The Importance of Physical Exercise in Cardiovascular Fitness in Breast Cancer Survivors. A Cross-sectional Study: Women in Motion 2.0.”

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Abstract

Purpose

To compare the cardiovascular fitness of breast cancer (BC) survivors with an active lifestyle to those with a sedentary lifestyle.

Methods

A cross-sectional study was conducted. Participants were classified into four different groups: sedentary with BC (Sed-BCW), active with BC (Act-BCW), sedentary without BC (Sed-HW) and active without BC (Act-HW). VO_2max was estimated by the 6-minute walking test (6MWT); speed was measured by the 35-meter test; isometric strength was measured by dynamometry tests; lower body maximum strength was measured by the squat test; explosive strength was measured by the Sargent Jump Test; balance was measured by the 30-second balance test; and body composition was measured by bioimpedance.

ANOVA was used to analyze group differences and post hoc comparisons were developed with the Bonferroni test.

Results

A total of 92 women were recruited. Significant differences were found in VO_2max between the Act-BCW and Sed-BCW groups (MeanDif=5.86, $p<0.001$). No differences in VO2max were observed between the active groups (MeanDif= 0.42, p= 0.753).

Related body composition and fat mass levels were significantly lower in the Act-BCW group than in the sedentary groups (Sed-BCW MeanDif= -6.78; p= 0.012 and Sed-HW MeanDif= -12.07; $p<0.001$)

Conclusions

Women who are Act-BCW can achieve similar values in physical condition as women who are Act-HW and have better values than women in who are sedentary. Moreover, physical exercise might be a stronger determinant of body composition than a previous history of BC.

1. Introduction

Breast cancer (BC) is the most common tumor in women worldwide. In 2020, 34,088 new cases were estimated in Spain, assuming a 3.81% percent increase from 2018. Approximately 130,000 women have been living with a breast tumor diagnosis in the last five years [1]. Despite this, BC treatments lead to long-term side effects such as physical impairments (i.e., cardiorespiratory fitness reduction) [2] and changes in body composition (i.e., fat gain) [3]. These effects may negatively impact quality of life and survival rates of these women [4, 5]

In this sense, obesity has been described as a promoter of different cancer biomarkers, especially those related to general inflammation, such as IGF-1 [6, 7], C-reactive protein [8, 9], some interleukins, estradiol, and TNF-α [10–12], and can impair immune function, altering leucocyte counts, and cell-mediated immune responses [13, 14].

For this reason, obesity is becoming an important topic of interest due to the possible relationship with cancer prognosis by the role of inflammatory cells in tumor proliferation, survival, and migration [15, 16]. This highlights the relevance of obesity and weight control in breast cancer patients [17]. Severe obesity is associated with a

significant increase in relapses and deaths in patients with operable breast cancer receiving adjuvant chemotherapy [18].

In the last ten years, there has been a strong interest in the role of exercise for breast cancer patients as an effective tool to prevent different side effects resulting from cancer treatments [19], in particular, reducing obesity, [20] fatigue and depression levels and increasing cardiovascular fitness (VO_{2max}), functional capacity, and strength [21]. These benefits have been observed in patients during any stage of the illness, including in survivors [22], and are related to the improvement of the quality of life of BC patients [23].

In addition, multiple studies have observed that physical exercise helps to rebalance the alterations in body composition resulting from cancer treatments, reducing fat mass levels, and increasing lean mass. These factors prevent different metabolic diseases and reduce relapse risk, which are associated with obesity. [24] [20]

It is important to note that VO_{2max} has been described as an independent parameter of better survival in BC [25] patients as well as in healthy women [26, 27]. However, several treatments used for BC patients in reducing VO_{2max} not only worsen fatigue perception and functional capacity but also negatively impact patients' QoL and mortality [28, 29].

Despite the relevance of VO_{2max} in cancer survivors, little is known about the extent to which physically active BC survivors are able to recover and achieve similar VO_{2max} values compared to their healthy counterparts and whether the impact of sedentary behavior on women's VO_{2max} and health is similar in cancer patients and healthy women.

With this in mind, we developed a cross-sectional study to compare the VO_{2max} of BC patients to the VO_{2max} of controls with active and sedentary behaviors.

2. Methods

Study Hypothesis

BC patients can achieve the same level of VO_{2max} as paired healthy women performing the same level of exercise.

