How changes in physical activity relate to fatigue interference, mood, and quality of life during treatment for non-metastatic breast cancer


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ABSTRACT

Objective: Physical activity (PA) following surgery for breast cancer may improve depressive symptoms and quality of life (QoL) via reduction in fatigue-related daily interference (FRDI). Less is known about how change in PA may relate to these psychosocial factors throughout the course of treatment. In a secondary analysis of a previous psychosocial intervention trial, we examined relationships between change in PA, depressive symptoms, and functional QoL, as mediated by change in FRDI, and whether naturally occurring change in PA provided benefit independent of the intervention.

Method: Women (N = 240) with non-metastatic stage 0–III breast cancer were randomized to cognitive-behavioral stress management (CBSM) or a control 2–10 weeks post-surgery. PA, FRDI, clinician-rated depressive symptoms, self-reported depressed mood, and functional QoL were assessed at baseline and three months post-intervention.

Results: Increased PA was associated with reductions in clinician-rated depressive symptoms, depressed mood, and improved QoL, mediated by a reduction in FRDI. This was above and beyond the effect of CBSM.

Conclusions: Increased PA may mitigate FRDI and improve depressive symptoms and functional QoL for women undergoing breast cancer treatment, beyond effects of a psychosocial intervention. Benefits of an integrated PA and psychosocial approach should be investigated further.

1. Introduction

Fatigue, depressive symptoms, and diminished quality of life (QoL) are among the serious breast cancer treatment-related side effects [1]. Physical activity may mitigate the severity of physical and psychological sequelae associated with a breast cancer diagnosis and treatment [2–4]; women with breast cancer who engage in physical activity have less fatigue [5,6], depressive symptoms [6], and better quality of life (QoL) [5–7]. The process by which physical activity reduces these symptoms is less understood [8]. Previously, women with non-metastatic breast cancer reported greater physical activity and had less concurrent perceived daily interference due to fatigue, less clinician- and self-rated depressive symptoms, and better functional QoL following surgery [9]. Moreover, fatigue interference served an intermediary role; greater physical activity was related to less depressive symptoms and better functional QoL via reduced fatigue interference [9]. While these findings suggest a potential mechanism relating physical activity to mood outcomes, the relationships must be examined longitudinally for better understanding.

Despite potential benefits, most women with breast cancer do not meet the American College of Sports Medicine (ACSM) physical activity recommendations, which encourage patients to engage in at least 150 min of moderate or 75 min of vigorous intensity activity each week during treatment [10]. Unfortunately, physical activity often decreases after diagnosis, especially among women undergoing radiation or chemotherapy [11]. Given previous evidence of the concurrent relationships between physical activity, fatigue interference, depressive symptoms, and QoL post-surgically [9], understanding how changes in physical activity may influence these outcomes over time is relevant as women manage treatment-related symptoms.
In addition to physical activity, psychosocial interventions involving cognitive-behavioral, relaxation, and mindfulness techniques have shown efficacy in improving fatigue, depressive symptoms, and QoL in breast cancer [12–14]. Group-based cognitive-behavioral stress management (CBSM) has been particularly efficacious in reducing fatigue interference and depressed mood and improving QoL for women during breast cancer treatment [15–17]. As such, researchers have investigated whether an integrative approach combining physical activity and cognitive-behavioral techniques may attenuate treatment-related symptoms for women with non-metastatic breast cancer [18]. However, whether increased physical activity may be additionally beneficial for women who participate in CBSM has not been explored. Support for the additive effect of increased physical activity on psychosocial adjustment may encourage consistent promotion of physical activity among breast cancer patients.

The current study was a secondary analysis that aimed to (1) examine whether the relationships between physical activity and physical and psychosocial factors in the previously reported post-surgical cross-sectional study [9] are observed longitudinally during treatment, such that change in physical activity from pre- to post-intervention predicts changes in fatigue interference, clinician- and self-rated depressive symptoms, and functional QoL; (2) assess whether the influence of modified physical activity involvement on changes in depressive symptoms and functional QoL is mediated by change in fatigue interference; and (3) explore whether change in physical activity contributes additional benefit above and beyond CBSM. We hypothesized that an increase in physical activity would be associated with a reduction in fatigue interference, clinician- and self-rated depressive symptoms, and an increase in functional QoL, that the effect of increased physical activity on mood outcomes would be mediated by reduced fatigue interference, and that an increase in physical activity would be independently related to reduction in FRDI and improved QoL outcomes, above and beyond the effect of CBSM.

