.413

*Results adjusted by baseline assessment. Abbreviations: CI= confidence interval; Kg = kilograms; % = percentage; MET= metabolic equivalent of task; m = meters; min/wk = minutes per week; MWT = minutes walking test; Nº = number; SD= standard deviation.

4.5. Fatigue and quality of life

In addition, fatigue improved significant at the end of the exercise program in the intervention group, (p=0.006) although in control group remains in similar levels (p=0.19), showed significant lower levels of fatigue in the intervention group compared with the control group (p=0.014). General quality of life perception did not show significant improvements in any of the groups (p=0.19 for intervention and p=0.94 for control). Quality of life did not show significant differences in between groups comparisons (p=0.413). Significant improvements in pre-post comparisons in the intervention group were found in physical well-being subscale (p=0.014), in social well-being subscale (p=0.001) and in emotional well-being subscale (p=0.032). However, not significant differences were observed in functional well-being subscale (p=0.062). Related to the control group, no significant differences were achieved in any of the quality-of-life subscales (Table 2).

In other exploratory analysis, possible correlations between time from diagnosis and physical activity levels were evaluated results were not significant. All the results with significance, differences between means are presented in "(Supplementary Table 3)".

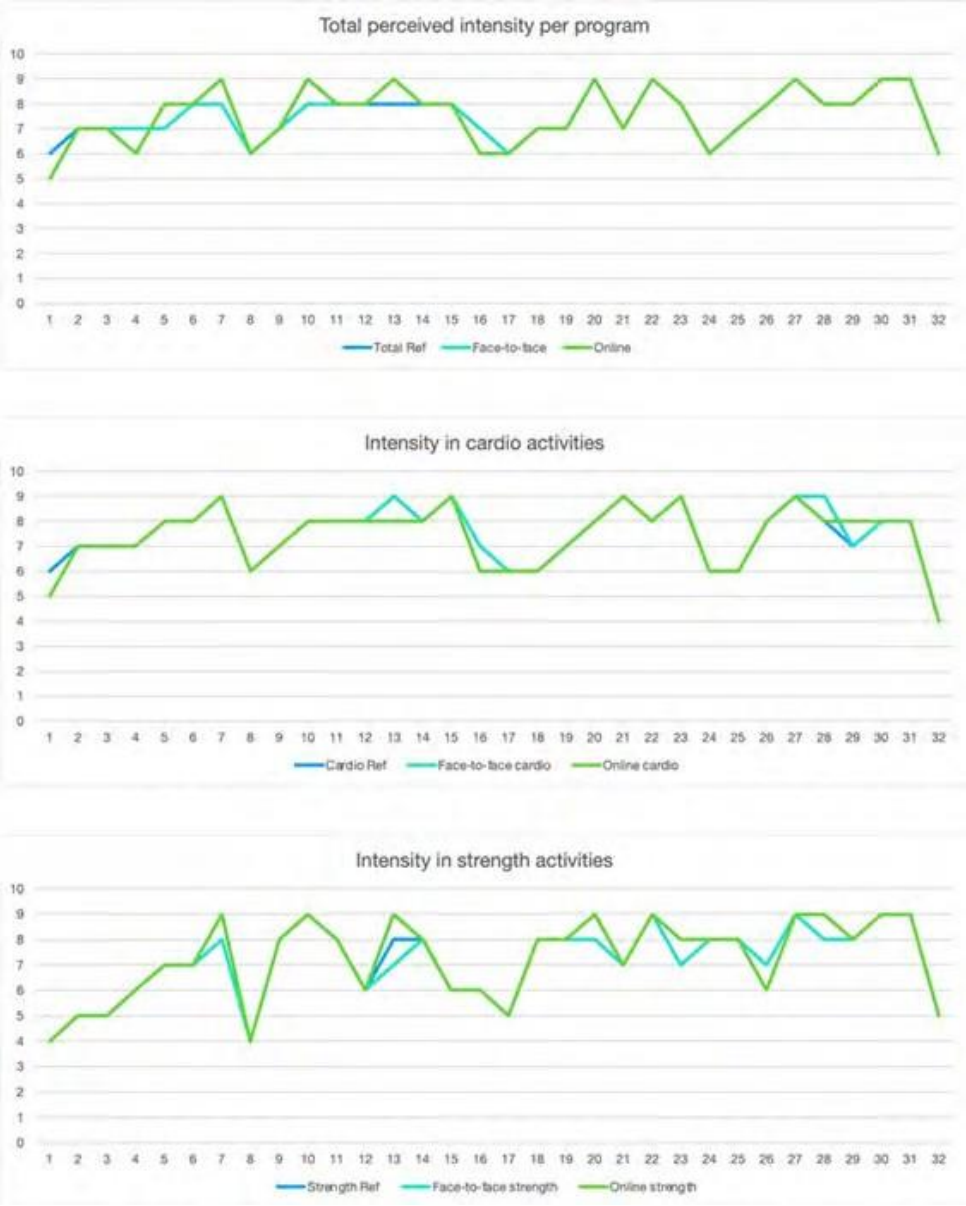
4.6. Body composition

Body composition was significantly improved in the intervention

group, with an improvement of 5.24% in lean mass and -4.67 kg of body fat mass. Intervention group achieve significant higher percentage of lean mass ($p<0.001$) and significantly lower percentage of fat mass ($p=0.033$) (Table 2).

