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Home-Based Physical Activity in Patients With Breast Cancer: During and/or After Chemotherapy? Impact on Cardiorespiratory Fitness. A 3-Arm Randomized Controlled Trial (APAC)

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Abstract

Objectives: Physical activity (PA) programs are recommended for breast cancer care. However, their modalities remain to be discussed. This study determined the best time to begin a personalized or adapted program based on cardiopulmonary exercise test function. This randomized controlled trial evaluated the effect of home-based adapted PA (APA) performed during or after treatment on cardiorespiratory fitness (CRF) at 12 months. **Method:** The primary endpoint was the peak oxygen consumption (VO_{2peak}) at 12 months (group A vs C and B vs C). Secondary endpoints included the 6-minute walking test, assessment of muscle strength, fatigue, quality of life, anxiety, and depression, and a questionnaire on PA levels. All tests were evaluated at baseline and at 6 and 12 months. A total of 94 patients with breast cancer were randomized to 3 different groups: group A, performing 6 months of APA during adjuvant care; group B, 6 months of APA after adjuvant care; and group C, 12 months of APA during and after specific care. The program combined 1 resistance session and 2 aerobic sessions per week. Analysis of variance was used for repeated measures, Student's *t*-test or the Mann–Whitney *U*-test for continuous variables, and χ^2 test for binary or categorical variables. **Results:** The study assessed 81 participants at 6 months and 73 at 12 months. The majority of patients completed more than 85% of the exercise sessions. The baseline for VO_{2peak} and secondary outcomes did not differ among the groups. VO_{2peak} increased during the exercise period and decreased during the chemotherapy period without APA, but at 12 months no significant difference was observed. The same variation was observed in the 6-minute walking test, with significance at 6 months between A+C versus B ($P = .04$), but no difference among the groups at 12 months. In the 3 groups, no decreases in other studied parameters were noted, except at 6 months in group B without APA. **Conclusion:** Home-based APA in breast cancer patients has a positive effect on CRF and physical functions, with no differences based on the timing of this program based on specific cancer treatment. **Trial Registration:** ClinicalTrials.gouv.fr (NCT01795612). *Registered 20 February 2013.*

Keywords

adapted physical activity, breast cancer, home training, peak oxygen consumption, chemotherapy

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Background

The health benefits of exercise, both during and following treatment in cancer patients, have been well-described in systematic reviews and meta-analyses.[1-5] Physical activity (PA) has gained attention as a promising method to reduce fatigue, depression, and anxiety, and to improve psychological and physiological functions based on health-related

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quality of life (QOL), muscle strength, and cardiorespiratory fitness (CRF).[6,7] Studies have observed significant improvements in cardiorespiratory fitness for breast cancer populations (during and after adjuvant therapy) participating in physical activity (PA) interventions within randomized controlled trials, showing an impact on well-being.[1,8,9] The best indicator of cardiorespiratory fitness is the maximal peak oxygen consumption (VO_{2peak}), which assesses global cardiovascular function, cardiopulmonary reserve, and the efficiency of oxygen transport. It is impaired in breast cancer patients and correlated with survival in both breast cancer patients and the general population.[10,11] This parameter is the gold standard for adapting PA and evaluating the impact of APA in patients deconditioned by pathology and its treatment.

During the treatment of cancer, physical activity programs must be adapted to each patient to produce better adherence. To devise a personalized program, physical activity was adapted based on the heart rate determined at the first ventilator threshold assessed in a cardiopulmonary exercise test.

However, the best period to begin a PA program remains unknown. APA performed during or after breast cancer treatment has shown benefits compared to controls,[12] and these benefits seem to differ as a function of when the program begins. Few randomized controlled studies have examined the best time to begin an APA program during or after breast cancer chemotherapy.[13]

Patient preference may be important for deciding when to begin an APA program, but may not be the only indicator. A total of 22 quantitative studies asked participants when they would prefer to start a PA program and 2 qualitative studies reported program start preferences. Of the 9 studies assessing this variable, 6 found that starting a program 3 to 6 months following treatment was the most common preference,[14-17] followed by immediately after treatment.[18,19] Because cancer treatment leads to rapid patient deconditioning, the impact of an APA program on fatigue and QOL is commonly explored at the beginning of chemotherapy and radiotherapy treatment.[20] However, the best time to begin APA remains unclear.

Existing randomized controlled trials for breast cancer patients on PA during and after treatment are home-based, telephone-supported, and supervised and unsupervised interventions.

Supervised described APA programs are difficult to realize in real life and are cost-limiting. Home-based PA interventions can avoid some barriers of PA, such as transportation and cost.[21] We prefer home-based programs based on previous experience (SAPA study),[22] but with regular coaching.

Few randomized controlled trials have explored the effects of home-based interventions on cardiorespiratory fitness in breast cancer,[23] and most studies have used 6-minute walking tests as evaluation tests. In our previous clinical trial, we showed that without an APA program, all women decreased their maximum oxygen uptake (VO_{2peak}) during adjuvant chemotherapy for breast cancer.[20,22] With APA training, they increased their VO_{2peak} at the end of 6 months, maintained at 12 months.

In this report, we evaluated the effects of 3 home-based programs combining aerobic and resistance exercises beginning during and/or after adjuvant or neoadjuvant chemotherapy. The primary objective was to assess impact on VO_{2peak}, and secondary objectives were to assess the impact on the 6-minute walking test, muscle strength, QOL, and fatigue 12 months after starting the protocol.

Methods

Setting and Participants

Women aged 18 to 75 years with early-stage breast cancer treated with chemotherapy (adjuvant or neoadjuvant) followed by radiotherapy were eligible for the study. All patients were surgically treated before entry into the protocol or during the protocol if neoadjuvant chemotherapy was administered.

All patients received the same chemotherapy with 6 courses administered every 21 days (3 FEC100, 3 docetaxel) and trastuzumab for 12 months if the breast tumor was HER2 positive. All patients had normal initial left ventricular ejection fraction confirmed after chemotherapy if they were treated with trastuzumab. Women on hormone therapy who completed other primary cancer treatments were considered post-treatment. Exclusion criteria included metastatic disease, symptomatic cardiac pulmonary disease, a left ventricular ejection fraction $<50\%$, family history of sudden death in a first-degree relative, and ongoing treatment with a beta-blocker. The trial was conducted at Limoges University Hospital (France) from March 2013 to May 2015. Medical oncologists enrolled the patients, explained the study, and obtained informed consent. The study was approved by the Ethics Committee of Limoges Hospital (no. 2012-A01401-42) (France) and registered in ClinicalTrials.gouv.fr (NCT01795612).

