# Design of a randomized controlled trial of adapted physical activity during adjuvant treatment for localized breast cancer: the PASAPAS feasibility study

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# Design of a randomized controlled trial of adapted physical activity during adjuvant treatment for localized breast cancer: the PASAPAS feasibility study

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## Abstract

**Introduction**: After a diagnosis of localized breast cancer, overweight, obesity and weight gain are negatively associated with prognosis. In contrast, maintaining an optimal weight through a balanced diet combined with regular physical activity appears to be effective protective behaviours against comorbidity or mortality after a breast cancer diagnosis. The primary aim of the PASAPAS randomized controlled trial is to evaluate the feasibility of implementing an intervention of adapted physical activity (APA) for 6 months concomitant with the prescription of a first line of adjuvant chemotherapy. Secondary aims include assessing acceptability of the intervention, compliance to the program, process implementation, patients' satisfaction, evolution of biological parameters and medico-economic impact of the intervention.

**Methods and analysis**: The study population consists in 60 women eligible for adjuvant chemotherapy after a diagnosis of localized invasive breast cancer. They will be recruited during a 2-year inclusion period and randomly allocated between an APA intervention arm and a control arm following a 2:1 ratio. All participants should benefit from personalized dietetic counselling and patients allocated to intervention arm will be offered an APA program of two to three weekly sessions of Nordic walking and aerobic fitness. During the 6-month intervention and 6-month follow-up, four assessments will be performed including blood draw, anthropometrics and body composition measurements, and questionnaires about physical activity level, diet, lifestyle factors, psychological criteria, satisfaction for the intervention and medical data.

**Ethics and dissemination**: The study was approved by the local ethics review board (Comité de Protection des Personnes Sud-Est IV) and the national agencies for biomedical studies and for privacy. All participants will give written informed consent. Study findings will be disseminated

through the scientific public and serve for foundation of future randomized controlled trials of efficacy.

## Article summary

**Article focus:** This article presents the rationale and protocol for a single-centre randomized controlled trial, which was designed to evaluate the feasibility of implementing a 6-month program of adapted physical activity among breast cancer patients undergoing adjuvant chemotherapy.

**Key messages:** The study results will provide feasibility evidence and preliminary data for a future full-scale multicenter randomized controlled trial testing the effectiveness of a physical activity program during breast cancer treatment on survival-related outcomes.

This study should help transpose the international evidence for physical activity benefits after a breast cancer diagnosis to the French population and context, given major cultural and lifestyle differences.

**Strengths and limitations of this study:** The physical activity program presented has the advantage of being performed during breast cancer adjuvant treatment, personalized and supervised by trained professionals. It reflects growing evidence showing the necessity to maintain or start physical activity as soon as possible after a cancer diagnosis and avoid loss of physical fitness. As most feasibility studies, sample size is small. But the study will test procedure adequacy for formalizing the design of a definitive trial.

## Introduction

Throughout the world, breast cancer is the leading cause of cancer in women and the leading cause of cancer death, with circa 1,383,500 new cases and 458,400 deaths in 2008.[1] Thanks to progress in diagnostic tools, care and treatments in Western countries, survival after diagnosis is greater than 80% at 5 years.[2] Overall, breast cancer seems to be a disease of developed countries and particularly affects Western countries or those with a Western lifestyle. Therefore, it is important for breast cancer patients and survivors to maintain optimal health and minimize the deleterious effects of cancer and its treatment such as fatigue, stress, anxiety or obesity. Weight gain in adulthood,[3] overweight, obesity,[4] the lack of physical activity[5] and alcohol consumption are risk factors commonly associated with risk of breast cancer (mainly in post-menopause for overweight and obesity).[6] After a diagnosis of breast cancer, obesity appears to double the risk of recurrence and death in these patients, regardless of the state of menopause.[7;8] Weight gain after diagnosis is also recognized as a risk factor for increased risk of recurrence and mortality and increases the risk of comorbidities.[8;9] In contrast, physical activity done appropriately could improve many prognostic factors as well as survival in women after breast cancer. Several large cohort studies of women with breast cancer have shown an average reduction of 45% mortality associated with moderate exercise compared to sedentary lifestyle.[10-14] Randomized control trials have also shown that physical activity improves fitness, quality of life, self-esteem and treatment adherence and reduces fatigue.[7;15;16] Thus, maintaining an optimal weight through a balanced diet combined with regular physical activity appear to be effective protective behaviours against breast cancer as well as comorbidity or mortality after a diagnosis of breast cancer.[11]