4.7. Secondary analysis between interventions

No differences in attendance between interventions were observed ($p=0.997$). In addition, no significant differences between interventions were observed in physical neither emotional variable (Table 1). Furthermore, the perception of total BORG intensity was similar in both groups, with a correlation level of 0.94 for the perceived intensity of the whole session, 0.96 for cardio activities and 0.95 for strength activities. No significant differences were found between the pre-planned Borg intensity in either part of the class (cardio or strength) (Supplementary Figure 1).



Supplementary Figure 1: Comparative intensity differences among interventions

Supplementary Table 4: Attendance variables. Differences between online and onsite groups (n=74).

	Total	Face to face sessions attendance	Online sessions attendance	p
	N / %			
Attendance (n/% attendance)	40 / 85.13	14/ 89.51	25/ 89.50	0.998
Online intervention (n/%)	14 / 35.90	23.35	84.02	
In person intervention (n/%)	25 / 64.10	76.64	15.98	

5. Discussion

The intervention group exhibited significantly improved levels of CRF, body composition, functional levels, fatigue, and physical activity levels to the control group. These results confirm the effectiveness of this multimodal 16-week training program in reducing significant side effects associated with cancer post-treatment comorbidities.

The main outcome of our study revealed a noteworthy enhancement in CRF following our multimodal exercise program, showing a significant increase of 5.95ml/kg*min (23%) from the baseline measurement. This improvement surpasses the findings of the systematic review and meta-analyses, conducted by Scott et al. 7, comprising of 48 studies investigating exercise and VO2peak in cancer patients. In this study, improvements in CRF of 2.80 ml/kg/min were reported among cancer patients undergoing different interventions. The extent of improvement observed in our study surpasses that reported in previous research, likely attributable to our higher intensity exercise program and the high adherence exhibited by participants. The increase of 5.95 ml/kg*min in CRF observed in our study holds significance, as each 3.39 mL/kg/min increment has been linked to a 13% reduction in all-cause mortality [21]. Remarkably, this substantial enhancement in CRF was achieved irrespective of cancer treatment modality, cancer type, comorbidities, and BMI. In contrast, patients in the control group experienced a decline in their CRF by approximately of 6.7%, with an average of 23,94 ml/kg*min, falling below the thresholds established by ACSM and associated with poorer survival [6]. In relation with the body composition, our study revealed significant reductions in fat mass and noteworthy improvements in lean mass within the groups following the 16-weeks of exercise intervention. Interestingly, the intervention group exhibited a substantial 10% reduction in fat mass. This decrease in fat mass has been related with improvements in metabolic syndrome biomarkers such as leptin, IGF-1 and adiponectin levels [22]. Lean mass was preserved in patients within the intervention group, whereas those in the control group exhibited a 10.5% reduction. This decline is associated with diminished functional and fitness capacity, consistent with findings from our prior research [23].

Participants within the intervention group demonstrated significantly higher levels of overall intensity activity. These higher activity levels are linked to a reduced risk of cardiotoxicity and better physiological adaptations [24,25]. There were no differences in outcomes between the interventions, showing that a combined intervention can be effective in working with patients who are homebound or live far from a sports center. Even when treating international patients. Among all enrolled patients, 36% favored the online intervention, leading to a decrease in program drop-outs. Furthermore, nearly 16% of in-person classes were replaced by online classes, enhancing program adherence and effectiveness. These outcomes align with previous studies employing remote interventions, indicating improvements in CRF, functionality, and a reduction in associated side-effects [26–28]. The novelty of our intervention lies in the potential combination of face-to-face and online programs, resulting in comparable outcomes in both modalities. The study had limitations, including a higher drop-out rate in the control group and the use of the BORG scale instead of direct instruments to monitor intensity, primarily due to limited funding.

6. Conclusion

This RTC has demonstrated that a multimodal exercise program significantly improves CRF, body composition, and physical function in breast cancer patients. Participants saw a 22.4% increase in CRF and notable improvements in body composition, with a 10% reduction in fat mass and a 5.24% increase in lean mass. Functional capacity also improved significantly. Notably, the study found comparable outcomes between in-person and online exercise modalities, suggesting the potential of remote interventions. Despite some limitations, including a higher dropout rate in the control group, the findings advocate for integrating structured exercise programs into the treatment plan for breast cancer patients, with potential long-term benefits for survival and quality of life. Future research should explore the sustainability of these benefits and extend the investigation to a wider range of cancer patients.

7. Competing Interests

The authors declare that they have no competing interests.

8. Practical Implications

•This study shows that a multimodal exercise program (face-to-face and online) is feasibility to increase CRF in women diagnosed with breast cancer (stages IA to IIIB).

• High adherence levels (over 80%) were observed in both exercise programs, which explains the high the extent of improvement in the participants.

•Two of the most relevant findings are that the decrease in fat mass has been associated with improvements in biomarkers of metabolic syndrome and a lower risk of cancer recurrence, and on the other hand that the increase in CRF has been associated with a lower risk

of cardiovascular disease in the long term.

•Thanks to the novelty of this intervention, a combination of face-to-face and online exercise programs makes physical exercise more accessible to these patients.

9. Author's Contribution

SC participated in the design of the study, contributed to data collection and data reduction/analysis; MC participated in the design of the study and contributed to data collection and data reduction; HP contributed to data analysis and interpretation of results. All authors contributed to the manuscript writing. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

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