Study design

A cross-sectional study was designed to include active and sedentary adult women with and without a diagnosis of BC. The study was approved by the ethics committee at the Carlos III Health Institute. The study was conducted following the principles of the Declaration of Helsinki. Participants received all necessary information, and they signed written informed consent forms to participate.

In total, 92 women were recruited on an ongoing basis from April to June 2018 at a sport center in Madrid, Spain (Tigers Running Club). The patients were divided into four groups meeting the following inclusion criteria:

Two groups of active women were defined as those who performed more than 150 minutes of exercise per week, with a minimum of 60 minutes of resistance exercise and 90 minutes of cardiovascular exercise [30]:

- Group 1: active healthy women.
- Group 2: active women with a diagnosis of BC in the last five years.

Two groups of sedentary women were defined as those who performed less than 90 min/week of physical exercise:

- Group 3: sedentary healthy women.
- Group 4: sedentary women with BC in the last five years.

The exclusion criteria included women with bone metastatic disease, as well as any musculoskeletal, cardiovascular, or neurological disorder that could constitute a contraindication to exercise. Eligible women were scheduled for their testing appointment.

The participants underwent initial testing in the following order: body composition, the 6MWT, 35-meter test, dynamometry tests, balance test, Sargent jump test, and squat test. The women completed the following questionnaires: the quality of life, depression, fatigue, memory, and oncology physical exercise questionnaires. All tests were performed in a single session.

Objectives

- Primary objective

To compare the VO_{2max} of BC patients with an active lifestyle to those with a sedentary lifestyle.

VO_{2max} was estimated using the 6MWT, collecting the final distance. VO_{2max} was estimated using the following formula [31]:

22.506-0.271*weight+0.051*distance(6MWT)-0.065*years.

- Secondary objectives

To compare the fitness conditions and body compositions of BC patients with an active lifestyle to those with a sedentary lifestyle.

To assess the participants' fitness conditions, the following tests were developed: a 35-meter test (speed); dynamometry tests (isometric strength); a 60" squat test (lower body maximum strength); a Sargent jump test (explosive strength); and a 30 second balance test (balance).

Body composition was measured by bioimpedance (Tanita BC-601) at the beginning of the assessment to determine weight, fat mass, lean mass, water percentage, bone mass, and visceral fat. All women had to follow the same dietary recommendations before the test.

Statistical Analyses

- Sample size

The sample size of 23 participants per group was estimated with a statistical power of 80% to detect a minimum difference in VO_{2max} of 3.9 ml/kg/min (1.67-5.1 ml/kg/min) between groups, assuming a total sample of 92 women [32].

- Statistical Analyses

Descriptive analyses using the mean and standard deviation for continuous variables and percentages for categorical variables were used.

Analyses of variance (ANOVA) were used with continuous variables to compare the groups. Post hoc comparisons were calculated using the Bonferroni test. Comparisons between categorical variables were performed using the chi-square test.

All statistical analyses were performed using SPSS version 21 software (SPSS Inc., Chicago, IL). Confidence intervals were set at 95%, and the significance value was set at $p<0.05$.

3. Results

Of the 106 participants who were contacted at the beginning of the study, fourteen refused to participate after initial acceptance. (Figure 1)

Patient Characteristics

Baseline Demographic and Medical profile of Cancer Patients Participating in the study are shown in Table 1.

Table 1
Baseline demographic and medical profile of each group of participants.

	Act- BCW n (%)	Sed- BCW n (%)	Act- HW n (%)	Sed- HW n (%)
Employment Situation				
Worker	19 (82.6)	12 (63.16)	18(90)	21(95.5)
Retired	1 (4.4)	4(21.05)	1(5)	0 (0)
Housewife	0 (0)	0 (0)	0 (0)	1 (4.6)
Student	1(4.3%)	0 (0)	0 (0)	0 (0)
Unemployed	1 (4.4)	3 (15.8)	1 (5)	0 (0)
Treatment received				
Chemotherapy:	19 (90.5)	16 (88.9)		
-Anthracycline scheme	10 (43.48)	11 (47.82)		
-Non anthracycline scheme	13 (56.52)	12 (52.18)		
Radiotherapy	17 (77.3)	16 (84.2)		
Endocrine therapy	19 (86.4)	18 (94.7)		
Targeted therapies (Herceptin):	10 (45.5)	10 (52.6)		
-Herceptin at the measuremnt´s time	3 (13.04)	1 (4.35)		
Lymphedema	10 (50)	6 (33.4)		
Comorbidities				
No comorbidities	14 (66.7)	7 (43.8)	17 (89.5)	7 (35)
1-3 comorbidities	7 (33.3)	9 (56.2)	2 (10.5)	12 (60)
> 3 comorbidities	-	-	-	1 (5)

Patient age was the first considered variable. All women were paired with a ratio of ± three years of age. There were no differences in age between the BC patient (49.48 vs. 50.57: p=0.687) or healthy women groups (52.26 vs. 47.43 years, p=0.076).