Study Design

The APAC trial was an open interventional single-center, prospective, 3-arm, phase III, randomized controlled trial. The trial compared 3 groups, as shown in the flow chart in Figure 1:

- Group A: 6-month home-based APA program during adjuvant or neoadjuvant therapy
- Group B: 6-month home-based APA program after adjuvant or neoadjuvant therapy

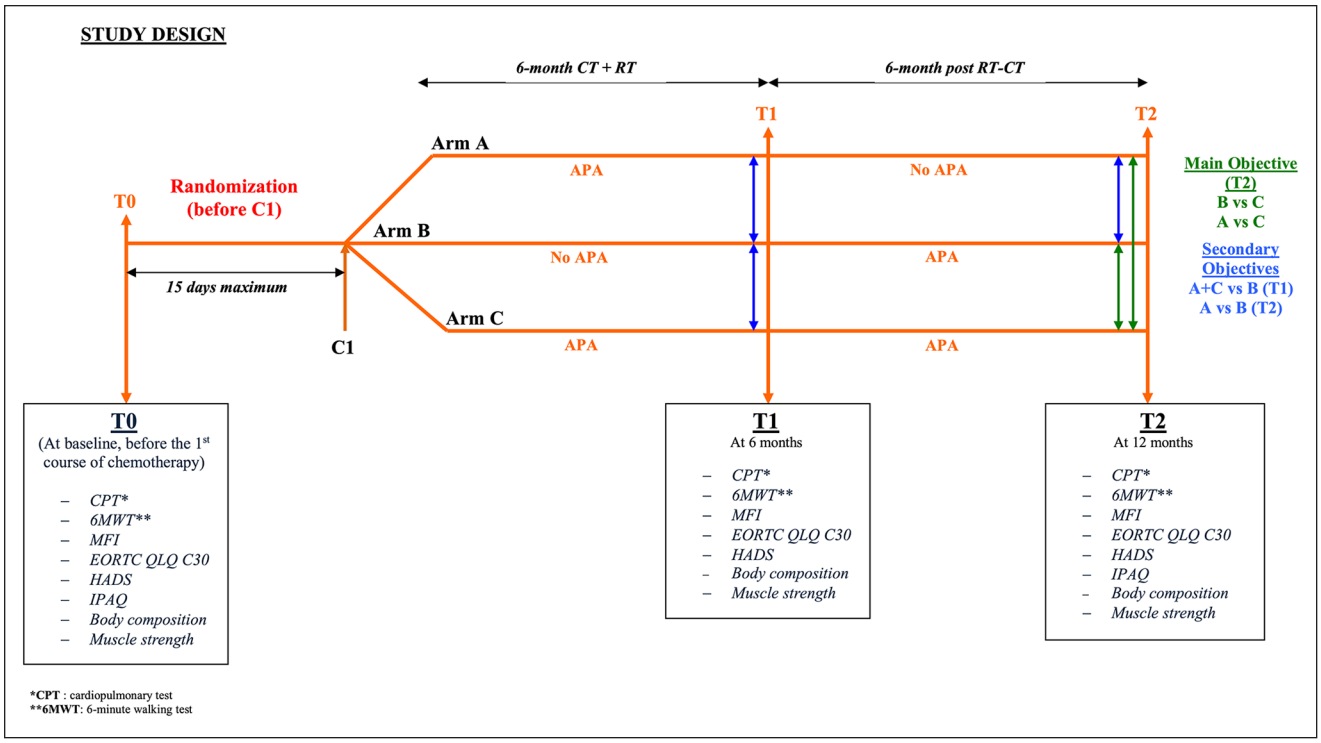

Figure 1. Study design.

- Group C: 12-month home-based APA program during and after adjuvant or neoadjuvant therapy

After completing all baseline assessments, participants were randomized 1:1:1 to 1 of the 3 exercise intervention groups without stratification. Randomization was balanced by blocks of variable size.

Adverse events were monitored and registered during the study. The study sample completed questionnaires and physical tests before chemotherapy (T0), after 6 months of treatment (T1), and at 12 months (T2). The main criterion was cardiorespiratory fitness at 12 months measured by VO_{2peak} (mL min^{-1} kg^{-1}) based on incremental cardiopulmonary exercise tests. All patients received the same nutrition counselling as per public health nutrition recommendations.

Exercise Training Intervention

An exercise specialist provided detailed information about the APA program to each patient and evaluated their actual home activity and fitness at each course of chemotherapy. The specialist contacted patients by phone weekly to check on progress and overcome any barriers to activity. The intervention consisted of a home-based exercise program combining aerobic and resistance sessions. Aerobic exercises were to be performed a minimum of twice per week (54 or 108 sessions depending on the randomized group).

Cardiovascular training was performed on a bicycle ergometer (Ergobike Fitness 3; Daum Electronic) at constant wattage. Each patient was provided a bicycle. At baseline, all patients performed a cardiopulmonary exercise test (CPET) to determine VO_{2peak}, maximum aerobic power, and heart rate at ventilatory threshold. For an exercise session, the participants began to pedal 3 series of 8 minutes at 60% of their maximum aerobic power obtained at ventilatory threshold with 1-minute rest intervals, and gradually rode 30 minutes continuously at 70%. The patients could also choose to perform brisk walking in addition to the bicycle. Resistance training was performed once a week on 5 muscle groups, including the abdominal, hamstrings, quadriceps, triceps, and surae and gluteus maximus using elastic bands. Each resistance training session consisted of 2 sets of 8 initially and was increased to 12 repetitions after an initial supervised session. The first session lasted 20 minutes and the length was increased progressively by 1 repetition each 6 weeks; the delay between the second series was 1 minute 30 seconds. A total of 27 or 54 resistance sessions were scheduled.

Study Outcomes

The primary objective of the APAC trial was to evaluate the effects of the training program performed for 6 or 12 months on VO_{2peak} at 12 months. The VO_{2peak} results were compared between group A (APA 6 months during specific treatment)

versus C (APA for 12 months) and B (APA 6 months after specific treatment) versus C (APA for 12 months).

Secondary Objectives

The following secondary objectives were included:

- Comparison at 12 months of VO_{2peak} between group A and B.
- Comparison at 6 months of VO_{2peak} between group B and A + C (groups A and C, who performed the same program for 6 months, were combined)
- Comparison of functional capacity, muscle strength, 6-minute walking test, fatigue, QOL, anxiety or depression, and anthropometric (body mass and body mass index [BMI]) measures of body composition based on impedance and PA evaluation at 6 months between group B and groups A + C and at 12 months between A versus B, B versus C, and A versus C.

All assessments were made at baseline (T0) and within 2 weeks around 6 months (T1) and 12 months (T2).

Primary and Secondary Endpoint Measures

Cardiopulmonary exercise tests. To determine VO_{2peak}, an incremental supervised cardiopulmonary exercise test with 12-lead electrocardiogram monitoring (Corina; GE Medical Systems IT Inc., Milwaukee, WI, USA) was performed according to cardiopulmonary exercise test guidelines for clinical and cancer populations.[24] All CPET was performed on an electronically braked cycle ergometer (model 900; ergoline, Bitz, Germany) with breath-by-breath expired gas analysis (Vmax spectra metabolic cart, Model 29n; SensorMedics, Yorba Linda, CA, USA). The analysis of expired air allowed the determination of oxygen uptake (VO_2), carbon dioxide production (VCO_2), ventilation (VE), and the respiratory exchange ratio (RER; VCO_2–VO_2) during rest and exercise. The peak oxygen uptake was the highest oxygen uptake during exercise.