2. Methods

2.1. Participants

Participants were part of a larger, single center, single blind, randomized, parallel assignment efficacy trial, testing a CBSM intervention. A detailed description of the original study design is available elsewhere [16,17]. Study approval was granted by the University of Miami’s Institutional Review Board (National Institutes of Health Clinical Trial NCT01422551). Women diagnosed with non-metastatic stage 0-IIb breast cancer were recruited through physician referrals and community advertising. Participants were required to have had surgery for primary breast cancer in the 2–10 weeks prior to enrollment (lumpectomy, mastectomy, or bilateral mastectomy). Exclusion criteria included: (1) diagnosis of stage IV breast cancer or prior cancer (except minor skin cancers such as squamous or basal cell carcinomas); (2) ongoing neoadjuvant or post-surgical adjuvant treatment; (3) a major medical condition other than cancer; (4) < 21 or > 75 years of age; (5) non-fluency in English; (6) previous hospitalization for psychiatric conditions; and (7) current psychosis, substance use disorder, suicidality, major depressive disorder, or panic disorder.

2.2. Procedures

Eligible women who were interested in participating gave informed consent and were enrolled. Following the baseline assessment, participants were randomized to CBSM or a 1-day psychoeducational control group. Randomization and assessments were completed by blinded study coordinators. Initial assessments took place at approximately 2–10 weeks post-surgery and prior to adjuvant cancer treatment (chemotherapy and/or radiation). Women were reassessed 3 months post-intervention. Assessments included blood and saliva samples, patient-reported psychosocial questionnaires, and a clinician-administered measure.

2.3. CBSM intervention

Women randomized to the CBSM intervention met 2 h per week for 10 weeks. CBSM is a structured, manualized psychosocial intervention that combines relaxation (e.g., muscle relaxation and imagery) and cognitive behavioral therapy (e.g., cognitive re-structuring, coping effectiveness training, assertiveness, and anger management skills) [19]. CBSM aims to attenuate muscle tension and increase relaxation, replace negative cognitions pertaining to breast cancer and treatment, improve coping strategies, and build and maintain social support networks. Interventionists were trained in the protocol, and sessions were videotaped and monitored weekly for fidelity by two clinical psychologists.

2.4. Control

Participants assigned to the 1-day psycho-educational control seminar received an abbreviated dose (i.e., 5–6 h) of information about CBSM, which was delivered in a classroom lecture format. This seminar took place one weekend during the corresponding 10-week CBSM intervention. Women primarily received information related to breast cancer and its treatment. The seminar did not involve any in-session or at-home practice of CBSM techniques and was designed to emulate an informational self-help seminar.

2.5. Measures

2.5.1. Demographic and medical characteristics

Women self-reported demographics, medical condition, and cancer-treatment at baseline and follow-up assessment. Characteristics included age, ethnicity, employment status, marital status, income, education, stage of disease, type of surgery, days elapsed from surgery to baseline assessment, and type of adjuvant treatment. Self-reported information was verified with medical record review.

2.5.2. Physical activity

Intensity, frequency, and duration of physical activity were measured using a brief version of the Seven-Day Physical Activity Recall Questionnaire [20]. This measure is widely utilized in cancer populations [21]. Participants recorded the time engaged in vigorous and/or moderate activity each day of the previous week. Vigorous intensity activities require substantial energy expenditure and increased heart rate (e.g., jogging, running, sustained swimming). Moderate intensity activities increase heart rate, yet conversation is possible (e.g., yard work, heavy housecleaning, brisk walking). Since moderately to vigorously intense activity is most beneficial for health outcomes [22], minutes of moderate and vigorous activity per week were combined. The reliability in the current sample was strong (α = 0.90).

