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ORIGINAL ARTICLE

Feasibility of an exercise and nutritional intervention for weight management during adjuvant treatment for localized breast cancer: the PASAPAS randomized controlled trial

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Abstract

Purpose Lack of physical activity (PA), weight gain, and overweight have been associated with increased risk of recurrence and mortality after breast cancer diagnosis. We evaluated the feasibility of implementing an individualized exercise program and nutritional counseling during adjuvant treatment of localized invasive breast cancer.

Methods Sixty-one patients eligible for adjuvant chemotherapy were randomized 2:1 to receive a 6-month program of weekly aerobic exercises associated with nutritional counseling (n = 41) or usual care with nutritional counseling (n = 20, one withdrawal). The primary endpoints were the proportion of patients compliant with two weekly supervised sessions and their overall adherence (i.e., proportion of supervised and unsupervised sessions completed versus planned sessions).

Results Ten percent of patients in the intervention group were compliant with the two weekly supervised sessions for 6 months, but the overall median adherence rate was 85% of supervised and non-supervised sessions completed. Non-adherence was mainly due to intrinsic reasons (medical, organizational, psychological barriers). Adherence was positively associated with education and baseline PA level and inversely associated with baseline weight and tumor grade. No statistically significant benefits were observed in the intervention group, even if overall PA level and body composition improved and anthropometrics were maintained over time ($p < 0.05$).

Conclusions Overall, there was good adherence with the 6-month exercise program during adjuvant treatment for breast cancer, despite poor compliance to twice-weekly supervised sessions. This study highlights the need for flexible exercise modalities and innovative experimental design to reach patients who would most adhere and benefit from intervention.

Trial registration: ClinicalTrials.gov Identifier: NCT01331772. Registered 8 April 2011, https://clinicaltrials.gov/ct2/show/NCT01331772?term=pasapas&rank=1

Keywords Breast cancer · Physical activity · Exercise · Clinical trial · Nutrition · Obesity

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Background

Weight gain [1] and overweight [2] have been associated with increased risk of recurrence and mortality after breast cancer (BC) diagnosis. Almost 50% of patients are overweight or obese at the time of diagnosis and the majority of them gain weight after treatment [3]. Less than 30% of BC patients meet minimal recommendations of 150 min of moderate physical activity (PA) weekly [4]. Furthermore, there is a significant decrease in PA levels during adjuvant therapy for BC [5] and levels remain low after treatment termination [6], stressing the importance of setting up exercise programs early after diagnosis. The reduction in PA is greater in overweight women and those who receive chemotherapy and radiotherapy compared with those receiving only surgery [7]. This is associated with low energy expenditure which contributes to weight gain, and with deterioration of body composition, increased mortality, and lower quality of life [8].

Regular PA during treatment reduces cancer-related fatigue [9], improves quality of life [10], and maintains weight [11] and body composition [12]. It has been associated with better overall survival and lower risk of recurrence in observational studies [13]. Despite the health benefits of regular PA, the majority of BC patients and survivors do not respect public health PA guidelines [4, 14]. Maintaining regular PA during BC treatment can be challenging as 60% of patients experienced adverse effects related to treatment [15]. Personal and environmental barriers to regular PA include pain, fatigue, lack of energy, exercise perception, transportation, equipment, and cost [16].

Studies evaluating exercise programs during adjuvant treatment for BC have been already reported in Europe [17, 18], but not in France. We performed a randomized clinical trial to evaluate the feasibility and acceptability of implementing a program of adapted PA (APA) associated with nutritional counseling, compared with usual care and nutritional counseling for 6 months in a population of French women receiving adjuvant treatment for localized BC. Here we present the main outcome and secondary outcomes, i.e., effects on PA level, anthropometrics, body composition, diet, and biological parameters.

Methods

Study design

The design and methods of the PASAPAS trial (www.ClinicalTrials.gov, n°:NCT01331772) have already been described [19]. Briefly, PASAPAS was an interventional, controlled, randomized, single-center trial conducted at the Léon-Bérard comprehensive cancer center, Lyon, France.

Ethics, consent, and permissions

A French Research Ethics Committee (Comité de Protection des Personnes Sud-Est IV, No. 11-023) and the National Security Agency of Medicines and Health Products (No. B110268-80) approved the protocol. Written informed consent was obtained from all participants. The CONSORT guidelines were followed to conduct and report the research.

Recruitment and randomization

French-speaking women aged 18–75 years, diagnosed with a first primary invasive non-metastatic BC, who were initiating adjuvant chemotherapy, living ≤ 60 km from the center, with no contraindications to exercise and able to afford travel expenses to attend the program, were eligible.

The protocol was presented to patients by their oncologist during their first consultation for adjuvant chemotherapy and a clinical research assistant provided further information. Women were randomized 2:1 to either an exercise intervention or a control group using a computer-generated allocation. The total sample size of this pilot study was fixed based on the pragmatics of recruitment and we estimated that 60 participants were sufficient to assess the feasibility of the intervention. We used an unbalanced randomization (2:1 ratio) to emphasize the size of the group of patients supported by the exercise intervention (main target of the study). Moreover, inclusion of 40 patients in the intervention group was sufficient to obtain a precision of at least ± 15% around our estimates for the compliance rate (i.e., primary endpoint), with a confidence level of 95%. The reasons for non-participation of eligible patients were recorded. Age, height, current weight, and Scarff-Bloom-Richardson (SBR) tumor grade of non-participants were obtained from their medical records.

Interventions

Usual care

Participants in both groups received usual care, including dietary and PA counseling delivered by a registered dietician and a certified APA trainer, according to guidelines for cancer survivors [4]. Personalized dietary care was possible on request for 6 months. The patients in the control group had no restriction for PA.

