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Effects of a multicomponent physical activity behavior change intervention on fatigue, anxiety, and depressive symptomatology in breast cancer survivors: Randomized trial

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Abstract

Objectives—To determine the effects of the 3-month multicomponent Better Exercise Adherence after Treatment for Cancer (BEAT Cancer) physical activity behavior change intervention on fatigue, depressive symptomatology, and anxiety.

Methods—Post-primary treatment breast cancer survivors ($n=222$) were randomized to BEAT Cancer or usual care (UC). Fatigue Symptom Inventory and Hospital Anxiety and Depression Scale were assessed at baseline, post-intervention (month 3; M3), and follow-up (month 6; M6). Potential demographic, medical, and psychosocial moderators were assessed at baseline.

Results—Adjusted linear mixed-model analyses demonstrated significant effects of BEAT Cancer versus UC on fatigue intensity (M3 mean between group difference [M] = -0.6 ; 95% confidence interval [CI] = -1.0 to -0.2 ; effect size [d] = -0.32 ; $p=.004$), fatigue interference (M3 M = -0.8 ; CI = -1.3 to -0.4 ; $d = -0.40$; $p < .001$), depressive symptomatology (M3 M = -1.3 ; CI = -2.0 to -0.6 ; $d = -0.38$; $p < .001$), and anxiety (M3 M = -1.3 ; CI = -2.0 to -0.5 ; $d = -0.33$; $p < .001$). BEAT Cancer effects remained significant at M6 for all outcomes (all p values $< .05$; $d =$

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Conflict of Interest and Adherence to Ethical Standards

Laura Rogers and all contributing authors declare they have no personal or professional relationships that may represent a potential conflict of interest. All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

–0.21 to –.35). Clinically meaningful effects were noted for fatigue intensity, fatigue interference, and depressive symptomatology.

Conclusions—BEAT Cancer reduces fatigue, depressive symptomatology, and anxiety up to 3 months post-intervention in post-primary treatment breast cancer survivors. Further study is needed to determine sustainable methods for disseminating and implementing the beneficial intervention components.

Keywords

oncology; survivorship; psychosocial; exercise; cancer

Background

Current oncologic treatment modalities have improved 5-year breast cancer survival rates to 89%, resulting in over 3.5 million women living with a history of breast cancer in the U.S. [1]. Many of these women continue to experience fatigue, depression, and/or anxiety months to years after their breast cancer diagnosis with these symptoms being associated with greater disability and a poorer quality of life [2–5]. Importantly, the symptoms of fatigue, depression, and anxiety were among the top 10 highest ranked issues of importance related to quality of life and patient-reported outcomes when over 1000 breast cancer survivors were surveyed [6].

Exercise has demonstrated promise as a non-pharmacologic therapy for these symptoms with potential underlying mechanisms including beneficial changes in inflammation, hormone profiles, body composition, cardiorespiratory endurance, and autonomic function [7–14]. These exercise benefits, along with others, documented by exercise training trials have motivated the development and testing of physical activity behavior change interventions aimed at translating these findings to a larger number of breast cancer survivors by focusing on increasing physical activity adherence. Because such interventions focus on changing behavior rather than testing exercise health outcomes with strict exercise training [15], it is important to report whether the physical activity increase resulting from a behavior change intervention is sufficient for achieving the same benefits reported by exercise training trials.

Of the 14 randomized controlled trials explicitly testing behavior change interventions focused on physical activity behavior in breast cancer survivors, only seven reported fatigue [16–22] and only two reported mood [16, 17]. Moreover, the results have been inconsistent; fatigue improved in only three of the seven trials [16, 17, 20] and neither of the two studies assessing mood reported improvements in depressive symptomatology and anxiety [16, 17]. A floor effect (low baseline levels), insufficient increases in physical activity with the intervention, and/or differences in measure sensitivity may have contributed to this lack of improvement. Therefore, additional research is needed to determine if physical activity behavior change interventions can effectively translate exercise training benefits related to psychosocial outcomes in breast cancer survivors.