Observational cohorts of breast cancer patients conducted in France have shown that currently almost half of French patients are overweight or obese at diagnosis,[9;17] then nearly half gain weight within one year after chemotherapy.[17] Patients treated for breast cancer practice less physical exercise of moderate to vigorous intensity than the healthy population for a similar energy expenditure.[18] Indeed, reduced physical activity is a factor most likely implicated in weight gain among women receiving adjuvant chemotherapy for localized breast cancer.[19-21] Given the poor prognosis associated with overweight, weight gain and insufficient physical activity, supportive care including physical activity and dietetic care is necessary in breast cancer patients.

Despite the encouraging results of mainly North American studies on the impact of physical activity after breast cancer, no intervention studies of physical activity were conducted until recently in France.[22] Therefore, our aim was to transpose the international evidence to the French population and context, given major cultural differences concerning food, the practice of physical activity and other lifestyle-related factors with North American populations. In this article, we described the design of the randomized controlled trial PASAPAS (acronym for “Programme pour une Alimentation Saine et une Activité Physique Adaptée pour les patientes atteintes d’un cancer du Sein” in French, meaning "Program for healthy eating and adapted physical activity for patients with breast cancer" in English). This study aims at evaluating the feasibility in human, material and financial terms of implementing an individualized program of dietary counselling and adapted physical activity (APA) in a French population of women being treated for breast cancer. The APA intervention program was tailored to prevent the risk of

overweight, obesity or weight gain and to maintain and/or increase the patients' physical activity level.

The main objective of the PASAPAS study is to evaluate, in a cohort of adult patients with a first localized (i.e., non-metastatic) breast cancer, the feasibility of implementing an APA intervention for 6 months, in addition to a dietary management, concomitant with the prescription of a first line of adjuvant chemotherapy (which lasts between 12 and 18 weeks according to the protocol). Secondary objectives are to: (i) assess the acceptability of the intervention and randomization and the recruiting capabilities; (ii) assess the patients' adherence to the intervention program and analyze of the reasons for non-adherence; (iii) verify the adequacy between the procedures of the intervention program (APA and dietetic), as well as the data collection and management, and the constraints of implementing the study in real conditions; (iv) describe the patients' satisfaction with the dietetic and APA programs ; (v) perform a health economics analysis; (vi) describe baseline state and evolution of a numbers of variables (physical activity level and profile, dietary intake, anthropometrics, body composition, lipid profiles, quality of life, body satisfaction/self-perception, self-esteem, depression, anxiety); (vii) finally, as part of a joint biological study, describe metabolomic profiles, lipidomic profiles, as well as the expression of endocrine factors and adipokines linked to breast cancer at initial diagnosis (i.e., comparing between tumor and circulating blood before surgery in a cross-sectional study) and metabolic changes during the interventions (longitudinal study).

## Methods and Design

## Study design

The PASAPAS study is an interventional, controlled, randomized, single centre, open label, parallel-group study with two arms: an intervention (or "APA") group where patients are invited to a 6-month exercise program in supervised groups in addition to usual and personalized dietetic care; a control group receiving usual dietetic care and physical activity national guidelines. The 6-month intervention is followed by a 6-month monitoring, that is a 12-month study duration for each participant. The enrolment is planned over a period of 24 months, which corresponds to a total study duration of 36 months.

The trial was registered on the website www.clinicaltrials.gov (registration number: NCT01331772).