Exercise intervention

In the intervention group, a free-of-charge 6-month supervised exercise program was offered in addition to the usual care. The program consisted of moderate-to-vigorous intensity [i.e., ≥ 3 metabolic equivalents of task (METs)] sessions of outdoor Nordic walking (60 min) and indoor aerobic fitness

(45 min) (i.e., aerobic-based exercises involving major muscle groups), personalized according to the initial PA level of the patient, in small groups supervised by a certified APA trainer [19]. To ensure that the exercise was of moderate intensity, the talk test was used [20]. The principle aim of the program was to maintain weight and body composition [21]. During chemotherapy (i.e., 12 to 18 weeks of 3-week courses or weekly courses in case of non-tolerance to the 3-week chemotherapy regimen), the program consisted of two weekly sessions, one outdoor and one indoor. To take into account treatment-related side effects in the first week after chemotherapy injection [22] and the necessary physiological recovery [23], exercise sessions were not scheduled the first week of each chemotherapy course. Participants able to exercise were encouraged to participate in additional supervised sessions or to perform non-supervised exercise sessions during this week. After chemotherapy completion, the exercise program consisted of three weekly-supervised sessions (two outdoor), including during radiotherapy. The number of sessions planned over the program for each woman varied according to the duration of her chemotherapy protocol. Women anticipating not being able to attend a planned supervised session could replace it by a non-supervised home-based aerobic-based session planned with the APA trainer. Beside the program, participants were encouraged to be physically active for at least 30 min per day in accordance with guidelines [4].

All participants received Nordic walking poles and a pedometer at the beginning of the program. Attendance at each supervised session was recorded. Attendance to non-supervised sessions and reasons for non-adherence were reported by the patient in a PA diary that was collected by a research assistant at each follow-up visit. Reported adverse events were classified as a consequence of either cancer treatment or the intervention and those related to the intervention were graded for severity (five toxicity grades, NCI-CTC.V.4.0).

Endpoints

The primary endpoints were the percentage of patients who were compliant with the entire exercise program, i.e., completed at least two supervised exercise sessions every week of the 6-month program (except for the first week of each chemotherapy course) [19], and the overall adherence to the exercise program defined as the proportion of planned sessions completed, i.e., number of supervised, non-supervised, and additional sessions completed, divided by total number of sessions planned over 6 months.

Secondary endpoints were the acceptability of the intervention and randomization, evaluated as the proportion of eligible patients who accepted to participate in the trial, the identification of barriers to recruitment, the overall satisfaction that was evaluated at 6 months using a scale of 0 to 10, the evolution of PA level, anthropometrics, body composition, diet, circulating biological values, and the effects of the intervention on these parameters.

Data collection

There were four data collection points: at baseline (T1, first day of chemotherapy), 9 weeks after chemotherapy initiation (T2, first day of the fourth 3-week course of chemotherapy), at 6 months (T3, end of intervention), and at 12 months (T4, 6-month post-intervention) [19].

Sociodemographic, lifestyle, and epidemiologic risk factors were collected at baseline (T1) using a questionnaire-based interview. Travel distance from home to the cancer center was recorded. Menopausal status and clinical characteristics were obtained from the patients' medical records.

PA level and sedentary behavior were assessed by the validated interviewer-based software questionnaire PAQAP© [24]. The questionnaire provided detailed classification of PA levels for all participants at each data collection point. The mean time spent during occupational, leisure time, household, transportation activities, and basic activities of daily living were collected for a usual week preceding the evaluation. These data were analyzed to provide the number of hours per week spent in at least moderate intensity PA (≥ 3 METs), in moderate-to-vigorous intensity PA (≥ 4 METs), and in screen activities (e.g., television, computer). The maximal oxygen uptake (VO_{2max}, mL/min/kg) was estimated using the mean daily energy expenditure (DEE, kilocalories/day) [24].

Dietary intake was assessed using a 3-day food diary completed by patients in the week preceding T1, T3, and T4 evaluations. The dietician assessed smoking status and usual consumption of alcohol over the previous 6 months. Calorie intake was estimated using GENI software (Micro 6, Villers-les-Nancy, France, V.7.4) [19].

Anthropometrics were measured by the research assistant at each evaluation, including height (using a fathom accurate to 0.1 cm), body weight (using a mechanical scale recalibrated at each measurement: SECA, 7617019004, 2011, Seca GmbH&Co, Hamburg, Germany; accurate to 0.5 kg), and waist and hip circumferences (using a measuring tape accurate to 0.1 cm). Body mass index (BMI, kg/m^2) was calculated and categorized as underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30.0 kg/m^2).

Body composition was measured at each evaluation using bioelectrical impedance analysis (QuadScan 4000, Bodystat) to assess percentage of body fat (%BF) and fat free mass (FFM, kg) [25].

Circulating concentrations of fasting glucose, albumin, total cholesterol, its high-density lipoprotein (HDL), and low-density lipoprotein (LDL) fractions, and triglycerides were analyzed in fasting blood samples collected at each evaluation (before chemotherapy infusion at T1 and T2) as these

biomarkers of cardio-vascular and metabolic risks might improve with PA.

Statistical methods

Baseline characteristics of the population and their longitudinal variations were described by group and overall (frequency and percentage of categorical data, median and minimum-maximum of quantitative data). Absolute %BF values were individually compared with the European reference data for healthy women in the same age category to identify metabolically obese women [26]. The characteristics of women who declined to participate were compared with those of participants using chi-square test and Student's *t* test.

The trial was powered for assessing compliance with the program expressed in frequencies and percentages. The main reasons for non-participation were reported by proportion of unattended sessions. Potential determinants of adherence to the program were explored by multivariable logistic regression with odds ratio (OR) and their 95% confidence interval (CI), using a limited number of predictor variables given the small sample size of the intervention group. The analysis was performed in the intent-to-treat population.

For secondary outcomes, group and time effects and their interaction with continuous parameters (anthropometrics, body composition, PA level, diet, and biological values) were evaluated in exploratory analyzes using repeated-measure analysis of variance on ranks. If the analyzes revealed significant effects, multiple post hoc comparisons were performed. Spearman correlation analyzes explored potential effects of PA on continuous variables. The threshold of statistical significance was $\alpha = 0.05$. Analyzes were conducted using SAS software (V9.4; SAS Institute, Cary, NC).