2.5.3. Fatigue-related daily interference

The 7-item Perceived Interference subscale of the 12-item Fatigue Symptom Inventory (FSI) was used to measure the extent to which respondents perceive that fatigue interferes with daily life, roles, and responsibilities, hereinafter referred to as fatigue-related daily interference (FRDI). The FSI was developed and validated for cancer populations [23]. Items (e.g., “Rate how much, in the past week, fatigue has interfered with your normal work activity”) are rated on a Likert-scale of 0 (no interference) to 9 (extreme interference). Items are averaged to obtain a total FRDI score ranging from 1 to 9, with higher scores indicating greater FRDI. The reliability for the FRDI subscale within the current sample was strong (α = 0.93).
2.5.4. Clinician-rated depression

Depressive symptoms were measured with the Hamilton Rating Scale for Depression (HRSD) [24], administered by a master's level clinical psychology student under the supervision of a clinical psychologist. The HRSD is a 17-item, interview-based measure assessing symptoms of depression over the past week. The HRSD has sound psychometric properties [25] and has been used to assess depression in breast cancer [26,27]. Items are rated on 3- and 5-point scales and summed to obtain a total score ranging from 0 to 54, with higher scores indicating more severe depressive symptoms. Reliability in the current sample was fair (α = 0.66).

2.5.5. Depressed mood

Depressed mood was measured using the Depression subscale of the 40-item Affect Balance Scale (ABS) [28]. This self-report measure assesses frequency of positive and negative affective states over the past week using a 5-point Likert-type scale (1 = never; 5 = always). Items are averaged to obtain a subscale score ranging from 1 to 5, with higher scores indicating more depressed mood. Previous research has demonstrated that the ABS is a valid and reliable measure of mood in breast cancer populations [29,30]. The reliability for the current sample was good (α = 0.80).

2.5.6. Functional QoL

The 7-item Functional Well-Being subscale of The Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) [31,32] was used to assess functional QoL. Using a Likert-type scale, participants rate each item from 0 (not at all) to 4 (very much). Scores are summed to obtain a functional QoL score. Scores range from 0 to 28, with higher scores indicating better functional status. The FACT-B was developed, validated, and normed for use in breast cancer populations [31]. The Functional Well-Being subscale had good reliability in the current sample (α = 0.84).

2.6. Analytic strategy

Data were screened, and three outliers for physical activity were Winsorized to fall within three standard deviations of the mean [33]. Descriptive statistics were examined to inspect variable distributions and ensure that multivariate assumptions of normality were met [34]. The physical activity Seven-Day Recall score, originally measured in minutes, was transformed into hours to meet the assumption of relative variance [34].

Path analysis was conducted using structural equation modeling (SEM) in Mplus [35] to test the direct and indirect pathways by which change in physical activity relates to changes in FRDI, clinician-rated depressive symptoms, depressed mood, and functional QoL. First, difference scores were computed to reflect the change from pre- to post-intervention. Second, the model was specified identically to that by Stagl and colleagues [9], with changes in depressive symptoms, depressed mood, and functional QoL regressed on change in FRDI, and change in FRDI regressed on change in physical activity. Correlations were specified between changes in depressive symptoms, depressed mood, and QoL. Next, to examine whether change in physical activity accounted for additional variability above and beyond the known effect of CBSM on reductions in FRDI, this model was estimated first with study condition (CBSM vs. control) as the predictor, and then with change in physical activity as an additional predictor. Congruent with findings from Stagl and colleagues, in which fatigue intensity was not associated with physical activity, clinician- and self-rated depressive symptoms, and/or QoL, the current investigation only examined fatigue interference [9]. Finally, to consider potential alternative models, reverse directionality was assessed by examining model fit when each outcome variable (i.e., clinician-rated depressive symptoms, depressed mood, and functional QoL) served as the intermediary variable. In these models, FRDI was specified as an outcome variable.

Theoretically-supported demographic (i.e., age, education, and income) and cancer-specific (i.e., stage of disease, type of surgery, and days elapsed from surgery to assessment) factors that may influence outcomes were included as covariates [1,36] and regressed on the proposed mediator (FRDI) and each outcome variable (clinician-rated depressive symptoms, depressed mood, and functional QoL). Missing data were estimated using full information maximum likelihood, which derives population estimates using all observed data. Four indices were estimated and interpreted for model fit: chi-square test ($\chi^2$ > 0.05, confirmatory fit index (CFI) > 0.95, root mean square error of approximation (RMSEA) < 0.06, and standardized root mean square residual (SRMR) < 0.08 [34,37]. The z-statistic of the unstandardized regression coefficients was examined to interpret direct and indirect pathways, with a two-tailed level of significance, $p < 0.05$. Standardized coefficients were examined as measures of effect sizes as follows: 0.1 = small; 0.3 = medium; 0.5 = large [38].