## Study participants

*Inclusion criteria*

The study sample is composed of adult women, aged 18 years or older and under 75 years, being diagnosed with a first invasive non-metastatic breast carcinoma that has been histologically confirmed, and requiring the prescription for a first line of adjuvant chemotherapy. Other inclusion criteria are: being treated in the clinical site (Léon Bérard Cancer Centre, Lyon, France); being able to participate in the APA intervention and providing a medical certificate of no contraindications to exercise issued by the general practitioner, the referring physician or the main investigator physician; living within a 60-km perimeter and agreeing to support travel expenses to attend group exercise sessions; available and willing to participate in the PASAPAS study for the duration of the program (6 months) and during the post-program monitoring (6 months); able to understand, read and write French; affiliated with a social security system; having dated and signed informed consent.

*Non-inclusion criteria*

Non-inclusion criteria are: woman with metastatic or inflammatory breast cancer; personal history or coexistence of another primary carcinoma (except another *in situ* carcinoma regardless of the site and/or basal cell skin carcinoma and/or non-mammary cancer in complete remission for more than 5 years); contraindications to exercise according to the investigator such as serious or unstable cardiac or respiratory pathology, uncontrolled diabetes, bone metastases and severe osteoporosis; state of severe malnutrition under the criteria of the French National Health Authority [23]; personal history of eating disorders; unable to be followed for medical, social, family, geographical or psychological reasons, for the study duration; deprived of their liberty by court or administrative decision; pregnant or nursing or of childbearing age without effective contraception during the study.

**Recruitment and randomization**

Patients eligible for the study are identified during the multidisciplinary meeting following surgery. They are presented and offered the study protocol by the oncologist during the consultation done for planning the chemotherapy (pre-chemotherapy consultation). If a patient agrees to participate, she has to sign an informed consent form. Inclusion and randomization are conducted within 15 days before the start of chemotherapy (Figure 1). Participants are randomly allocated between the APA intervention arm and the control arm following a 2:1 ratio in favour of APA intervention.

**Interventions**

*Dietetic intervention*

All participants (both intervention and control arms) benefit from dietetic and physical activity support, according to the recommendations of the second French National Health and Nutrition

Program (PNNS2).[24] At the first visit (beginning of adjuvant chemotherapy), the participants meet the dietician and receive individualized dietary counselling according to dietary analysis, and a print material (entitled "Tips for a healthy diet and practicing physical activity" and labelled in accordance with the PNNS2). Moreover, a dietary management is offered to each participant; in case of acceptance, dietetic consultations are offered on patient's request for the duration of the intervention (6 months).

*APA intervention*

Women randomized to the intervention arm are offered, in addition to dietary management (see Dietetic intervention), to participate in group sessions of APA over a period of 6 months, including: (i) two sessions per week throughout the duration of chemotherapy (four to six 3-week courses depending on the protocol, i.e., for 12-18 weeks), except during the first week of each course as a recovery from exercise and to take into account fatigue and other side effects related to chemotherapy; (ii) three sessions per week after cessation of chemotherapy, until the end of the 6-month intervention (i.e., for 8-14 weeks). For the duration of chemotherapy, the APA program includes one session of Nordic walking outdoors and one session of aerobic fitness indoors (combining cardiovascular workouts such as step, muscle strengthening and stretching or relaxation) per week. After chemotherapy, the APA program includes two sessions of Nordic walking and one session of aerobic fitness per week.

The group sessions of maximum eight patients are supervised by an APA professional. Exercises consists in aerobic of moderate intensity (4-6 METs) adapted according to the initial physical activity profile of each participant. The APA program is an individualized exercise according to co-morbidities and defined by the PA level (jointly defined by PA profile or time spent in physical activities of different intensities and by aerobic capacity) and the body composition

status. Each session comprises a warm-up of 10 min, a core period (20-30 minutes for aerobic fitness exercise or 30-40 min for Nordic walking) and a cool-down period of 10 min. The progressive increase in workload is conducted by an increased frequency (from two sessions early in the program to three sessions at the end of program), then the actual duration and, lastly (after the end of chemotherapy) the intensity upon patient's desire and capacity. In all cases, the intensity of activity remains less than 80 % of age-adjusted maximal heart rate [equal to 220 – age expressed in years].

