BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030911
Article Type:	Protocol
Date Submitted by the Author:	08-Apr-2019
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Keywords:	Breast tumours < ONCOLOGY, SPORTS MEDICINE, PREVENTIVE MEDICINE, CLINICAL PHYSIOLOGY

BMJ Open ***Study protocols***

Effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors: the habit-B study protocol for a randomized controlled trial

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ABSTRACT

Introduction

Maintaining high levels of physical activity not only helps to maintain and improve physical health and quality of life, but also plays a role in reducing short- and long-term adverse effects due to cancer treatments. Moreover, a greater degree of cardiorespiratory fitness is associated with reduced risk of all-cause mortality. However, there are no home-based programs for improving cardiorespiratory fitness using body weight exercises for breast cancer survivors. This study will assess the efficacy of the newly developed habit-B program on maximum oxygen uptake compared with treatment as usual. The effects of this program on exercise habits, level of physical activity, physical fitness, and subjective indices will also be investigated.

Methods and analysis

This is a 12-week, parallel-group, single blind, randomized controlled trial. Allocation will be managed by a central server using a computer-generated random allocation sequence provided by an independent data center. Participants will be assigned to the Habit-B Program (high-intensity interval training [HIIT] exercise, exercise counseling + guidance, home-based exercise support using information and communication technology [ICT], and a wearable device) or treatment as usual with a wearable device. Subjects will be sedentary women aged 20 to 59 years who have received breast surgery in the past 2 to 13 months after diagnosis of invasive breast cancer (Stage I-IIa) and have never received neo-

adjuvant or adjuvant chemo-therapy except for hormone therapy. The primary endpoint is the amount of change in peak oxygen uptake (VO_{2peak}; mL/kg/min) between the groups after 12 weeks of intervention.

Ethics and dissemination

The study protocol was approved by the Institutional Review Board of the National Cancer Center Japan on 28 February 2019 (ID: 2018-274).

Trial status Study enrolment, intervention, and data collection are ongoing. The estimated end date for this study is on March 31, 2021.

Trial registration number UMIN000036400; Pre-results.

Strengths and limitations of this study

1. If the findings of this trial suggest that the intervention is effective, it is expected to lead to establishing an effective exercise program for breast cancer survivors in Asia; VO_{2peak} of breast cancer survivors will be improved and exercise habits will be formed.
2. By achieving the trial objectives, it will become possible to suggest a home exercise program.
3. Data on clinical problems and participants' opinions obtained in this study can subsequently be utilized in the dissemination and implementation of future programs.

4. Even if implementation, effectiveness, or usefulness are not demonstrated, analyzing the cause of this should contribute to planning a new exercise program.
5. Collaborative work with professionals in the field of clinical oncology, exercise science, mental health, rehabilitation, public health, nursing, and cancer survivors constitutes a new model for cancer survivorship care.

INTRODUCTION

Breast cancer, which is one of the most common cancers affecting women, newly affects over 86,000 women each year[1]. Advances in early detection and treatment have improved survival rates, with the current 10-year survival rate at over 90%[1]. It is recommended that cancer survivors acquire and maintain healthy behaviors to extend survival, such as staying reasonably fit through appropriate physical exercise and having a healthy diet [2]. High levels of physical activity not only help to maintain and improve physical health and quality of life (QOL), but also play a role in reducing short- and long-term side effects of cancer treatment[3]. The American Cancer Society guidelines recommend a minimum of 150 min moderate physical activity or 75 min intensive physical activity per week, in addition to usual physical activity in daily life[4], and the Japan Breast Cancer Society's Clinical Guidelines for Breast Cancer strongly recommend maintaining a high level of physical activity[5 6]. Exercise is effective in treating breast cancer because it significantly improves physical function, mental health, and physiological markers before, during, and after cancer treatment[5 6]. A US study previously reported that following breast cancer diagnosis, less than half of patients maintained a level of physical activity at or above the recommended standards[7]. We assume that the proportion of individuals with a habit of exercising is low among breast cancer survivors as well and that very few maintain a high level of physical activity in Japan.

Previous studies of physical activity and exercise intervention among breast cancer survivors have mainly focused on weight gain[8 9], impairment of endothelial function[10], lower bone density in post-menopausal women[11], and lower physical fitness[12 13]. The ENERGY Trial, an early and representative study conducted in the US, demonstrated the effectiveness of a home exercise program and nutritional advice to promote weight loss among breast cancer survivors[8]. However, because the proportion of overweight adults in Japan is lower than that in the US[14], it is not appropriate to adopt the US-developed program in Japan. It would appear suitable though to develop intervention around measurements of VO_{2peak}, the globally important health indicator of cardiorespiratory fitness [15 16].

VO_{2peak} decreases with age, and a meta-analysis has suggested that women who are sedentary have a decrease of 3.2 mL/kg/min over 10 years[17]. A cohort study suggested that the all-cause mortality rate decreased by 17% for each 1 metabolic equivalent (MET) increase (3.5 mL/kg/min) in VO_{2peak} for women[18]. Also, individuals who met the standards for physical activity had a relative risk of 0.76 compared with those engaging in no physical activity, and individuals with a moderate VO_{2peak} had a relative risk of 0.56 compared with those with a low VO_{2peak}. Thus, maintaining a high VO_{2peak} has great benefits in terms of all-cause mortality rate[19]. A systematic review demonstrated that the median VO_{2peak} of breast cancer survivors not receiving chemotherapy was lower than that of healthy sedentary women (25.3 mL/kg/min vs. 29.7 mL/kg/min)[13]. In a 16-year follow-up study of breast cancer survivors[13], hazard ratios were 0.67 for the

moderate VO_{2peak} group (8.5 METs) and 0.45 for the high group (11.1 METs) compared with the low VO_{2peak} group (6.7 METs). In this report, the mortality rate was reduced by maintaining a VO_{2peak} of 8 METs or above[13]. Against this background, it is necessary to develop an exercise program that will increase $VO_{2peak\ in}$ breast cancer survivors.

When considering how to increase VO_{2peak}, research has advanced in recent years with the use of HIIT for athletes and sedentary populations[20-22]. HIIT allows subjects to exercise at vigorous intensity within 10 min, resulting in improved cardiorespiratory fitness[16 23]. A recent systematic review showed, based on the findings of 12 studies of HITT conducted in supervised experimental settings, that HITT appeared to be more beneficial than treatment as usual for improving physical fitness and health-related outcomes in cancer survivors during any stage of treatment and aftercare[23]. To our knowledge, only one study has evaluated changes in cardiorespiratory fitness following a home-based HITT program, which involved healthy young women[24]. Given that no home-based HIIT programs with body weight exercises have been reported for breast cancer survivors to date, it is necessary to develop such programs and examine their efficacy and feasibility.

Recent emerging technologies such as apps and wearable devices are promising tools for the monitoring of cancer patients' daily activity levels and for facilitating coaching, self-monitoring, feedback, and encouragement to exercise[25,26]. Apps[27] and wearable devices[28] are being used for both subjective and objective measures in the field of clinical oncology. However, further investigations

are needed of their potential utility in objective evaluations of physical activity as well as in lifestyle modification and maintenance and enhancement of QOL in real-world settings.

The aim of this study is to investigate the effect of the newly developed habit-B program, comprising **h**ome-based high-intensity interval training **a**nd **b**ehavioral modification using **i**nformation and communication **t**echnology on cardiorespiratory fitness and exercise habits for sedentary **b**reast cancer survivors. We will investigate whether the habit-B program improves VO_{2peak} compared with a control group as well as investigate the safety and feasibility of program. The secondary objectives are to investigate the effect of this program on exercise habits, physical activity level, physical function, and subjective measures.

METHODS AND ANALYSIS

Trial design (Figure 1)

In this study 12-week, parallel-group, single blind, randomized controlled trial, participants will be randomly assigned to intervention either with the habit-B program (HIIT exercise, exercise counseling + guidance, home-based exercise support using ICT, and a wearable device) or treatment as usual with a wearable device. An independent data center will provide computer-generated random allocation. The allocation sequences will be maintained centrally and the results of the assignment will be automatically displayed on each participant's app.

Participants

The eligibility criteria for participants are as follows: (1) female, aged between 20 and 59 years at diagnosis (stages I-IIa); (2) diagnosed with invasive breast cancer within 2 to 13 months after surgery; (3) not requiring cancer chemotherapy aside from hormone therapy; (4) currently engages in not more than moderate intensity exercise for 30 min on 2 separate days per week (total of 60 min); (5) ability to complete an electronic patient reported outcome (e-PRO) questionnaire via a smartphone; (6) consent to trial participation obtained in writing from the patient themselves; and (7) ability to read, write, and understand Japanese. The exclusion criteria are as follows: (1) judged to have severely reduced cognitive function by a primary physician; (2) exercise judged to be risky by a primary physician; (3) history of smoking within the previous 12 months; (4) body

mass index of 30 or above; (5) abnormal electrocardiogram in preoperative testing, resting heart rate (HR) below 60 beats/min or above 100 beats/min, or stage III hypertension or above (diastolic blood pressure over 110 mmHg or systolic blood pressure over 180 mmHg); and (6) judged unfit for the trial by a primary physician for other reasons.

Interventions

This will be a randomized, single-blind study. Participants will be enrolled and assigned using an electronic data capture system with an app. The protocol intervention will be started within 21 days of enrollment. If for some reason the start is delayed beyond 21 days, the reason will be entered into the electronic Case Report Form (eCRF). If it is determined that the intervention cannot be started, the details will be noted in the eCRF as "protocol intervention stopped."

The habit-B program group

The habit-B program comprises home-based exercise support utilizing 6 weeks of exercise counseling/exercise guidance and 12 weeks of ICT intervention (e-mail, app, wearable device; shown in Figure 2). Participants will be encouraged to complete the following program HIIT using specific body weight exercises for a 10-min training session 3 times a week for 12 weeks (total of 36 sessions during the trial period; Figure 3): (1) one 10-min session of exercises focused on the lower

limbs; (2) a total of 10 min exercises, comprising a 3-min warm-up, 4-min training (8 sets of 20 s exercise + 10 s rest), and a 3-min cool-down; (3) these training exercises are designed to increase in intensity each week; and (4) the details of these exercises are divided into three stages according to cardiorespiratory fitness (VO_{2peak}) at Week 0 and the contents of training are designed to increase physical strength incrementally in accordance with the individual's level of strength. In addition, we will continue to follow up on the between-group differences in e-PRO data of change from baseline to 24 and 36 weeks post-intervention.

The social cognitive theory proposed by Bandura et al. may be helpful to apply when considering interventions for behavioral change[29], chiefly in that it affords a framework for understanding the underlying reasons for making and maintaining health behaviors[30]. Its key concepts involve (1) understanding of health risks and benefits, (2) perceived self-efficacy of being able to control one's own health habits, (3) projected costs and benefits or expected outcomes, (4) specified health goals with short- and long-term intentions to engage in the behavior, (5) perceived facilitators and social support, and (6) barriers to instituting change[29 30]. In the present study, we developed the exercise program applying the first 5 concepts.

We will also provide the participant a brochure as a reminder to exercise and will check the type of physical activity they engage in in daily life (Figure 4). When developing the habit-B program, we collaborated closely with exercise scientists, oncologists, physical therapists, nurses, mental health practitioners, and breast

cancer survivors.

Control group

The control group will be provided a wearable device and setup support at the start of intervention. Self-monitoring using the wearable device will be recommended during the trial period. While there are no reports of increasing VO_{2peak} with the use of a wearable device alone, other reports have ruled out their efficacy with regard to effects on exercise habits[31]. In this study, the wearable devices are used only to monitor physical activity in the control group.

PROCEDURE

Data collection, management, monitoring, and auditing

We will collect all data except qualitative interview data, blood samples, fecal samples, and medical economic costs through the e-PRO system. Those who provide consent will be enrolled in the app-based e-PRO system on their smartphone. If the entered data is insufficient, enrollment will not be accepted until all fields are completed at baseline. The electronic data capture system will be used for data management and central monitoring. Because this exercise program will not be invasive, there is no need to establish a data monitoring committee or to complete auditing in this study.