Six-minute walking test. The 6-minute walking test was performed according to the ATS guidelines[25]: under the supervision of a respiratory physiologist, patients were instructed to walk as quickly as possible for up to 6 minutes, and the total distance was recorded. Patients were allowed to stop at any time during the 6-minute test. Age- and sex-predicted 6-minute walking test results were calculated using Enright's equation.[26]

Body composition. BMI was determined from height and body mass using the formula BMI = mass (kg)/height^2 (m). Fat and lean mass were assessed using dual-energy X-ray absorptiometry using Z-Metrix (BioparHom).[27]

Peripheral muscular strength. The strength of the quadriceps muscle was measured in the sitting position and determined using the best of 3 repetitions on an isometric bench with a strain gauge (Globus System). Peak force was measured in kg during a 5-second period; the maximum force of 3 consecutive repetitions was recorded. Each test was followed by 1 minute of rest (3 trials).

Fatigue. Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20), a 20-item questionnaire consisting of 5 dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Scores of the subscales range from 4 to 20, and a high score indicates significant fatigue.[28]

Quality of life. Quality of life was assessed using the EORTC QLQ-C30.[29] This questionnaire assesses 5 functional scales (physical, role, cognitive, emotional, and social) and 9 symptoms caused by cancer or its treatment (fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) and includes a global health and quality of life scale. Regarding functions, higher scores represent a better QOL; for symptoms, higher scores represent a worse QOL. This questionnaire has been validated for individuals with cancer[30] and, more specifically, those with breast cancer.

Anxiety and depression. Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS),[31] a self-administered questionnaire of 14 items rated from 0 to 3. A higher score is related to greater anxiety or depression.

Assessment of exercise performance. The APA program performance was monitored using 2 methods: Polar monitor and exercise diary. Participants were provided with a heart rate monitor (Polar RS400SD; Polar Electro, Kempele, Finland) and asked to wear it during exercise. Results measured using the polar monitor provided a calculated metabolic equivalent of tasks (MET) estimated based on caloric expenditure.[32] APA programs were considered valuable if the patient realized ≥85% of the scheduled sessions while wearing the Polar monitor. Participants were also asked to record in a diary the number of minutes and kilometers of exercise performed without wearing the monitor.

Assessment of PA globally performed over 1 week. Patients completed the validated long-form International Physical Activity Questionnaire (IPAQ).[33] Over the previous week (7 days), PA was collected to assess the duration (number of days, minutes per day) that an individual engaged in low, moderate, and vigorous PA across 4 domains (occupational, active transportation, domestic, and leisure). PA

data were then used to calculate the MET-based IPAQ score by weighing each type of activity by its MET energy requirement (3.3 × walking, duration; 4 × moderate PA duration; 8 × vigorous PA duration). Data were summed to estimate a total PA at T0, T1, and T2. For each patient, it was determined whether the totals were categorized as low, moderate, or high following international recommendations (www.ipaq.ki.se).

Statistical Analysis and Sample Size Calculation

The sample size was calculated to detect a difference of 3.3 mL min^{-1} kg^{-1} of VO_{2peak} between the groups (A vs C, B vs C) at 12 months (T2), based on Thorsen et al[34] and our publication of the SAPA trial.[22] Each group required 27 patients to achieve 90% power, with an α value set at 5% overall for this study (2.5% for each comparison 2-sided test). To account for an expected dropout rate of 20%, 30 patients were included in each arm. The analysis was conducted on an intention-to-treat basis. Results were presented as the means and standard deviation for continuous variables and as percentages and numbers for categorical variables. Comparisons between groups were made using Student's *t*-test or the non-parametric Mann–Whitney *U*-test, as appropriate, for continuous variables, and using the χ^2 test for binary or categorical variables. Analysis of variance was used for repeated measures. Change scores were not imputed for patients who had data missing at either time-point and these patients were excluded from the analysis. Analyses were performed using SAS ver. 9.3 (SAS Institute, Cary, NC, USA).

Results

From March 2013 to May 2015, 105 patients were eligible and 94 patients were enrolled in the APAC trial (Figure 2). All patients completed assessments upon admission to the study (T0). One patient in group B and 1 in group C refused to participate in the program after baseline assessment (T0). For the primary objective analysis at 12 months, 21 patients were excluded.

Participant Characteristics at Baseline

Patient characteristics at baseline are presented in Table 1. The 3 groups were mostly homogenous for tumor characteristics and treatments. The average age for patients in the groups was 53.0 ± 8.9 years. No statistical difference was observed between the 3 groups. For BMI and when subcategories were studied, there were more overweight and obese patients in group C ($P = .042$). All patients received radiotherapy and hormonotherapy according to estrogen receptor and progesterone receptor positivity.

Effect of Home-Based Activity on Aerobic and Functional Capacity

At T0, VO_{2peak} did not differ among the 3 groups, with relatively low values of 20.8 ± 5, 20.9 ± 4.1, and 21.1 ± 4 mL min^{-1} kg^{-1} in group A, B, and C, respectively ($P = .31$) (Table 3). Regarding criteria for maximal efforts, a plateau in VO_{2peak} was achieved in all participants. At T2, VO_{2peak} increased in the 3 groups without significant differences (B vs C: $P = .78$, A vs C: $P = .64$) (Table 3).

In group A, a significant increase in VO_{2peak} was achieved at T1 ($P = .029$) without a difference between T1 and T2 ($P = .20$). In group B, after a significant decrease at T1 ($P = .009$), VO_{2peak} increased significantly at T2 ($P = .002$). In group C, the VO_{2peak} increase was not significant at T1 ($P = .34$) and persisted between T1 and T2 (Figure 3). A trend was observed in group C when we studied VO_{2peak} (T2 − T0) without a significant difference between the 3 groups (B vs C: $P = .27$, A vs C: $P = .41$).

At T1 (secondary objective), the VO_{2peak} decreased in group B (patients under chemotherapy without an APA program) and increased in groups A and C (patients included in an APA program), but changes between the groups were not significant (Table 4). To study the VO_{2peak} in patient populations as a function of PA performed, we created 3 subgroups whose patients participated in ≥85% of the sessions in each randomized group: A′ (n = 25), B′ (n = 23), and C′ (n = 21). The mean values of the VO_{2peak} compared to the baseline (T2 − T0) were 0.97 ± 3.65, 0.84 ± 2.69, and 1.95 ± 2.56, respectively, for A′, B′, and C′ (no statistical difference), with a trend towards an increase in group C′, which was twice as high as group A′ (Table 5).

Significant heterogeneity in VO_2 variation was observed among patients. In group A, a 66% increase in VO_2 with a mean value of 3.1 to 4.6 mL min^{-1} kg^{-1} was observed; however, we also observed a 34% decrease with a mean of −2.8 to −4.8 mL min^{-1} kg^{-1}. In group B, a 63% increase in VO_2 was observed, while in group C an 83% increase was observed. The variables associated with VO_{2max} at T2 in univariate analysis were age ($\beta = -0.013$, $P < .001$), muscle strength ($\beta = 0.011$, $P = .0002$), HADS anxiety ($\beta = -0.027$, $P = .003$), FEV (force expiratory volume per second) ($\beta = 0.193$, $P = .003$), and bone mass ($\beta = 0.221$, $P = .019$). These variables were not found in multivariate analysis.

