Home-based physical activity in breast cancer patients and cardiorespiratory fitness: during and/or after chemotherapy? A three-arm randomized controlled trial (APAC)

François Vincent  
Centre Hospitalier Universitaire de Limoges

Elise Deluche (elise.deluche@chu-limoges.fr)  
Centre Hospitalier Universitaire de Limoges  
https://orcid.org/0000-0001-8474-3116

Joelle Bonis  
Université de Limoges Faculté de Médecine

Sophie Leobon  
Centre Hospitalier Universitaire de Limoges

Marie-Thérèse Antonini  
Centre Hospitalier Universitaire de Limoges

Caroline Laval  
Centre Hospitalier Universitaire de Limoges

Florent Favard  
Centre Hospitalier Universitaire de Limoges

Eloïse Dobbels  
Centre Hospitalier Universitaire de Limoges

Sandrine Lavau-Denes  
Centre Hospitalier Universitaire de Limoges

Anaïs Labrunie  
Centre Hospitalier Universitaire de Limoges

Frédéric Thuillier  
Centre Hospitalier Universitaire de Limoges

Laurence Venat  
Centre Hospitalier Universitaire de Limoges

Nicole Tubiana-Mathieu  
Centre Hospitalier Universitaire de Limoges
Keywords: Adapted physical activity, breast cancer, home training, peak oxygen consumption, chemotherapy

DOI: https://doi.org/10.21203/rs.3.rs-33269/v1

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Abstract

Objectives

Adapted physical activity (APA) program is recommended for breast cancer care. However, their modalities have not been defined. The aim of this study was to determine the best time to begin APA. This randomized controlled trial evaluated at 12 months the effect of home-based APA performed during and/or after treatment on cardiorespiratory fitness. The primary endpoint was peak oxygen consumption \((V_{O2peak})\) compared at 12 months (group A vs C and B vs C). Secondary endpoints included the 6-min walking test (6MWT), assessment of muscular strength, fatigue, quality of life, anxiety, and depression, and a questionnaire of PA levels. All tests were evaluated at baseline, 6 months, and 12 months.

Method

A total of 94 patients with breast cancer were randomized to three 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 one resistance session and two 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 \(\chi^2\) test for binary or categorical variables.

Results

A total of 81 participants were assessed at 6 months and 73 participants at 12 months. The majority of patients completed more than 85% of the exercise sessions. The baseline for \(V_{O2peak}\) and secondary outcomes did not differ among the groups. \(V_{O2peak}\) increased during the exercise period and decreased during the chemotherapy period without APA, but at 12 months no significant difference was observed. The same variations were observed in the 6MWT, with a significance at 6 months between A+C vs. B \((p=0.04)\), but no difference among the groups at 12 months. In the three groups, no decrease in other studied parameters were noted, except at 6 months in group B without APA.

Conclusions

Home-based APA in breast cancer survivors can decrease some of the negative side effects of cancer treatment and has a positive effect on physical function with no differences based on the timing of this program.

TRIAL REGISTRATION

ClinicalTrials.gov (NCT01795612). Registered 20 February 2013,

https://clinicaltrials.gov/ct2/show/NCT01795612?term=APAC&draw=2&rank=3

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). Adapted physical activity (APA) has gained attention as a promising method to reduce fatigue, depression, and anxiety, and to improve psychological and physiological functions based on health-related quality of life (QOL), muscle strength, and cardiorespiratory fitness (6, 7). Studies have observed significant improvements in cardiorespiratory fitness for breast cancer populations (during and after adjuvant therapy) participating in physical activity (PA) program within randomized controlled trials, showing an impact on well-being (1, 8, 9). Peak oxygen consumption (VO$_{2\text{peak}}$), an indicator of cardiorespiratory fitness, is correlated with survival in the general population and in breast cancer patients (10, 11).

However, it is difficult to perform a APA regimen during cancer treatment, especially chemotherapy, and the appropriate period to begin a APA program remains unknown. Although various clinical trials have shown benefits of APA performed during or after breast cancer treatment compared to a control group (12), the benefits varied between these different periods.