Random assignment and assignment adjustment factors

After enrollment and the additional input of the VO_{2peak} value, patients will be randomly assigned. In the process of random assignment, VO_{2peak} (obtained from the baseline measurement performed after obtaining informed consent) and age will be used as assignment adjustment factors, and automatic assignment will be performed using the data center's assignment feature. Only the measurer will be blinded in this study, because interventions differ for the intervention group and control group.

Dataset availability

The data sharing policy in this study is defined with reference to the example proposed by the International Committee of Medical Journal Editors (ICMJE): Individual participant data will be made publicly available for a 5-year period through the University Hospital Medical Information Network – Individual Case Data Repository (UMIN-ICDR) (https://www.umin.ac.jp/icdr/index-j.html).

Concomitant treatments

There are no regulated concomitant therapies or supportive therapies in this study.

Stopping rules for participants

Situations in which the intervention protocol is terminated for any of the following reasons will be defined as stopping of the protocol intervention: (1)

dropping out due to withdrawal of consent or inability to measure the primary endpoint (VO_{2peak}); (2) if a primary physician deems it necessary to stop the protocol intervention for a participant due to adverse events such as stress; (3) death of the patient during the protocol intervention period; (4) sudden worsening of the participant's condition after enrollment or discovery of a protocol violation or ineligibility. A researcher will report the reason for stopping the protocol intervention to the data center. In this event, as long as consent is not withdrawn, follow-up including the questionnaire survey will be continued.

Stopping of the assessment

Situations in which the participant declines assessment will effectively stop the assessment. A researcher will confirm the possibility of implementing the remaining parts of the intervention and follow-up with the participant. Stopping of the assessment will be recorded along with the details of the reason for stopping. As a rule, the remaining aspect of follow-up will be implemented as stipulated per protocol.

Assessment measures

Table 1 shows the outcome measurement schedule.

Primary outcome measure: Cardiorespiratory fitness (VO_{2peak})

VO_{2peak} is the maximum oxygen uptake observed during exercise tolerance testing and is used as an indicator of cardiorespiratory fitness[32 33]. For each participant, VO_{2peak} will be measured using the incremental multistage load method with a bicycle ergometer (Ergomedic 828E, Monark, Stockholm, Sweden) at 60 revolutions per min (rpm). The test will begin at 0.5 kp and increase by 0.25 kp per min until exhaustion. When the participant's pedal rotation speed drops below 55 rpm 3 times, the test will be deemed concluded. Respiratory gases will be analyzed using an automatic gas analyzer (Air Monitor AE-310S, Minato Medical Science Co., Ltd., Osaka, Japan). Rated perceived exertion and HR will be recorded after 45 s in each stage. The maximum value of VO_2 observed during exercise will be used as the VO_{2peak}.

Secondary outcome measures

Physical function

An alternative indicator of VO_{2peak}, the 6-min walk test (m), will be performed[34]. Walking speed (m/s), a diagnostic criterion for sarcopenia, will also be measured. A 5-m section in the middle of an 11-m line will be measured to calculate walking speed [35]. One-repetition maximum for leg press, which reflects muscle strength in the lower body, will be assessed using a leg press machine [36 37]. After a thorough warm-up, measurements will be performed by incrementally increasing the load until a weight, which can be lifted only once, is reached. Load will be increased by two levels at a time. Grip strength will also be measured[37 38].

The chair stand test, which reflects combined leg strength for the lower limbs as a whole, will be performed[37 39]. Participants will sit and stand from a chair for 10 s and the number of chair stands will be measured. The timed up and go test, which is used in clinical settings as an assessment of functionality as well as muscular strength, will also be performed[37]. The functional reach test, which as a method of assessing dynamic balance is considered an indicator of expected fall risk, will also be performed[40]. While keeping the hand at the same height, the participant will extend their arm forward as far as possible, without moving the feet, to make a mark at the farthest point they can reach. Lifting the heels and standing on tiptoe is allowed. The two-step test will also be performed[41]. This test comprehensively assesses ability to walk, including leg strength, balance, and flexibility. Based on bioelectrical impedance analysis, a body composition meter (MC-780A-N, TANITA, Japan) will be used to send a weak electrical current through the body via electrodes.

Physical activity level

The Global Physical Activity Questionnaire (GPAQ) was developed in 2002 as an internationally standardized questionnaire for surveying physical activity level. The GPAQ is widely used in policy development by the World Health Organization[42-44]. The face validity of the Japanese version has been confirmed[45]. In addition, as an objective measure of physical activity during the research period, resting HR, steps, distance, calorie expenditure, and the duration of each sleep

stage as well as wake up time will be measured using an activity monitor and logged for 24-h periods (Fitbit versa, Fitbit Inc., San Francisco, CA). Maximum HR during exercise will also be measured to confirm whether the intensity of the exercise being implemented is appropriate. The accurately measured group will be defined as the group who wears the Fitbit versa at least 60% of the time during the 12-week intervention period.

Subjective measures

Fear of cancer recurrence (FCR) will be assessed by the overall fear index score on the Concerns About Recurrence Scale[46 47]. This instrument comprises 4 items scored on a 6-point Likert scale (range, 1–6), with a higher score indicating worse FCR. Depression will be assessed using the Patient Health Questionnaire-9 [48]. Fatigue will be assessed by the Cancer Fatigue Scale. Sleep will be assessed by the Athens Insomnia Scale[49 50]. Health-related QOL will be assessed using the EuroQol 5 Dimensions questionnaire[51 52].

Biological assessments

To assess changes in gut microbiota, intestinal metabolites, and intestinal immunity, a 1-g fecal sample will be obtained at baseline and at 12 weeks. Blood concentrations of polyunsaturated fatty acids will be assessed from capillary dried blood spot samples (approximately 80 μL) at baseline[53].

Medical economic costs

For cost-benefit analysis, the number of staff, working hours, labor costs, equipment costs, office expenses, number of unexpected medical consultations, direct medical costs, and costs of other medical services used will be obtained.

Harms

The intervention in this research will potentially place stress on participants physically and in terms of their time, because it will take approximately 1 h and 30 min. There will also be temporary exhaustion, although individual differences will be considered in exercise implementation. There are no financial risks associated with participation in the study.

Compensation

If participants develop unexpected health issues due to study participation during or after completion of the study, treatment will be provided appropriately in the same way as standard medical care. Medical expenses at that time will be handled within the medical insurance to which the participant is enrolled. No financial compensation, except for providing the wearable device, will be given in this study.

DATA ANALYSIS

The primary endpoint, VO_{2peak}, will be calculated as follows. Measurements will be taken at the start of the intervention (0 week) and at the conclusion of the intervention (12 weeks). The analysis set for primary analyses will consist of all randomized subjects. After completing primary endpoint data locking, analyses centering on the primary endpoint will be performed. The objective of primary analysis in this study is to investigate whether the habit-B program group (trial treatment group) surpasses the group receiving treatment as usual (control) in VO_{2peak}, the primary endpoint. One-sided tests will be used, because, if the trial intervention group is inferior to the control group, it is not important in this trial whether that difference is statistically significant. The trial will adopt a one-sided significance level of 2.5%. A between-groups comparison will be performed using an independent two-sample t-test to determine the significance of amount of change in VO_{2peak} (mL/kg/min) from 0 week to 12 weeks (after intervention completion) between the trial intervention and the control groups. Secondary endpoint analyses will be performed with the goal of supplementing the primary analyses. Once all data has been locked following conclusion of the primary analysis period and follow-up, final analyses will be performed.

Sample size estimation

The main hypothesis of this study is that the intervention group will significantly surpass the control group in terms of the amount of change in VO_{2peak}

from 0 week to 12 weeks. Regarding the clinical significance of the results of an exercise program, it is common to use an increase of 10% in VO_{2peak} to evaluate the effects of an exercise program[54]. As such, an increase of 10% from VO_{2peak} at the start of exercise has been established for this trial. According to a previous study of intervention similar to that in the present study[55], the standard deviation for the VO_{2peak} of the intervention group was 2.6 mL/kg/min. Based on the above hypothesis, by estimating the number of subjects required for a one-sided 2.5% and a power of 80% in the analysis, 28 individuals per group are necessary for a total of 56 in both groups (SAS 9.4 software; SAS Institute Inc., Cary, NC). With the estimation that 4 participants will drop out, enrollment of 60 patients is planned.

Study period

The study period of this trial will be from April 2019 to March 2021; the participant entry period will be from April 2019 to March 2020. Study enrolment, intervention, and data collection are ongoing.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

This study protocol was designed with the involvement of a breast cancer survivor who participated in this study as a researcher and coauthor. She discussed issues with other survivors in instances where survivors' preferences and opinions should be considered. In the process of creating the habit-B program,

we conducted a preliminary confirmation of the feasibility and safety of this program in 5 breast cancer survivors.

ETHICAL CONSIDERATIONS AND DISSEMINATION

The protocol was approved by the Institutional Review Board of the National Cancer Center Research Ethical Review Committee on 28 February 2019 (ID: 2018-274). The results obtained will be submitted for publication in a peer-reviewed international journal, and the main relevant findings will be presented at conferences.

DISCUSSION

An excellent review by Shapiro et al. affirms the positive role that high levels of physical activity play in improving not only health-related QOL and symptom management (e.g., chronic pain, fatigue, insomnia, sexual dysfunction, metabolic syndrome, bone loss, cognitive dysfunction, and depression), but also return to work in cancer survivors [3]. In addition, increased cardiorespiratory fitness may decrease all-cause mortality among cancer survivors[12,56]. However, there are currently no effective home-based exercise programs available for improving cardiorespiratory fitness for breast cancer survivors. No studies have precisely investigated cardiorespiratory fitness [57], although a small pilot study did estimate VO_2 based on subjective exercise intensity among Japanese breast cancer survivors. Accordingly, the present study seeks to confirm whether our originally developed home-based exercise program (habit-B program) improves VO_{2peak} compared with treatment as usual in sedentary breast cancer survivors in Japan. With the assumption that the program will be widely implemented if successful, it was designed to be (1) home based, (2) quick to implement (only 10 min in total), (3) use only body weight exercises involving the lower limbs, and (4) utilize a wearable device for which personalized ICT support is available. We believe that no similar studies have been implemented.

If it is found that the habit-B program is effective in increasing VO_{2peak}, we will then proceed to the next trial, aiming for its widespread implementation in society. Specifically, the aims of the next study will be (1) to investigate whether

intervention using the program developed in this research but presented in a simpler format is effective in establishing exercise habits and (2) to assess whether the program can be implemented in societies in Eastern Asia, including in both urban and rural Japan and other East Asian countries.

We strongly believe that a successful support team comprising specialists in the field of exercise science, medicine, rehabilitation, nursing, and patient advocacy, as involved in this study, will provide a new horizon in cancer survivorship care.

Acknowledgements

We sincerely thank Dr. Hiroji Iwata, Dr. Hirokazu Arai, Ms. Noriko Watanabe, Dr. Noriaki Tatematsu, Dr. Hikaru Ihira, Mr. Tomoyasu Chigahara, Dr. Taro Ueno, Dr. Shinji Fukuda, and Dr. Eiko Saito for their generous support for the study. We also thank Ms. Ayako Sato for her role as an exercise model.

Contributors KT, EO, RO, YS, TK, and YM conceived the study and drafted the original protocol. KT, EO, RO, YS, TS, AK, TK, and YM participated in refining the protocol. AK played a major role in the statistical analysis. KT, EO, TK, and NS contributed to developing the exercise program. EO and YM drafted the manuscript. All authors participated in, read, and approved the final manuscript.

Funding This study is supported by a National Cancer Center Research and Development Fund (30-A-17).