We have previously reported the main outcomes of the Better Exercise Adherence after Treatment for Cancer (BEAT Cancer) intervention for improving physical activity behavior, cardiorespiratory fitness, and quality of life [23, 24]. BEAT Cancer participants were significantly more likely to meet exercise recommendations of 150 weekly minutes of moderate intensity activity immediately post-intervention (accelerometer odds ratio [OR] = 2.2; 95% confidence interval [CI] = 1.0 – 4.8 and self-report OR = 5.2; CI = 2.6 – 10.4) and 3 months later (OR = 2.4; CI = 1.1 – 5.3 and self-report OR = 4.8; CI = 2.3 – 10.0). Moreover, significant between group differences favoring BEAT Cancer versus usual care were reported for Functional Assessment of Cancer Therapy (FACT)-Breast at both time points with significant fitness benefits occurring 3 months post-intervention [23]. Our primary aim for this report was to compare the effects of the 3-month BEAT Cancer to usual care on fatigue, depressive symptomatology, and anxiety in breast cancer survivors using data from our multicenter randomized controlled efficacy trial. We hypothesized that, when compared with usual care, BEAT Cancer would result in significant decreases in fatigue, depressive symptomatology, and anxiety immediately post-intervention (month 3; M3) and at 3 months post-intervention follow-up (month 6; M6). Although our original protocol (written in 2009) proposed assessing depression and anxiety as sources of physical activity self-efficacy [25], we report these as health outcomes because updated literature reviews indicate a significant burden of suffering caused by psychosocial symptoms and a clear knowledge gap regarding the ability of behavior change interventions to translate exercise training benefits.

Methods

Study design, setting, participants, and randomization

This multicenter, randomized controlled trial has been previously described [23, 24]. In summary, two Midwestern and one Southeastern academic institutions randomized 222 breast cancer survivors to receive BEAT Cancer or usual care. Women ages 18 to 70 were included if they had a history of ductal carcinoma in situ (DCIS) or stage I-IIIa breast cancer and had completed primary treatment (i.e., surgery, radiation, and/or chemotherapy). Other inclusion criteria included being 8 weeks post-surgery, English speaking, medically cleared by physician, and insufficiently physically active (i.e., 30 minutes of vigorous physical activity or 60 minutes of moderate activity per week, on average, during the past six months). Individuals were excluded if they had dementia, inability to ambulate or fully participate in study activities, contraindication to physical activity participation, metastatic or recurrent breast cancer, plans for elective surgery during the intervention, travel plans interfering with the scheduled study sessions, and current participation in another exercise study. The study protocol was approved by the institutional review board (IRB) at each recruiting site and written informed consent was obtained prior to initiating study procedures. Direct and indirect recruitment strategies were used (e.g., newspaper advertisements, announcements in electronic newsletters, website postings, support groups, flyers in patient waiting areas and retail/service outlets, invitation letters to potential participants identified by the institutional cancer registry, physician referral, and prior participant referrals). As described [24], randomization was based on computer generated numbers in blocks of 4 within each recruiting site. Randomization occurred in the order in

which the participants completed baseline testing with study staff being unaware of the randomization until the moment the randomization result was revealed by opening an opaque sealed envelope.