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 two qualitative studies reported program start preferences. Of the nine studies assessing this variable, six found that starting a program 3 to 6 months following treatment was the most common preference (13–16), followed by immediately after treatment (17, 18). 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 (19). However, the best time to begin APA remains unclear.

Existing randomized controlled trials on APA during and after treatment comprise home-based, telephone-supported, and supervised and unsupervised interventions. There are no specific recommendations for breast cancer patients.

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. We prefer home-based programs based on previous experience (SAPA study) but with regular coaching. Few randomized controlled trials have explored the effects of home-based interventions on cardiorespiratory fitness in breast cancer (20, 21), and most studies have used walking tests for evaluation. In a previous clinical trial, we showed that without an APA program, all women decreased their maximum oxygen uptake (VO$_{2\text{max}}$) during adjuvant chemotherapy for breast cancer (22). With APA training, they increased their VO$_{2\text{max}}$ at the end of 6 months, maintained it at 12 months without difference with the control group.

In this study, we evaluated the effects of three different home-based programs combining aerobic, resistance, and flexibility exercises during and/or after adjuvant specific treatment. The impact of APA was assessed for a primary objective on VO$_{2\text{max}}$ and as well as on 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 six courses administered every 21 days (three FEC100, three 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 patient, and ongoing treatment with beta-blocker. The trial was conducted at Limoges University Hospital (France) from March 2013 to May 2015. Medical oncologists enrolled patients, explained the study and obtained written informed consent. The study was approved by the Ethics Committee of Limoges Hospital (no. 2012-A01401-42) (France) and registered in ClinicalTrials.gov (NCT01795612).

Study design

The APAC trial was an open interventional single-center, prospective, three-arm, phase III, randomized controlled trial (Fig. 1). The trial compared three groups, as shown in the flow chart in Fig. 2:

- 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
- 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 one of the three exercise intervention groups without stratification. 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.

Exercise training intervention

An exercise specialist provided detailed information about the APA program adapted to each patient and the same specialist evaluated home activity and patient fitness during 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 sessions or 108 sessions in the randomized group).
Cardiovascular training was performed on a bicycle ergometer at constant wattage. At baseline, all patients performed a cardiopulmonary exercise test to determine VO$_{2\text{peak}}$, maximum aerobic power, and heart rate at ventilatory threshold. Participants began to pedal three series of 8 min at 60% of their maximum aerobic power obtained at ventilatory threshold with 1-min rest intervals, and gradually rode 30 min 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 five muscle groups, including abdominal, hamstring, quadriceps, triceps, and surae and gluteus maximus using elastic bands. Each resistance training session consisted of two sets of 8 to 12 repetitions. A total of 27 or 54 resistance sessions were performed.

All patients received the same nutrition counselling.

**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$_{2\text{peak}}$ at 12 months. The VO$_{2\text{peak}}$ 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$_{2\text{peak}}$ between group A and B.
- Comparison at 6 months of VO$_{2\text{peak}}$ between group B and A + C.
- Comparison of functional capacity, muscle strength, 6-min 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$_{2\text{peak}}$, 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 (23).

**Six-minute walking test**
Under the supervision of a respiratory physiologist, patients were instructed to walk as quickly as possible for up to 6 min, and the total distance was recorded. Patients were allowed to stop at any time during the 6-min test. Age- and sex-predicted 6-min walking test was calculated from Enright's Eq. (24).

**Body composition**

BMI was obtained from height and body mass using the formula \(\text{BMI} = \frac{\text{mass (kg)}}{\text{height}^2 \text{ (m)}}\). Fat and lean mass were assessed using dual-energy X-ray absorptiometry.

**Peripheral muscular strength**

Muscular strength of the quadriceps was determined using the best of three repetitions on an isometric bench with a strain gauge (Globus System). For a valid measurement, it was necessary that the patient's strength reached a plateau and was supported for at least 0.5 s. Each test was followed by 1 min of rest (three trials). Force was measured in kg.

**Fatigue**

Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI-20). The MFI-20 is a 20-item questionnaire consisting of five 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 (25).