3. Results

3.1. Participant characteristics

From a total screening sample of 502 women, 240 were consented and randomized to CBSM intervention ($n$ = 120) or the 1-day psycho-educational control ($n$ = 120). Women were an average of 50.3 (SD = 9.0) years old, with > 50% having completed college or advanced degrees, and 36.3% being a member of a racial or ethnic minority group. At baseline, women reported minimal use of medication for depression, anxiety, and/or sleep concerns (Table 1). The number of days elapsed from surgery to baseline assessment was significantly different between the CBSM and control groups, F(2,299) = 5.84, $p < 0.05$. No other significant difference was found between study conditions (Table 1).

At the pre-intervention assessment, women reported an average of 158 min (SD = 285) of moderate intensity and 24 min (SD = 150) of vigorous intensity physical activity per week. Based on guidelines from the ACSM, 32.5% of the women in the sample met the recommendation for 150 min of moderate activity per week, while 7.5% met the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Years education</td>
<td>15.5 (2.3)</td>
<td>15.7 (2.5)</td>
</tr>
<tr>
<td>Time since surgery (days)</td>
<td>44.7 (25.5)</td>
<td>36.6 (19.9)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>74 (61.7%)</td>
<td>78 (65.0%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>31 (25.8%)</td>
<td>30 (25.0%)</td>
</tr>
<tr>
<td>African American</td>
<td>10 (8.3%)</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>American</td>
<td>4 (3.3%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Married/partnered</td>
<td>75 (62.5%)</td>
<td>75 (62.5%)</td>
</tr>
<tr>
<td>Employed</td>
<td>92 (76.7%)</td>
<td>86 (71.7%)</td>
</tr>
<tr>
<td>Stage</td>
<td>19 [I]; 51 [II]; 41 [III]; 8 [IV]</td>
<td>19 [I]; 39 [II]; 50 [III]; 11 [IV]</td>
</tr>
<tr>
<td>Procedure</td>
<td>52 (43.3%)</td>
<td>66 (55.0%)</td>
</tr>
<tr>
<td>Lymph node surgery</td>
<td>68 (56.7%)</td>
<td>54 (45.0%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>51 (42.5%)</td>
<td>48 (40.0%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>48 (40.0%)</td>
<td>55 (45.8%)</td>
</tr>
<tr>
<td>Hormonal</td>
<td>50 (41.7%)</td>
<td>56 (46.7%)</td>
</tr>
<tr>
<td>Using anti-depressant medication</td>
<td>12 (10.0%)</td>
<td>14 (11.7%)</td>
</tr>
<tr>
<td>Using anti-anxiety medication</td>
<td>20 (16.7%)</td>
<td>22 (18.3%)</td>
</tr>
<tr>
<td>Using sleep medication</td>
<td>19 (15.8%)</td>
<td>24 (20.0%)</td>
</tr>
<tr>
<td>Using pain medication</td>
<td>32 (26.7%)</td>
<td>28 (23.3%)</td>
</tr>
</tbody>
</table>
recommendation for 75 min of intense activity per week. Post-intervention, women reported an average of 275 min (SD = 439) of moderate-intensity physical activity per week, with 57.1% of the women meeting the ACSM recommendation for moderate physical activity. On average, women reported 55 min (SD = 130) of vigorous intensity physical activity per week, with 36.3% of the women meeting the ACSM guideline for vigorous physical activity at this time point. From T1 to T2, 75.6% of the women increased their level of moderate physical activity, and this change was significant (t(192) = 2.86, p < 0.01). Similarly, the vast majority of women increased their engagement in vigorous physical activity (92.3%), and this increase was also significant (t(192) = 2.08, p < 0.05) (Table 2). There were no differences on demographic (e.g., age and ethnicity) or medical variables (e.g., stage, surgical procedures, and adjuvant treatment) when comparing women who increased moderate and/or vigorous physical activity versus those who did not.