Competing interests EO has received research support from Nippon Suisan Kaisha, Ltd. YJM has received speaker fees from Pfizer, Mochida, Eli Lilly, Morinaga Milk, and NTT Data and is conducting collaborative research with Morinaga Milk. AK has received speaking fees from Chugai Pharmaceutical Co., Ltd. All other authors declare that they have no competing interests regarding this work.

Ethics approval. The protocol was approved by the Institutional Review Board of the National Cancer Center on 28 February 2019 (ID: 2018-274).

FIGURE LEGENDS

Figure 1. Flow diagram of study participants. HIIT, high-intensity interval training; ICT, information and communication technology.

Figure 2. Study design of the habit-b program (**h**ome-based high-intensity interval training **a**nd **b**ehavioral modification using information and communication **t**echnology on cardiorespiratory fitness and exercise habits for sedentary **b**reast cancer survivors). HIIT, high-intensity interval training; ICT, information and communication technology.

Figure 3. Sample of high-intensity interval training using body weight exercise.

Figure 4. Brochure reminding participants about the importance of exercise and providing instructions about physical activity in daily life.

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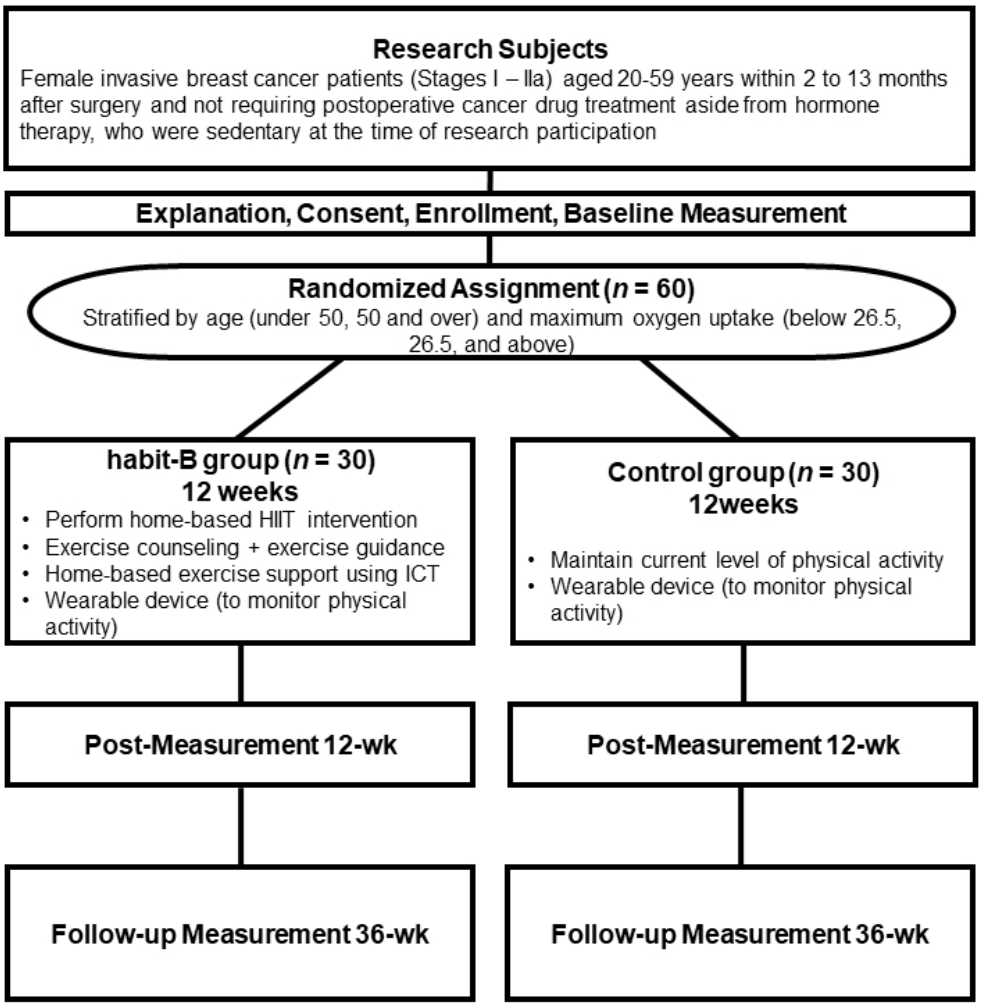
Table 1 Schedule for outcome measurement

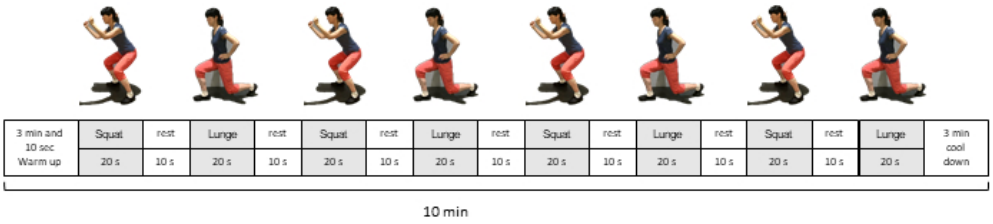
	Time points			
	Protocol Intervention Period		Follow-up Intervention Period	
Assessment	**0 week**	**12 weeks**	**24 weeks**	**36 weeks**
Confirmation of eligibility	×			
Explanation, consent, enrollment	×			
Assignment	×			
Demographics, laboratory data, blood fatty acids	×			
Maximum oxygen uptake, physical function	×	×		
GPAQ	×	×	×	×
Objective activity level (according to Fitbit versa®)	←	—	—	→
Subjective indexes	×	×	×	
Assessment of protocol intervention feasibili	×	×		
Interview regarding satisfaction of the intervention		×		
Exercise log	←	→		
Adverse events	←	→		
Gut microbiota	×	×		
Medical Economic Cost	←	—	—	→

Table 1. Schedule for outcome measurement.



190x191mm (96 x 96 DPI)

190x101mm (96 x 96 DPI)



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166x236mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors: the habit-B study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030911.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Jun-2019
Complete List of Authors:	Tsuji, Katsunori; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences Ochi, Eisuke; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences; Hosei University, Faculty of Bioscience and Applied Chemistry Okubo, Ryo; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences Shimizu, Yoichi; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences Kuchiba, Aya; National Cancer Center Japan, Division of Biostatistical Research, Center for Public Health Sciences; National Cancer Center Japan, Biostatistics Division, Center for Research Administration and Support Ueno, Taro; SUSMED, Inc. Shimazu, Taichi; National Cancer Center Japan, Division of Prevention, Center for Public Health Sciences Kinoshita, Takayuki; National Cancer Center Hospital, Department of Breast Surgery Sakurai, Naomi; Cancer Solutions Matsuoka, Yutaka; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Mental health, Oncology
Keywords:	Breast tumours < ONCOLOGY, SPORTS MEDICINE, PREVENTIVE MEDICINE, CLINICAL PHYSIOLOGY

BMJ Open ***Study protocols***

Effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors: the habit-B study protocol for a randomized controlled trial

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ABSTRACT

Introduction

Maintaining high levels of physical activity not only helps to maintain and improve physical health and quality of life, but also plays a role in reducing adverse effects due to cancer treatments. Moreover, a greater degree of cardiorespiratory fitness is associated with reduced risk of all-cause mortality. However, there are no home-based programs for improving cardiorespiratory fitness using body weight exercises for breast cancer survivors. This study will assess the efficacy of the newly developed habit-B program on maximum oxygen uptake compared with treatment as usual. The effects of this program on exercise habits, level of physical activity, physical fitness, and subjective indices will also be investigated.

Methods and analysis

This is a 12-week, parallel-group, single blind, randomized controlled trial. Allocation will be managed by a central server using a computer-generated random allocation sequence provided by an independent data center. Participants will be assigned to the habit-B Program (high-intensity interval training exercise, exercise counseling + guidance, home-based exercise support using information and communication technology, and a wearable device) or treatment as usual with a wearable device. Subjects will be sedentary women aged 20 to 59 years who have received breast surgery in the past 2 to 13 months after diagnosis of invasive breast cancer (Stage I-IIa) and have never received chemo-therapy except for

hormone therapy. The primary endpoint is the change in peak oxygen uptake (VO_{2peak}; mL/kg/min) between the groups after 12 weeks of intervention.

Ethics and dissemination

The study protocol was approved by the Institutional Review Board of the National Cancer Center Japan on 28 February 2019 (ID: 2018-347). The findings will be disseminated through peer reviewed publications and conference presentations.

Trial status Study enrolment, intervention, and data collection are ongoing. The estimated end date for this study is on March 31, 2021.

Trial registration number UMIN000036400; Pre-results.

Strengths and limitations of this study

1. This clinical trial will be the world's first home-based HIIT program using ICT to increase cardiorespiratory fitness in sedentary breast cancer survivors.
2. The habit-B program is designed based on the theory of Bandura for sedentary breast cancer survivors to develop exercise habits.
3. Collaborative work with professionals in the field of clinical oncology, exercise science, mental health, rehabilitation, public health, nursing, and cancer survivors constitutes a new model for cancer survivorship care.
4. We cannot rigorously exclude breast cancer survivors who may have exercise habits because the definition of sedentary subjects will be based on self-report.

INTRODUCTION

Breast cancer, which is one of the most common cancers affecting women, newly affects over 86,000 women each year[1]. It is recommended that cancer survivors acquire and maintain healthy behaviors to extend survival, such as staying reasonably fit through appropriate physical exercise and having a healthy diet [2]. High levels of physical activity not only help to maintain and improve physical health and quality of life (QOL), but also play a role in reducing short- and long-term side effects of cancer treatment. The American Cancer Society guidelines recommend a minimum of 150 min moderate physical activity or 75 min intensive physical activity per week, in addition to usual physical activity in daily life[3], and the Japan Breast Cancer Society's Clinical Guidelines for Breast Cancer strongly recommend maintaining a high level of physical activity[4 5].

The ENERGY Trial, an early and representative study conducted in the US, demonstrated the effectiveness of a home exercise program and nutritional advice to promote weight loss among breast cancer survivors[6]. However, because the proportion of overweight adults in Japan is lower than that in the US[7], it is not appropriate to adopt the US-developed program in Japan. It would appear suitable though to develop intervention around measurements of VO_{2peak}, the globally important health indicator of cardiorespiratory fitness [8 9].

VO_{2peak} decreases with age, and a meta-analysis has suggested that women who are sedentary have a decrease of 3.2 mL/kg/min over 10 years[10]. A cohort study suggested that the all-cause mortality rate decreased by 17% for each 1 metabolic equivalent (MET) increase (3.5 mL/kg/min) in VO_{2peak} for women[11]. A

systematic review demonstrated that the median VO_{2peak} of breast cancer survivors not receiving chemotherapy was lower than that of healthy sedentary women (25.3 mL/kg/min vs. 29.7 mL/kg/min)[12]. In a 16-year follow-up study of breast cancer survivors[12], hazard ratios were 0.67 for the moderate VO_{2peak} group (8.5 METs) and 0.45 for the high group (11.1 METs) compared with the low VO_{2peak} group (6.7 METs). In this report, the mortality rate was reduced by maintaining a VO_{2peak} of 8 METs or above[12]. Against this background, it is necessary to develop an exercise program that will increase VO_{2peak} in breast cancer survivors.

When considering how to increase VO_{2peak}, research has advanced in recent years with the use of HIIT for athletes and sedentary populations[13-15]. HIIT allows subjects to exercise at vigorous intensity within 10 min, resulting in improved cardiorespiratory fitness[9 16]. A recent systematic review showed, based on the findings of 12 studies of HIIT conducted in supervised experimental settings, that HIIT appeared to be more beneficial than treatment as usual for improving physical fitness and health-related outcomes in cancer survivors during any stage of treatment and aftercare[16]. To our knowledge, only one study has evaluated changes in cardiorespiratory fitness following a home-based HIIT program, which involved healthy young women[17]. Given that no home-based HIIT programs with body weight exercises have been reported for breast cancer survivors to date, it is necessary to develop such programs and examine their efficacy and feasibility.