**Quality of life**

QOL was assessed using the EORTC QLQ-C30 (26). This questionnaire assesses five functional scales (physical, role, cognitive, emotional and social) and nine symptoms caused by cancer or its treatments (fatigue, nausea and vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties) and a global health and quality of life scale. For functions, higher scores represent a better QOL; for symptoms, higher scores represent a worse QOL. This questionnaire has been validated for individuals with cancer (27) and more specifically with breast cancer.

**Anxiety and depression**

Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS) (28), 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**

APA program performance was monitored using two 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 (29). APA programs were considered valuable if the patient realized \(\geq 85\%\) 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) (30). Over the previous week (7 days), AP was collected to assess the duration (number of days, minutes per day) that an individual engaged in low, moderate, and vigorous PA across four 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 VO₂peak between the groups (A vs. C, B vs. C) at 12 months (T2), based on Thorsen et al. (31) and our publication of the SAPA trial (22). A total of 27 patients were required in each group to achieve 90% power, with an α value set at 5% overall for this study (2.5% for each comparison two-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 χ² 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 software (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 (Fig. 1). All patients completed assessments upon admission to the study (T0). One patient in group B and one in group C refused to participate in the program after baseline assessment (T0). For primary objective analysis at 12 months, 21 patients were excluded.

**Participant characteristics at baseline**

Patient characteristics at baseline are presented in Table 1. The three 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 three groups. For BMI and when subcategories were
studied, there were more overweight and obese patients in group C (p = 0.042). All patients received radiotherapy and hormonotherapy according to estrogen receptor and progesterone receptor positivity.
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)    | 0.83    |
| Cancer Stage number, n (%)       |                 |                 |                 |         |
| I                               | 8 (25.0)        | 4 (12.9)        | 8 (25.8)        | 0.61    |
| 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)         |         |
| RH- n (%)                       | 6 (18.7)        | 4 (12.9)        | 4 (12.9)        | 0.75    |
| RH+ n (%)                       | 26 (81.3)       | 27 (87.1)       | 27 (87.1)       |         |
| Mastectomies n (%)              | 10 (31.2)       | 7 (22.6)        | 9 (29.0)        | 0.72    |
| Lumpyectomy n (%)               | 22 (68.8)       | 24 (77.4)       | 22 (71.0)       |         |
| Adjuvant chemotherapy n (%)     | 22 (68.8)       | 20 (64.5)       | 24 (77.4)       | 0.52    |
| Neoadjuvant chemotherapy n (%)  | 10 (31.2)       | 11 (35.5)       | 7 (22.6)        |         |
| Trastuzumab n (%)               | 6 (18.7)        | 6 (19.3)        | 5 (16.1)        | 0.94    |
| BMI kg/m² (mean ± sd)           | 25.2 ± 5.2      | 25.5 ± 4.5      | 25.9 ± 4.8      | 0.64    |
| 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      | 0.46    |
| characteristics                  | Group A (N = 32) | Group B (N = 31) | Group C (N = 31) | p-value |
|----------------------------------|------------------|------------------|------------------|---------|
| Muscular mass (kg) (mean ± sd)   | 19.7 ± 3.1       | 18.9 ± 2.6       | 20.7 ± 5.1       | 0.13    |
| 6MWT (m) (mean ± sd)             | 520.3 ± 9.5      | 523.0 ± 57.2     | 528.1 ± 62.3     | 0.87    |
| 6MWT (% theoretical) (mean ± sd) | 96.6 ± 12.3      | 97 ± 12.1        | 96.4 ± 11.6      | 0.51    |
| Hemoglobin (g/dl) (mean ± sd)    | 13.2 ± 0.9       | 13.7 ± 0.7       | 13.4 ± 1.0       | 0.11    |
| Muscular strength (kg) (mean ± sd)| 27.8 ± 8.9      | 29.3 ± 10.6      | 32.7 ± 10.7      | 0.15    |
| Bone mass (kg) (mean ± sd)       | 1.7 ± 0.4        | 1.7 ± 0.4        | 1.7 ± 0.4        | 0.55    |
| Comorbidities, n (%              | 19 (59.4)        | 14 (45.2)        | 11 (35.5)        | 0.16    |
| 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)          |         |