In terms of employment, more than 60% of the patients were working at the time. Almost 70% of the BC patients were receiving endocrine therapy at the time of the analysis.

The participants reported different comorbidities: osteoporosis, cholesterol problems, high sugar levels, high fat levels, high blood pressure, cardiac problems, and thyroid problems. Interestingly, significant differences were found between the breast cancer groups (p=0.017).

Finally, no relationship was found among the treatment types (chemotherapy, radiotherapy, endocrine therapy, and targeted therapies) or in the number of comorbidities in women with BC.

Table 2 presents fitness profile, body composition and physical activity levels of each of group of women.

Table 2
Health-related fitness and quality of life of each group of participants

OUTCOMES	Act-BCW (n=23) M ±SD	Sed-BCW (n=23) M±SD	Act-HW (n=23) M±SD	Sed-HW (n=23) M±SD
Age (years)	49.48± 8.73	50.57 ± 10.06	47.43 ± 8.31	52.26 ± 9.27
Height (cm)	163.04 ±4.74	162.78 ± 5.08	163.65 ±6.27	162.30 ± 4.47
Physical status				
VO2max (ml/kg/min)	38.35±3.11	34.11±4.40	37.68±3.01	32.187+5.31
6MWT (m)	766.74± 51.69	695.21± 47.47	769.78± 67.94	690.17 ± 63.63
35 meters (sec)	7.2 ± 0.89	8.9±2.41	6.9 ±0.91	9.6± 4.6
Strength Index	2.40±0.46	1.76± 0.42	2.50±0.42	2.02±0.42
Squat test (reps)	46.09±7.39	40.61±6.88	48.96±7.14	41.17±5.85
Sargent jump (cm)	18.19±4.45	14.85±6.04	18.53±6.29	14.65±3.81
Balance test (OE- RL) (sec)	29.87±0.46	26.94±7.43	28.65±4.49	25.49±9.27
Balance test (OE-LL) (sec)	29.52±2.29	25.42±9.02	29.61±1.88	26.07±9.02
Balance Test (CE-RL) (sec)	13.66±10.78	9.53±10.14	10.87±9.71	7.53±6.10
Balance Test (CE-LL) (sec)	13.23± 10.92	8.02±8.27	12.17±9.39	10.06±10.17
Body Composition				
Total weight (kg)	60.05± 7.20	67.94 ± 12.22	62.70 ±8.63	71.38 ± 13.29
BMI (kg/m²)	22.65 ±2.99	25.65 ± 4.76	23.57 ± 2.71	27.74 ± 4.72
Fat mass (%)	28.51± 6.45	35.30 ± 6.9	40.09 ± 12.57	40.58 ± 8.49
Lean mass (%)	67.75± 6.03	62.55 ±5.92	67.02 ± 5.17	59.16 ± 7.15
Water (%)	52.13± 4.53	47.48 ±4.73	51.48 ± 3.98	46.22 ± 4.02
Bone weight (kg)	2.05 ± 0.13	2.06 ± 0.22	2.13 ± 0.34	2.10 ± 0.29
Visceral fat	5.00 ±2.09	7.26 ± 3.06	5.22 ± 1.95	7.83± 2.40
Physical Activity Level				
IPAQ (mets)	2465.84±1922.65	1064.84±1144.55	1626.23±1552.80	879.96±1067.08

Cardiovascular fitness

In terms of the cardiovascular fitness of active women, VO_{2max} levels were significantly better in comparison with the sedentary groups ($p<0.001$). No significant differences were found between the Act-HW and Act-BCW groups ($p=0.75$). No differences were found between the sedentary groups ($p=0.214$). However, there were significant

differences in VO_{2max} between the Act-BCW and Sed-BCW groups (p=0.000). These results are presented in Tables 3 and 4 and in the box plot graphic in Figure 2. Women in the Sed-BCW group did not show significant differences compared with their healthy counterparts (p=0.21).