Results

Patients

From June 2011 to June 2013, 61 of the 202 screened, eligible women (30%) were included in the trial according to the CONSORT flow diagram (Fig. 1). The main reasons for refusal were as follows: not interested (62%), logistic barriers (frequency/distance, 20%), medical condition or treatment (diabetes, health condition, depression, fear of treatment side-effects, refused chemotherapy; 9%), reason(s) related to the exercise program or the study modalities (refusal to be randomized, already exercising, program too time-consuming, preference for exercising alone or with non-sick individuals, not interested; 5%) and organizational barriers (childcare, professional activity; 4%). Non-participants had similar age ($p = 0.36$), BMI ($p = 0.40$), and SBR tumor grade ($p = 0.93$) as participants.

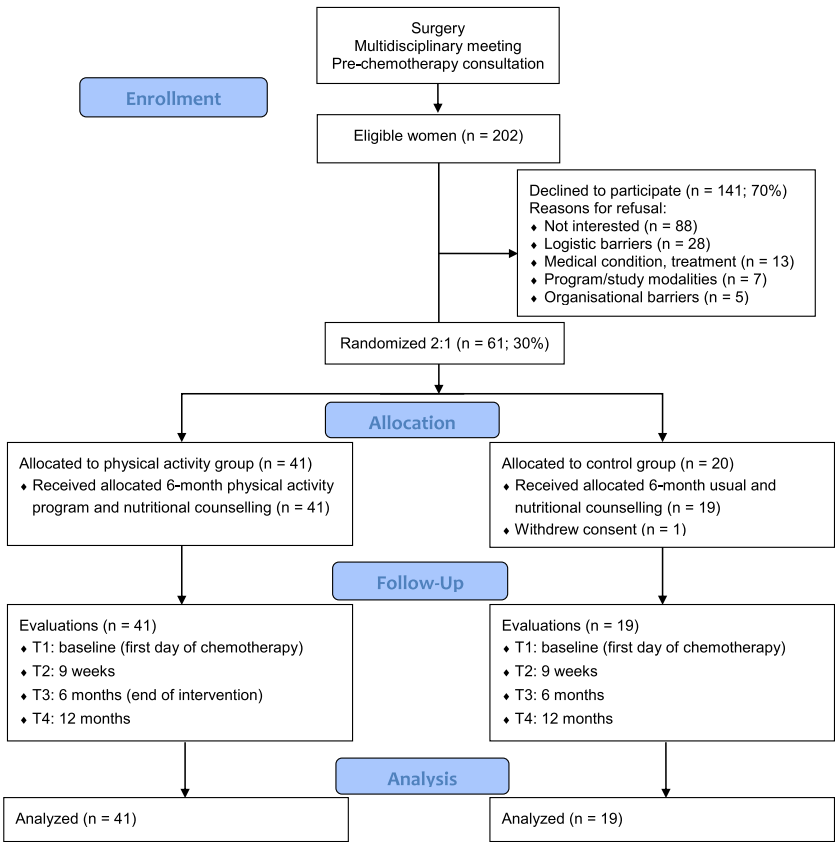

Fig. 1 CONSORT flow diagram of the PASAPAS randomized controlled trial

Table 1 Sociodemographic and clinical characteristics of patients in the PASAPAS trial at baseline overall and by group ($N = 60$)

Characteristics	Overall ($N = 60$)	Exercise group ($n = 41$)	Usual care group ($n = 19$)
Age (years), median (min-max)	52.7 (26.2–71.5)	53.9 (26.2–71.5)	49.4 (27.0–69.3)
Menopausal status, *n* (%)			
Premenopausal	23 (38.3)	16 (39.0)	7 (36.8)
Post- or perimenopausal[a]	32 (53.4)	22 (53.7)	10 (52.7)
Unknown	5 (8.3)	3 (7.3)	2 (10.5)
Family status, living with significant other, *n* (%)	49 (81.7)	33 (80.5)	16 (84.2)
Education status, *n* (%)			
No diploma or lower than high school	21 (35.0)	14 (34.1)	7 (36.8)
High school	8 (13.3)	7 (17.1)	1 (5.3)
University and higher	31 (51.7)	20 (48.8)	11 (57.9)
Occupational status, *n* (%)			
Retired, unemployed, or housewife	19 (31.7)	14 (34.1)	5 (26.3)
Professional activity at T1	6 (10.0)	5 (12.2)	1 (5.3)
On sick leave at T1	35 (58.3)	22 (53.7)	13 (68.4)
Smoking status, *n* (%)			
Current smoker	10 (16.7)	6 (14.6)	4 (21.1)
Former smoker	20 (33.3)	14 (34.1)	6 (31.6)
Never smoked	30 (50.0)	21 (51.2)	9 (47.4)
Personal medical history[b], *n* (%)	36 (60.0)	26 (63.4)	10 (52.6)
Cardiovascular	13 (60.0)	7 (17.1)	6 (31.6)
Respiratory	6 (10.0)	4 (9.8)	2 (10.5)
Diabetes	3 (5.0)	1 (2.4)	2 (10.5)
Dyslipidemia	7 (11.7)	5 (12.2)	2 (10.5)
Tumor histological type, *n* (%)			
Ductal	50 (83.3)	34 (82.9)	16 (84.2)
Lobular	7 (11.7)	6 (14.6)	1 (5.3)
Ductal and lobular	3 (5.0)	1 (2.4)	2 (10.5)
Tumor size, *n* (%)			
pT1	30 (50.0)	19 (46.3)	11 (57.9)
pT2 or pT3	29 (48.3)	21 (51.3)	8 (42.1)
pTx	1 (1.7)	1 (2.4)	0 (0.0)
Node stage, *n* (%)			
pN0	30 (50.0)	23 (56.1)	7 (36.8)
pN1	25 (41.7)	14 (34.1)	11 (57.9)
pN2 or pN3	4 (6.6)	3 (7.4)	1 (5.3)
pNx	1 (1.7)	1 (2.4)	0 (0.0)
SBR grade, *n* (%)			
I	6 (10.5)	4 (10.3)	2 (11.1)
II	26 (45.6)	18 (46.2)	8 (44.4)
III	25 (43.9)	17 (43.6)	8 (44.4)
ER status, positive, *n* (%)	44 (73.3)	29 (70.7)	15 (78.9)
PR status, positive, *n* (%)	40 (66.7)	26 (63.4)	14 (73.7)
HER2 status, positive[c], *n* (%)	13 (21.7)	9 (22.0)	4 (21.1)
Type of surgery before baseline, *n* (%)			
Tumorectomy	40 (66.7)	24 (58.5)	16 (84.2)
Mastectomy	20 (33.3)	17 (41.5)	3 (15.8)
Distance from home to cancer center (km), median (min-max)	10.3 (1.3–55.0)	8.9 (1.7–54.0)	12.0 (1.30–55.0)

pT pathological tumor size, *pTx* tumor size not evaluable, *pN* pathological regional lymph node metastases, *pNx* regional lymph nodes not evaluable, *SBR* Scarff-Bloom-Richardson, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