**Effect of home-based activity on aerobic and functional capacity**

At T0, VO$_{2peak}$ did not differ among the three 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 = 0.31) (Table 3). Regarding criteria for maximal efforts, a plateau in VO$_{2peak}$ was achieved in all participants. At T2, VO$_{2peak}$ increased in the three groups without significant differences (B vs. C: p = 0.78, A vs. C: p = 0.64) (Table 3).
### Table 3
Effects on cardiopulmonary function (Intention-to-treat Analysis)

| Variable | Group A mean (sd) | Group B mean (sd) | Group C mean (sd) |
|----------|------------------|------------------|------------------|
|          | p-value          | p-value          | p-value          |
|          | (at T2)          | (T0 vs T1)      | (T0 vs T2)      | (T1 vs T2) |
|          | A vs B           | C vs C          |                  |

#### Primary endpoint at T2

| Var  | Group A | Group B | Group C | p-value |
|------|---------|---------|---------|---------|
| VO   | 2.0     | 2.2     | 2.0     | 0.029   |
| 2p   | 8.0     | 2.3     | 2.0     | 0.61    |
|      | (5)     | (6)     | (5)     | (5)     |
| ek   | 0.0     | 0.0     | 0.0     | 0.34    |
| kga  | 1.0     | 2.0     | 1.0     | 0.41    |

#### Secondary endpoints at T2

| Var  | Group A | Group B | Group C | p-value |
|------|---------|---------|---------|---------|
| M    | 2.0     | 4.1     | 1.0     | 0.002   |
| W    | 0.0     | 5.0     | 7.0     | 0.029   |
| T    | 3.0     | 7.0     | 5.0     | 0.002   |
|      | (5)     | (5)     | (5)     | (5)     |

In group A, a significant increase in VO$_{2peak}$ was achieved at T1 ($p = 0.029$) without difference between T1 and T2 ($p = 0.20$). In group B, after a significant decrease at T1 ($p = 0.009$), VO$_{2peak}$ increased significantly at T2 ($p = 0.002$). In group C, the VO$_{2peak}$ increase was not significant at T1 ($p = 0.34$) and persisted between T1 and T2 (Fig. 3). A trend was observed in group C when we studied VO$_{2peak}$ (T2 − T0) without a significant difference between the three groups (B vs. C: $p = 0.27$, A vs. C: $p = 0.41$).

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 in function of PA performed, we created three subgroups whose patients participated in $\geq 85\%$ 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 $\pm$ 3.65, 0.84 $\pm$ 2.69, and 1.95 $\pm$ 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).
Table 4: Effects on secondary end points at 6 months (T1) (Intention-to-treat Analysis)

| Variable       | Group A mean (sd) | Group C mean (sd) | Group A + C mean (sd) | Group B mean (sd) | \( p\)-value (T1) | \( p\)-value (T1-T0) |
|----------------|-------------------|-------------------|-----------------------|-------------------|------------------|------------------|
| VO2peak        | 20.8 (5.0)        | 22.0 (5.0)        | 21.9 (4.0)            | 21.9 (4.0)        | 0.8              | (3.0)            |
| 6MWT           | 52.3 (59.5)       | 53.7 (55.1)       | 52.1 (48.8)           | 52.1 (48.8)       | 6.9              | (33.1)           |
| HADS anxiety   | 9.3 (4.0)         | 7.7 (2.0)         | 9.6 (2.9)             | 9.6 (2.9)         | -1.9             | (3.01)           |
| HADS depression| 3.8 (2.0)         | 4.1 (3.0)         | 0.0 (7.7)             | 0.0 (7.7)         | -0.7             | (2.59)           |
| MF1            | 59.7 (5.7)        | 62.2 (7.08)       | 59.5 (5.0)            | 59.5 (5.0)        | 0.6              | (6.90)           |