Table 3
Mean difference, 95% Confidence Interval (CI) and p value of health-related fitness and quality of life between Act-BCW and the other groups.

	Act-BCW vs Sed-BCW			Act-BCW vs Act-HW			Act-BCW vs Sed-HW		
	Mean Dif	95% CI	p-value	Mean Dif	95% CI	p-value	Mean Dif	95% CI	p-value
Physical status									
$V0_2$ (ml/kg/min)	5.86	3.16 to 8.55	<0.001	0.42	-2.26 to 3.12	0.75	7.55	4.86 to 10.24	<0.001
6MWT (meters)	71.52	37.36 to 105.68	<0.001	-3.04	-37.20 to 31.11	0.86	76.57	42.41 to 110.72	<0.001
35m (seconds)	-1.87	-3.44 to -0.30	0.020	0.17	-1.40 to 1.74	0.83	-2.39	-3.96 to -0.82	0.003
Jump (cm)	5.48	1.47 to 9.49	0.008	-2.87	-6.88 to 1.14	0.16	4.91	0.90 to 8.92	0.017
Strength Index	0.63	0.31 to 0.95	<0.001	-0.09	-0.40 to 0.21	0.53	0.376	0.07 to 0.68	0.015
Body Composition									
BMI	-3.00	-5.29 to -0.71	0.11	-0.91	-3.21 to -1.38	0.43	-5.09	-7.38 to -2.79	<0.001
Fat Mass (%)	-6.78	-12.52 to -1.54	0.012	-11.57	-16.80 to -6.33	<0.001	-12.07	-17.31 to -6.83	<0.001
Lean Mass (%)	5.20	1.62 to 8.78	0.05	0.72	-2.86 to 4.3	0.70	8.59	3.72 to 13.45	<0.001
Water (%)	4.65	2.11 to 7.19	<0.001	0.65	-1.89 to 3.19	0.61	5.91	3.37 to 8.45	<0.001
Bone Mass (%)	-0.17	-1.70 to 0.14	0.82	-0.87	-0.24 to 0.65	0.26	-0.61	-0.21 to 0.91	0.43
Visceral fat	-2.26	-3.68 to -0.84	0.002	-0.22	-1.64 to -1.20	0.76	-2.83	-4.24 to -1.41	<0.001
Physical Activity Level									
IPAQ (mets)	1400.10	543.90 to 2258.09	0.002	839.60	-17.49 to 1696.70	0.055	1585.87	728.77 to 2442.97	0.055

Table 4
Mean difference, 95% Confidence Interval (CI)and p value of health-related fitness and quality of life between Sed-BCW and other groups.

	Sed-BCW vs Act-HW			Sed-BCW vs Sed-HW			Act-HW vs Sed-HW		
	Mean Dif	95% CI	p-value	Mean Dif	95% CI	p-value	Mean Dif	95% CI	p-value
Physical status									
V02 (ml/kg/min)	-5.42	-8.12 to -2.73	<0.001	1.70	-0.99 to 4.40	0.21	7.12	4.43 to 9.82	<0.001
6MWT (meters)	-74.57	-108.72 to -40.41	<0.001	5.04	-29.11 to 39.20	0.77	-79.61	45.45 to 113.77	<0.001
35m (seconds)	2.04	0.47 to 3.61	0.011	-0.052	-2.09 to 1.05	0.51	-2.57	-4.14 to -0.99	0.002
Jump (cm)	-8.35	-12.36 to -4.34	<0.001	-0.57	-4.57 to 3.44	0.78	7.78	3.77 to 11.79	<0.001
Strength Index	-0.73	-1.04 to -0.41	<0.001	-0.25	-0.56 to 0.06	0.11	047	0.18 to 0.77	0.002
Body Composition									
BMI	2.09	-0.21 to 4.38	0.74	-2.09	-4.38 to 0.21	0.07	-4.17	-6.47 to -1.88	<0.001
Fat Mass (%)	-4.79	-10.03 to 0.44	0.012	-5.29	-10.52 to -0.05	0.07	-0.50	-5.74 to -4.73	0.85
Lean Mass (%)	-4.48	-8.06 to -0.90	0.015	3.39	-0.19 to 6.97	0.06	7.87	4.29 to 11.45	<0.001
Water (%)	-4.00	-6.54 to -1.46	0.002	1.26	-1.28 to 3.80	0.33	5.26	2.72 to 7.80	<0.001
Bone Mass (%)	-0.70	-0.22 to 0.83	0.37	-0.43	-0.20 to 0.109	0.57	0.026	-0.13 to 0.18	0.73
Visceral fat	2.04	0.62 to 3.46	0.005	-0.57	-1.98 to 0.85	0.43	-2.61	-4.03 to -1.19	0.43
Physical Activity Level									
IPAQ (mets)	1585.87	728.77 to 2442.97	<0.001	184.88	-672.22 to 1041.97	0.67	746.27	-110.82 to 1603.36	0.09

