Long-term physical activity and body composition after exercise and educational programs for breast cancer: A randomized controlled trial from the Setouchi Breast Project-10

Takayuki Iwamoto (✉ tiwamoto@cc.okayama-u.ac.jp)
Okayama University Hospital

Yukiko Kajiwara
Okayama University Hospital

Kengo Kawada
Okayama University Hospital

Daisuke Takabatake
Kochi Health Science Center

Yuichiro Miyoshi
NHO Shikoku Cancer Center

Shinichiro Kubo
Fukuyama Citizens Hospital

Yoko Suzuki
Okayama University Hospital

Mari Yamamoto
Fukuyama Citizens Hospital

Yutaka Ogasawara
Kagawa Prefectural Center Hospital

Minami Hatono
Okayama University Hospital

Seiji Yoshitomi
Red Cross Okayama Hospital

Kyoko Hara
Red Cross Okayama Hospital

Asako Sasahara
Okayama University Hospital

Shozo Ohsumi
NHO Shikoku Cancer Center

Masahiko Ikeda
Fukuyama Citizens Hospital
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Abstract

Background

It is unclear what interventions can sustain long-term higher physical activity (PA) to improve breast cancer outcomes. Thus, this study aimed to evaluate the long-term effects of interventions on PA after breast cancer treatment.

Methods

This was an open-label randomized controlled trial for patients with stage 0-III breast cancer evaluating the efficacy of exercise and educational programs on long-term PA compared with usual care. The primary endpoint was proportion of patients with recreational PA (RPA) ≥ 5 metabolic equivalents (METs)/week at 1 year after registration.

Results

From 01/03/2016 to 15/03/2020, breast cancer patients were registered in the control (n = 120), education (n = 121), or exercise (n = 115) group. There were no significant differences in proportion of RPA ≥ 5 METs/week at 1 year between the exercise and control groups (54% and 53%, P = 0.492) and between the education and control groups (62% and 53%, P = 0.126). Significant difference in reductions from baseline at 1 year were noted on body weight (P = 0.0083), BMI (P = 0.0034), and body fat percentage (P = 0.0027) between education and control groups. Similarly, the exercise group showed significant difference in reduction in body fat percentage (P = 0.0038) compared to control group.

Conclusions

Although there were no significant effects on RPA 1 year after exercise and educational programs for breast cancer survivors, both interventions reduced body composition. Future studies on PA should investigate appropriate interventions to improve overall survival.

Trial registration

UMIN000020595 at UMIN Clinical Trial Registry

Date of first registration: 01/03/2016

Background

Breast cancer is one of the most commonly diagnosed cancers worldwide, accounting for 11.7% of new cancer diagnosis and 6.9% of cancer mortality among women in 2020 [1]. Improving the mortality of breast cancer survivors is a significant social concern. In the last two decades, the association between higher amounts of physical activity (PA) and all-cause and breast cancer-specific mortalities has been investigated [2, 3]. Other studies have revealed whether PA and obesity after the diagnosis of breast
cancer might influence the progression and recurrence of breast cancer. A meta-analysis of four cohort studies showed that women with high to moderate PA after the diagnosis of breast cancer had a significantly reduced risk of breast cancer-specific mortality (relative risk rate 0.71, 95% confidence interval [CI] 0.58–0.87) and all-cause mortality (relative risk rate 0.57, 95% CI 0.45–0.72) [4]. Another meta-analysis by the World Cancer Research Fund and American Institute for Cancer Research Continuous Expert Update Project found that PA before the diagnosis of breast cancer reduced the risk of all-cause and breast cancer mortalities, and PA 1 year after breast cancer diagnosis reduced the risk of all-cause mortality [5]. Despite these data, cancer survivors have low levels of PA [6, 7] and a decreased PA during cancer treatment without returning to the PA pre-diagnosis levels [8]. A global survey in 2016 reported that more than a quarter of all adults might have insufficient PA [9]. Most people, including cancer survivors, find it difficult to shift from a mostly sedentary lifestyle to a physically active lifestyle [10]. Although the association between higher PA and better breast cancer prognosis is becoming clearer, it is unclear what interventions can sustain long-term higher PA to improve breast cancer outcomes. Currently, medical staff may provide vague guidance for PA to breast cancer survivors in daily clinical settings. The promotion of PA can be considered a part of cancer treatment, and it is necessary to establish exercise programs for breast cancer survivors based on evidence. However, the generalization of exercise programs in the modern healthcare system may be difficult because of the limitations of human, facility, and economic resources for exercise programs. Recently, due to increasing health awareness, there have been many private facilities that provide exercise programs out of hospitals.