[a] Two perimenopausal patients in the intervention group

[b] Including also psychiatric, neurological diseases, and other unclassified diseases (data not shown)

[c] HER2 status, positive: IHC3+ or FISH+

After inclusion, 41 women were randomized to the intervention group and 20 women to the control group. One patient in the control group withdrew consent just after being randomized, leaving 60 evaluable participants, 41 in the intervention group, and 19 in the control group (Fig. 1). Participants were followed until June 2014.

At baseline (T1), all data were similar between groups (Tables 1 and 2). The majority was post-menopausal, had a university education or higher, was on sick leave since diagnosis, and lived a median of 10.3 km from the cancer center. Median BMI was 23.5 kg/m^2, 27 (45%) women were overweight or obese, 45 (75%) were metabolically obese including 18 (30%) who were normal-weight obese (i.e., high %BF despite normal weight BMI). The time spent in PA ≥ 3 METs was 14.30 h/week, including only 0.50 h/week in PAs ≥ 4 METs. Women spent 24.55 h/week in screen time activities. The DEE (1732 kcal/day) and energy intake (1688 kcal/day) were balanced.

Primary endpoints

Compliance with the exercise program

Four (10%) women were compliant with the entire program and 22 (54%) were compliant with 70% of the

Table 2 Nutritional characteristics of the patients of the PASAPAS trial at baseline overall and by group ($N = 60$)

	All ($N = 60$)	Exercise group ($n = 41$)	Usual care group ($n = 19$)
Anthropometric variables, median (min-max)			
Height (cm)	162 (146–174)	162 (147–174)	161 (146–174)
Weight (kg)	62.5 (40.0–115.0)	62.0 (45.0–115.0)	63.0 (40.0–112.5)
Body mass index (kg/m^2)	23.5 (17.7–44.9)	23.4 (17.7–44.9)	23.7 (18.8–40.8)
< 18.5 kg/m^2, *n* (%)	1 (1.7)	1 (2.4)	0 (0.0)
18.5–24.9 kg/m^2, *n* (%)	32 (53.3)	22 (53.7)	10 (52.6)
25.0–29.9 kg/m^2, *n* (%)	16 (26.7)	11 (26.8)	5 (26.3)
≥ 30.0 kg/m^2, *n* (%)	11 (18.3)	7 (17.1)	4 (21.1)
Waist circumference (cm)	85.0 (64.0–131.0)	85.0 (66.0–131.0)	85.0 (64.0–123.0)
≥ 80.0 cm, *n* (%)	38 (63.3)	24 (58.5)	17 (73.7)
Waist circumference/height	0.53 (0.40–0.82)	0.54 (0.41–0.82)	0.52 (0.40–0.74)
≥ 0.50, *n* (%)	35 (58.3)	23 (56.1)	12 (63.2)
Hip circumference (cm)	100.0 (85.0–133.5)	100.0 (87.0–133.5)	100.0 (85.0–128.0)
Body composition, median (min-max)			
%Body fat	34.7 (19.6–55.1)	35.7 (19.6–55.1)	33.7 (24.4–50.1)
Fat mass (kg)	20.8 (10.2–63.4)	20.5 (10.2–63.4)	21.3 (12.7–56.4)
Fat free mass (kg)	40.8 (26.0–56.5)	40.1 (28.8–56.5)	42.1 (26.0–56.1)
Physical activity and sedentary behavior, median (min-max)			
PA ≥ 3METs (h/week)	14.30 (2.69–28.23)	14.34 (2.69–28.23)	14.27 (4.72–27.26)
PA ≥ 4METs (h/week)	0.50 (0.00–8.33)	0.42 (0.00–8.33)	0.56 (0.00–6.98)
Screen time activities (h/week)	24.55 (0.00–62.63)	25.47 (0.00–62.63)	21.42 (1.67–51.27)
Estimated VO_{2max} (mL/min/kg)	26.5 (17.5–34.5)	26.1 (17.5–34.5)	27.9 (19.9–32.2)
Daily energy expenditure (kcal/day)	1732 (1450–2186)	1722 (1450–2186)	1802 (1467–2098)
Energy intake excluding alcohol (kcal/day)	1688 (765–2920)	1682 (1078–2920)	1726 (765–2273)
Alcohol (g/day)	1.3 (0.0–25.9)	1.4 (0.0–25.9)	1.2 (0.0–5.4)
Albuminemia (g/L)	44.0 (32.0–53.0)	44.0 (32.0–53.0)	44.0 (38.0–53.0)
Fasting glycemia (mmol/L)	5.05 (3.90–10.40)	4.90 (3.90–8.00)	5.30 (4.20–10.40)
Triglycerides (mmol/L)	0.85 (0.31–3.56)[b]	0.90 (0.31–2.35)[b]	0.77 (0.33–3.56)
Total cholesterol (mmol/L)	5.58 (3.08–8.71)[b]	5.55 (3.08–8.71)[b]	5.60 (4.06–7.10)
HDL cholesterol (mmol/L)	1.79 (0.93–3.11)[c]	1.82 (1.22–3.11)[b]	1.56 (0.93–2.60)[b]
LDL cholesterol (mmol/L)	3.35 (1.02–6.17)[c]	3.32 (1.02–6.17)[b]	3.52 (1.82–4.84)[b]

METs metabolic equivalents of task, VO_{2max} oxygen uptake, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

[a] One missing value

[b] Two missing values

[c] Four missing values

program (number of weeks with ≥ 2 supervised sessions).