\( A + C \text{ vs } B \)
| Variable               | Group A    | Group C    | Group A + C | Group B    | \( p\)-value (T1) | \( p\)-value (T1 - T0) |
|------------------------|------------|------------|-------------|------------|-------------------|----------------------|
|                        | mean (sd)  | mean (sd)  | mean (sd)   | mean (sd)  |                  |                      |
| QL QC 30 (global score) | 52.3 (16.2) | 52.1 (21.0) | 0.4 (2.28)  | 56.7 (21.3) | 50.4 (20.1) (2.72) | 54.5 (18.86) (22.44) |
| BMI                    | 25.2 (5.2)  | 25.5 (6.8)  | 0.1 (1.68)  | 25.9 (4.8)  | 0.2 (4.5) (1.65)  | 25.3 (4.98) (4.92)  |
| Fat mass               | 22.4 (11)   | 23.1 (9.5)  | 0.5 (6.08)  | 24.1 (8.3)  | 1.2 (10) (6.90)   | 23.3 (9.67) (9.65)  |
| Muscular mass          | 19.7 (3.1)  | 18.3 (2.8)  | -1 (3.76)   | 20.2 (5.1)  | -0.5 (4.0) (6.55) | 20.2 (4.26) (4.48)  |
| Muscular strength      | 27.8 (8.9)  | 30.4 (8.1)  | 3.0 (6.87)  | 32.7 (10.7) | 0.0 (11.8) (6.37) | 30.2 (10.00) (10.14) |
| Bone mass              | 1.7 (0.4)   | 1.6 (0.4)   | -0.1 (0.48) | 1.7 (0.4)   | 1.7 (0.4) (0.40)  | 1.7 (0.40) (0.43)   |

Note: The table shows the mean and standard deviation (sd) for different variables across three groups (A, C, and B) with p-values for the comparison of Group A with Group C (T1) and Group A with Group B (T1 - T0).
Table 5
Effects on secondary end points at 12 months (T2) (Intention-to-treat Analysis)

| Variable | Group A mean (sd) | Group B mean (sd) | Group C mean (sd) | p-value (T2) | p-value (T2-T0) |
|----------|------------------|------------------|------------------|-------------|----------------|
| T0       | T2 - T0          | T0               | T2 - T0          | A vs B      | A vs C         |
| VO₂peak  | 20.8 (5.0)       | 22.3 (4.0)       | 20.9 (4.1)       | 0.9 / 8     |                 |
|          | (5.0)            | (6.0)            | (4.0)            |             |                 |
| MWT      | 52.0 (5.9)       | 54.7 (5.2)       | 55.2 (5.8)       | 0.7 / 7     |                 |
|          | (5.9)            | (5.2)            | (5.8)            |             |                 |
| IPAQ     | low 62 (6.5)     | 71 (9)           | 48.9 (13.8)      | 0.9 / 0     |                 |
|          | (6.5)            | (9)              | (13.8)           |             |                 |
|          | moderate 51.4 (9.4) | 44 (3)         | 56.3 (8.5)       | 0.7 / 5     |                 |
|          | (9.4)            | (3)              | (8.5)            |             |                 |
|          | high 87.5 (8.8)  | 35 (8)           | 24 (8)           | 0.2 / 4     |                 |
|          | (8.8)            | (8)              | (8)              |             |                 |