Recent emerging technologies such as smartphone applications (apps) and wearable devices are promising tools for the monitoring of cancer patients' daily

activity levels and for facilitating coaching, self-monitoring, feedback, and encouragement to exercise[18,19]. Apps[20] and wearable devices[21] are being used for both subjective and objective measures in the field of clinical oncology. However, further investigations are needed of their potential utility in objective evaluations of physical activity as well as in lifestyle modification and maintenance and enhancement of QOL in real-world settings.

The aim of this study is to investigate the effect of the newly developed habit-B program, comprising **h**ome-based high-intensity interval training **a**nd **b**ehavioral modification using **i**nformation and communication **t**echnology on cardiorespiratory fitness and exercise habits for sedentary **b**reast cancer survivors. We will investigate whether the habit-B program improves VO_{2peak} compared with a control group as well as investigate the safety and feasibility of program. The secondary objectives are to investigate the effect of this program on exercise habits, physical activity level, physical function, and subjective measures.

METHODS AND ANALYSIS

Trial design

In this study 12-week, parallel-group, single blind, randomized controlled trial (Figure 1), participants will be randomly assigned to intervention either with the habit-B program (HIIT exercise, exercise counseling + guidance, home-based exercise support using ICT, and a wearable device) or treatment as usual with a wearable device (Fitbit Versa smart watch; Fitbit Inc., San Francisco, CA). An independent data center will provide computer-generated random allocation. Participants will be assigned by the minimization method, a form of dynamic randomization, using two prognostic factors: VO_{2peak} and age. Based on the allocation sequences, the contents of the app that participants use during the trial will be assigned automatically to either the habit-B program or control.

Participants

The eligibility criteria for participants are as follows: (1) female, aged between 20 and 59 years at diagnosis (stages I-IIa); (2) diagnosed with invasive breast cancer within 2 to 13 months after surgery; (3) not requiring cancer chemotherapy aside from hormone therapy; (4) currently engages in not more than moderate intensity exercise for 30 min on 2 separate days per week (total of 60 min), which is based on the National Health and Nutrition Survey Japan[22]; (5) ability to complete an electronic patient reported outcome (e-PRO) questionnaire via a smartphone; (6) consent to trial participation obtained in writing from the

patient themselves; and (7) ability to read, write, and understand Japanese. The exclusion criteria are as follows: (1) judged to have severely reduced cognitive function by a primary physician; (2) exercise judged to be risky by a primary physician; (3) history of smoking within the previous 12 months; (4) body mass index of 30 or above; (5) abnormal electrocardiogram in preoperative testing, resting heart rate (HR) below 60 beats/min or above 100 beats/min, or stage III hypertension or above (diastolic blood pressure over 110 mmHg or systolic blood pressure over 180 mmHg); and (6) judged unfit for the trial by a primary physician for other reasons.

Interventions

This will be a randomized, single-blind study. Participants will be enrolled and assigned using an electronic data capture system with an app. The protocol intervention will be started within 21 days of enrollment. If for some reason the start is delayed beyond 21 days, the reason will be entered into the electronic Case Report Form (eCRF). If it is determined that the intervention cannot be started, the details will be noted in the eCRF as “protocol intervention stopped.”

The habit-B program group

The habit-B program (Figure 2) comprises home-based exercise support utilizing 6 weeks of exercise counseling/exercise guidance (once per week, 6 times

total, 30 min per session) and 12 weeks of ICT interventions, which are provided with personalized e-mail (once per week, 12 times in total), and a newly developed exercise app (during each exercise session, shown in Figure 3). Participants will be encouraged to complete the following program HIIT using specific body weight exercises for one 10-min training session 3 times a week for 12 weeks (total of 36 sessions during the trial period, as shown in Figures 2 and 4): (1) one bout of 10-min exercises; (2) a total of 10 min exercise, comprising a 3-min warm-up, 4-min training (8 sets of 20 s exercise + 10 s rest), and a 3-min cool-down; (3) these training exercises are designed to increase in intensity each week; and (4) the details of these exercises are divided into three stages according to cardiorespiratory fitness (VO_{2peak}) at Week 0 and the contents of training are designed to increase physical strength incrementally in accordance with the individual's level of strength. In addition, we will continue to follow up on the between-group differences in e-PRO data of change from baseline to 24 and 36 weeks post-intervention.

The social cognitive theory proposed by Bandura et al. may be helpful to apply when considering interventions for behavioral change[23], chiefly in that it affords a framework for understanding the underlying reasons for making and maintaining health behaviors[24]. Its key concepts involve (1) understanding of health risks and benefits, (2) perceived self-efficacy of being able to control one's own health habits, (3) projected costs and benefits or expected outcomes, (4) specified health goals with short- and long-term intentions to engage in the behavior, (5)

perceived facilitators and social support, and (6) barriers to instituting change[23 24]. In the present study, we developed the exercise program applying the first 5 concepts.

We will also provide the participant a brochure as a reminder to exercise and will check the type of physical activity they engage in in daily life (Figure 5). When developing the habit-B program, we collaborated closely with exercise scientists, oncologists, physical therapists, nurses, mental health practitioners, and breast cancer survivors.

Control group

The control group will be provided a wearable device and setup support at the start of intervention. Self-monitoring using the wearable device will be recommended during the trial period. While there are no reports of increasing VO_{2peak} with the use of a wearable device alone, other reports have ruled out their efficacy with regard to effects on exercise habits[25]. In this study, the wearable devices are used only to monitor physical activity in the control group.

PROCEDURE

Data collection, management, monitoring, and auditing

We will collect all data except qualitative interview data, blood samples, fecal samples, and medical economic costs through the e-PRO system. Those who provide consent will be enrolled in the app-based e-PRO system on their

smartphone. If the entered data is insufficient, enrollment will not be accepted until all fields are completed at baseline. The electronic data capture system will be used for data management and central monitoring. Because this exercise program will not be invasive, there is no need to establish a data monitoring committee or to complete auditing in this study.

Random assignment and assignment adjustment factors

After enrollment and the additional input of the VO_{2peak} value, patients will be randomly assigned. In the process of random assignment, VO_{2peak} (obtained from the baseline measurement performed after obtaining informed consent) and age will be used as assignment adjustment factors, and automatic assignment will be performed using the data center's assignment feature. Only the measurer will be blinded in this study, because interventions differ for the intervention group and control group.

Dataset availability

The data sharing policy in this study is defined with reference to the example proposed by the International Committee of Medical Journal Editors (ICMJE): Individual participant data will be made publicly available for a 5-year period through the University Hospital Medical Information Network – Individual Case Data Repository (UMIN-ICDR) (https://www.umin.ac.jp/icdr/index-j.html).

Concomitant treatments

There are no regulated concomitant therapies or supportive therapies in this study.

Stopping rules for participants

Situations in which the intervention protocol is terminated for any of the following reasons will be defined as stopping of the protocol intervention: (1) dropping out due to withdrawal of consent or inability to measure the primary endpoint (VO_{2peak}); (2) if a primary physician deems it necessary to stop the protocol intervention for a participant due to adverse events such as stress; (3) death of the patient during the protocol intervention period; (4) sudden worsening of the participant's condition after enrollment or discovery of a protocol violation or ineligibility. A researcher will report the reason for stopping the protocol intervention to the data center. In this event, as long as consent is not withdrawn, follow-up including the questionnaire survey will be continued.

Stopping of the assessment

Situations in which the participant declines assessment will effectively stop the assessment. A researcher will confirm the possibility of implementing the remaining parts of the intervention and follow-up with the participant. Stopping of the assessment will be recorded along with the details of the reason for stopping.

As a rule, the remaining aspect of follow-up will be implemented as stipulated per protocol.

Assessment measures

Table 1 shows the outcome measurement schedule.

Primary outcome measure: Cardiorespiratory fitness (VO_{2peak})

VO_{2peak} is the maximum oxygen uptake observed during exercise tolerance testing and is used as an indicator of cardiorespiratory fitness[26 27]. For each participant, VO_{2peak} will be measured using the incremental multistage load method with a bicycle ergometer (Ergomedic 828E, Monark, Stockholm, Sweden) at 60 revolutions per min (rpm). The test will begin at 0.5 kp and increase by 0.25 kp per min until exhaustion. When the participant's pedal rotation speed drops below 55 rpm 3 times, the test will be deemed concluded. Respiratory gases will be analyzed using an automatic gas analyzer (Air Monitor AE-310S, Minato Medical Science Co., Ltd., Osaka, Japan). Rated perceived exertion and HR will be recorded after 45 s in each stage. The maximum value of VO_2 observed during exercise will be used as the VO_{2peak}.

Secondary outcome measures

Physical function

An alternative indicator of VO_{2peak}, the 6-min walk test (m), will be performed[28]. Walking speed (m/s), a diagnostic criterion for sarcopenia, will also be measured. A 5-m section in the middle of an 11-m line will be measured to calculate walking speed [29]. One-repetition maximum for leg press, which reflects muscle strength in the lower body, will be assessed using a leg press machine (Powertec Leg Press P-LP16; Powertec, Paramount, CA) [30 31]. After a thorough warm-up, measurements will be performed by incrementally increasing the load until a weight, which can be lifted only once, is reached. Load will be increased by two levels at a time. Grip strength (TKK 5401 Grip-D; Takei, Niigata, Japan) will also be measured[31 32]. The chair stand test, which reflects combined leg strength for the lower limbs as a whole, will be performed[31 33]. Participants will sit and stand from a chair for 10 s and the number of chair stands will be measured. The timed up and go test, which is used in clinical settings as an assessment of functionality as well as muscular strength, will also be performed[31]. The functional reach test, which as a method of assessing dynamic balance is considered an indicator of expected fall risk, will also be performed[34]. While keeping the hand at the same height, the participant will extend their arm forward as far as possible, without moving the feet, to make a mark at the farthest point they can reach. Lifting the heels and standing on tiptoe is allowed. The two-step test will also be performed[35]. This test comprehensively assesses ability to walk, including leg strength, balance, and flexibility. Based on bioelectrical impedance analysis, a body

composition meter (MC-780A-N, TANITA, Japan) will be used to send a weak electrical current through the body via electrodes.

Physical activity level

The Global Physical Activity Questionnaire (GPAQ) was developed in 2002 as an internationally standardized questionnaire for surveying physical activity level. The GPAQ is widely used in policy development by the World Health Organization[36-38]. The face validity of the Japanese version has been confirmed[39]. In addition, as an objective measure of physical activity during the research period, resting HR, steps, distance, calorie expenditure, and the duration of each sleep stage as well as wake up time will be measured using an activity monitor and logged for 24-h periods (Fitbit versa, Fitbit Inc., San Francisco, CA). Maximum HR during exercise will also be measured to confirm whether the intensity of the exercise being implemented is appropriate. The accurately measured group will be defined as the group who wears the Fitbit versa at least 60% of the time during the 12-week intervention period.

Subjective measures

Fear of cancer recurrence (FCR) will be assessed by the overall fear index score on the Concerns About Recurrence Scale[40 41]. This instrument comprises 4 items scored on a 6-point Likert scale (range, 1–6), with a higher score indicating worse FCR. Depression will be assessed using the Patient Health Questionnaire-9

[42]. Fatigue will be assessed by the Cancer Fatigue Scale. Sleep will be assessed by the Athens Insomnia Scale[43 44]. Health-related QOL will be assessed using the EuroQol 5 Dimensions questionnaire[45 46].

Biological assessments

To assess changes in gut microbiota, intestinal metabolites, and intestinal immunity[47], a 1-g fecal sample will be obtained at baseline and at 12 weeks. Blood compositions of n-3 polyunsaturated fatty acids[48] will be assessed from capillary dried blood spot samples (approximately 80 μL) at baseline[49].