Body compositions, physical conditions, and physical activity levels

In terms of body composition, the Act-BCW group showed significantly better results in total weight, body mass index, lean mass, water percentage, and visceral mass compared to the sedentary groups. Moreover, the Act-BCW group had a significantly lower body fat percentage than the Act-HW group (p<0.001). No significant differences were found in the rest of the measured variables between the active groups (Table 3) or between the sedentary groups (Table 4).

Regarding physical conditions, the Act-BCW group showed significantly higher results than the sedentary groups in the 35-meter test, dynamometry tests (right hand, left hand, legs and back) squat test, and Sargent jump test. There were no differences between the Act-BCW and Act-HW groups.

4. Discussion

In this work, we found that women who are Act-BCW can achieve the same values in cardiovascular fitness, physical condition and body composition as active healthy women and significantly better values than sedentary women with BC.

Our results confirm that women who were Act-BCW presented an 11.8% higher $V0_{2max}$ than their counterparts who were Sed-BC, a significant difference that might impact not only BC patients´ health but also the survival of women with BC. In addition, the results of this investigation confirm the main hypothesis of the study, showing that women who are Act-BCW can achieve the same values in $V0_{2max}$, or even higher values, than women who are Act-HW.

Bearing in mind that cardiovascular capacity is an independent predictor of mortality in cancer [33] and is 25% lower than the $V0_{2max}$ (relative to age and sex) in healthy individuals, the results of our trial are an important scientific contribution that once again emphasizes the importance of physical exercise in improving cancer patient health during and after treatments, which can lead clinicians to consider approaching the treatment of cancer patients in an integral way.

Related to body composition, our results show that physical activity is an effective, supportive care method in BC patients to achieve fat mass and lean mass levels that are similar to healthy active women. In contrast, body composition values were not significantly worse in sedentary patients than in their healthy counterparts, suggesting that BC by itself does not imply a body composition imbalance. Therefore, physical exercise is a stronger determinant of a balance or imbalance in body composition than a previous history of BC.

This study aligns with previous evidence [34] showing that approximately 65% of all breast cancer survivors are overweight or have obesity; it is also known that a sedentary lifestyle and obesity are associated with poorer outcomes after a BC diagnosis and a significant increase in recurrence and elevated total mortality [35], possibly through their relationships with some biomarkers that are promoters of inflammation [36].

Findings from a recent report suggested that BC patients with obesity had a 35% higher risk of BC-related death [37] [18]. Additionally, BC treatment is related to an increase in body fat as well as a decrease in lean body mass and bone mineral density. These changes can put these women at increased risk for frailty fractures and osteoporosis, as well as further risk for comorbid chronic diseases and cancer recurrence [38].

Apart from maximum oxygen consumption and body composition, we observed that active women had a better functional capacity than sedentary women, again showing the importance of exercise to maintain body functionality and prevent the most common physical disabilities in these patients, such as arthralgia or muscle pain, which might promote medication withdrawal [39].

When analyzing patients' limitations in being more active, a lack of time was the main barrier to performing physical exercise, given the impression that they do not perceive exercise as a key factor in maintaining and recovering their health. Therefore, this could be an aspect to be considered in future studies. Developing strategies that include oncologists, nurses, other care providers and exercise-oncology specialists not only encourages

patients to practice exercise but also highlights the importance of patients having an active lifestyle because it has been demonstrated that BC survivors who maintain an active lifestyle can achieve the same values in physical condition as active healthy women.