Note: T0 = baseline, T2 = 12 months, T2-T0 = change from baseline to 12 months.
| Variable               | Group A mean (sd) | Group B mean (sd) | Group C mean (sd) | p-value (T2) | p-value (T2-T0) |
|------------------------|-------------------|-------------------|-------------------|--------------|-----------------|
| HA Anxiety             | 9.3 (4.2)         | 7.8 (3.6)         | -1.6 (3.3)        | 0.90         | 0.9             |
|                        |                   |                   |                   |              |                 |
| HA Depression          | 3.8 (2.7)         | 4.4 (2.9)         | 0.4 (3.0)         | 0.80         | 0.7             |
|                        |                   |                   |                   |              |                 |
| MFI Score              | 59.7 (5.7)        | 59.1 (4.4)        | -0.6 (5.5)        | 0.30         | 0.2             |
|                        |                   |                   |                   |              |                 |
| QL QC 30               | 52.3 (1.6)        | 52.3 (2.4)        | 8.7 (2.8)         | 0.30         | 0.2             |
| (global score)         |                   |                   |                   |              |                 |
| BMI                    | 25.2 (5.2)        | 25.0 (5.3)        | 0.1 (2.1)         | 0.80         | 0.5             |
|                        |                   |                   |                   |              |                 |
| Fat mass               | 22.4 (1.1)        | 22.1 (2.9)        | 2.1 (6.5)         | 0.20         | 0.1             |
|                        |                   |                   |                   |              |                 |
| Muscle mass            | 19.7 (3.1)        | 18.9 (3.3)        | -0.4 (3.8)        | 0.20         | 0.1             |
| Variable        | Group A mean (sd) | Group B mean (sd) | Group C mean (sd) | p-value (T2) | p-value (T2-T0) |
|-----------------|-------------------|-------------------|-------------------|-------------|----------------|
| **Muscular strength** | 27.8 (8.9)        | 32.2 (8.3)        | 3.6 (7.9)         | 4.4 (9.7)   | 0.3 (2.7)      |
| **Bone mass**   | 1.7 (0.4)         | 1.7 (0.5)         | 0.1 (0.3)         | -0.2 (0.5)  | 0.9 (2.7)      |

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$_2_{\text{max}}$ at T2 in univariate analysis were age ($\beta = -0.013$, $p < 0.001$), muscle strength ($\beta = 0.011$, $p = 0.0002$), HADS anxiety ($\beta = -0.027$, $p = 0.003$), FEV (force expiratory volume per second) ($\beta = 0.193$, $p = 0.003$), and bone mass ($\beta = 0.221$, $p = 0.019$). These variables were not found in multivariate analysis.

**Adherence assessment**

Aerobic exercise program $\geq 85\%$ 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 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 $\geq 85\%$ of the program because of difficulties using the monitor; 90% of patients performed moderate PA.
Table 2
AP 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          | 40    | 16 (55)          | 10 (42)          | 14 (61)          |
| MET 3–6         |       | 12 (75)          | 8 (80)           | 11 (79)          |
| MET > 6         |       | 3 (19)           | 2 (20)           | 2 (14)           |
| N (mean ± sd)   |       |                 |                  |                  |
| Walking (km)    | 87    | 78 ± 84          | 94.3 ± 122.1     | 150.8 ± 219.8    |
| Walking (hours) | 87    | 21 ± 23.7        | 25.2 ± 31.4      | 33.6 ± 41.1      |
| Biking (km)     | 87    | 417.8 ± 229.1    | 423.3 ± 219.6    | 773.4 ± 459.4    |
| Biking (hours)  | 87    | 18.2 ± 9.5       | 18.9 ± 9.6       | 35.6 ± 20.9      |

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-min walking test**

The results of the 6-min walking test are shown in Table 3. At baseline (T0), no difference was observed between the three groups (p = 0.87). At 6 months (T1), patients in group A and C significantly increased their distance compared to group B, who decreased their distance (p = 0.042) (Table 6). At 12 months (T2), all groups increased their performance from baseline without a statistical difference (Table 3). In group A, patients had a delta (T1 – T0) at 17 m ± 48.9 and a lower increase 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 < 0.0001). In group C, the increase in distance was slow until T1 (p = 0.48), and continued to increase until T2 with a significant change (p = 0.001), 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 three groups, without difference between the groups.

**Quadriceps strength**

No change in quadriceps strength was observed between the three groups at T2 (Table 5). At T2, the values were about the same among the three 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 three 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 performance. 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 versus B, in favor of APA groups (p = 0.010). 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 three 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. Fatigue global score was 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 two 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 ten, five, and eight patients in group A, B, and C, respectively. More specifically, tendinitis in two patients of group B and C and a calf snap in one patient in group C may have been associated with AP.

Discussion

The APAC study does not show different physiological functional impacts between three strategies of a home-based APA program during and/or after specific adjuvant treatment in patients with early-stage breast cancer. The between-group difference in VO$_{2peak}$ observed in the APAC study was not significant.