Better Exercise Adherence after Treatment for Cancer (BEAT Cancer) intervention

As described [24], the 3-month social cognitive theory-based BEAT Cancer intervention included 12 supervised exercise sessions with an exercise specialist that were tapered over the first 6 weeks to an exclusively unsupervised home-based program. Face-to-face update counseling sessions with the exercise specialist every two weeks occurred during the final 6 weeks of the intervention. Home-based exercise was monitored by the exercise specialist by reviewing the exercise and heart rate monitor log sheets. Exercise intensity and progression has been published [24]. Additional behavior change counseling was provided during six discussion group sessions led by trained facilitators during the first 9 weeks of the intervention. The social cognitive theory constructs targeted by the exercise specialists and group sessions included self-efficacy, exercise barriers, behavioral capability, goal setting with self-monitoring, behavioral modification strategies, time management, stress management, safety, cognitive reframing, relapse prevention, and role models (see previous publication for a description of how each intervention component addressed each construct [24]). The behavioral modification strategies and cognitive reframing focused specifically on physical activity behavior. However, cognitive reframing may have expanded, when indicated, to include dealing with stress and lack of time as these were significant and frequent barriers to physical activity behavior change. Participants randomized to receive the BEAT Cancer intervention were also given a personal heart rate monitor, educational notebook, and printed materials identical to that given to the usual care group. The educational notebook included additional detail regarding the group discussion topics (e.g., stress management, time management, etc.), notes pages, basic exercise concepts (e.g., F.I.T.T. principles, heart rate, rating of perceived exertion, exercise safety, resuming exercise after missed sessions, relapse prevention, etc.), instructions for stretching exercises, brief nutrition information for optimal physical energy (pilot testing suggested this was needed for safety reasons), exercise log sheets, behavioral modification worksheets, and logistical information (e.g., session schedules, etc.). Quality control activities to ensure fidelity included written evaluations, observation, and/or videotaping [24]. Participant adherence to the intervention activities has been previously reported [23].

Usual care intervention

The usual care participants received publically available, printed materials from the American Cancer Society. No physical activity-related counseling or instructions were given to the usual care participants beyond that contained in the printed materials.

Measures

As described [24], assessments occurred at baseline, M3 (immediately post-intervention), and M6 (3 months after intervention completion). Demographic and medical characteristics were self-reported. The Fatigue Symptom Inventory [26] measured fatigue intensity (mean of 4 items, 1 to 10 scale) and fatigue interference (mean of 7 items, 1 to 10 scale) over the past 7 days (possible range 1 to 10). Items related to intensity asked about level of fatigue on

day felt most fatigued, day felt least fatigued, average in past 7 days, and today. Items related to fatigue interference asked how much fatigue interfered with general activity level, bathing/dressing, work activity, ability to concentrate, relationships, enjoyment of life, and mood. The reliability (e.g., α coefficient $>.90$) and validity (construct and convergent) of the Fatigue Symptom Inventory has been confirmed in cancer survivors (multiple cancer types including but not limited to breast) and treatment status (e.g., on or off treatment) [26–28]. Importantly, the Fatigue Symptom Inventory has been proven to discriminate between breast cancer survivors with and without clinically meaningful fatigue [28]. The 14-item Hospital Anxiety and Depression Scale (HADS) measured depression and anxiety symptomatology (7 items for each subscale; 0 to 3 Likert scale for a possible range of 0 to 21 for each subscale) [29]. The HADS has proven reliable in multiple chronic disease populations including but not limited to breast cancer survivors (i.e. mean α coefficients of .82 and .83 for depression and anxiety subscale, respectively) [30]. Its concurrent and discriminant validity have also been documented [30, 31]. Higher scores indicated greater fatigue, depression, or anxiety [29]. Although participant blinding to study group was not possible, data entry and management was performed by individuals blinded to the participant's group allocation [24].

Sample size calculation and statistical analyses

Sample size was based on the primary study outcome as previously reported [24]. Retaining 213 participants at M6 [23] allowed detection of a small to medium effect size = 0.39 ($p < .05$, power of .80). For the analyses reported here, we used adjusted linear mixed models incorporating an unstructured covariance matrix to test BEAT Cancer effects on fatigue intensity, fatigue interference, depressive symptomatology, and anxiety at M3 and M6. SAS[®] statistical software (Cary, NC) was used and statistical significance was determined by two-sided p -value $< .05$. These analyses (i.e., all models testing intervention effects on outcomes) were adjusted for previously identified covariates associated with the primary study outcome and time point (i.e., baseline value of the outcome, site [stratification variable for randomization], breast cancer stage, history of chemotherapy, history of radiation, hormonal therapy [none versus on hormonal therapy for ≤ 1 year versus on hormonal therapy for > 1 year], number of comorbidities using the validated self-report scale by Groll *et al.* [32], and marital status [i.e., married or living with significant other versus other]) [23]. Body mass index (BMI) was not considered a covariate because the study groups did not differ at baseline with regard to BMI and baseline BMI was not associated with any psychosocial outcomes (data not shown). Effect sizes were calculated by dividing the estimated least square mean for the between group difference by the standard deviation of mean calculated using the pooled baseline values [33]. All analyses were intention-to-treat with all available data being used.