STRENGTHS AND LIMITATIONS

The main strength of this study is its originality since no previous studies were found comparing the physical condition of these four groups of women. Moreover, using field tests added a pragmatic element to the study, making it a more real-life scenario than a research laboratory.

The main limitations include the small sample size, the cross-sectional nature of the study, and the lack of resources.

Despite the limitations of the study, we can conclude that performing at least 150 minutes/week of physical exercise is crucial for BC patients, given that there is an improvement in their physical capacity and $V0_{2max,}$ which is directly linked with better survival.

Moreover, exercise helps breast cancer patients recover a healthy body composition, increasing lean mass and decreasing body fat. This effect counteracts the negative impact of several treatments on women's weight a characteristic that is associated with a worse prognosis.

Declarations

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Availability of data and material: all the used data were accurate and come from the official source. Authors confirm the absence of data manipulation, the consistency and reliability of the research, and the originality of the manuscript.

Code availability: The authors confirm that the data supporting the findings of this study are available within the article and are also available from the corresponding author (S.C) upon reasonable request.

Authors' contributions: all the authors contributed equally, dividing the work into study design, data collection, structure, drafting and revision, bringing a well stablished structure, consistency, and quality to the manuscript.

Ethics approval: The study was approved by the ethics committee at the Carlos III Health Institute, Spain.

Consent to participate: Participants received all necessary information, and they signed written informed consent forms to participate.

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Figures

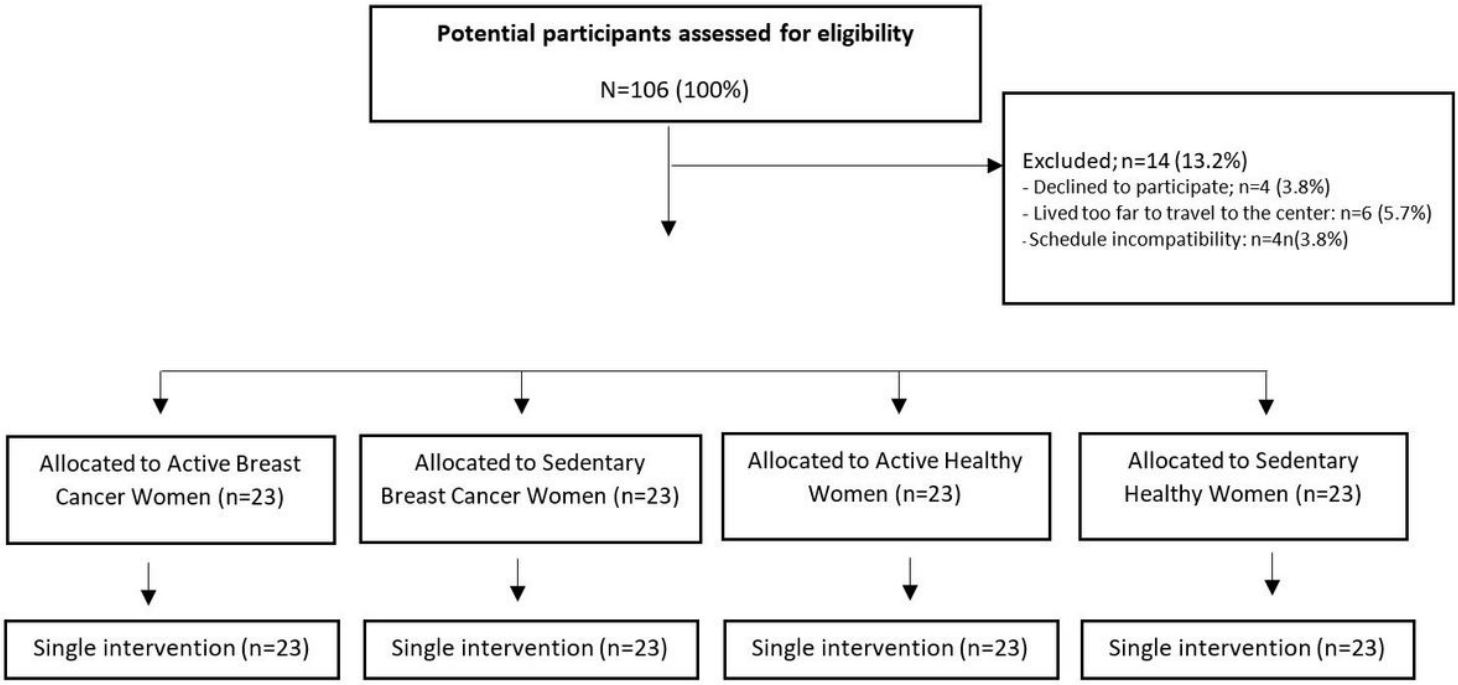

Figure 1

CONSORT diagram: flow of participants.