Adherence Assessment

Aerobic exercise program ≥85% was performed by 91%, 80%, and 77% of patients in group A, B, and C, respectively (Table 2). The results measured in METs were determined

Table 1. Patient Characteristics at Baseline (N = 94).

Characteristics	Group A (N = 32)	Group B (N = 31)	Group C (N = 31)	*P*-value
Age. years median (min-max)	56.5 (30-69)	50.0 (37-72)	50.0 (29-72)	.83
Cancer stage number, n (%)				
I	8 (25.0)	4 (12.9)	8 (25.8)	.61
II	21 (65.6)	25 (80.6)	19 (61.3)	
III	3 (9.4)	2 (6.5)	3 (9.7)	
Unknown	0 (0)	0 (0)	1 (3.2)	
HR− n (%)	6 (18.7)	4 (12.9)	4 (12.9)	.75
HR+ n (%)	26 (81.3)	27 (87.1)	27 (87.1)	
Mastectomies n (%)	10 (31.2)	7 (22.6)	9 (29.0)	.72
Lumpectomy n (%)	22 (68.8)	24 (77.4)	22 (71.0)	
Adjuvant chemotherapy n (%)	22 (68.8)	20 (64.5)	24 (77.4)	.52
Neoadjuvant chemotherapy n (%)	10 (31.2)	11 (35.5)	7 (22.6)	
Trastuzumab n (%)	6 (18.7)	6 (19.3)	5 (16.1)	.94
BMI (kg/m²) (mean ± SD)	25.2 ± 5.2	25.5 ± 4.5	25.9 ± 4.8	.64
Thin (<18.5)	1 (3.1)	0 (0.0)	1 (3.2)	/
Normal (≥18.5 et <25)	20 (62.5)	17 (54.8)	11 (35.5)	
Overweight (≥25 et <30)	5 (15.6)	9 (29.0)	15 (48.4)	
Obesity (≥30)	6 (18.8)	5 (16.1)	4 (12.9)	
Fat mass (kg) (mean ± SD)	22.4 ± 11	23.3 ± 8.9	24.1 ± 8.3	.46
Muscular mass (kg) (mean ± SD)	19.7 ± 3.1	18.9 ± 2.6	20.7 ± 5.1	.13
6 MWT (m) (mean ± SD)	520.3 ± 9.5	523.0 ± 57.2	528.1 ± 62.3	.87
6 MWT (% theoretical) (mean ± SD)	96.6 ± 12.3	97 ± 12.1	96.4 ± 11.6	.51
Hemoglobin (g/dl) (mean ± SD)	13.2 ± 0.9	13.7 ± 0.7	13.4 ± 1.0	.11
Muscular strength (kg) (mean ± SD)	27.8 ± 8.9	29.3 ± 10.6	32.7 ± 10.7	.15
Bone mass (kg) (mean ± SD)	1.7 ± 0.4	1.7 ± 0.4	1.7 ± 0.4	.55
Comorbidities, n (%)	19 (59.4)	14 (45.2)	11 (35.5)	.16
Hypertension (n = 11)	6 (18.7)	2 (6.5)	3 (9.7)	/
Metabolic disorder (n = 18)	9 (28.1)	4 (12.9)	5 (16.1)	
Anxiety—depression (n = 9)	2 (6.2)	6 19.3)	1 (3.2)	
Rheumatological symptoms (n = 6)	2 (6.2)	2 (6.5)	2 (6.5)	

Abbreviations: HR, hormone receptors; BMI, body mass index; 6MWT, 6-minute walking test; SD, standard deviation.

using the polar monitor, as described in the Methods. Adherence measured using the monitor (Table 2) was registered in less than 50% of patients who performed ≥85% of the program because of difficulties using the monitor; 90% of patients performed moderate PA.

Quantity and duration of walking and biking were registered with diary recording independently of polar wearing and did not differ between group A and B (Table 2), but was almost doubled in group C. Resistance training assessment was performed in a mean of 66.8% of sessions (±30.2) in group A, 84.2% (±20.3) in group B, and 74.4% (±24.3) in group C.

Changes in the 6-Minute Walking Test

The results of the 6-minute walking test are shown in Table 3. At baseline (T0), no difference was observed between the 3 groups ($P = .87$). At 6 months (T1), patients in group A and C significantly increased their distance compared to group B, who decreased their distance ($P = .042$) At 12 months (T2), all groups increased their performance from baseline without statistical difference (Table 3). In group A, patients had a delta (T1 − T0) at 17 m ± 48.9 and a lower but continued to increase after T1 with a delta (T2 − T1) at 5.8 m ± 32. In group B, the distance performed by patients decreased at T1 and increased after starting APA, and T2 was significantly higher than T1 ($P < .0001$). In group C, the increase in distance was slow until T1 ($P = .48$), and continued to increase until T2 with a significant change ($P = .001$), and was twice as high as the values obtained in group A and B.

Changes in Body Composition

Table 5 shows the stability in body composition variables at 6 and 12 months across the 3 groups, without difference between the groups.

Table 2. PA Program Assessment.

	Total	Group A (N = 32)	Group B (N = 30)	Group C (N = 30)
	N	n (%)	n (%)	n (%)
Pts (number of sessions ≥85%)	76	29 (91)	24 (80)	23 (77)
Pts with evaluable activity in MET	40	16 (55)	10 (42)	14 (61)
MET<3		1(6)	0 (0)	1 (7)
MET 3-6		12 (75)	8 (80)	11 (79)
MET>6		3 (19)	2 (20)	2 (14)
	N	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)
Walking (km) (mean ± SD)	87	78 ± 84	94.3 ± 122.1	150.8 ± 219.8
Walking (hours) (mean ± SD)	87	21 ± 23.7	25.2 ± 31.4	33.6 ± 41.1
Biking (km) (mean ± SD	87	417.8 ± 229.1	423.3 ± 219.6	773.4 ± 459.4
Biking (hours) (mean ± SD)	87	18.2 ± 9.5	18.9 ± 9.6	35.6 ± 20.9

Abbreviations: PA, physical activity; MET, metabolic equivalent of task (1 MET is considered equivalent to the consumption of 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$); SD, standard deviation.

Quadriceps Strength

No change in quadriceps strength was observed between the 3 groups at T2 (Table 5). At T2, the values were about the same among the 3 groups, but with an increase in all patients compared to values obtained at baseline in groups A (3.6 ± 7.9), B (2.6 ± 6.5), and C (4.4 ± 7.7). At 6 months, decreased strength was observed in group B, with a difference between T1 and T0 of −0.17 ± 2.8, while there was an increase in group A (1.52 ± 3.4) and C (0.02 ± 3.2) (Table 5).