Adherence to the exercise program

A total of 2146 sessions were planned for the 41 patients in the intervention group [median 50 (min-max 33–60) sessions per patient]. The median adherence to the program was 85% (0%–182%), counting supervised, non-supervised, and additional sessions. A total of 17 (41%) patients were adherent to the program (one woman attended all the sessions planned and 16 attended additional sessions). One patient attended none of the session. Among the sessions, 70.3% were planned supervised sessions and 29.7% were non-supervised or additional supervised sessions. More than half of the patients (54%) did not attend any non-supervised or additional supervised sessions during the week following chemotherapy. Three and two women requested personalized dietary care in the intervention and control groups, respectively.

The main intrinsic reasons for non-attendance to the exercise program session were medical (mainly second or reconstructive surgery; $n = 27$), logistic or organizational barriers ($n = 25$), and patients' vacations ($n = 18$) (Fig. 2). The main extrinsic reasons were the program being closed during vacations ($n = 17$) and cancelation of outdoor sessions due to weather conditions ($n = 15$). Women with higher educational level and those performing PA ≥ 4 METs at baseline were more likely to be adherent (OR = 11.42 [95% CI 2.10–62.23]; OR = 3.54 [95% CI 1.06–11.79], respectively). Patients with higher SBR tumor grade and those with greater baseline weight were less likely to be adherent (OR = 0.16 [95% CI 0.04–0.76]) and (OR = 0.92 [95% CI 0.85–0.99], respectively). Adherence did not differ with age, %BF, family status, duration of chemotherapy, and distance between home and cancer center. Satisfaction after the 6-month PA program was 8.6 (5.0–10.0) in the intervention group.

Safety

For the first 6 months, no serious adverse events occurred; 59 (98%) patients reported ≥ 1 non-serious adverse event related to either cancer treatment or the intervention. In the intervention group, adverse events that were certainly, probably, or possibly due to the exercise program according to the patient's judgment concerned 23 (56%) patients. These included fatigue ($n = 27$), various pain ($n = 28$), muscle pain or cramps ($n = 6$), asthenia ($n = 3$), dyspnea ($n = 1$), shortness of breath ($n = 1$), and altered general health ($n = 1$). They were classified as grade 1 severity (i.e., asymptomatic or mild, medical intervention not indicated; $n = 53$) or grade 2 (i.e., moderate severity, minimal medical intervention indicated; $n = 14$).

Secondary endpoints

There were no significant group effects for anthropometrics, body composition, PA level, and biological parameters and no interactions between time and groups (Table 3). The repeated-measure analysis of variance showed a time effect, with a statistically significant increase in PA ≥ 3 METs, PA ≥ 4 METs, and DEE at 6 months followed by maintenance at 12 months, a transitory improvement in body composition (decreased %BF, increased FFM) while anthropometrics were stable, a decrease followed by a stabilization of total cholesterol, LDL, and fasting glycemia, a transitory decrease in HDL, a transitory increase in triglycerides, and a transitory decrease in alcohol consumption at 6 months followed by a return to baseline values at 12 months (Table 4). Time spent in screen-time activities, aerobic capacity, and albuminemia did

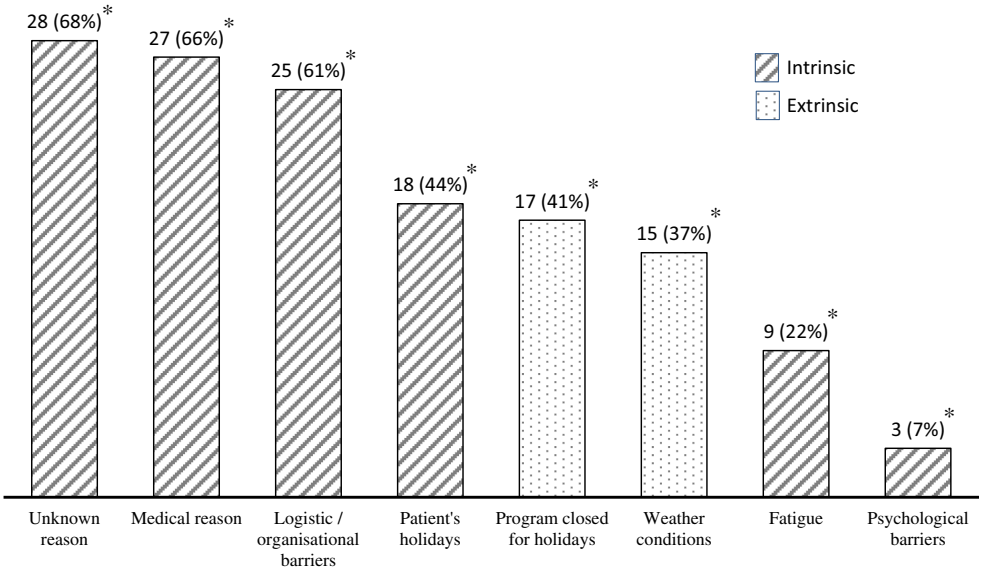

Fig. 2 Main intrinsic and extrinsic reasons for non-attendance for the exercise program ($n = 41$). Number (percentage) of women who missed ≥ 1 planned session and reported the reason at least once; *$n = 41$, ≥ 1 reason was possible

Table 3 Variations of characteristics during follow-up in the PASAPAS trial ($N = 60$)