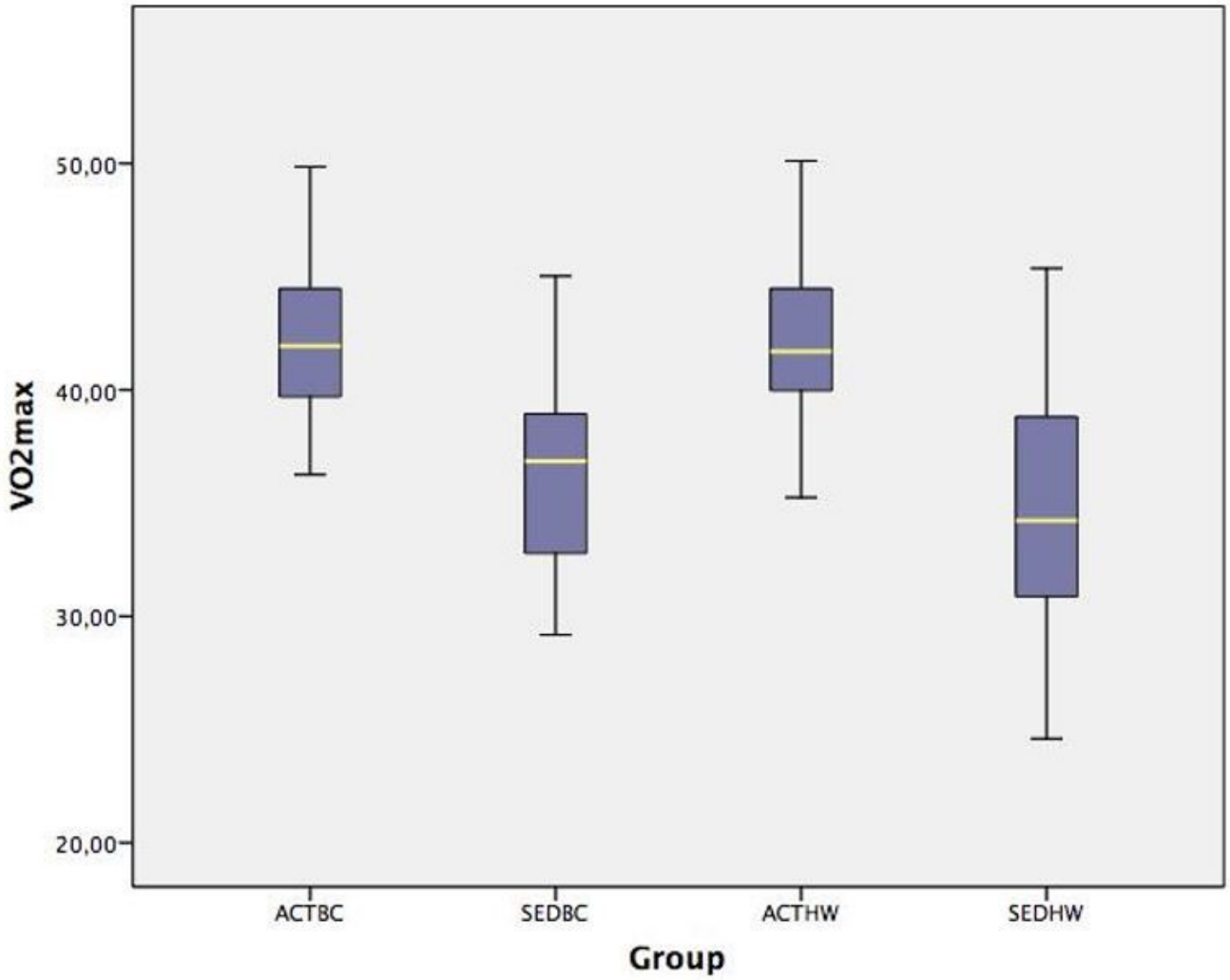

Figure 2

Box plot of VO_2 levels of the four different groups of participants

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