Medical economic costs

For cost-benefit analysis, the number of staff, working hours, labor costs, equipment costs, office expenses, number of unexpected medical consultations, direct medical costs, and costs of other medical services used will be obtained.

Harms

The intervention in this research will potentially place stress on participants physically and in terms of their time, because it will take approximately 1 h and 30 min. There will also be temporary exhaustion, although individual differences will be considered in exercise implementation. There are no financial risks associated with participation in the study.

Compensation

If participants develop unexpected health issues due to study participation during or after completion of the study, treatment will be provided appropriately in the same way as standard medical care. Medical expenses at that time will be handled within the medical insurance to which the participant is enrolled. No financial compensation, except for providing the wearable device, will be given in this study.

DATA ANALYSIS

The primary endpoint, VO_{2peak}, will be calculated as follows. Measurements will be taken at the start of the intervention (0 week) and at the conclusion of the intervention (12 weeks). The analysis set for primary analyses will consist of all randomized subjects. Our primary analysis is intention-to-treat analysis and patients without outcome data will be excluded from the analyses. After completing primary endpoint data locking, analyses centering on the primary endpoint will be performed. The objective of primary analysis in this study is to investigate whether the habit-B program group (trial treatment group) surpasses the group receiving treatment as usual (control) in VO_{2peak}, the primary endpoint. One-sided tests will be used, because, if the trial intervention group is inferior to the control group, it is not important in this trial whether that difference is statistically significant. The trial will adopt a one-sided significance level of 2.5%. A between-groups comparison will be performed using an independent two-sample

t-test to determine the significance of amount of change in VO_{2peak} (mL/kg/min) from 0 week to 12 weeks (after intervention completion) between the trial intervention and the control groups. Secondary endpoint analyses will be performed with the goal of supplementing the primary analyses. The detailed methods for supplementary analyses will be specified in the Statistical Analysis Plan before the study data is fixed. Once all data has been locked following conclusion of the primary analysis period and follow-up, final analyses will be performed.

Sample size estimation

The main hypothesis of this study is that the intervention group will significantly surpass the control group in terms of the amount of change in VO_{2peak} from 0 week to 12 weeks. Regarding the clinical significance of the results of an exercise program, it is common to use an increase of 10% in VO_{2peak} to evaluate the effects of an exercise program[50]. As such, an increase of 10% from VO_{2peak} at the start of exercise has been established for this trial. According to a previous study of intervention similar to that in the present study[51], the standard deviation for the VO_{2peak} of the intervention group was 2.6 mL/kg/min. Based on the above hypothesis, by estimating the number of subjects required for a one-sided 2.5% and a power of 80% in the analysis, 28 individuals per group are necessary for a total of 56 in both groups (SAS 9.4 software; SAS Institute Inc., Cary, NC). With the estimation that 4 participants will drop out, enrollment of 60 patients is planned.

Study period

The study period of this trial will be from April 2019 to March 2021; the participant entry period will be from April 2019 to March 2020. Study enrolment, intervention, and data collection are ongoing.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

This study protocol was designed with the involvement of a breast cancer survivor who participated in this study as a researcher and coauthor. She discussed issues with other survivors in instances where survivors' preferences and opinions should be considered. In the process of creating the habit-B program, we conducted a preliminary confirmation of the feasibility and safety of this program in 5 breast cancer survivors.

ETHICAL CONSIDERATIONS AND DISSEMINATION

The protocol was approved by the Institutional Review Board of the National Cancer Center Research Ethical Review Committee on 28 February 2019 (ID: 2018-274). The results obtained will be submitted for publication in a peer-reviewed international journal, and the main relevant findings will be presented at conferences.

DISCUSSION

An excellent review by Shapiro et al. affirms the positive role that high levels of physical activity play in improving not only health-related QOL and symptom management (e.g., chronic pain, fatigue, insomnia, sexual dysfunction, metabolic syndrome, bone loss, cognitive dysfunction, and depression), but also return to work in cancer survivors [52]. In addition, increased cardiorespiratory fitness may decrease all-cause mortality among cancer survivors[53,54]. However, there are currently no effective home-based exercise programs available for improving cardiorespiratory fitness for breast cancer survivors. No studies have precisely investigated cardiorespiratory fitness [55]; however, a small pilot study did estimate VO_2 based on subjective exercise intensity among Japanese breast cancer survivors. Accordingly, the present study seeks to confirm whether our originally developed home-based exercise program (habit-B program) improves VO_{2peak} compared with treatment as usual in sedentary breast cancer survivors in Japan. With the assumption that the program will be widely implemented if successful, it was designed to be (1) home based, (2) quick to implement (only 10 min in total), (3) use only body weight exercises involving the lower limbs, and (4) utilize a wearable device for which personalized ICT support is available. We believe that no similar studies have been implemented.

If it is found that the habit-B program is effective in increasing VO_{2peak}, we will then proceed to the next trial, aiming for its widespread implementation in society. Specifically, the aims of the next study will be (1) to investigate whether

intervention using the program developed in this research but presented in a simpler format is effective in establishing exercise habits and (2) to assess whether the program can be implemented in societies in Eastern Asia, including in both urban and rural Japan and other East Asian countries.

We strongly believe that a successful support team comprising specialists in the field of exercise science, medicine, rehabilitation, nursing, and patient advocacy, as involved in this study, will provide a new horizon in cancer survivorship care.

Acknowledgements

We sincerely thank Dr. Hiroji Iwata, Dr. Hirokazu Arai, Ms. Noriko Watanabe, Dr. Noriaki Tatematsu, Dr. Hikaru Ihira, Mr. Tomoyasu Chigahara, Dr. Taro Ueno, Dr. Shinji Fukuda, and Dr. Eiko Saito for their generous support for the study. We also thank Ms. Ayako Sato for her role as an exercise model.

Contributors KT, EO, RO, YS, TK, and YM conceived the study and drafted the original protocol. KT, EO, RO, YS, TS, AK, TU, TK, and YM participated in refining the protocol. TU developed app and EDC system and managed datacenter. AK played a major role in the statistical analysis. KT, EO, TK, and NS contributed to developing the exercise program. KT, EO and YM drafted the manuscript. All authors participated in, read, and approved the final manuscript.

Funding This study is supported by a National Cancer Center Research and Development Fund (30-A-17).

Competing interests EO has received research support from Nippon Suisan Kaisha, Ltd. YJM has received speaker fees from Pfizer, Mochida, Eli Lilly, Morinaga Milk, and NTT Data and is conducting collaborative research with Morinaga Milk. AK has received speaking fees from Chugai Pharmaceutical Co., Ltd. All other authors declare that they have no competing interests regarding this work.

Ethics approval. The protocol was approved by the Institutional Review Board of the National Cancer Center on 28 February 2019 (ID: 2018-347).

FIGURE LEGENDS

Figure 1. Flow diagram of study participants. HIIT, high-intensity interval training; ICT, information and communication technology.

Figure 2. Study design of the habit-b program (**h**ome-based high-intensity interval training **a**nd **b**ehavioral modification using information and communication **t**echnology on cardiorespiratory fitness and exercise habits for sedentary **b**reast cancer survivors). HIIT, high-intensity interval training; ICT, information and communication technology.

Figure 3. Screenshots of the application for the smartphone-based exercise movie.

Figure 4. Sample of high-intensity interval training using body weight exercise.

Figure 5. Brochure reminding participants about the importance of exercise and providing instructions about physical activity in daily life.

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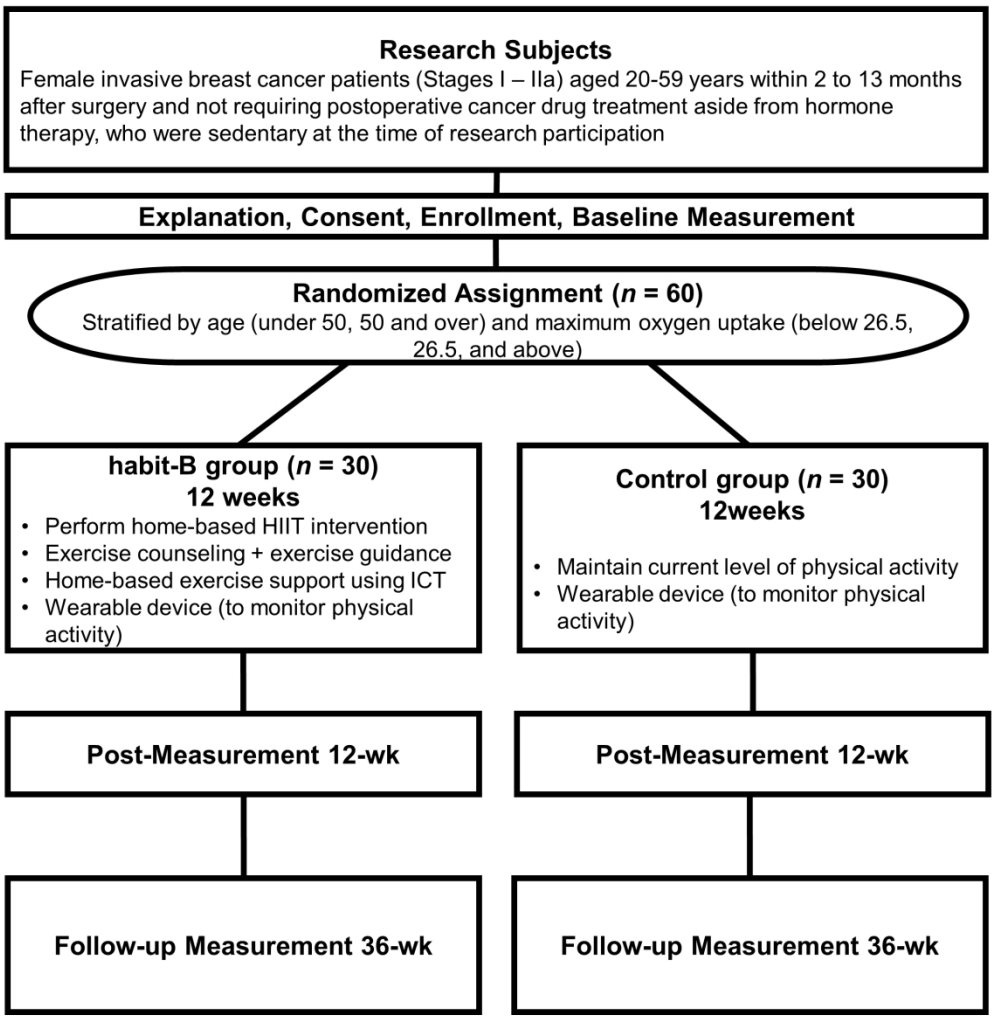
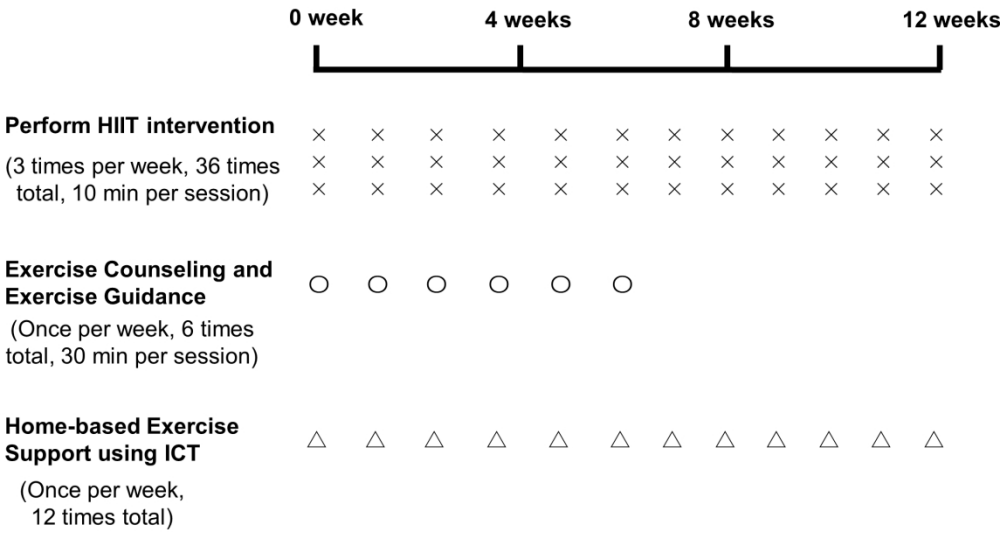
Table 1 Schedule for outcome measurement