Although many APA studies involving breast cancer patients have been performed, few randomized controlled studies have been conducted during or after breast cancer chemotherapy. In addition, these studies showed that the performance of a home-based APA program increases VO$_{2peak}$, but intensity, duration, and schedule 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 (32). Exercise post-treatment aims to accelerate recovery, improve physical fitness and QOL, and reduce fatigue. The aim of our study was to assess changes in VO$_{2peak}$, an indicator of cardiorespiratory fitness, after an APA program started at different times in breast cancer patients.

In this trial, we compared the feasibility and benefits 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 (33). We did not compare the VO$_2$ values with a control group without AP because it would not have been ethical 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-month 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 22–25% lower compared to their age-matched healthy, sedentary non-cancer peers (11, 34). Low cardiorespiratory fitness is known to be inversely associated with breast cancer-related deaths, cardiovascular, and all-cause mortality (10, 35). 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 three groups A, B, and C. Group A maintained at T2 the improvement in VO_{2} obtained after 6 months of APA (as shown previously in SAPA trial), whereas Group B increased VO_{2} after their APA program despite a decrease in T1, and this increase recovered the value obtained in group A and C.

At T1, patients received chemotherapy and radiotherapy and comparison between groups A+C versus B showed the classical decrease in VO_{2} with chemotherapy alone and an increase when AP was performed concomitantly with chemotherapy. 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. (36) (2.7 ± 2.6 mL min^{-1} kg^{-1}) 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). 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} 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 explications of the coach to patients highlighted 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 (37, 38); the majority of patients in the three 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 same variations were obtained in the 6-min walking tests than in VO_{2peak}, supporting the concordance of these tests. 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 walking meters 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 (39–41).
Cancer-related fatigue has been reported in up to 90% of people with cancer during adjuvant treatment with radiation therapy, chemotherapy, and endocrine therapy (42). Meta-analysis has shown that APA has a significant positive effect on fatigue (43–47) and QOL (48). 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 without deterioration was present in the three 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 (49). Only emotional state was considered at T1 to differ significantly when patients performed APA during specific treatments. All patients decreased their anxiety based on the HADS questionnaires, as described previously.

No change was observed in BMI and body composition based on absorptiometry. This stability was significant, as described previously (37), and may be explained by the absence of diet control. 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 Wanderson (50); two or three sessions were recommended in other previous reports (51) and the maintenance of muscular strength is known to have repercussions on QOL. In a study by Shilz et al. (53), 60% of breast cancer survivors suffered from significant decreases in muscle strength, thereby reducing QOL.

These results on VO$_{2\text{peak}}$ 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 (52); VO$_{2\text{peak}}$ can predict aerobic exercise behaviors and muscular fitness resistance. The moderate PA performed in these three groups may affect long-term exercise behavior since previous studies reported controversial results depending on the PA intensity with no impact of PA level (53) or intensity (54). A strength of our study is the exhaustive assessments with validated measures and addressing areas of physical performance, body composition, symptoms, and QOL.

**Conclusions**

A home-based program combining aerobic and resistance training is feasible without serious adverse events, leading to a maintenance of QOL, stable body composition, and improvement in fatigue, VO$_{2\text{peak}}$, and muscular strength. Adherence to an APA program is highly variable and novel tools are required to evaluate motivation and rate of participation in specific programs that may need to be supervised. The timing of the PA program did not strongly affect well-being 12 months after diagnosis, but this trial confirms the negative impact of no APA program during chemotherapy and highlights that it may be performed at home from the beginning of treatment.

**Declarations**
Ethics 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).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

The work was supported by Limoges University Hospital. The work was supported by a grant from the Ligue Contre le Cancer (87) and the CPAM (87).

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.

Acknowledgements

We thank “Textcheck” for their assistance with the English language editing. The English in this document has been checked by at least two professional editors, both of whom are native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/PXwBkn

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Figures
Figure 1

Study design
Figure 2

Flowchart
Figure 3

VO2peak changes between T0, T1, and T2

Supplementary Files

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