We hypothesized that exercise programs after the diagnosis of breast cancer using private facilities or educational programs by medical staff would improve all courses of mortality for breast cancer survivors. This study aimed to evaluate the long-term effects of an educational program by medical staff or an exercise program by private facilities outside of hospitals on long-term PA in breast cancer survivors.

**Methods**

**Patients**

Eligible participants had stage 0–III histologically diagnosed breast cancer, were within 1 year of completion of initial treatment (surgery or adjuvant chemotherapy), and were able to provide informed consent to participate in this trial. Patients were excluded if they were expected to have difficulty implementing the exercise program. Patients should receive standard therapies, including surgery, chemotherapy, human epidermal growth factor receptor 2 (HER2) targeted therapy, hormone therapy, and radiotherapy based on the Japanese Breast Cancer Society Clinical Practice Guidelines during the study [11, 12], and patients on hormone therapy or HER2 targeted therapy were allowed to enroll.

**Trial Design and Procedures**

The Setouchi Breast Project-10 (http://setouchi-bp.com/index.html) is an open-label randomized controlled trial (RCT) evaluating long-term PA by exercise and educational programs, compared with
usual care (Figure 1). Randomization was performed at the data center after confirming patient eligibility with assignment adjustment factors, as follows: age (<50 v ≥ 50 years), chemotherapy (Yes v No), and participating institution. This study has been performed in accordance with the Declaration of Helsinki and received an approval from the Ethics Committee of Okayama University Hospital and the respective institution, and each participant provided written informed consent. Participants were randomly assigned (in a 1:1:1 ratio) to usual care (control), educational program, or exercise program. This trial was registered in the UMIN Clinical Trial Registry (https://www.umin.ac.jp/) as UMIN000020595.

Participants in the control group were provided with an educational brochure on lifestyle after breast cancer treatment without any additional direct instruction by medical staff. In the education group, participants had to attend at least one instructional class on lifestyle (exercise and diet) for breast cancer survivors by breast medical doctors within 3 months of registration using an educational brochure. In the exercise program group, participants received a 30-min exercise program consisting of three parts, including aerobic exercise, workout, and stretching, three times a week for 4 months (16 weeks). The exercise program was outsourced to Curves Japan Co. (Tokyo, Japan), which is a fitness club for women only and has approximately 2,000 stores in Japan. For the first four months, the exercise program was provided free for the study participants and after that, they had to pay for program fee by themselves if they wished to continue. It can provide exercise programs of similar quality in each store, thus eliminating bias in a multi-institutional study. Details of the exercise program can be found on the webpage [13]. All participants were surveyed for their PA at baseline and at 2 months, 4 months, 6 months, and 1 year. PA levels were assessed using the questionnaire on PA at work and leisure time, which was validated by the Japan Public Health Center-based prospective study [14]. The primary endpoint was proportion of patients with recreational PA (RPA) ≥ 5 metabolic equivalents (metabolic equivalents [METs])/week at 1 year after registration. The key secondary endpoints were mean of change for RPA, total PA (tPA) (METs/day), and body composition (body weight, body mass index [BMI], and body fat percentage) from baseline at 1 year. Body fat percentage was measured with Karada Scan: HBF-701 (COMRON HEALTHCARE Co., Ltd. Kyoto Japan). PA was calculated using METs, which is a unit of measurement that shows the intensity of PA as a number of times greater than that at rest. The validation of METs for PA has been published by the National Institute of Nutrition and Health [15].

**Statistical Analyses**

This study was designed to randomly assign approximately 400 participants for the evaluation of the primary endpoint of RPA at 1 year. The sample size was estimated as follows: In a previous meta-analysis of four cohort studies examining the association between PA and prognosis after the diagnosis of breast cancer, dose-response analysis showed that the risk of total and breast cancer mortalities was reduced in women who had PA for at least 5 METs/week [4]. Therefore, in this study, we set a clinically meaningful threshold of 5 METs/week for PA after breast cancer diagnosis. In our previous analysis of 476 cases, a case-control study between December 2010 and November 2011 to examine lifestyle and breast cancer risk, the percentage of women with 5 METs/week or more was 43% [16]. In this study, we set an intervention to be clinically meaningful if the intervention increases the percentage of women with
5 METs/week or more by 20% compared to the control group (43% to 63%) for the exercise group and 15% for the education group (43% to 58%). Bonferroni correction was planned for the adjustment of multiplicity due to two tests for the primary endpoint: control group and education group and control group and exercise group. To detect a 20% increase in the proportion of 5 METs/week with a power of 90%, 129 cases per group were needed (α = 0.025, one-tailed, Fisher exact test), while it also has the power of 68% to detect 15% increase. The total sample size in this study was set at 400, with the expectation of missing cases and dropouts.