Characteristics	Intervention group ($n = 41$)				Control group ($n = 19$)				Group × time interaction[a]	Group effect[a]	Time effect[a]
	Median (min-max)				Median (min-max)						
	T1	T2	T3	T4	T1	T2	T3	T4	*p*	*p*	*p*
Weight (kg)	62.0 (45.0–115.0)	63.0 (46.0–115.0)	60.5 (45.5–110.0)	62.0 (46.0–116.0)	63.0 (40.0–112.5)	62.0 (40.0–113.5)	61.0 (41.0–106.0)	63.0 (40.5–98.0)	0.67	0.48	0.07
BMI (kg/m^2)	23.4 (17.7–44.9)	23.9 (17.7–44.9)	23.2 (18.4–43.0)	23.6 (18.2–43.1)	23.7 (18.8–40.8)	23.9 (18.8–41.2)	23.5 (19.2–38.5)	23.4 (19.0–36.3)	0.63	0.83	0.07
Waist circumference (cm)	85.0 (66.0–131.0)	85.0 (67.5–132.0)	81.0 (67.0–128.0)	83.5 (68.0–126.0)	85.0 (64.0–123.0)	82.0 (64.0–126.0)	84.0 (65.0–121.5)	82.0 (64.0–111.5)	0.65	0.79	0.22
Waist circumference/height	0.54 (0.41–0.82)	0.54 (0.43–0.83)	0.51 (0.43–0.80)	0.51 (0.43–0.78)	0.52 (0.40–0.74)	0.54 (0.42–0.76)	0.52 (0.43–0.73)	0.52 (0.44–0.68)	0.28	0.94	0.29
Hip circumference (cm)	100.0 (87.0–133.5)	97.0 (88.0–134.0)	98.0 (87.5–132.0)	100.0 (89.0–137.0)	100.0 (85.0–128.0)	100.0 (85.0–123.0)	101.5 (86.0–121.0)	102.0 (87.0–120.0)	0.88	0.43	0.007
% Body fat	35.7 (19.6–55.1)	35.3 (17.6–53.7)	33.7 (14.6–55.1)	35.7 (17.8–53.0)	33.7 (24.4–50.1)	32.2 (23.3–51.6)	33.9 (22.5–46.2)	33.8 (25.8–46.8)	0.90	0.55	< 0.001
Fat mass (kg)	20.5 (10.2–63.4)	19.1 (9.5–61.8)	18.7 (9.8–60.6)	20.7 (8.8–58.8)	21.3 (12.7–56.4)	19.0 (12.7–69.1)	19.5 (13.6–48.1)	20.3 (14.4–45.4)	0.96	0.96	< 0.001
Fat free mass (kg)	40.1 (28.8–56.5)	41.7 (30.6–55.8)	41.3 (29.2–59.9)	39.9 (29.6–57.2)	42.1 (26.0–56.1)	42.8 (27.3–57.90)	43.5 (27.1–57.9)	43.2 (26.1–55.5)	0.35	0.16	0.016
PA ≥ 3 METs (h/week)	14.34 (2.69–28.23)	11.44 (2.39–28.03)	15.32 (3.92–37.39)	14.80 (3.10–29.85)	14.27 (4.72–27.26)	12.37 (4.90–29.18)	13.10 (4.87–36.45)	16.22 (7.06–55.49)	0.40	0.85	0.012
PA ≥ 4 METs (h/week)	0.42 (0.00–8.33)	0.83 (0.00–8.24)	1.88 (0.00–7.28)	1.66 (0.00–10.78)	0.56 (0.00–6.98)	0.70 (0.00–3.46)	1.07 (0.09–7.12)	1.29 (0.19–5.78)	0.11	0.69	< 0.001
Screen time activities (h/week)	25.47 (0.00–62.63)	26.95 (7.21–72.73)	24.65 (0.87–57.87)	21.87 (5.52–38.74)	21.42 (1.67–51.27)	21.93 (5.12–49.00)	20.35 (1.38–39.36)	17.46 (0.11–57.36)	0.97	0.38	0.07
Estimated VO_{2max} (mL/min/kg)	26.1 (17.5–34.5)	25.8 (16.3–33.2)	26.9 (16.9–34.1)	26.6 (16.9–35.3)	27.9 (19.9–32.2)	27.2 (21.0–33.1)	27.1 (19.7–32.9)	28.0 (21.1–32.9)	0.13	0.41	0.36
Daily energy expenditure (kcal/day)	1722 (1450–2186)	1751 (1488–2006)	1839 (1465–2253)	1794 (1509–2220)	1802 (1467–2098)	1792 (1466–1938)	1823 (1531–2202)	1824 (1590–2373)	0.13	0.66	< 0.001
Energy intake excluding alcohol (kcal/day)	1682 (1078–2920)	–	1681 (1031–3100)	1552 (833–3399)	1726 (765–2273)	–	1686 (1023–2478)	1608 (1120–2045)	0.98	0.70	0.26
Alcohol (g/day)	1.4 (0.0–25.9)	–	0.7 (0.0–41.2)	1.7 (0.0–28.7)	1.2 (0.0–5.4)	–	0.6 (0.0–10.0)	1.1 (0.0–8.6)	0.22	0.14	0.001
Albuminemia (g/L)	44.0 (32.0–53.0)	42.0 (33.0–52.0)[b]	43.0 (30.0–48.0)[b]	44.0 (33.0–50.0)	44.0 (32.0–53.0)	41.0 (34.0–48.0)[b]	43.0 (36.0–48.0)	42.50 (11.0–48.0)[b]	0.50	0.28	0.19
Fasting glycemia (mmol/L)	4.90 (3.90–8.00)	5.25 (3.30–8.60)[d]	4.50 (3.10–7.40)[b]	4.60 (3.10–7.00)	5.30 (4.20–10.40)	5.90 (4.30–9.60)	4.70 (3.70–7.80)	4.70 (1.60–6.40)[b]	0.73	0.41	< 0.001
Triglycerides (mmol/L)	0.90 (0.31–2.35)[b]	1.02 (0.49–2.54)[b]	1.10 (0.52–2.66)[b]	0.97 (0.49–2.65)	0.77 (0.33–3.56)	1.43 (0.37–3.95)	1.28 (0.34–5.51)	0.98 (0.44–2.63)[b]	0.25	0.93	< 0.001
Total cholesterol (mmol/L)	5.55 (3.08–8.71)[b]	5.87 (3.71–9.07)	5.30 (3.26–8.08)[b]	5.03 (3.34–10.40)	5.60 (4.06–7.10)	5.74 (3.90–9.15)	4.99 (3.78–9.19)	4.86 (1.29–8.42)[b]	0.96	0.51	< 0.001
HDL cholesterol (mmol/L)	1.82	1.68	1.68	1.78	1.56	1.34	1.51	1.53	0.92	0.07	0.004

Table 3 (continued)