Level of Physical Activity Estimated From the IPAQ Questionnaire

The assessment of PA with the IPAQ questionnaire did not reveal a difference between the 3 groups in terms of classes of Met-min/w low or moderate and high PA at T2 or T1 (Table 5). More than 50% of patients were globally considered to have moderate activity, with a small percentage in high activity (from T0 to T2: 3 to 12% in group A, 6 to 13% in group B, and 6 to 4% in group C).

Quality of Life, Symptoms, and Functions From the EORTC QLQ-C30

The EORTC QLQ-C30 results are presented in Tables 4 and 5. Global score of QOL measured by QLQC30 was stable during the protocol. No significant decrease was observed during chemotherapy treatment. No significant difference between groups was observed at the various times when the questionnaires were assessed. When the different functions were studied, at 6 months group B showed decreases in all functional areas but only emotional state showed a significant difference between groups A+C (10.3 ± 21.1) versus B (–3.5 ± 27.2), in favor of APA groups ($P = .010$). At 12 months, group B showed a decreased global score and functional score, but no significant difference was observed between groups.

Anxiety and Depression From the HADS Questionnaire

The results showed an overall reduced symptomatology of anxiety in all groups during the protocol and a decrease in depressive symptoms in group C, but without a significant difference between the groups at 6 or 12 months (Tables 4 and 5).

Fatigue Measured Using the MFI Scale

At T0, no difference was observed between the 3 groups with an MFI score of 59.7 ± 5.6, 60.9 ± 5.7, and 59.4 ± 5 in group A, B, and C, respectively (Tables 4 and 5). Fatigue global score decreased at T1 in group B, who did not perform APA (−0.9 ± 6.4), but with no significant difference between groups A+C versus B. The fatigue global score and all subscales analyzed were stable, with no between-group differences at T2.

Adverse Events

No grade 3 or 4 toxicity was observed in patients in relation with APA, but 2 types of adverse events were reported for whom it was difficult to determine their origin (cancer, chemotherapy, or APA). Fatigue was reported during the APA program in 21 patients in group A, 10 in group B, and 21 in group C. Myalgia or arthralgia was observed in 10, 5, and 8

Table 3. Effects on Cardiopulmonary Function (Intention-to-Treat Analysis).

	Group A mean (SD)			*P*-value		Group B mean (SD)			*P*-value		Group C mean (SD)			*P*-value		*P*-value at T2	
Variable	T0	T1	T2	T0 vs T1	T1 vs T2	T0	T1	T2	T0 vs T1	T1 vs T2	T0	T1	T2	T0 vs T1	T1 vs T2	A vs C	B vs C
Primary endpoint at T2																	
VO_{2peak} ($ml.min^{-1}.kg^{-1}$)	20.8 (5.0)	22.2 (5.0)	22.3 (6.5)	**.02***	.20	20.9 (4.0)	20.1 (3.6)	21.7 (4.1)	.009	.002	21.0 (4.0)	21.9 (4.2)	22.7 (5.1)	.34	.07	.78	.64
Secondary endpoints at T2																	
6 MWT (m)	520.3 (59.5)	535.7 (55.1)	547.3 (52.9)	.12	.42	522.9 (57.2)	513.7 (44.6)	551.5 (45.8)	.08	**<.0001***	528.1 (62.3)	540.9 (59.9)	564.6 (62.5)	.46	**.001***	.27	.42

Abbreviations: VO_{2peak}, peak volume of oxygen consumed; 6MWT, 6-minute walking test; SD, standard deviation.
*significant difference $p < 0.05$.

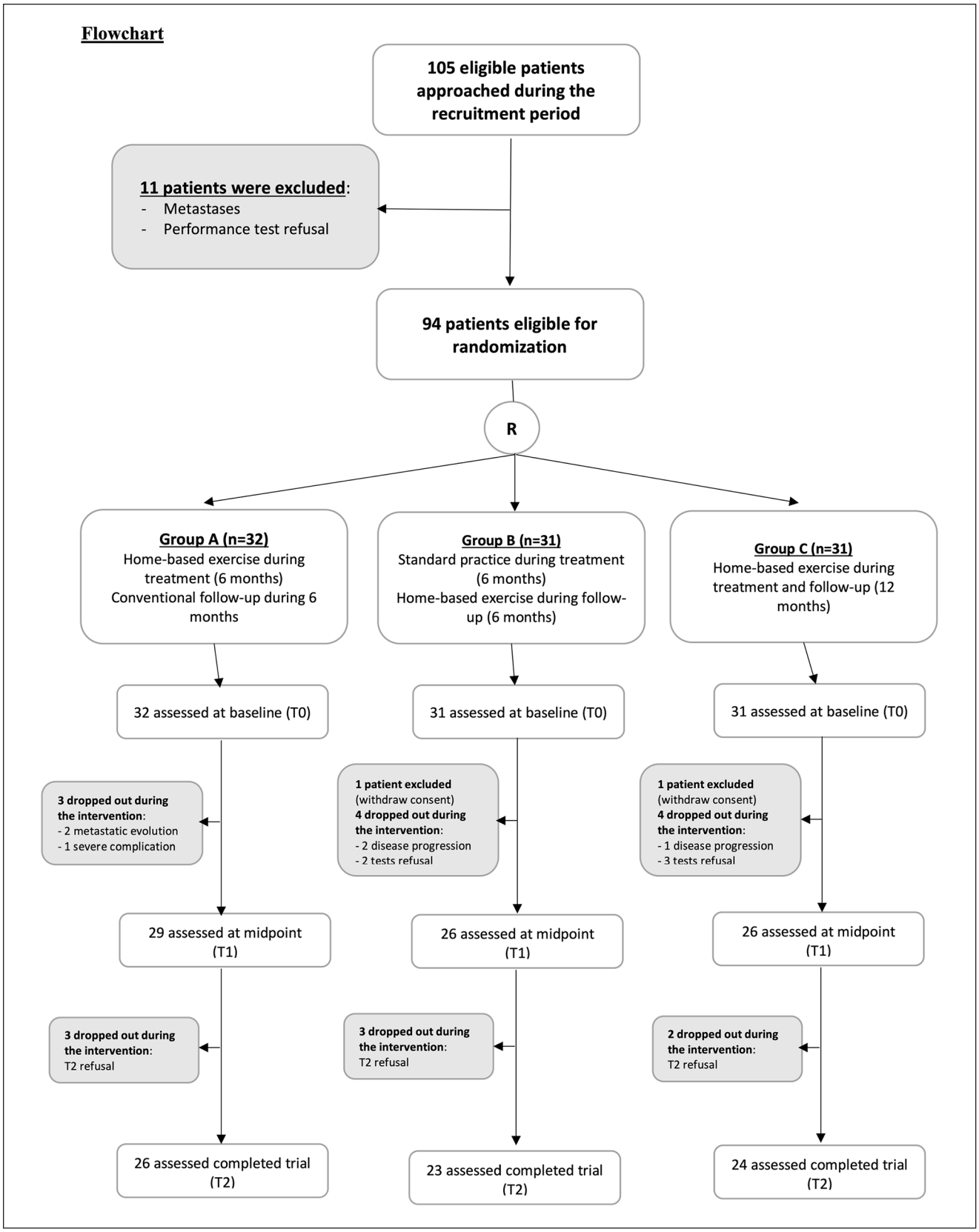

Figure 2. Flowchart.