Results

As previously reported [23], 222 participants completed baseline testing and were randomized (110 to BEAT Cancer and 112 to usual care). Retention was similar in both groups (97% at M3 and 96% at M6). Study groups were balanced with the exception that percentage reporting hormonal therapy for ≤ 1 year was 17% in the BEAT Cancer group and

30% in the usual care group ($p = .02$). For both groups combined, mean (SD) age was 54.4 (8.5) and education was 15.5 (2.6) years. Four (2%) were Hispanic and 98% were non-Hispanic; 84% were White, 11% were African-American and 5% were other. With regard to stage, 11% had DCIS, 42% had stage I, 35% had stage II, and 12% had stage III. Mean (SD) months since cancer diagnosis was 54 (54.5) with 58% reporting history of chemotherapy and 68% reporting history of radiation therapy. About half (49%) were currently on hormonal therapy [23].

BEAT Cancer effects on fatigue, depressive symptomatology, and anxiety

After adjusting for covariates, BEAT Cancer significantly reduced fatigue intensity at both time points [mean between group difference (M) = -0.61 ; 95% confidence interval (CI) = -1.04 to -0.19 ; effect size (d) = -0.32 ; $p = .004$ at M3 and M = -0.46 ; 95% CI -0.89 to -0.03 ; $d = -0.26$; $p = .038$ at M6]. Significant and greater reductions in fatigue interference occurred (M = -0.84 ; 95% CI = -1.26 to -0.43 ; $d = -0.40$; $p < .001$ at M3 and -0.66 ; CI -1.08 to -0.24 ; $d = -0.35$; $p = .002$ at M6). BEAT Cancer also significantly reduced depressive symptomatology (M = -1.31 ; 95% CI = -1.98 to -0.64 ; $d = -0.38$; $p < .001$ at M3 and M = -0.71 ; 95% CI = -1.39 to -0.02 ; $d = -0.21$; $p = .042$ at M6) and anxiety (M = -1.25 ; 95% CI = -1.98 to -0.53 ; $d = -0.33$; $p < .001$ at M3 and M = -0.75 ; CI = -1.49 to -0.02 ; $d = -0.21$; $p = .044$ at M6) (Table 1). All effects sizes indicated small to medium size intervention effects.

Conclusions

Compared to usual care, the BEAT Cancer intervention significantly improved fatigue intensity, fatigue interference, depressive symptomatology, and anxiety in post-treatment breast cancer survivors. Importantly, statistically significant intervention effects on these outcomes continued 3 months after intervention completion. These findings are of substantial clinical relevance because anxiety, depression, and fatigue are among the top 10 most important patient-reported outcomes influencing quality of life among breast cancer survivors [6].

With the exception of fatigue intensity at M6, our effect sizes on fatigue were within the range of reported effect sizes discriminating cancer patients from non-cancer controls supporting the BEAT Cancer's ability to exceed a clinically important difference [34]. Moreover, the fatigue interference mean for the participants receiving the BEAT Cancer intervention dropped and remained below the clinically meaningful cutpoint of 3 [28]. It is noteworthy that the intervention continued to offer benefit 3 months after intervention completion and significant intervention effects occurred without restricting enrollment to participants who reported fatigue (a study design strategy sometimes used to avoid the detrimental impact of a floor effect on intervention benefit). These effects hold considerable potential for improving the quality of life of post-treatment breast cancer survivors given the frequency of persistent fatigue and its association with poorer quality of life [6].

It is notable that BEAT Cancer is the first physical activity behavior change intervention for breast cancer survivors demonstrating significant improvements in depressive symptomatology and anxiety immediately post-intervention and 3 months after intervention

completion. The mean between group difference at M3 of -1.3 represents a minimally important difference (MID) for depressive symptomatology and nearly reached the MID of 1.4 for anxiety [35]. Improvements may relate to a combination of increased physical activity along with the behavioral support provided during supervised exercise and group counseling sessions [7]. Because the objectives of behavior change interventions are to improve health and well-being of participants through increased physical activity rather than determine the effects of a specific exercise type or amount, the delivery methodology may be as important as the physical activity increases when designing for optimal intervention effects on mood. The intervention's ability to reach the MID for depressive symptomatology offers substantial potential for addressing persistent symptoms negatively impacting the well-being of breast cancer survivors [6].