Attending the group sessions is required to determine the compliance of each participant to the APA program, but participants are free to practice more exercise individually or attend additional group sessions. In case a participant cannot attend a group session (for medical or personal reason or for exceptional circumstances such as holidays), she must replace it the same week by an individual session of another aerobic exercise (e.g., Nordic walking, free-swimming, hiking, biking), which is planned in advance with the APA professional; this intends to avoid a decrease in physical fitness. To verify attendance in the program, exercise is recorded in a notebook and the number of steps is recorded by a pedometer given to participants.

If side effects occur during 3-week cycles of chemotherapy, patients may be prescribed a weekly chemotherapy (mainly paclitaxel). The APA program remains the same for these patients, meaning they have no session during each weekly chemotherapy cycle and resume APA at the end of chemotherapy, but they can attend group sessions if they wish.

**Data collection and evaluations**

As part of this study, patients of both arms are followed over a total duration of 12 months (i.e., for the 6-month dietetic and APA intervention program and a 6-month follow-up after the intervention). Four evaluations are performed (see Figure 1): at baseline (T1, day 1 of

chemotherapy), at 9 weeks (T2, day 1 of the fourth 3-week course of chemotherapy), at 26 weeks ± 1week (T3, end of the intervention 6 months after initiation of chemotherapy) and at 52 weeks ± 4 weeks (T4, end of the 6-month follow-up post-intervention), which corresponds to the end of the study for patients. All following data are collected at each evaluation, except dietary and psychological assessments that are performed at T1, T3 and T4 only and patients' satisfaction for the intervention in both arms that is evaluated at T3 only.

*Physical activity*

The level and profile of physical activity are assessed at each evaluation using the PAQAP© questionnaire[25] administered by interview; the IPAQ questionnaire is filled at the same time for international comparison. Physical activity before the time of diagnosis is also assessed retrospectively at T1, to distinguish between activities that are no longer practiced since diagnosis and new activities practiced since surgery. The PAQAP© questionnaire provides the estimated aerobic capacity ($\dot{V}O_{2max}$, ml/min/kg), usual average daily energy expenditure (kJ/day), physical activity profile (i.e., time spent in activities of the following intensities: below 2 METs or sedentary, 2–2.9 METs, 3–3.9 METs, 4–5.9 METs, 6–9.9 METs, and >10 METs) and time spent sitting and lying.

*Anthropometrics and body composition*

The following anthropometric data is measured at each evaluation: weight (kg) using the same scale throughout the study, height (cm) using a fathom, waist circumference (cm) and hip circumference (cm) using a measuring tape. For standardizing measurements, waist circumference is measured midway between the last floating rib and the iliac crest and the hip circumference is measured at the tip of the pubis. Body mass index (BMI) is calculated as weight

(kg) divided by the square of height (m). Weight one month ago (close to surgery), 6 months ago (close to diagnosis) and one year ago is also declared retrospectively at baseline.

Risk of metabolic diseases is identified for this population as follows: metabolic risk[26] if waist circumference to height ratio >0.5; insulin-resistance risk[27] if waist circumference >80cm; and additionally cardiovascular risk[28] if waist circumference >88cm.

Body composition is evaluated using a multifrequency bioelectrical impedance analysis (QuadScan4000, Bodystat®; measure duration of about 30 seconds, after lying for 10 minutes) that provides body fat (%, kg), lean mass (%, kg), dry lean mass, basal metabolic rate, basal metabolic rate to weight ratio and body water (%, l; total, intracellular, extracellular). Normal-weight obese women are identified using the waist circumference and more particularly the percentage of body fat in comparison to BMI status.[29;30] Body composition is also assessed at the time of diagnosis by analysing a CT-scan (systematically done for clinical management) at the L3 lumbar position and measuring the area occupied by adipose (subcutaneous and visceral) and lean tissue (Slice-O-Matic Software, V4.3, Tomovision).