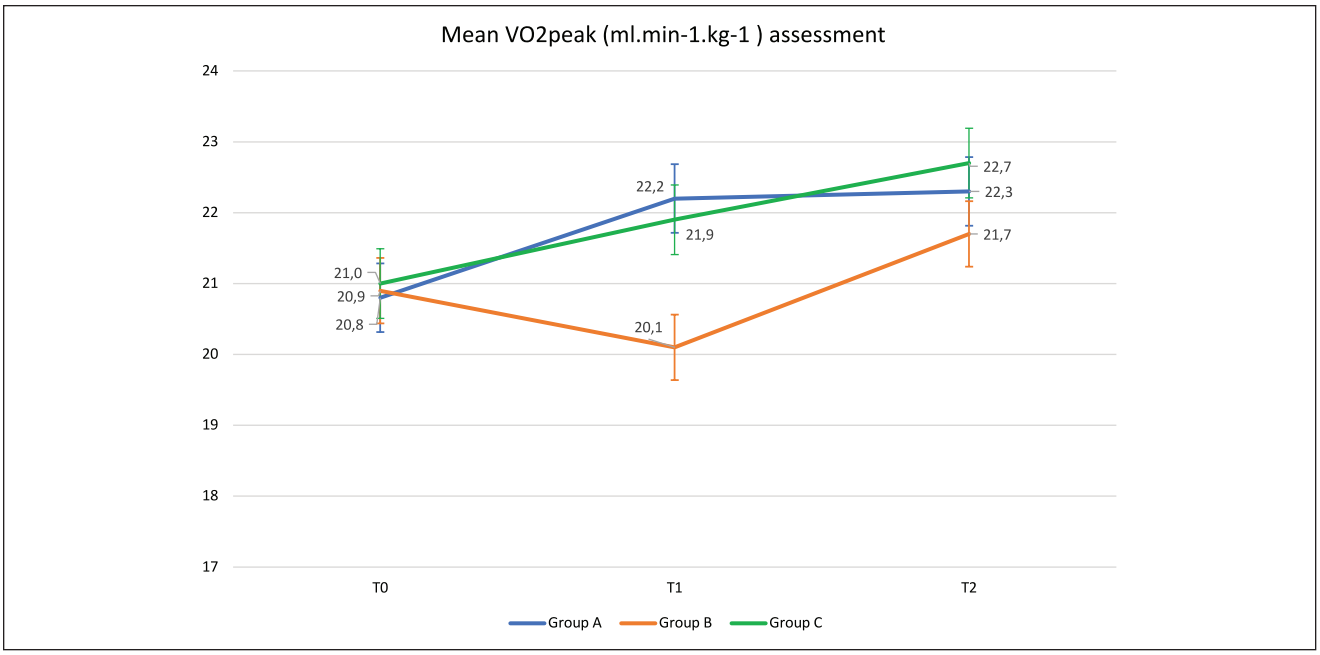

Figure 3. VO_{2peak} changes between T0, T1, and T2.

patients in group A, B, and C, respectively. More specifically, tendinitis in 2 patients of group B and C and a calf snap in 1 patient in group C may have been associated with AP.

Discussion

The APAC study does not highlight different long-term physiological functional impacts among the 3 home-based APA programs in patients with breast cancer, during and/or after chemotherapy and radiotherapy. The between-group difference in VO_{2peak} observed 12 months after the beginning of the trial was not significant. Although many APA studies involving breast cancer patients have been performed, few randomized controlled studies have compared PA programs during or after chemotherapy. It has been shown that home-based APA programs increase VO_{2peak}, compared to controls, but the intensity, duration, and schedule of the APA programs vary among studies. During cancer-specific treatment, APA may increase treatment effectiveness to limit secondary effects, maintain physical fitness preventing muscle loss, fat gains, and fatigue, and improve QOL.[35] The aim of exercise post-treatment is to accelerate recovery, improve physical fitness and QOL, and reduce fatigue.

In this trial, we compared the feasibility and benefits with regard to physical fitness and health-related outcomes of a home-based PA program during or after specific cancer treatment to provide recommendations for patients undergoing breast cancer treatment. This AP program combined aerobic and resistance exercises, as proposed for the majority of trials for cancer patients.[36,37] We did not compare the cardiorespiratory fitness of patients performing APA with a control group without AP because it would have been unethical to perform breast cancer adjuvant treatment without proposing an APA program, even if the modality is not precise. Previous reports have mostly assessed the impact of AP at the end of the AP program. In our study, the first objective was home-based exercise training impact on VO_{2max} evaluated at 12 months after starting the AP program. In this trial, we measured cardiorespiratory fitness with VO_{2max} using a cycle ergometer with breath-by-breath expired gas analysis, while many studies on home-based PA apply the 6-minute walking test. Secondary objectives included exhaustive assessments on physical capacity, body composition, QOL, and anxiety and depression.

Breast cancer survivors have been reported as having VO_{2max} values 22% to 25% lower compared to their age-matched healthy, sedentary non-cancer peers.[11,38] Low cardiorespiratory fitness is known to be inversely associated with breast cancer-related deaths, cardiovascular, and all-cause mortality.[10,39] In this trial, the significant increase in VO_2 after APA was confirmed. However, at 12 months, APA did not increase the VO_{2max} differently between the 3 groups A, B, and C. At T2, group A maintained the improvement in VO_2 obtained after 6 months of APA (as shown previously in the SAPA trial), whereas Group B increased VO_2 after their APA program despite a decrease in T1, and this increase reached the level attained in groups A and C.

At T1, patients have finished their chemotherapy and radiotherapy treatments and comparison between groups A+C versus B showed the classical decrease in VO_{2peak} with cancer treatment alone and an increase when PA was

Table 4. Effects on Secondary End Points at 6 Months (T1) (Intention-to-Treat Analysis).