Our study strengths include its rigorous randomized controlled trial design, multicenter implementation (improved generalizability among post-treatment breast cancer survivors), and excellent retention rates. Although our intervention was multicomponent (i.e., effects should not be attributed solely to exercise effects), the value of our study results are further enhanced by the following: 1) the beneficial changes in fatigue, depression, and anxiety are similar to that achieved with exercise outcome trials [10], behavioral support is often provided in exercise outcome studies to improve adherence to the prescribed exercise dose [15], and our data is consistent with prior studies indicating that home-based physical activity counseling that utilizes behavioral support for increasing adherence is beneficial for cancer survivors [17]. Our study limitations include the small percentage of ethnic minorities represented and unknown generalizability to survivors of cancer types other than breast and/or on primary treatment. Also, our intervention focused on physical activity alone and applying our results to interventions that also include a diet and/or weight loss component should be done with caution.

In summary, a multicomponent physical activity behavior change intervention previously reported as efficacious in increasing physical activity behavior [23] also significantly improved fatigue, depressive symptomatology, and anxiety immediately post-intervention and 3 months post-intervention when compared to usual care. These intervention effects were clinically meaningful for fatigue intensity, fatigue interference, and depressive symptomatology immediately post-intervention. Clinically meaningful benefits continued for fatigue interference at 6 months (i.e., 3 months post-intervention). Importantly, our data suggest that multicomponent physical activity behavior change interventions can translate psychosocial benefits reported in exercise training to the target population. Further study is needed to determine intervention components most responsible for improved psychosocial outcomes, individuals most likely to respond to the intervention, and sustainable methods for disseminating and implementing the beneficial intervention components.

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Table 1

Effects of the BEAT Cancer intervention on fatigue intensity, fatigue interference, depressive symptomatology, and anxiety at post-intervention (month 3) and 3 months after intervention completion (month 6) in breast cancer survivors

Outcome	Unadjusted means		Adjusted ^a between-group differences		Estimated least square mean with (95% CI); <i>p</i> value
	Baseline mean (SD)	Month 3 mean (SD)	Month 6 mean (SD)	BEAT Cancer vs usual care at month 3 (post-intervention)	BEAT Cancer vs usual care at month 6 (3 months post-intervention)
Fatigue intensity					
BEAT Cancer	4.5 (1.7)	4.0 (1.8)	4.1 (1.7)		
Usual care	4.7 (2.0)	4.7 (2.0)	4.6 (2.0)	-0.6 (-1.0 to -0.2); .004	-0.5 (-0.9 to -0.0); .038
Fatigue interference					
BEAT Cancer	3.3 (1.9)	2.7 (1.7)	2.9 (1.9)		
Usual care	3.5 (2.2)	3.6 (2.2)	3.6 (2.3)	-0.8 (-1.3 to -0.4); <.001	-0.7 (-1.1 to -0.2); .002
Depression					
BEAT Cancer	4.8 (3.3)	3.0 (2.6)	3.5 (3.3)		
Usual care	4.7 (3.5)	4.3 (3.1)	4.3 (3.5)	-1.3 (-2.0 to -0.6); <.001	-0.7 (-1.4 to -0.0); .042
Anxiety					
BEAT Cancer	7.1 (3.9)	5.6 (3.4)	5.8 (3.9)		
Usual care	7.0 (3.9)	6.8 (3.5)	6.5 (3.7)	-1.3 (-2.0 to -0.5); <.001	-0.8 (-1.5 to -0.0); .044

CI, confidence interval; SD, standard deviation

^a Adjusted for baseline value, study site, breast cancer stage, history of chemotherapy, history of radiation therapy, current hormonal therapy, comorbidities, and marital status