*Nutritional intake*

Dietary intake is assessed by a 3-day food diary (two week days and one week-end day) completed by the patient the week preceding the evaluation and reviewed by the dietician using standardized portions.[31] A dietary analysis using the GENI software (Micro 6, Villers-les-Nancy, France, version 7.4) provides caloric, macronutrient and fluid intake. The dietician also assesses usual consumption of alcoholic beverages over the preceding 6 months, the use of dietary supplements and the compliance with the PNNS2 guidelines.[32]

*Biological samples*

A fasting blood sample is collected at each evaluation as part of the biological study (in particular, blood will be drawn before infusion of chemotherapy at T1 and T2). Two tubes are drawn each time (one dry tube of 10 ml and one EDTA tube of 10 ml). Blood parts (i.e., serum, plasma and buffy coat) are separated and stored in aliquots of 300 µl in liquid nitrogen. After completion of the study, the following analyses will be performed longitudinally:

- Levels of plasma biomarkers of dietary intake of antioxidants (total carotenoids, lycopene, β-carotene, α-tocopherol);

- Lipidomics analysis: complete profile of about 50 fatty acids, including the circulating levels of saturated, monounsaturated *cis*, n-6 polyunsaturated, n-3 polyunsaturated and *trans* fatty acids, as well as ω3 to ω6 ratio;

- Levels of cytokinic factors (leptin, adiponectin, TNFα, TGFβ) and endocrine factors (insulin, IGF1, SHBG) in plasma;

- Metabolomics analysis: measurement of serum metabolites identified by the profile obtained by nuclear magnetic resonance (NMR) such as amino acids, sugars, organic acids, and all identifiable metabolites of molecular weight below 1 kDa; identification of multivariate metabolic profiles characteristics for each study arm.

For the cross-sectional study at surgery, a tumour sample (frozen if tumor size ≥ 20 mm) and a circulating blood sample that were collected whenever possible during surgery, will be obtained retrospectively from the clinic biobank. Then, complete profile of fatty acids, measurement of cytokinic and endocrine factors and metabolomics analysis will also be performed on them.

Finally, levels of fasting glucose, albumin, lipids (total cholesterol and its HDL and LDL fractions, triglycerides) are measured at each evaluation.

*Psychological criteria*

Psychological criteria are assessed at each evaluation using self-administered questionnaires: quality of life using the EORTC QLQ-C30 questionnaire with its module BR-23 specific for breast cancer[33;34] and the MOS SF-36 questionnaire[35;36] (version 4.0 in French language); body satisfaction and global self-perception using the QSCPGS questionnaire;[37] self-esteem using the Scale of Rosenweig;[38;39] depression using the Beck Depression Inventory (BDI) questionnaire;[40-42] and anxiety using the State Trait Anxiety Inventory (STAI) questionnaire.[43;44]

*Patients' satisfaction*

Overall satisfaction of the patients for the intervention in both arms is assessed at the end of the program (T3) using a graduated scale.

*Other data collection*

Clinical data, demographic data, medical history and reproductive history are collected at baseline. Tobacco use is collected at each evaluation.

In the intervention group, adherence to the APA sessions (primary outcome) is monitored by the APA professionals and reasons for non-adherence are recorded.

All adverse events (except hematological adverse events, gastrointestinal and hepatobiliary events that are frequently linked to adjuvant treatment of cancer) and all concomitant medications are reported by the patients continuously during the 6-month intervention period using a booklet.

Globally, the duration of each evaluation is estimated to be approximately 2 hours per patient (10 min for anthropometric measurements, 10 min for the rest necessary for impedance measurements, 45-60 min for physical activity assessment and 35–45 min for the dietary evaluation).

**Study outcomes**

The primary endpoint will be the proportion of patients in the intervention group who participate in at least two group sessions of APA per week for the duration of the APA program (i.e., 26 weeks from day 1 of chemotherapy), except during the first week of each course (see APA intervention).