	Group A mean (SD)			Group C mean (SD)			Group A + C mean (SD)			Group B mean (SD)			*P*-value (T1)	*P*-value (T1-T0)
Variable	T0	T1	T1-T0	T0	T1	T1-T0	T0	T1	T1-T0	T0	T1	T1-T0	A + C vs B	A + C vs B
VO_{2peak} ($ml.min^{-1}.kg^{-1}$)	20.8 (5.0)	22.2 (5.0)	0.7 (4.4)	21.0 (4.0)	21.9 (4.2)	0.8 (3.0)	20.9 (4.5)	22 (5.2)	0.9 (2.7)	20.9 (4.0)	20.1 (3.6)	−0.3 (4.5)	.46	.27
6 MWT (m)	520.3 (59.5)	535.7 (55.1)	17 (48.8)	528.1 (62.3)	540.9 (59.9)	6.9 (33.1)	524.1 (60.51)	538.3 (57.05)	12 (41.75)	522.9 (57.2)	513.7 (44.6)	−17 (47.5)	**.04***	**.02***
HADS anxiety (score)	9.3 (4.2)	7.7 (2.9)	−2 (2.99)	9.6 (3.4)	7.7 (3.7)	−1.9 (3.01)	9.5 (3.80)	7.7 (3.30)	−1.8 (2.7)	9.3 (3.6)	8.0 (3.9)	−1.4 (2.6)	1.0	.53
HADS depression (score)	3.8 (2.7)	4.1 (3.1)	0.07 (3.16)	3.5 (2.5)	3.5 (2.7)	−0.07 (2.59)	3.6 (2.59)	3.8 (2.92)	0 (2.9)	3.8 (3.0)	4.4 (3.1)	0.3 (4)	.34	.66
MFI score	59.7 (5.7)	62.2 (5)	2.5 (7.08)	59.5 (5.0)	59.3 (5.0)	0.6 (6.90)	59.6 (5.29)	60.8 (5.54)	1.5 (7.1)	61.0 (5.7)	60.6 (6.9)	−0.9 (6.4)	.44	.13
EORTC QLQC30 (global score)	52.3 (16.2)	52.1 (21.0)	0.4 (2.28)	56.7 (21.3)	50.3 (20.1)	−0.4 (2.72)	54.5 (18.86)	51.2 (22.44)	0.6 (20.9)	58.1 (17.4)	50.0 (20.5)	−6.2 (20.6)	.64	.11
BMI (kg/m^2)	25.2 (5.2)	25.2 (5.4)	0.1 (1.68)	25.9 (4.8)	25.4 (4.5)	0.2 (1.65)	25.5 (4.98)	25.4 (4.92)	0.1 (1.7)	25.5 (4.5)	25.1 (3.6)	0.2 (1.2)	.98	.91
Fat mass (kg)	22.4 (11)	23.1 (9.5)	0.5 (6.08)	24.1 (8.3)	24.4 (10)	1.2 (6.90)	23.3 (9.67)	23.7 (9.65)	0.8 (6.4)	23.3 (8.9)	22.8 (7.7)	0.9 (3.2)	.92	.56
Muscular mass (kg)	19.7 (3.1)	18.6 (2.8)	−1.3 (3.76)	20.7 (5.1)	20.2 (4.0)	−0.5 (6.55)	20.2 (4.26)	19.4 (3.48)	−0.9 (5.3)	18.9 (2.6)	18.1 (4.4)	−0.8 (3.5)	.26	.98
Muscular strength (kg)	27.8 (8.9)	30.4 (8.1)	3.0 (6.87)	32.7 (10.7)	33.8 (11.8)	0.04 (6.37)	30.2 (10.00)	32.1 (10.14)	1.5 (6.7)	29.3 (10.6)	30.0 (10.5)	−0.3 (5.7)	.37	.21
Bone mass (kg)	1.7 (0.4)	1.6 (0.4)	−0.01 (0.48)	1.7 (0.4)	1.7 (0.4)	−0.04 (0.40)	1.7 (0.40)	1.7 (0.43)	0 (0.4)	1.7 (0.4)	1.6 (0.5)	−0.1 (0.4)	.29	.39

Abbreviations: VO_{2peak}, peak volume of oxygen consumed; 6MWT, 6-minute walking test; HADS, hospital anxiety and depression score; MFI questionnaire, multidimensional. fatigue inventory; EORTC QLQC30 questionnaire, European organization for research and treatment of cancer quality of life questionnaire score 30; BMI, body mass index; SD, standard deviation.
P-value was determined by Student's *t*-test of the difference between groups or the non-parametric Mann-Whitney U-test as appropriate.
*significant difference $p<0.05$.

Table 5. Effects on Secondary End Points at 12 Months (T2) (Intention-to-Treat Analysis).

	Group A mean (SD)			Group B mean (SD)			Group C mean (SD)			*P*-value (T2)			*P*-value (T2-T0)		
Variable	T0	T2	T2-T0	T0	T2	T2-T0	T0	T2	T2-T0	A vs B	A vs C	B vs C	A vs B	A vs C	B vs C
VO_{2peak} ($ml.min^{-1}.kg^{-1}$)	20.8 (5.0)	22.3 (6.5)	1 (3.6)	20.9 (4.0)	21.7 (4.1)	0.8 (2.7)	21.0 (4.0)	22.7 (5.1)	1.7 (2.5)	.98	/	/	.90	.40	.27
6MWT (m)	520.3 (59.5)	547.3 (52.9)	18.8 (53.7)	522.9 (57.2)	551.5 (45.8)	17.2 (39.8)	528.1 (62.3)	564.6 (62.5)	30.4 (37.7)	.77	.27	.42	.55	.24	.09
IPAQ (METS-min/week)															
Low	626.5 (667.8)	714.2 (957.7)	48.9 (913.8)	707.3 (596.1)	662.8 (869)	45.8 (1035.6)	468.1 (564.4)	137.8 (692.3)	−155.1 (476)	.90	.43	.23	.77	.65	1
Moderate	519.4 (585.4)	441.7 (361.5)	−151.1 (608.5)	563.3 (876.2)	816.5 (1717.3)	319.1 (2004)	397.3 (579.8)	727.3 (1147)	420.7 1308.8	.75	.41	.20	.40	.02	.17
High	87.5 (388.4)	352 (906)	240 (820.1)	0 (0)	52.2 (176.6)	52.2 (176.6)	232 (827.8)	170 (594.1)	−60 (1092.4)	.24	.68	.45	.97	.50	.49
HADS anxiety (score)	9.34 (4.2)	7.8 (3.4)	−1.6 (3.3)	9.3 (3.6)	8.5 (4.7)	−1 (4.1)	9.6 (3.4)	7.9 (3.4)	−1.8 (2.4)	.93	.98	.90	.95	.78	.65
HADS depression (score)	3.8 (2.7)	4.4 (2.9)	0.4 (3)	3.8 (3.0)	4.8 (4.1)	0.6 (4.3)	3.5 (2.5)	3.1 (3.0)	−0.4 (2.9)	.89	.07	.13	0.81	.26	.34
MFI score	59.7 (5.7)	59.1 (4.7)	−1 (7.5)	61.0 (5.7)	60.4 (4.3)	−0.8 (5.4)	59.5 (5.0)	58.9 (5.4)	0.8 (5.9)	.32	.89	.29	.94	.36	.34
EORTC QLQC30 (global score)	52.3 (16.2)	52.3 (24.1)	8.7 (12.8)	58.1 (17.4)	49.7 (25.1)	−1.1 (18)	56.7 (21.3)	52.1 (28.5)	5.2 (19.3)	.34	.97	.59	.04	.26	.25
BMI (kg/m^2)	25.2 (5.2)	25.6 (5.3)	0.5 (2.1)	25.5 (4.5)	25.8 (3.5)	0.4 (1.3)	25.9 (4.8)	26.0 (4.8)	0.8 (1.5)	.85	.75	.86	.88	.58	.37
Fat mass (kg)	22.4 (11)	22.1 (9.2)	2.1 (6.5)	23.3 (8.9)	25.6 (8.9)	3 (5)	24.1 (8.3)	25.8 (12.8)	2.3 (8.3)	.20	.31	.82	.63	.91	.83
Muscular mass (kg)	19.7 (3.1)	18.9 (3.7)	−0.4 (3.8)	18.9 (2.6)	20.7 (5.5)	1.3 (4.9)	20.7 (5.1)	19.5 (3.0)	−1.9 (3.9)	.28	.23	.98	.22	.24	.06
Muscular strength (kg)	27.8 (8.9)	32.2 (8.3)	3.6 (7.9)	29.3 (10.6)	34.8 (9.3)	2.6 (6.5)	32.7 (10.7)	37.6 (9.8)	4.4 (7.7)	.32	.04	.33	.64	.72	.40
Bone mass (kg)	1.7 (0.4)	1.7 (0.5)	0 (0.5)	1.7 (0.4)	1.6 (0.4)	−0.1 (0.3)	1.7 (0.4)	1.7 (0.5)	−0.2 (0.5)	.97	.82	.98	.96	.36	.49