### 3.2. Change in physical activity predicting FRDI and outcomes

The specified model relating change in physical activity to changes in FRDI, clinician-rated depressive symptoms, depressed mood, and functional QoL, adjusting for previously mentioned covariates, showed a good fit to the data, $\chi^2(3) = 4.21$, $p = 0.24$, CFI = 0.99, RMSEA = 0.05, SRMR = 0.02. Model identification and unstandardized paths estimates are shown in Fig. 1.

Table 2  
Means, standard deviations, and mean difference scores for study variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline FRDI</td>
<td>3.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Functional QoL</td>
<td>18.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Clinician-rated depression</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>9.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Hours of PA</td>
<td>2.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Baseline – post-intervention FRDI</td>
<td>−0.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Functional QoL Δ</td>
<td>2.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Clinician-rated depression Δ</td>
<td>−1.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Depressed mood Δ</td>
<td>−1.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Hours of PA Δ</td>
<td>2.2</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Note: FRDI = fatigue-related daily interference; PA = physical activity; QoL = quality of life.

### 3.3. Effects of change in physical activity on outcomes mediated by FRDI

Indirect effects were examined to assess mediation (not in table). The model showed significant indirect effects, such that the increase in physical activity predicting improved functional QoL ($B = 0.05$, $p = 0.03$) and less depressed mood ($B = −0.02$, $p = 0.04$) was mediated by reductions in FRDI. However, the indirect path from increased physical activity to reductions in clinician-rated depressive symptoms via reduced FRDI was not significant ($B = −0.02$, $p = 0.13$). This model explained 4.9%, 4.8%, 15.1%, and 20.9% of the variance of changes in FRDI, clinician-rated depressive symptoms, depressed mood, and functional QoL, respectively.

Alternative models were estimated to determine whether FRDI was the most appropriate mediator relationships. After assessing for reverse directionality with all possible outcome and intermediary variables, the originally specified model was retained due to superior model-data correspondence and significant direct and indirect effects.

### 3.4. Effects of physical activity and CBSM

To determine whether the increased physical activity accounted for additional variability in this model above and beyond what was accounted for by condition assignment, the model was first estimated with a path regressing change in FRDI on study condition only (CBSM vs. control); change in physical activity was not included in this model. This model was a good fit for the data, $\chi^2(3) = 1.23$, $p = 0.75$, CFI = 1.0, RMSEA < 0.000, SRMR = 0.01. The direct effect from condition to FRDI change was significant, such that women assigned to CBSM experienced reduced FRDI from pre- to post-intervention, $B = −0.54$, $p = 0.04$ (not in table).

Physical activity was then added back into the model, with FRDI...
change regressed on both physical activity change and study condition (Fig. 2), yielding good model fit, $\chi^2(3) = 4.19$, $p = 0.24$, CFI = 0.99, RMSEA = 0.05, SRMR = 0.02. Examination of the unstandardized direct effects revealed a borderline significant association between study condition and FRDI change, such that women assigned to the CBSM group showed a marginally significant reduction in FRDI from pre- to post-intervention. The path from change in physical activity to FRDI change was also significant, indicating that women who showed an increase in physical activity reported a decrease in FRDI from pre- to post-intervention, above and beyond the effect of condition.

Indirect effects were examined (not in table). The model showed significant indirect effects, such that the increase in physical activity predicting improved functional QoL ($B = 0.05$, $p = 0.03$) and less depressed mood ($B = -0.05$, $p = 0.04$) was mediated by reductions in FRDI. However, the indirect path from increased physical activity to reductions in clinician-rated depressive symptoms via reduced FRDI was not significant ($B = -0.02$, $p = 0.15$). This model explained 6.7%, 5.4%, 15.2%, and 20.9% of the variance of changes in FRDI, clinician-rated depressive symptoms, depressed mood, and functional QoL, respectively.

4. Discussion

This study examined associations between change in physical activity and changes in FRDI, clinician- and self-rated depressive symptoms, and functional QoL from pre- to post-intervention in women undergoing treatment for non-metastatic breast cancer. Despite undergoing treatment, women increased moderate and vigorous intensity physical activity, with nearly 60% of women meeting the ACSM recommendation for moderate physical activity post-intervention. This was accompanied by improved functional QoL, as assessed by the SF-36, and reductions in self-reported depressive symptoms, as measured by the PHQ-9. The model explained 6.7%, 5.4%, 15.2%, and 20.9% of the variance of changes in FRDI, clinician-rated depressive symptoms, depressed mood, and functional QoL, respectively.