Secondary endpoints are:

(i) assessment of the acceptability of the intervention and randomisation (proportion of eligible and invited patients that volunteer to participate in the study, rate of recruitment), as well as the qualitative analysis of barriers to recruitment (e.g., competition with other therapeutic trials, geographic distance, etc);

(ii) assessment of patients' compliance (percentage of patients who complete the full APA program), as well as the qualitative analysis of the reasons for noncompliance;

(iii) formalization of the APA and dietetic intervention program and the data collection and management process to implement in a future study (adequacy between procedures and study implementation in real conditions);

(iv) score of overall satisfaction of the patients with the intervention, at the end of the intervention;

(v) costs supported/avoided for health care providers;

(vi) baseline and changes in nutritional intake, physical activity level and profile, anthropometrics, body composition and psychological parameters;

(vii) baseline and changes in biological parameters (metabolome, lipidome, cytokines, endocrine factors) along the intervention, as well as their comparison between the tumor and circulating blood at the time of initial diagnosis (before surgery).

**Withdrawal from the PASAPAS study**

Participants may interrupt the study prematurely for the following various reasons: a relapse of disease; a decision of the Promotor or the investigator; death of the patient. Except in the last case, a final evaluation will be performed.

**Health economics analysis**

The literature shows a growing interest in health economics questions relating to physical activity for cancer patients.[45;46] Economics impact of an APA intervention in patients with localized invasive breast cancer undergoing chemotherapy will be assessed based on a cost analysis and a budget impact analysis.

*Cost analysis*

Costs will be assessed prospectively for each patient. Identification, measurement and valuation of costs will be performed based on the hospital's point of view. Hence, cost computations will focus on inpatient, outpatient, and home care. Length of stay within conventional medical unit, rehabilitation unit, home care, etc. will be identified and multiplied by their respective unit costs. The timeframe will be 12 months. Mean costs will be assessed for both APA intervention and control groups. All costs will be related to 2013 and will be given in euros.

*Budget impact analysis*

The hospital perspective will be retained and one-year baseline period presented. Target and prevalent populations will be estimated based on this study and Léon Bérard Cancer Centre data.

**Statistical analysis**

*Sample size*

The number of patients to include was defined empirically. A sample size of 60 patients seems sufficient to explore the feasibility of such a program and to identify potential corrective measures to take into account in interventions in the context of a future randomized clinical trial for efficacy. To emphasize the size of the group of patients supported by the APA intervention (main target of the study), an unbalanced randomization (2:1 ratio) has been proposed.

*Statistical analyses*

The analysis will be performed in the intent-to-treat (ITT) population, including all patients randomized in the arm allocated by randomization, in order to limit the possibility of bias associated with participants not receiving the intervention they were allocated for. Baseline characteristics will be summarised by treatment arms using standard descriptive statistics. Primary outcome will be described as the proportion of patients who participate in at least two planned APA sessions per week, with its 95% confidence interval. Participation in the APA program will be evaluated by the rate of patients who participate in all APA sessions and reasons for non-participation will be described. Tolerance analysis will be performed by studying the rate and its 95% confidence interval of patients who had at least one adverse event in the APA arm. For secondary outcome variables, changes in anthropometric measurements, body composition variables, physical activity profile and dietary, psychological and biological variables will be analysed by the absolute and relative variations of each of these endpoints between randomization (initial assessment at T1) and follow-up assessments (T2 to T4). These variations will be compared between both arms of randomization using a non-parametric test. A method for imputing missing data will be considered if necessary.

*Health economics analysis*

Descriptive statistics will be used to present costs. 95% confidence intervals will be calculated.

Costs will be compared using the Mann-Whitney test. When necessary, multiple regression analyses will be performed to examine the relationship between costs and a range of potentially explanatory clinical variables.

**Ethics considerations and dissemination**

The PASAPAS study was approved by the French ethics Committee (Comité de Protection des Personnes Sud-Est IV), the National Security Agency of Medicines and Health Products that applies for biomedical studies (ANSM, formerly AFSSAPS) and the French National Committee on Informatics and Privacy (CNIL). All participants give written informed consent. The study imposes no risks on the participants and the APA program is safe.

The study findings will be widely disseminated through the scientific public by publication in international peer-reviewed journals and presentation in national and international conferences. They will also be useful for optimising the intervention program and serve as a foundation for future full-scale randomized controlled trial.