Abbreviations: VO_{2peak}, peak volume of oxygen consumed; 6MWT, 6-minute walking test; IPAQ, international physical activity questionnaire; HADS, hospital anxiety and depression score; MFI questionnaire, Multidimensional. Fatigue Inventory; EORTC QLQC30 questionnaire, European organization for research and treatment of cancer quality of life questionnaire score 30; BMI, body mass index; SD, standard deviation.
P-value was determined by Student's *t*-test of the difference between groups or the non-parametric Mann-Whitney U-test as appropriate.

performed concomitantly with specific treatment. These changes were significantly different within each group but were not different between groups. These results support the findings of previous studies, but the VO_2 improvement of 0.9 ± 2.7 mL min^{-1} kg^{-1} was lower than those obtained by Courneya et al (2.7 ± 2.6 mL min^{-1} kg^{-1})[40] and in our previous SAPA protocol (2.26 ± 1.53 mL min^{-1} kg^{-1} in intention-to-treat analysis and 3.49 ± 1.64 mL min^{-1} kg^{-1} based on per-protocol analysis).[22] It was similar to that described in Dolan et al.[41] Typical curves of VO_{2peak} evolution during the protocol were observed, and the lack of difference among the groups may be explained based on the following hypotheses. The number of patients included in the protocol was calculated based on a planned difference in VO_{2peak} that was too high among the groups; in group C, the low adherence to APA from T0 to T1 may have been due to the high proportion of patients who were overweight or obese. The counselling of the patients by coaches to highlight the importance of PA and the aim of this protocol may explain why the majority of patients in group A maintained their adherence to PA after T1, contrary to published series.[42,43] The majority of patients in the 3 groups performed exercise at moderate levels based on the Polar monitor or questionnaires, which are commonly used for home-based exercise programs. These differences showed a heterogeneity of program performance and VO_{2peak} status was initially low in the majority of patients despite the average age being younger than normal in patients with breast cancer. Because we expressed the results as VO_{2peak} means, we cannot discuss the within-group and between-group heterogeneity of results: 66% of patients in group A showed increased VO_2 compared to 83% of group C. The impact of exercise intensity on the physical fitness of patients was not determined in the APAC trial, as shown in the meta-analysis of Mugele et al.[44]

The same variation was seen in the 6-minute walking test as in the VO_{2peak}, supporting the concordance of these tests.[45] A significant difference was observed at T1 between group A and C compared to group B, with a decrease in group B during chemotherapy performed without the AP program. A continued increase in meters walked was obtained in group C from T0 and T2, even if no significantly different values were present at T2 compared to group A and B.

Under any APA program performed by patients that was assessed with questionnaires, patients were considered to perform a moderate level of PA during the week. However, we found no associations between post-intervention changes in VO_{2max} and changes in self-reported moderate to vigorous PA, revealing some limitations of these questionnaires. With a more accurate evaluation of the percentage of the program performed by patients, we found that the majority of patients performed 85% or more of the APA program, but it was difficult to measure the true expended calories because of difficulties using the Polar monitor. The APA program was performed in accordance with international PA recommendations for adults.[46-48]

Cancer-related fatigue has been reported in up to 90% of people with cancer during adjuvant treatment with radiation therapy, chemotherapy, and endocrine therapy.[49] Meta-analysis has shown that APA has a significant positive effect on fatigue,[50-54] and QOL.[55] In our study, fatigue evaluated based on MFI was stable without aggravation despite chemotherapy, except in group B, in which fatigue increased during chemotherapy with no difference between groups. A positive effect on QOL with no deterioration was present in all 3 groups, but was smaller than expected. A bias in evaluation in these questionnaires highlights the meaning of the personal self-evaluation, with changes in internal standards values and conceptualization of QOL, as reported previously.[56] Only emotional state was considered at T1 to differ significantly when patients performed APA during specific treatments. All patients had decreased anxiety based on the HADS questionnaires, as described in Rogers et al, with amelioration of depressive symptoms and anxiety after 3 months of a physical program compared to the controls.[57] Moreover, in general populations more physically active subjects have better mental health.[58]

No change was observed in BMI and body composition based on absorptiometry. This stability was significant, as described previously[59] and may be explained by the absence of diet control. Muscle mass and strength are of clinical relevance because these parameters are associated with treatment complications and time to tumor progression.[60] Muscle strength increased after APA, and a decrease was only observed in group B at T1 but reached the other groups at T2. This result was important because resistance training was not supervised and performed only once a week. The same increase was described in a study by Dos Santos et al.[43,61] Two or 3 sessions were recommended in other previous reports[62] and the maintenance of muscular strength has repercussions on QOL.

These results on VO_{2peak} and muscular strength are encouraging to establish recommendations because they are known to facilitate PA behavior. It has been shown that exercise programs that improve or at least maintain physical fitness during breast cancer chemotherapy improve long-term exercise adherence.[63] VO_{2peak} can predict aerobic exercise behaviors and muscular fitness resistance. The moderate PA performed in these 3 groups may affect long-term exercise behavior since previous studies reported controversial results depending on the PA intensity with no impact of PA level[64] or intensity.[65] A strength of our study is the exhaustive assessments with validated measures and addressing areas of physical performance, body composition, symptoms, and QOL.

Conclusion

A home-based APA program combining aerobic and resistance training is feasible during and or immediately after

chemotherapy in breast cancer patients. This trial confirms the negative impact of the absence of an APA program during chemotherapy. The timing of the PA program did not affect cardiorespiratory fitness or well-being 12 months after beginning PA.

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Author Contributions

FV, JB, SL, SLD, and NTM participated in the conception and design. All authors participated in data acquisition. AL performed the statistical analysis. NTM, FV, SLD, ED, and SL analyzed the data. FV, NTM, and JB supervised the work. NTM, FV, JB, SL, and ED were the major contributors in writing the manuscript. All authors contributed to the manuscript, critically revised the manuscript, and approved the final version.

Declaration of Conflicting Interests

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Ethical Approval and Consent to Participate

Clinical data were collected in accordance with French bioethics laws regarding patient information and consent. The study was performed in accordance with the Declaration of Helsinki. Data collection and use were approved by Limoges Hospital Ethics Committee (approval number no. 2012-A01401-42).

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Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

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