	Time points			
	Protocol Intervention Period		Follow-up Intervention Period	
Assessment	**0 week**	**12 weeks**	**24 weeks**	**36 weeks**
Confirmation of eligibility	×			
Explanation, consent, enrollment	×			
Assignment	×			
Demographics, laboratory data, blood fatty acids	×			
Cardiorespiratory fitness, physical function	×	×		
GPAQ	×	×	×	×
Objective activity level (according to Fitbit versa®)	←	—	—	→
Subjective indexes	×	×	×	
Assessment of protocol intervention feasibility	×	×		
Interview regarding satisfaction of the intervention		×		
Exercise log	←	→		
Adverse events	←	→		
Gut microbiota	×	×		
Medical Economic Cost	←	—	—	→

Table 1. Schedule for outcome measurement





3 min and 10 sec Warm up	Squat	rest	Lunge	rest	Squat	rest	Lunge	rest	Squat	rest	Lunge	rest	Squat	rest	Lunge	3 min cool down
	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	

10 min

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (p1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry(p4, 20)
	2b	All items from the World Health Organization Trial Registration Data Set(n/a)
Protocol version	3	Date and version identifier(p4, 20)
Funding	4	Sources and types of financial, material, and other support (p23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (p23)
	5b	Name and contact information for the trial sponsor (p23)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (n/a)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (n/a)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (p6)
	6b	Explanation for choice of comparators (p11)
Objectives	7	Specific objectives or hypotheses (p6)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (p8)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained(p5)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (p8,9)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered(p9-11)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (p13)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (p11)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial(p12,13)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended(p14-18)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure 1,2, and Table 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations(p19)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size(n/a)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions(p8,12)

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned(p8,12)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions(p8,12)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how(p12)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial(n/a)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol(p18)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols(p10,13)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol(p11,12)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol(p18,19)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (p18,19)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (p18,19)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed(p11,12)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial(n/a)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct(p17)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor(p11,12)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval(p4)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (n/a)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (n/a)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable(n/a)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial(p12)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site(p23)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators(n/a)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation(p17,18)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions(p4,20)
	31b	Authorship eligibility guidelines and any intended use of professional writers(p11)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code(n/a)

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates(n/a)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable(p17)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors: the habit-B study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-030911.R2
Article Type:	Protocol
Date Submitted by the Author:	16-Jul-2019
Complete List of Authors:	Tsuji, Katsunori; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences Ochi, Eisuke; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences; Hosei University, Faculty of Bioscience and Applied Chemistry Okubo, Ryo; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences Shimizu, Yoichi; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences Kuchiba, Aya; National Cancer Center Japan, Division of Biostatistical Research, Center for Public Health Sciences; National Cancer Center Japan, Biostatistics Division, Center for Research Administration and Support Ueno, Taro; SUSMED, Inc. Shimazu, Taichi; National Cancer Center Japan, Division of Prevention, Center for Public Health Sciences Kinoshita, Takayuki; National Cancer Center Hospital, Department of Breast Surgery Sakurai, Naomi; Cancer Solutions Matsuoka, Yutaka; National Cancer Center Japan, Division of Health Care Research, Center for Public Health Sciences
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Mental health, Oncology
Keywords:	Breast tumours < ONCOLOGY, SPORTS MEDICINE, PREVENTIVE MEDICINE, CLINICAL PHYSIOLOGY

BMJ Open ***Study protocols***

Effect of home-based high-intensity interval training and behavioral modification using information and communication technology on cardiorespiratory fitness and exercise habits among sedentary breast cancer survivors: the habit-B study protocol for a randomized controlled trial

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ABSTRACT

Introduction

Maintaining high levels of physical activity not only helps to maintain and improve physical health and quality of life, but also plays a role in reducing adverse effects due to cancer treatments. Moreover, a greater degree of cardiorespiratory fitness is associated with reduced risk of all-cause mortality. However, there are no home-based programs for improving cardiorespiratory fitness using body weight exercises for breast cancer survivors. This study will assess the efficacy of the newly developed habit-B program on maximum oxygen uptake compared with treatment as usual with wearable device. The effects of this program on exercise habits, level of physical activity, physical fitness, and subjective indices will also be investigated.

Methods and analysis

This is a 12-week, parallel-group, single blind, randomized controlled trial. Allocation will be managed by a central server using a computer-generated random allocation sequence provided by an independent data center. Participants will be assigned to the habit-B Program (high-intensity interval training exercise, exercise counseling + guidance, home-based exercise support using information and communication technology, and a wearable device) or treatment as usual with a wearable device. Subjects will be sedentary women aged 20 to 59 years who have received breast surgery in the past 2 to 13 months after diagnosis of invasive breast cancer (Stage I-IIa) and have never received chemo-therapy except for

hormone therapy. The primary endpoint is the change in peak oxygen uptake (VO_{2peak}; mL/kg/min) between the groups after 12 weeks of intervention.

Ethics and dissemination

The study protocol was approved by the Institutional Review Board of the National Cancer Center Japan on 28 February 2019 (ID: 2018-347). The findings will be disseminated through peer reviewed publications and conference presentations.

Trial status Study enrolment, intervention, and data collection are ongoing. The estimated end date for this study is on March 31, 2021.

Trial registration number UMIN000036400; Pre-results.

Strengths and limitations of this study

1. This clinical trial will be the world's first home-based HIIT program using ICT to increase cardiorespiratory fitness in sedentary breast cancer survivors.
2. The habit-B program is designed based on the theory of Bandura for sedentary breast cancer survivors to develop exercise habits.
3. Collaborative work with professionals in the field of clinical oncology, exercise science, mental health, rehabilitation, public health, nursing, and cancer survivors constitutes a new model for cancer survivorship care.
4. We cannot rigorously exclude breast cancer survivors who may have exercise habits because the definition of sedentary subjects will be based on self-report.

INTRODUCTION

Breast cancer, which is one of the most common cancers affecting women, newly affects over 86,000 women each year[1]. It is recommended that cancer survivors acquire and maintain healthy behaviors to extend survival, such as staying reasonably fit through appropriate physical exercise and having a healthy diet [2]. High levels of physical activity not only help to maintain and improve physical health and quality of life (QOL), but also play a role in reducing short- and long-term side effects of cancer treatment. The American Cancer Society guidelines recommend a minimum of 150 min moderate physical activity or 75 min intensive physical activity per week, in addition to usual physical activity in daily life[3], and the Japan Breast Cancer Society's Clinical Guidelines for Breast Cancer strongly recommend maintaining a high level of physical activity[4 5].

The ENERGY Trial, an early and representative study conducted in the US, demonstrated the effectiveness of a home exercise program and nutritional advice to promote weight loss among breast cancer survivors[6]. However, because the proportion of overweight adults in Japan is lower than that in the US[7], it is not appropriate to adopt the US-developed program in Japan. It would appear suitable though to develop intervention around measurements of VO_{2peak}, the globally important health indicator of cardiorespiratory fitness [8 9].

VO_{2peak} decreases with age, and a meta-analysis has suggested that women who are sedentary have a decrease of 3.2 mL/kg/min over 10 years[10]. A cohort study suggested that the all-cause mortality rate decreased by 17% for each 1 metabolic equivalent (MET) increase (3.5 mL/kg/min) in VO_{2peak} for women[11]. A

systematic review demonstrated that the median VO_{2peak} of breast cancer survivors not receiving chemotherapy was lower than that of healthy sedentary women (25.3 mL/kg/min vs. 29.7 mL/kg/min)[12]. In a 16-year follow-up study of breast cancer survivors[12], hazard ratios were 0.67 for the moderate VO_{2peak} group (8.5 METs) and 0.45 for the high group (11.1 METs) compared with the low VO_{2peak} group (6.7 METs). In this report, the mortality rate was reduced by maintaining a VO_{2peak} of 8 METs or above[12]. Against this background, it is necessary to develop an exercise program that will increase VO_{2peak} in breast cancer survivors.

When considering how to increase VO_{2peak}, research has advanced in recent years with the use of HIIT for athletes and sedentary populations[13-15]. HIIT allows subjects to exercise at vigorous intensity within 10 min, resulting in improved cardiorespiratory fitness[9 16]. A recent systematic review showed, based on the findings of 12 studies of HIIT conducted in supervised experimental settings, that HIIT appeared to be more beneficial than treatment as usual for improving physical fitness and health-related outcomes in cancer survivors during any stage of treatment and aftercare[16]. To our knowledge, only one study has evaluated changes in cardiorespiratory fitness following a home-based HIIT program, which involved healthy young women[17]. Given that no home-based HIIT programs with body weight exercises have been reported for breast cancer survivors to date, it is necessary to develop such programs and examine their efficacy and feasibility.

Recent emerging technologies such as smartphone applications (apps) and wearable devices are promising tools for the monitoring of cancer patients' daily

activity levels and for facilitating coaching, self-monitoring, feedback, and encouragement to exercise[18,19]. Apps[20] and wearable devices[21] are being used for both subjective and objective measures in the field of clinical oncology. However, further investigations are needed of their potential utility in objective evaluations of physical activity as well as in lifestyle modification and maintenance and enhancement of QOL in real-world settings.

The aim of this study is to investigate the effect of the newly developed habit-B program, comprising **h**ome-based high-intensity interval training **a**nd **b**ehavioral modification using **i**nformation and communication **t**echnology on cardiorespiratory fitness and exercise habits for sedentary **b**reast cancer survivors. We will investigate whether the habit-B program improves VO_{2peak} compared with a control group as well as investigate the safety and feasibility of program. The secondary objectives are to investigate the effect of this program on exercise habits, physical activity level, physical function, and subjective measures.

METHODS AND ANALYSIS

Trial design

In this study 12-week, parallel-group, single blind, randomized controlled trial (Figure 1), participants will be randomly assigned to intervention either with the habit-B program (HIIT exercise, exercise counseling + guidance, home-based exercise support using ICT, and a wearable device) or treatment as usual with a wearable device (Fitbit Versa smart watch; Fitbit Inc., San Francisco, CA). An independent data center will provide computer-generated random allocation. Participants will be assigned by the minimization method, a form of dynamic randomization, using two prognostic factors: VO_{2peak} and age. Based on the allocation sequences, the contents of the app that participants use during the trial will be assigned automatically to either the habit-B program or control.

Participants

The eligibility criteria for participants are as follows: (1) female, aged between 20 and 59 years at diagnosis (stages I-IIa); (2) diagnosed with invasive breast cancer within 2 to 13 months after surgery; (3) not requiring cancer chemotherapy aside from hormone therapy; (4) currently engages in not more than moderate intensity exercise for 30 min on 2 separate days per week (total of 60 min), which is based on the National Health and Nutrition Survey Japan[22]; (5) ability to complete an electronic patient reported outcome (e-PRO) questionnaire via a smartphone; (6) consent to trial participation obtained in writing from the

patient themselves; and (7) ability to read, write, and understand Japanese. The exclusion criteria are as follows: (1) judged to have severely reduced cognitive function by a primary physician; (2) exercise judged to be risky by a primary physician; (3) history of smoking within the previous 12 months; (4) body mass index of 30 or above; (5) abnormal electrocardiogram in preoperative testing, resting heart rate (HR) below 50 beats/min or above 100 beats/min, or stage III hypertension or above (diastolic blood pressure over 110 mmHg or systolic blood pressure over 180 mmHg); and (6) judged unfit for the trial by a primary physician for other reasons such as the administration of beta-adrenergic blocking agents.