## Discussion

The goal of this article was to describe the protocol of a multidisciplinary 6-month intervention study of APA and dietary management for breast cancer patients undergoing adjuvant chemotherapy. This single centre feasibility study is designed to evaluate the feasibility of implementing an APA program and test the study process prior to a multicentre full-scale randomised controlled trial testing the effectiveness of an APA program during breast cancer treatment on survival-related outcomes. Inclusions in the PASAPAS study started in June 2011 and the study will be closed in June 2014.

The optimal management for improved physical activity level of a healthy individual appears to be at least three sessions per week, 30 to 60 minutes each and of moderate intensity, allowing a sufficient dose of exercise. Intensity and type of exercise included in the APA program for breast cancer patients were based on literature evidence that recommends moderate-intensity exercise that combines aerobic and resistance exercise.[47;48] Therefore, sessions of aerobic and resistance exercise of at least 4 MET intensity, such as Nordic walking and aerobic fitness, were planned twice to three times a week to permit a progressive increase in exercise frequency. An interval of at least 48 hours between sessions allows a complete recovery and sessions are close enough to promote metabolic responses.[49] The APA program is individualized in terms of intensity (above 4 METs) and duration of the sessions according to initial physical activity level, anthropometrics, body composition and comorbidities. APA sessions are supervised by trained APA professionals (similar to exercise physiologists).

The APA program was designed to be feasible for breast cancer patients undergoing treatment and obtain a metabolic response to exercise. The APA program aims at: (i) to prevent physical deconditioning (i.e., to preserve the initial physical activity level or improve it if it is insufficient or below recommendations); (ii) to avoid weight gain, which is common during or after breast cancer treatment; (iii) to improve quality of life; (iv) and to reduce fatigue. Improvements are expected in terms of body composition (maintenance or increase in lean mass, no increase or decrease in body fat), cardio-respiratory capacity, balance and flexibility. Physical activity has been shown to be safe in cancer patients.[50]

Strengths of the study include first the physical activity intervention that is personalized and supervised by trained professionals. Group sessions provide support to cancer patients for being physically active and following an exercise program. Moreover, meeting other cancer patients

with similar health conditions and creating social links or friendship are reinforcement techniques for successfully modifying lifestyle habits such as physical activity or sedentary behaviors. Second, the timing of the APA intervention during adjuvant treatment makes the study original. Most physical activity interventions in cancer patients are performed after treatment[51-53] and are not necessary randomized.[54] However, growing evidence shows the necessity to maintain or start physical activity as soon as possible after a cancer diagnosis and avoid loss of physical fitness.[55;56] Third, the 6-month program is relatively long compared to other programs published in the literature and may help patients sustain in a regular practice of physical activity. Fourth, a biological substudy will provide insight into the mechanisms involved in cancer and during an exercise intervention. Though the small size of this feasibility study, biological results will raise mechanistic hypotheses for a future large-scale randomized controlled trial. Fifth, a medico-economic evaluation is original and will guide the institution in integrating physical activity in cancer patient's care. Finally, the 6-month program is relatively long compared to other programs published in the literature and may help patients sustain in a regular practice of physical activity.

The authors also recognize limits for the study. The small sample size does not provide statistical power to test efficacy of the APA intervention in modifying prognosis factors, but it is sufficient for the primary goal of the study to test feasibility of implementing the program. Feasibility studies are often of very small size indeed.[57;58] Because the APA program is supervised and performed locally, the target population is limited to patients living in the close area of the clinic. Recruitment in the study is strongly limited for this reason.

Given the large and growing population affected by breast cancer worldwide and the important benefit of physical activity on breast cancer survival identified in observational studies, it is now

necessary to study the impact of physical activity on disease-free survival and overall survival in a multicenter randomized study design. However, studying overall survival might be difficult, if not impossible, to achieve given the relatively good prognosis of breast cancer[59] and the growing efforts for national nutrition and physical activity prevention programs. Therefore, a valid intermediate survival endpoint might be necessary, which might be related to body composition or a composite endpoint based on biological mechanisms.[60]

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## Ethics approval

Ethics approval was provided by the Comité de Protection des Personnes Sud-Est IV.