For the primary analyses, the effect of the intervention on PA was examined using the Fisher exact test for the proportion of RPA ≥ 5 METs/week at 1 year (α = 0.025, one-tailed) in the intgention-to-treat population, which included all the patients who underwent randomization. The mean and 95% CI of change from baseline at 1 year were calculated for tPA, RPA, body weight, BMI, and body fat percentage, and were compared between groups (control group vs. education group, control group vs. exercise group) using t-test. The proportions of obese patients between groups at 1 year were compared using the Fisher exact test. Obesity was defined as a BMI of 25 or higher by the Japan Society for the Study of Obesity. The change from the baseline at 2, 4, 6, and 12 month for each group and the difference between groups were modeled for tPA, RPA, body weight, BMI, and body fat percentage using mixed-effects models for repeated measures (MMRM). Bonferroni correction was not performed for comparisons between groups other than the primary endpoint, and the significance level was set to a P value of 0.05. All statistical analyses were Full Analysis Set (FAS) and performed using JMP Pro version 14.2.0 (SAS Institute Inc.).

Results

Participants and Interventions

From 01/03/2016 to 15/03/2020, 356 patients with breast cancer were enrolled at six sites (Fukuyama City Hospital, Japanese Red Cross Okayama Hospital, Kagawa Prefectural Central Hospital, Kochi Health Science Center, National Hospital Organization Shikoku Cancer Center, and Okayama University Hospital) and randomly assigned to the control (n = 120), education (n = 121), or exercise (n = 115) group. The full analysis set was defined as the population excluding cases of ineligible exclusion, withdrawal of consent, relocation, chemotherapy after enrollment, and breast cancer recurrence during the study period. Participant's owchart is shown in Figure 1. Overall, the characteristics of the patients at baseline were well balanced among the three groups, except for HER2 status (P = 0.026) and anti-HER2 therapy (P = 0.046) (Table 1).

Ninety-seven of the 120 (80.8%) participants in the education group received one or two instructional classes within 3 months of registration. In the exercise group, 45 of the 108 (41.7%) participants attended the exercise program at least three times a week within 2 months after registration. Forty nine of the 108 (45.4%) participants received the exercise program for 3 to 4 months after registration (Sup. Figure 1).

Primary and Secondary Outcomes
The primary endpoint was that there were no significant differences in the effect of the intervention on RPA ≥5 METs/week at 1 year between the exercise and control groups (54% and 53%, \( P = 0.492 \)) and between the education and control groups (62% and 53%, \( P = 0.126 \)) (Figure 2). The secondary endpoints were the mean of the change from baseline at 1 year in tPA, PA, body weight, BMI, and body fat percentage as shown in Figure 3. Although change of tPA and RPA had no significant differences in intergroups (education versus control group and exercise versus control group), there were significant difference in reductions on body weight (education versus control: \( P = 0.0083 \)), BMI (education versus control: \( P = 0.0034 \)), and body fat percentage (education versus control: \( P = 0.0027 \) and exercise versus control: \( P = 0.0038 \)) (Figure 3). Marginal significance in reductions were also observed in body weight (\( P = 0.0644 \)) and BMI (\( P = 0.0500 \)) in the exercise group (Figure 3-C and D). The proportion of obese patients at 1 year in the education group was significantly smaller than the control (education group: 94% versus control group: 73%, \( P = 0.0088 \)), but no significance in the exercise group (exercise group: 78%, \( P = 0.1930 \)) (Figure 4). The change in PA from the baseline in each group is shown in Sup. Figure 2. MMRM analysis showed that there was a significant difference over time in educational intervention effects for tPA relative to the control group (difference in mean of change over time: 1.26, 95% CI 0.27 to 2.27, \( P = 0.0128 \)) and no significance in the exercise group (Sup. Figure 2-A) and for the RPA, both interventions (education and exercise) had no significant difference in mean of change over time compared to the control group (Sup. Figure 2-B). Next, we assessed the association between interventions and body composition, including body weight, BMI, and body fat percentage. We showed the mean of change from the baseline to each time point (Sup. Figure 2-C, D, and E). For bodyweight, educational intervention effects had significant differences in mean of change over time relative to the control group (difference in mean of change over time −0.42, 95% CI −0.82 to −0.02, \( P \) value = 0.0385), but no significance in the exercise group (Sup. Figure 2-C). Similar significant differences were observed in BMI (education group: estimated value −0.21, 95% CI −0.38 to −0.04, \( P = 0.0139 \)) (Sup. Figure 2-D). In body fat percentage, both interventions had significant differences (education group: difference in mean of change over time −0.69, 95% CI −1.17 to −0.21, \( P = 0.0047 \)); exercise group: difference in mean of change over time −0.63, 95% CI −1.12 to −0.13, \( P = 0.0127 \)) (Sup. Figure 2-D). The mean and standard deviation of tPA, RPA, BMI, body weight, and body fat percentage at each survey point are shown in Supplementary Table 1. No specific adverse events due to the intervention were reported.