Interventions

This will be a randomized, single-blind study. Participants will be enrolled and assigned using an electronic data capture system with an app. The protocol intervention will be started within 21 days of enrollment. If for some reason the start is delayed beyond 21 days, the reason will be entered into the electronic Case Report Form (eCRF). If it is determined that the intervention cannot be started, the details will be noted in the eCRF as “protocol intervention stopped.”

The habit-B program group

The habit-B program (Figure 2) comprises home-based exercise support utilizing 6 weeks of exercise counseling/exercise guidance (once per week, 6 times

total, 30 min per session) and 12 weeks of ICT interventions, which are provided with personalized e-mail (once per week, 12 times in total), and a newly developed exercise app (during each exercise session, shown in Figure 3). Participants will be encouraged to complete the following program HIIT using specific body weight exercises for one 10-min training session 3 times a week for 12 weeks (total of 36 sessions during the trial period, as shown in Figures 2 and 4): (1) one bout of 10-min exercises; (2) a total of 10 min exercise, comprising a 3-min warm-up, 4-min training (8 sets of 20 s exercise + 10 s rest), and a 3-min cool-down; (3) these training exercises are designed to increase in intensity each week; and (4) the details of these exercises are divided into three stages according to cardiorespiratory fitness (VO_{2peak}) at Week 0 and the contents of training are designed to increase physical strength incrementally in accordance with the individual's level of strength. In addition, we will continue to follow up on the between-group differences in e-PRO data of change from baseline to 24 and 36 weeks post-intervention.

The social cognitive theory proposed by Bandura et al. may be helpful to apply when considering interventions for behavioral change[23], chiefly in that it affords a framework for understanding the underlying reasons for making and maintaining health behaviors[24]. Its key concepts involve (1) understanding of health risks and benefits, (2) perceived self-efficacy of being able to control one's own health habits, (3) projected costs and benefits or expected outcomes, (4) specified health goals with short- and long-term intentions to engage in the behavior, (5)

perceived facilitators and social support, and (6) barriers to instituting change[23 24]. In the present study, we developed the exercise program applying the first 5 concepts.

We will also provide the participant a brochure as a reminder to exercise and will check the type of physical activity they engage in in daily life (Figure 5). When developing the habit-B program, we collaborated closely with exercise scientists, oncologists, physical therapists, nurses, mental health practitioners, and breast cancer survivors.

Control group

The control group will be provided a wearable device and setup support at the start of intervention. Self-monitoring using the wearable device will be recommended during the trial period. While there are no reports of increasing VO_{2peak} with the use of a wearable device alone, other reports have ruled out their efficacy with regard to effects on exercise habits[25]. In this study, the wearable devices are used only to monitor physical activity in the control group.

PROCEDURE

Data collection, management, monitoring, and auditing

We will collect all data except qualitative interview data, blood samples, fecal samples, and medical economic costs through the e-PRO system. Those who provide consent will be enrolled in the app-based e-PRO system on their

smartphone. If the entered data is insufficient, enrollment will not be accepted until all fields are completed at baseline. The electronic data capture system will be used for data management and central monitoring. Because this exercise program will not be invasive, there is no need to establish a data monitoring committee or to complete auditing in this study.

Random assignment and assignment adjustment factors

After enrollment and the additional input of the VO_{2peak} value, patients will be randomly assigned. In the process of random assignment, VO_{2peak} (obtained from the baseline measurement performed after obtaining informed consent) and age will be used as assignment adjustment factors, and automatic assignment will be performed using the data center's assignment feature. Only the measurer will be blinded in this study, because interventions differ for the intervention group and control group.

Dataset availability

The data sharing policy in this study is defined with reference to the example proposed by the International Committee of Medical Journal Editors (ICMJE): Individual participant data will be made publicly available for a 5-year period through the University Hospital Medical Information Network – Individual Case Data Repository (UMIN-ICDR) (https://www.umin.ac.jp/icdr/index-j.html).

Concomitant treatments

There are no regulated concomitant therapies or supportive therapies in this study.

Stopping rules for participants

Situations in which the intervention protocol is terminated for any of the following reasons will be defined as stopping of the protocol intervention: (1) dropping out due to withdrawal of consent or inability to measure the primary endpoint (VO_{2peak}); (2) if a primary physician deems it necessary to stop the protocol intervention for a participant due to adverse events such as stress; (3) death of the patient during the protocol intervention period; (4) sudden worsening of the participant's condition after enrollment or discovery of a protocol violation or ineligibility. A researcher will report the reason for stopping the protocol intervention to the data center. In this event, as long as consent is not withdrawn, follow-up including the questionnaire survey will be continued.

Stopping of the assessment

Situations in which the participant declines assessment will effectively stop the assessment. A researcher will confirm the possibility of implementing the remaining parts of the intervention and follow-up with the participant. Stopping of the assessment will be recorded along with the details of the reason for stopping.

As a rule, the remaining aspect of follow-up will be implemented as stipulated per protocol.

Assessment measures

Table 1 shows the outcome measurement schedule.

Primary outcome measure: Cardiorespiratory fitness (VO_{2peak})

VO_{2peak} is the maximum oxygen uptake observed during exercise tolerance testing and is used as an indicator of cardiorespiratory fitness[26 27]. For each participant, VO_{2peak} will be measured using the incremental multistage load method with a bicycle ergometer (Ergomedic 828E, Monark, Stockholm, Sweden) at 60 revolutions per min (rpm). The test will begin at 0.5 kp and increase by 0.25 kp per min until exhaustion. When the participant's pedal rotation speed drops below 55 rpm 3 times, the test will be deemed concluded. Respiratory gases will be analyzed using an automatic gas analyzer (Air Monitor AE-310S, Minato Medical Science Co., Ltd., Osaka, Japan). Rated perceived exertion and HR will be recorded after 45 s in each stage. The maximum value of VO_2 observed during exercise will be used as the VO_{2peak}.

Secondary outcome measures

Physical function

An alternative indicator of VO_{2peak}, the 6-min walk test (m), will be performed[28]. Walking speed (m/s), a diagnostic criterion for sarcopenia, will also be measured. A 5-m section in the middle of an 11-m line will be measured to calculate walking speed [29]. One-repetition maximum for leg press, which reflects muscle strength in the lower body, will be assessed using a leg press machine (Powertec Leg Press P-LP16; Powertec, Paramount, CA) [30 31]. After a thorough warm-up, measurements will be performed by incrementally increasing the load until a weight, which can be lifted only once, is reached. Load will be increased by two levels at a time. Grip strength (TKK 5401 Grip-D; Takei, Niigata, Japan) will also be measured[31 32]. The chair stand test, which reflects combined leg strength for the lower limbs as a whole, will be performed[31 33]. Participants will sit and stand from a chair for 10 s and the number of chair stands will be measured. The timed up and go test, which is used in clinical settings as an assessment of functionality as well as muscular strength, will also be performed[31]. The functional reach test, which as a method of assessing dynamic balance is considered an indicator of expected fall risk, will also be performed[34]. While keeping the hand at the same height, the participant will extend their arm forward as far as possible, without moving the feet, to make a mark at the farthest point they can reach. Lifting the heels and standing on tiptoe is allowed. The two-step test will also be performed[35]. This test comprehensively assesses ability to walk, including leg strength, balance, and flexibility. Based on bioelectrical impedance analysis, a body

composition meter (MC-780A-N, TANITA, Japan) will be used to send a weak electrical current through the body via electrodes.

Physical activity level

The Global Physical Activity Questionnaire (GPAQ) was developed in 2002 as an internationally standardized questionnaire for surveying physical activity level. The GPAQ is widely used in policy development by the World Health Organization[36-38]. The face validity of the Japanese version has been confirmed[39]. In addition, as an objective measure of physical activity during the research period, resting HR, steps, distance, calorie expenditure, and the duration of each sleep stage as well as wake up time will be measured using an activity monitor and logged for 24-h periods (Fitbit versa, Fitbit Inc., San Francisco, CA). Maximum HR during exercise will also be measured to confirm whether the intensity of the exercise being implemented is appropriate. The accurately measured group will be defined as the group who wears the Fitbit versa at least 60% of the time during the 12-week intervention period.

Subjective measures

Fear of cancer recurrence (FCR) will be assessed by the overall fear index score on the Concerns About Recurrence Scale[40 41]. This instrument comprises 4 items scored on a 6-point Likert scale (range, 1–6), with a higher score indicating worse FCR. Depression will be assessed using the Patient Health Questionnaire-9

[42]. Fatigue will be assessed by the Cancer Fatigue Scale. Sleep will be assessed by the Athens Insomnia Scale[43 44]. Health-related QOL will be assessed using the EuroQol 5 Dimensions questionnaire[45 46].

Biological assessments

To assess changes in gut microbiota, intestinal metabolites, and intestinal immunity[47], a 1-g fecal sample will be obtained at baseline and at 12 weeks. Blood compositions of n-3 polyunsaturated fatty acids[48] will be assessed from capillary dried blood spot samples (approximately 80 μL) at baseline[49].

Medical economic costs

For cost-benefit analysis, the number of staff, working hours, labor costs, equipment costs, office expenses, number of unexpected medical consultations, direct medical costs, and costs of other medical services used will be obtained.

Harms

The intervention in this research will potentially place stress on participants physically and in terms of their time, because it will take approximately 1 h and 30 min. There will also be temporary exhaustion, although individual differences will be considered in exercise implementation. There are no financial risks associated with participation in the study.

Compensation

If participants develop unexpected health issues due to study participation during or after completion of the study, treatment will be provided appropriately in the same way as standard medical care. Medical expenses at that time will be handled within the medical insurance to which the participant is enrolled. No financial compensation, except for providing the wearable device, will be given in this study.

DATA ANALYSIS

The primary endpoint, VO_{2peak}, will be calculated as follows. Measurements will be taken at the start of the intervention (0 week) and at the conclusion of the intervention (12 weeks). The analysis set for primary analyses will consist of all randomized subjects. Our primary analysis is intention-to-treat analysis and patients without outcome data will be excluded from the analyses. After completing primary endpoint data locking, analyses centering on the primary endpoint will be performed. The objective of primary analysis in this study is to investigate whether the habit-B program group (trial treatment group) surpasses the group receiving treatment as usual (control) in VO_{2peak}, the primary endpoint. One-sided tests will be used, because, if the trial intervention group is inferior to the control group, it is not important in this trial whether that difference is statistically significant. The trial will adopt a one-sided significance level of 2.5%. A between-groups comparison will be performed using an independent two-sample

t-test to determine the significance of amount of change in VO_{2peak} (mL/kg/min) from 0 week to 12 weeks (after intervention completion) between the trial intervention and the control groups. Secondary endpoint analyses will be performed with the goal of supplementing the primary analyses. The detailed methods for supplementary analyses will be specified in the Statistical Analysis Plan before the study data is fixed. Once all data has been locked following conclusion of the primary analysis period and follow-up, final analyses will be performed.

Sample size estimation

The main hypothesis of this study is that the intervention group will significantly surpass the control group in terms of the amount of change in VO_{2peak} from 0 week to 12 weeks. Regarding the clinical significance of the results of an exercise program, it is common to use an increase of 10% in VO_{2peak} to evaluate the effects of an exercise program[50]. As such, an increase of 10% from VO_{2peak} at the start of exercise has been established for this trial. According to a previous study of intervention similar to that in the present study[51], the standard deviation for the VO_{2peak} of the intervention group was 2.6 mL/kg/min. Based on the above hypothesis, by estimating the number of subjects required for a one-sided 2.5% and a power of 80% in the analysis, 28 individuals per group are necessary for a total of 56 in both groups (SAS 9.4 software; SAS Institute Inc., Cary, NC). With the estimation that 4 participants will drop out, enrollment of 60 patients is planned.