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## Contributorship statement

PB conceived the idea for the study. All authors contributed to the design of the study. AMF and SBA contributed to the development of the adapted physical activity program and are responsible for the physical activity analysis. MT, AMF, ASKL, SG and VBB contributed to the set up of the study. SC will be responsible for the statistical analysis. LP will be responsible for the medico-economic analysis. MT wrote the manuscript. All authors read, revised and approved the final manuscript.

### Competing Interests

None

## Figure legends

Figure 1: Flowchart of participants through the PASAPAS study.

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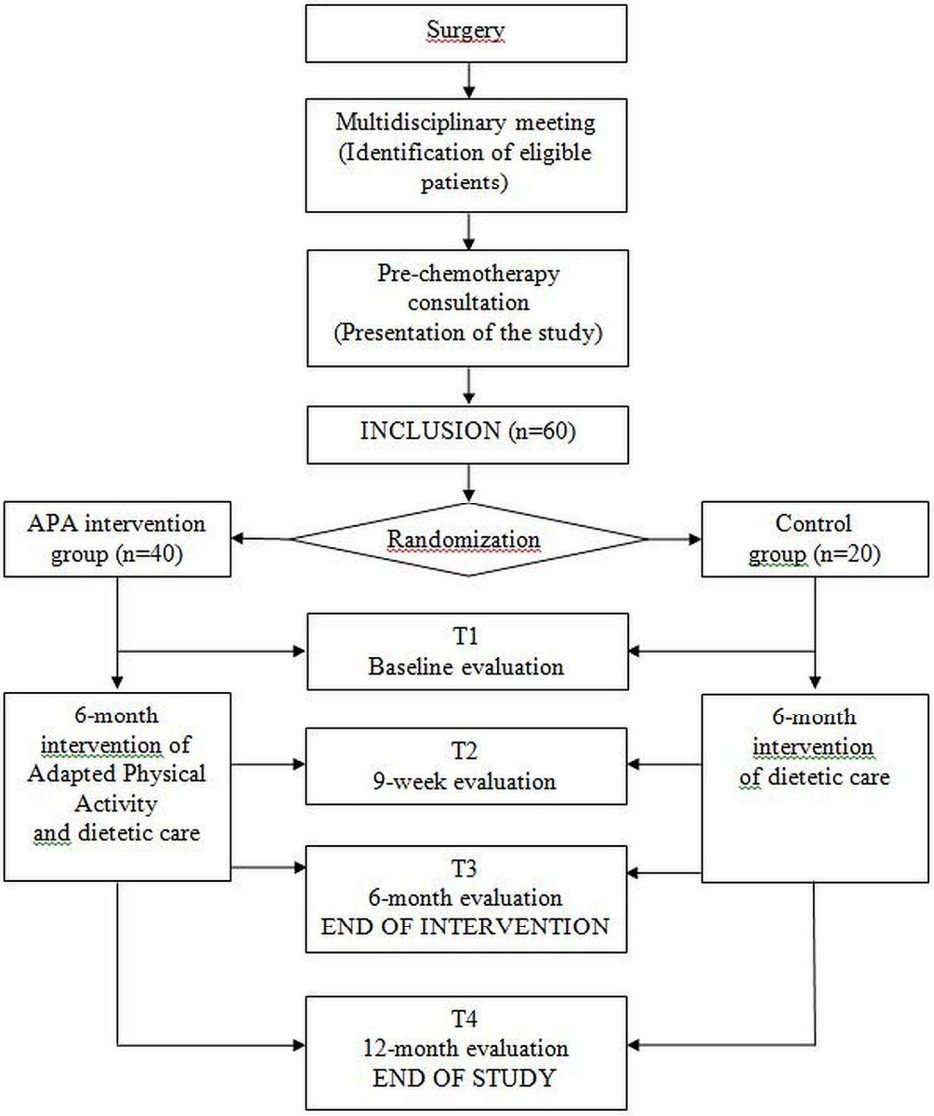


Flowchart of participants through the PASAPAS study
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