Discussion

This study evaluated the long-term effects of education or exercise program on PA levels 1 year after registration. We found that there were no significant differences in the RPA level by the interventions (education and exercise) at 1 year compared with usual care, although some significant improvements in body composition, including body weight, BMI, and body fat percentage, were observed. Behavioral change needs to be sustained to achieve long-term health outcomes, and we know significantly less about the efficacy of interventions for long-term change. In a study on the maintenance of outcomes following physical exercise and/or nutritional interventions in breast cancer survivors, only ten (16%) of the 63 trials assessed the outcomes at least 3 months after the intervention ceased [17]. Recently, another
systematic review and meta-analysis of maintenance of PA behavioral change in cancer survivors from 19 trials showed that existing interventions are successful in achieving small increases in PA for at least 3 months after they are completed [18], and that small changes may be insufficient to improve breast cancer outcomes. In trials for breast cancer in this meta-analysis, Mutrie et al. performed the longest follow-up of 5 years for an RCT to assess the psychological and functional benefits of a supervised exercise program with discussion of behavioral change techniques and showed more leisure time PA and more positive emotions than patients in the control group [19]. Leclerc et al. performed the second longest follow-up of 2 years for an RCT to assess the 3-month rehabilitation program, including physical training and psycho-educational session, and showed a maintenance of improvements in quality of life (QoL) and symptoms over 2 years [20]. Different from our study, their long-term maintenance of improvement might come from combination interventions, including psychological aspects and supervised exercise [21]. In our study, the reduction of body composition in the education group was one of the interesting findings. Face-to-face interviews with physicians may lead to long-term behavioral changes in patients and improve the patient-physician relationship. In future trials, a combination of the two interventions, education and exercise, to determine if they contribute to the improvement of breast cancer outcomes should be investigated.

In this study, RPA 1 year after registration was compared in groups from a previous meta-analysis that PA for at least 5 METs/week should be a surrogate to improve total and breast cancer mortalities [4]. In the adjuvant setting for cancer treatment, overall survival (OS) should be the absolute endpoint. The Nutrition and Physical Activity Guidelines for Cancer Survivors stated that they should engage in at least 150 min per week of moderately intense or 75 min per week of vigorously intense aerobic PA and should perform muscle-strengthening activities at least twice per week [22]. Distinct cancer types may require distinct recommendations. Majority of patients with breast cancer are women, and almost all patients with hormone receptor-positive breast cancer, which is approximately 70% of the total breast cancer cases, should receive hormone therapy for 5 to 10 years, which sometimes causes joint stiffness and muscle pain. Moreover, some patients who undergo total mastectomy have reconstruction of their breast by autologous or implant. These disease-specific treatments may affect the surrogate endpoints or these thresholds. Distinct surrogate endpoint may need distinct cancer types or settings (e.g., pre / post diagnosis and pre / post treatment).

Another interesting finding in our study was significant reductions in body composition at 1 year. When planning our study, RPA, not body composition, was set as a surrogate endpoint for overall survival based on previously reported meta-analyses in 2014 [4]. Some interesting papers have recently reported associations between body composition and breast cancer outcomes. From a prospective population-based study in breast cancer survivors (number of patients = 2,216) in 2021, compared with weight maintenance after diagnosis, large weight gain of > 10% increased all-cause mortality (HR 1.64, 95% CI 1.02 to 2.62) and breast cancer mortality (HR 2.25, 95% CI 1.25 to 4.04) [23], but the others showed no significances [24, 25]. Because our primary endpoint was not the body composition but RPA at 1 year, the results are not confirmative about whether these improvements in body composition directly improve
breast cancer prognosis from our study. Future prospective trials to investigate the associations between body composition and overall survival in breast cancer patients are needed.