Study period

The study period of this trial will be from April 2019 to March 2021; the participant entry period will be from April 2019 to March 2020. Study enrolment, intervention, and data collection are ongoing.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

This study protocol was designed with the involvement of a breast cancer survivor who participated in this study as a researcher and coauthor. She discussed issues with other survivors in instances where survivors' preferences and opinions should be considered. In the process of creating the habit-B program, we conducted a preliminary confirmation of the feasibility and safety of this program in 5 breast cancer survivors.

ETHICAL CONSIDERATIONS AND DISSEMINATION

The protocol was approved by the Institutional Review Board of the National Cancer Center Research Ethical Review Committee on 28 February 2019 (ID: 2018-274). The results obtained will be submitted for publication in a peer-reviewed international journal, and the main relevant findings will be presented at conferences.

DISCUSSION

An excellent review by Shapiro et al. affirms the positive role that high levels of physical activity play in improving not only health-related QOL and symptom management (e.g., chronic pain, fatigue, insomnia, sexual dysfunction, metabolic syndrome, bone loss, cognitive dysfunction, and depression), but also return to work in cancer survivors [52]. In addition, increased cardiorespiratory fitness may decrease all-cause mortality among cancer survivors[53,54]. However, there are currently no effective home-based exercise programs available for improving cardiorespiratory fitness for breast cancer survivors. No studies have precisely investigated cardiorespiratory fitness [55]; however, a small pilot study did estimate VO_2 based on subjective exercise intensity among Japanese breast cancer survivors. Accordingly, the present study seeks to confirm whether our originally developed home-based exercise program (habit-B program) improves VO_{2peak} compared with treatment as usual with wearable device in sedentary breast cancer survivors in Japan. With the assumption that the program will be widely implemented if successful, it was designed to be (1) home based, (2) quick to implement (only 10 min in total), (3) use only body weight exercises involving the lower limbs, and (4) utilize a wearable device for which personalized ICT support is available. We believe that no similar studies have been implemented.

If it is found that the habit-B program is effective in increasing VO_{2peak}, we will then proceed to the next trial, aiming for its widespread implementation in society. Specifically, the aims of the next study will be (1) to investigate whether

intervention using the program developed in this research but presented in a simpler format is effective in establishing exercise habits and (2) to assess whether the program can be implemented in societies in Eastern Asia, including in both urban and rural Japan and other East Asian countries.

We strongly believe that a successful support team comprising specialists in the field of exercise science, medicine, rehabilitation, nursing, and patient advocacy, as involved in this study, will provide a new horizon in cancer survivorship care.

Acknowledgements

We sincerely thank Dr. Hiroji Iwata, Dr. Hirokazu Arai, Ms. Noriko Watanabe, Dr. Noriaki Tatematsu, Dr. Hikaru Ihira, Mr. Tomoyasu Chigahara, Dr. Taro Ueno, Dr. Shinji Fukuda, and Dr. Eiko Saito for their generous support for the study. We also thank Ms. Ayako Sato for her role as an exercise model.

Contributors KT, EO, RO, YS, TK, and YM conceived the study and drafted the original protocol. KT, EO, RO, YS, TS, AK, TU, TK, and YM participated in refining the protocol. TU developed app and EDC system and managed datacenter. AK played a major role in the statistical analysis. KT, EO, TK, and NS contributed to developing the exercise program. KT, EO and YM drafted the manuscript. All authors participated in, read, and approved the final manuscript.

Funding This study is supported by a National Cancer Center Research and Development Fund (30-A-17).

Competing interests EO has received research support from Nippon Suisan Kaisha, Ltd. YJM has received speaker fees from Pfizer, Mochida, Eli Lilly, Morinaga Milk, and NTT Data and is conducting collaborative research with Morinaga Milk. AK has received speaking fees from Chugai Pharmaceutical Co., Ltd. All other authors declare that they have no competing interests regarding this work.

Ethics approval. The protocol was approved by the Institutional Review Board of the National Cancer Center on 28 February 2019 (ID: 2018-347).

FIGURE LEGENDS

Figure 1. Flow diagram of study participants. HIIT, high-intensity interval training; ICT, information and communication technology.

Figure 2. Study design of the habit-b program (**h**ome-based high-intensity interval training **a**nd **b**ehavioral modification using information and communication **t**echnology on cardiorespiratory fitness and exercise habits for sedentary **b**reast cancer survivors). HIIT, high-intensity interval training; ICT, information and communication technology.

Figure 3. Screenshots of the application for the smartphone-based exercise movie.

Figure 4. Sample of high-intensity interval training using body weight exercise.

Figure 5. Brochure reminding participants about the importance of exercise and providing instructions about physical activity in daily life.

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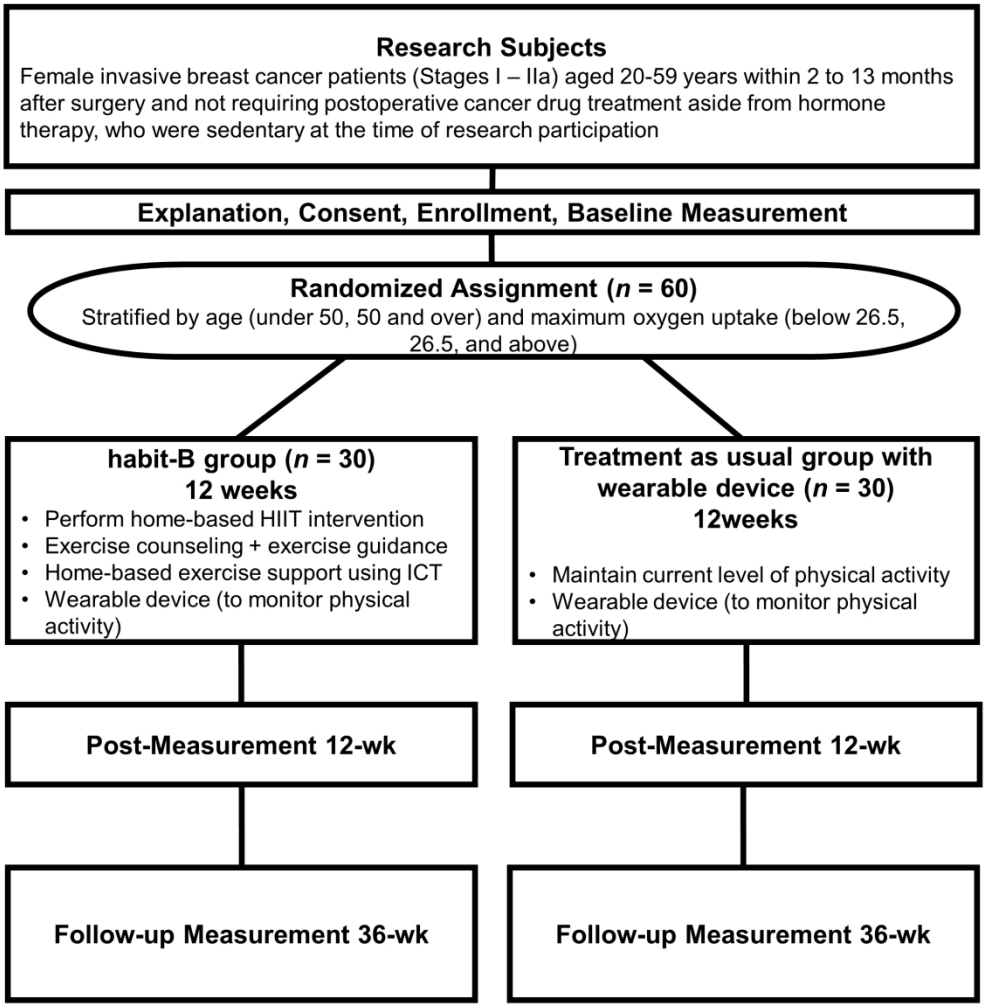
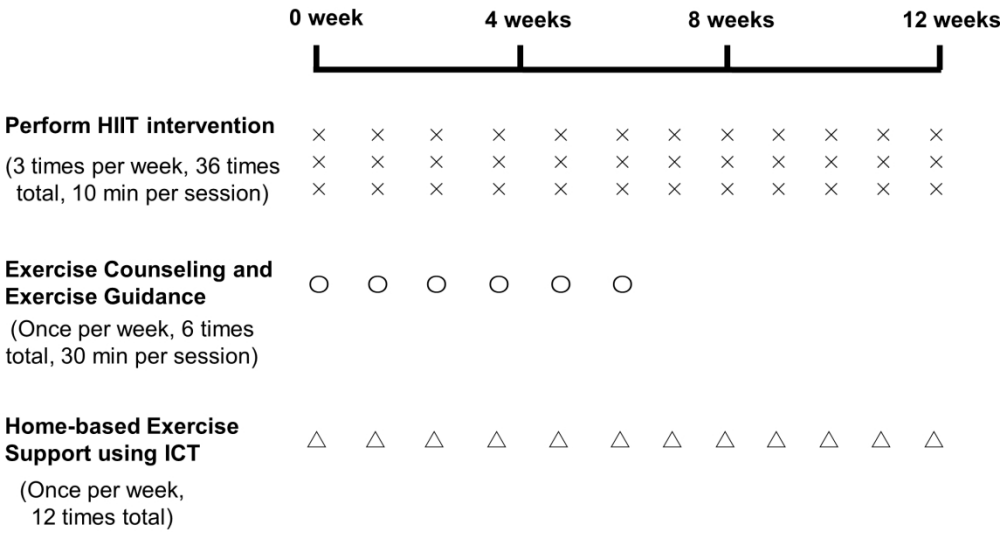
Table 1 Schedule for outcome measurement

	Time points			
	Protocol Intervention Period		Follow-up Intervention Period	
Assessment	**0 week**	**12 weeks**	**24 weeks**	**36 weeks**
Confirmation of eligibility	×			
Explanation, consent, enrollment	×			
Assignment	×			
Demographics, laboratory data, blood fatty acids	×			
Cardiorespiratory fitness, physical function	×	×		
GPAQ	×	×	×	×
Objective activity level (according to Fitbit versa®)	←	—	—	→
Subjective indexes	×	×	×	
Assessment of protocol intervention feasibility	×	×		
Interview regarding satisfaction of the intervention		×		
Exercise log	←	→		
Adverse events	←	→		
Gut microbiota	×	×		
Medical Economic Cost	←	—	—	→

Table 1. Schedule for outcome measurement



189x195mm (300 x 300 DPI)



3 min and 10 sec Warm up	Squat	rest	Lunge	rest	Squat	rest	Lunge	rest	Squat	rest	Lunge	rest	Squat	rest	Lunge	3 min cool down
	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	10 s	20 s	

10 min

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (p1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry(p4, 20)
	2b	All items from the World Health Organization Trial Registration Data Set(n/a)
Protocol version	3	Date and version identifier(p4, 20)
Funding	4	Sources and types of financial, material, and other support (p23)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (p23)
	5b	Name and contact information for the trial sponsor (p23)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (n/a)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (n/a)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (p6)
	6b	Explanation for choice of comparators (p11)
Objectives	7	Specific objectives or hypotheses (p6)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (p8)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained(p5)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (p8,9)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered(p9-11)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (p13)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (p11)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial(p12,13)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended(p14-18)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure 1,2, and Table 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations(p19)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size(n/a)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions(p8,12)

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned(p8,12)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions(p8,12)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how(p12)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial(n/a)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol(p18)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols(p10,13)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol(p11,12)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol(p18,19)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (p18,19)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (p18,19)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed(p11,12)

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial(n/a)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct(p17)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor(p11,12)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval(p4)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (n/a)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (n/a)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable(n/a)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial(p12)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site(p23)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators(n/a)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation(p17,18)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions(p4,20)
	31b	Authorship eligibility guidelines and any intended use of professional writers(p11)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code(n/a)

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates(n/a)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable(p17)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.