Characteristics	Intervention group (n = 41)				Control group (n = 19)				Group × time interaction[a]	Group effect[a]	Time effect[a]
	Median (min-max)				Median (min-max)						
	T1	T2	T3	T4	T1	T2	T3	T4	p	p	p
LDL cholesterol (mmol/L)	(1.22–3.11)[b] 3.32 (1.02–6.17)[b]	(0.76–3.41)[b] 3.82 (1.64–5.88)[b]	(0.99–2.98)[c] 2.96 (1.07–5.51)[b]	(1.02–3.42) 2.64 (1.21–6.52)	(0.93–2.60)[c] 3.52 (1.82–4.84)[c]	(0.82–2.79) 3.69 (1.49–5.05)[b]	(0.74–2.07) 2.85 (1.73–4.23)[b]	(0.23–4.08)[b] 3.02 (2.01–6.26)[c]	0.31	0.85	< 0.001

T1: baseline, T2: 9 weeks, T3: 6 months, T4: 12 months

METs metabolic equivalents of task, VO_{2max} oxygen uptake, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *BMI* body mass index

[a] Repeated-measures analysis of variance on ranks

[b] One missing value

[c] Two missing values

[d] Three missing values

not significantly change over the 1-year monitoring (Table 3). Most women (> 70%) successfully maintained or decreased their weight, waist circumference, and %BF, and maintained or increased their FFM.

During the first 6 months in the entire cohort, significant correlations between relative increase in PA ≥ 4 METs and a relative decrease in weight ($\rho = -0.31$, $p = 0.01$) and in fat mass ($\rho = -0.36$, $p = 0.004$) were observed. No correlations were observed with PA ≥ 3 METs. We also observed significant correlations between the relative decrease in sedentary behavior and the relative decrease in weight ($\rho = 0.29$, $p = 0.02$), in waist circumference ($\rho = 0.34$, $p = 0.008$), and in fat mass ($\rho = 0.29$, $p = 0.03$). Significant associations of the absolute decrease in sedentary behavior were observed with the absolute decrease in total cholesterol ($\rho = 0.30$, $p = 0.03$) and fasting glycemia ($\rho = 0.28$, $p = 0.04$).

Discussion

The PASAPAS trial showed that implementing a 6-month supervised exercise program, in addition to usual care, was feasible and safe during adjuvant treatment for localized BC in a French population. Although a small proportion of patients attended all or more than the two planned weekly supervised sessions, the global adherence to the program (overall volume of supervised and non-supervised sessions) was high. All patients finished the intervention as planned in the protocol and expressed high satisfaction. The observed 85% adherence rate for the exercise sessions was similar to or higher than that previously reported [18, 27, 28]. In one review, the adherence rate was higher than 60% in more than 50% of the studies [29].

The main reasons for non-adherence were treatment or disease-related adverse events and organizational barriers, similar to other studies conducted during chemotherapy [30]. A focus group highlighted that barriers to adherence to home-based PA programs during chemotherapy were side effects of chemotherapy, hospital admissions due to treatment complications, and body image [31]. In interventional studies, the patients' barriers were time constraints, change in physical appearance, and insufficient social support [32–34]. Other barriers to exercise sessions reported by patients have been procrastination, fatigue following exercise, and difficulties finding a bra suitable for exercise [35].

We found that higher education, being more active and slimmer at baseline, and a lower tumor grade were associated with better adherence to exercise, consistent with previous reports [32, 36]. In the PASAPAS trial, adherence did not differ according to the duration of the chemotherapy, unlike in other studies where adherence was better with shorter chemotherapy or when the exercise intervention was proposed post-treatment [36, 37]. We assume that multimodal program combining supervised and home-based sessions would improve adherence

by being more flexible [38, 39]. The exercise sessions could be possible during the week following chemotherapy for some patients. Various modalities could be proposed, such as flexible schedules, diverse program duration and session frequency [40, 41], diverse locations of practice [36], therapeutic education, and behavioral and mindfulness-based methods.

The absence of significant benefit from the intervention in the exploratory analyses was probably due to selection bias due to the enrolled women being aware of exercise and being highly motivated, contamination in the control group and the small sample size [28, 29]. Nevertheless, there was a trend to improved anthropometrics, body composition, and PA profile in the intervention group compared with the control group, which improved cholesterolemia and glycemia, consistent with previous studies [11] although the majority of BC patients gain weight and their body composition deteriorates before and during treatment [3, 12, 25]. Follow-up at 12 months showed that improvement was temporary, which supports the need of continued incentives to maintain PA behavior.

Study strengths

Compared with previous studies, this trial was original in the timing of the intervention, since the program started at chemotherapy onset, and continued for the duration of the adjuvant chemotherapy and radiotherapy treatment, thus lasting for up to 26 weeks. The feasibility of exercise as early as possible is an important point for the development of new complementary strategies in BC care since patients usually show a deterioration in PA level and metabolic risk factors since the diagnosis [25]. Also, the location, supervision, modality, and the choice of PA were original. The feasibility of the exercise program could be of interest to other countries that have a lower percentage of physically-active individuals compared with other EU countries [42, 43]. Only one patient withdrew consent after randomization, none of the patients were lost-to-follow-up compared with 15% in a similar trial [18]. Missing values were below 1%. There was comprehensive reporting of PA-related adverse events although there are

Table 4 Characteristics variations during follow-up of the PASAPAS trial measured at four time points (T1: baseline, T2: 9 weeks, T3: 6 months, T4: 12 months) with statistically significant time effect in repeated-measures analysis of variance on ranks ($p < .05$) ($N = 60$)