Another interesting finding was that the usual care group had a relatively better PA (53% at 1 year) than we estimated; they were provided with an educational brochure on lifestyle without any additional direct instruction in this study. We set the ratio of participants with 5 METs/week or more at 1 year PA in the control group to 43% in the sample size design. An educational brochure alone may have an effect on behavioral change. Vallance et al. reported that PA increased by 30 min/week in the standard group compared with 70 min/week in the print material group and concluded that print materials may be effective strategies for increasing PA and QoL in breast cancer survivors [26]. The higher PA of the control group above the estimation may be one of the reasons why the primary endpoint was not met.

This study has some limitations. First, we included not only participants who were inactive but also those who already had high PA at baseline. Approximately 40% of the participants already had RPA of 5 METs/week or more at baseline. The effect of intervention may have been less for those who already had high PA. It may be necessary to consider participants who need intervention to promote PA. Second, it is necessary to examine whether PA at 1 year and RPA with 5 METs/week as a surrogate for the endpoint of OS was appropriate. Due to limited resources, we decided to use the surrogate endpoint instead of OS as an absolute outcome. Different endpoints yield different results. We need longer follow-up data to show the association between the surrogate and absolute endpoints. Third, in some cases, the intervention was not performed even in the intervention group. Eighteen of the 120 (15%) participants in the education group never took the course, and approximately 40% of the participants in the exercise group participated less than three times per week, although they were required to perform exercise three times per week. Patients in the exercise group received the intervention program free of charge for only 4 months. After the first 4 months, they had to pay for it themselves if they wished to attend. Such economic barriers may also lead to poor compliance. Nevertheless, this study has the following strengths. First, we conducted a long-term outcome evaluation. Behavioral changes should be assessed by the long-term outcome after the intervention, not just after the intervention. Second, the intervention was outsourcing, which should be more feasible than the limited resources in the hospital. We believe that the use of local resources will lead to sustainability.

**Conclusions**

Although there were no significant effects on RPA 1 year after exercise and educational programs for breast cancer survivors, both interventions reduced body composition, including body weight, BMI, and body fat percentage. In future studies on PA, appropriate interventions to improve OS and endpoints to substitute for overall survival will be needed.

**Declarations**

**Ethics approval and consent to participate**
This study received an approval from the Ethics Committee of Okayama University Hospital and the respective institution. Informed consent was obtained from all individual participants included in the study.

**Consent for publication**

Not applicable

**Availability of data and materials**

The data that support the findings of this study are available from Takayuki Iwamoto but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Takayuki Iwamoto.

**Competing interests**


The other authors declare no competing interests.

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**Authors' contributions**

Conceptualization: Shozo Ohsumi, Masahiko Ikeda, Hiroyoshi Doihara, Yuri Mizota, Seiichiro Yamamoto, Hiroyoshi Doihara and Naruto Taira

Formal analysis; Seiichiro Yamamoto and Naruto Taira

Funding acquisition; Yuri Mizota, Seiichiro Yamamoto and Hiroyoshi Doihara

Investigation; Kengo Kawada, Daisuke Takabatake, Yuichiro Miyoshi, Kubo Shinichiro, Yoko Suzuki, Mari Yamamoto, Yutaka Ogasawara, Minami Hatono, Seiji Yoshitomi, Kyoko Hara and Naruto Taira

Methodology; Naruto Taira

Project administration; Naruto Taira

Resources; Naruto Taira
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References


**Table**

Table 1 is available in the Supplementary Files section

**Figures**

![Participants’ flowchart](image-url)

Figure 1

Participants’ flowchart.
Figure 2

Percentage of patients with recreational physical activity of $\geq 5$ metabolic equivalents (METs)/week in the assigned group at each survey point.

The bars indicate the percentage of participants with an RPA $\geq 5$ METs/week. The data labels indicate the number (or percentage) of the patients with RPA $\geq 5$ METs/week. Comparisons with the control group were performed using Fisher’s exact test. Blue: control group, red: education group, and green: exercise group.
Figure 3

Mean and 95%CI of change from baseline at 1 year

Dot showed the mean of change from baseline at 1 year. Horizontal line showed that 95%CI of change of them. The $P$ value was calculated by t-test.
Figure 4

Comparison of the proportion of obese patients at 1 year

The bars indicate the proportion of obese or non-obese patients at 1 year. Obese was defined as a BMI (body mass index) of 25 or higher. The data labels indicate the number of the patients. The $P$-value was calculated by Fisher's exact test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PAMS.Sup.Table1.xlsx
- SupFgurelegends.docx
- Sup.Figure1.jpg
- Sup.Figure2ab.jpg
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