	All ($N = 60$)			
	Median (min-max)			
	T1	T2	T3	T4
Hip circumference (cm)	100.0 (85.0–133.5)[a]	99.0 (85.0–134.0)[a]	100.5 (86.0–132.0)[a]	101.0 (87.0–137.0)
%Body fat (%)	34.7 (19.6–55.1)	33.5 (17.6–53.7)[b]	33.7 (14.6–55.1)[b]	34.5 (17.8–53.0)
Fat mass (kg)	20.8 (10.2–63.4)[c]	19.0 (9.5–69.1)[c, d]	19.1 (9.8–60.6)[d]	20.3 (8.8–58.8)
Fat free mass (kg)	40.8 (26.0–56.5)[e]	42.4 (27.3–57.9)[f]	41.7 (27.1–59.9)[f]	40.8 (26.1–57.2)[e]
Time spent in physical activity ≥ 3 METs (h/week)	14.30 (2.69–28.23)[g, h]	11.72 (2.39–29.18)[g]	14.45 (3.92–37.39)[h, i]	14.92 (3.10–55.49)[i]
Time spent in physical activity ≥ 4 METs (h/week)	0.50 (0.00–8.33)[j]	0.79 (0.00–8.24)[j]	1.73 (0.00–7.28)[k]	1.57 (0.00–10.78)[k]
Daily energy expenditure (Kcal/day)	1732 (1450–2185)[l]	1769 (1466–2006)[l]	1838 (1465–2253)[m]	1803 (1508–2373)[m]
Alcohol (g/day)	1.4 (0.0–25.9)[n]	–	0.7 (0.0–41.2)	1.6 (0.0–28.7)[n]
Fasting glycemia (mmol/L)	5.05 (3.90–10.40)	5.30 (3.30–9.60)[δ]	4.60 (3.10–7.80)[o; α]	4.60 (1.60–7.00)[o; α]
Triglycerides (mmol/L)	0.85 (0.31–3.56)[β]	1.18 (0.37–3.95)[p, q; α]	1.14 (0.34–5.51)[p; α]	0.97 (0.44–2.65)[q; α]
Total cholesterol (mmol/L)	5.58 (3.08–8.71)[r; β]	5.83 (3.71–9.15)[r]	5.26 (3.26–9.19)[s; α]	5.03 (1.29–10.40)[s; α]
HDL cholesterol (mmol/L)	1.79 (0.93–3.11)[t; ε]	1.54 (0.76–3.41)[u; α]	1.64 (0.74–2.98)[u, v; β]	1.65 (0.23–4.08)[t, v; α]
LDL cholesterol (mmol/L)	3.35 (1.02–6.17)[ε]	3.78 (1.49–5.88)[β]	2.90 (1.07–5.51)[w; δ]	2.68 (1.21–6.52)[w; β]

[a–w] Same letter indicates no significant difference ($p > .05$)

[α] One missing value. [β] Two missing values. [δ] Three missing values. [ε] Four missing values

METs metabolic equivalents of task, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein; %BF percentage of body fat, PA physical activity

All anthropometrics were stable during the 1-year follow-up except hip circumference that significantly increased during the 6-month follow-up following intervention and adjuvant treatments (T3 to T4, $p < .05$). %BF significantly decreased during the 6-month intervention (T1 to T3, $p < .05$) then significantly increased during the next 6-month follow-up (T3 to T4, $p < .05$) without reaching the baseline values (T1 to T4, $p < .05$). Inversely, fat free mass significantly increased during intervention (T1 to T3, $p < .05$) then significantly decreased during follow-up (T3 to T4, $p < .05$) without reaching the baseline values (T1 to T4, $p < .05$). Moderate (≥ 3 METs) PA, moderate-to-vigorous (≥ 4 METs) PA and daily energy expenditure significantly increased and fasting glycaemia, total cholesterol and LDL cholesterol significantly decreased during intervention (T1 to T3, $p < .05$ for all), then all remained steady for the next 6-month follow-up (T3 to T4, $p \geq .05$ for all). HDL cholesterol decreased during chemotherapy (T1 to T2, $p < .05$) then progressively returned to baseline values (T1 to T4, $p \geq .05$). Triglycerides significantly increased during intervention (T1 to T3, $p < .05$) then significantly decreased during the 6-month follow-up (T3 to T4, $p < .05$) without reaching the baseline values (T1 to T4, $p < .05$). Alcohol intake decreased significantly during the 6-month intervention (T1 to T3, $p < .05$) then returned to the baseline value (T1 to T4, $p \geq .05$)

only sparse data for the safety of exercise in BC survivors [44].

Study limitations

One limitation of our study is that measurement errors and reporting bias cannot be ruled out as PA questionnaires and diaries are subjective and non-exhaustive assessments. This could increase the risk of over- or under-estimation by the patients. Second, although there was no recruitment bias with respect to age, BMI, and tumor grade, we cannot exclude a selection bias through women highly motivated for PA, which may limit generalizability of the findings. This is a dilemma in PA intervention trials, since enrolled patients are the most likely to adhere but not the most likely to benefit [36]. Third, although the sample size was sufficient to explore the primary objective, the statistical power for the secondary outcomes may be limited. Fourth, contamination in the control group and the medium adherence in the intervention group could have increased the risk of effect dilution [28]. Baseline PA evaluations, possible compensatory response of evaluators and the sensitization of patients by counseling probably had an impact on feedback, self-evaluation, and reflexivity for patients about their behavior.

Conclusions

Exercise programs for BC patients should be flexible in terms of the activities offered and the schedule. The challenge for PA interventions is to allow all patients to practice regular PA both during and after treatment since regular PA could increase survival after BC diagnosis. Our results suggest that there is a need to develop innovative methodologies to overcome the challenge of evaluating complex interventions and the study should be implemented in a real-life setting with long-term follow-up. Future trials also need to focus on barriers and facilitators for regular PA.

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Authors' contributions AMF, ASKL, CB, RM, SG, VBB, DP, SB, ER, LP, PB, BF, OT, and MT contributed to conception and design of the trial. PB, BF, and OT were principal investigators. PR, PEH, TB, and OT were investigators. AMF, ASKL, CB, RM, SG, SM, VBB, EG, JC, SB, ER, PB, BF, OT, and MT acquired the data. MM and SC analyzed the data. AMF, MM, SB, PB, BF, OT, and MT participated in the interpretation of the findings. AMF, MM, BF, and MT drafted the manuscript. All of the authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the French Sud-Est IV ethics committee (Comité de Protection des Personnes), the National Security Agency of Medicines and Health Products that applies for biomedical studies (Agence Nationale de Sécurité du Médicament et des produits de santé), and the French National Committee on Informatics and Privacy (Commission Nationale de l'Informatique et des Libertés).

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

Abbreviations %BF, percentage of body fat; APA, adapted physical activity; BC, breast cancer; BMI, body mass index; CI, confidence interval; DEE, daily energy expenditure; FFM, fat free mass; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent of task; PA, physical activity; OR, odds ratio; SBR, Scarff-Bloom-Richardson

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