Fig. 2. Change model illustrating the additive effects of physical activity change and cognitive-behavioral stress management on fatigue-related daily interference (FRDI) change. Covariate paths have been removed for simplicity. **$p < 0.01$; *$p < 0.05$; §$p < 0.1$. 

Table 3

<table>
<thead>
<tr>
<th>Without CBSM</th>
<th>Change in FRDI</th>
<th>Change in clinic-rated depression</th>
<th>Change in depressed mood</th>
<th>Change in functional QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B$</td>
<td>$p$</td>
<td>$\beta$</td>
<td>$B$</td>
<td>$p$</td>
</tr>
<tr>
<td>Change in FRDI</td>
<td>$-0.05$</td>
<td>$0.02$</td>
<td>$-0.18$</td>
<td>$0.93$</td>
</tr>
<tr>
<td>Age</td>
<td>$0.01$</td>
<td>$0.63$</td>
<td>$0.04$</td>
<td>$-0.02$</td>
</tr>
<tr>
<td>Time since surgery</td>
<td>$0.003$</td>
<td>$0.54$</td>
<td>$0.04$</td>
<td>$0.10$</td>
</tr>
<tr>
<td>Procedure type</td>
<td>$-0.11$</td>
<td>$0.56$</td>
<td>$-0.04$</td>
<td>$0.13$</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>$0.29$</td>
<td>$0.31$</td>
<td>$0.08$</td>
<td>$-1.24$</td>
</tr>
<tr>
<td>Radiation</td>
<td>$0.212$</td>
<td>$0.39$</td>
<td>$0.07$</td>
<td>$-0.51$</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>$-0.24$</td>
<td>$0.37$</td>
<td>$-0.07$</td>
<td>$-0.05$</td>
</tr>
</tbody>
</table>

With CBSM

| Change in FRDI | $-0.05$ | $0.02$ | $-0.17$ | $-1.2$ | $<0.001$ | $0.14$ | $0.50$ | $<0.001$ | $0.29$ | $-1.19$ | $<0.001$ | $-0.42$ |
| Age          | $0.003$    | $0.86$ | $0.01$ | $0.02$ | $0.68$ | $0.03$ | $0.03$ | $0.26$ | $0.08$ | $0.01$ | $0.91$ | $0.01$ |
| Time since surgery | $0.002$ | $0.74$ | $0.02$ | $-0.02$ | $0.17$ | $-0.11$ | $0.01$ | $0.56$ | $0.04$ | $-0.03$ | $0.06$ | $-0.13$ |
| Procedure type | $-0.13$ | $0.51$ | $-0.05$ | $0.06$ | $0.92$ | $0.01$ | $-0.26$ | $0.41$ | $-0.06$ | $0.64$ | $0.21$ | $0.08$ |
| Chemotherapy  | $0.30$     | $0.29$ | $0.08$ | $0.16$ | $0.85$ | $0.02$ | $-1.20$ | $0.01$ | $-0.19$ | $0.31$ | $0.68$ | $0.03$ |
| Radiation     | $0.22$     | $0.38$ | $0.07$ | $-1.26$ | $0.09$ | $-0.13$ | $-0.13$ | $0.76$ | $-0.02$ | $-0.84$ | $0.20$ | $-0.09$ |
| Hormone therapy | $-0.22$ | $0.42$ | $-0.06$ | $-0.47$ | $-0.05$ | $-0.77$ | $0.08$ | $-0.12$ | $0.29$ | $0.69$ | $0.03$ |

Note: FRDI = fatigue-related daily interference; PA = physical activity; QoL = quality of life. Unstandardized ($B$) and standardized estimates ($\beta$); $p$-values for unstandardized estimates.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

§ $p < 0.1$. 

Consistent with our hypothesis, we observed a direct effect of condition.

FRDI = fatigue-related daily interference; PA = physical activity; QoL = quality of life. Unstandardized ($B$) and standardized estimates ($\beta$); $p$-values for unstandardized estimates.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

§ $p < 0.1$. 

This model explained 6.7%, 5.4%, 15.2%, and 20.9% of the variance of changes in FRDI, clinician-rated depressive symptoms, depressed mood, and functional QoL, respectively.
activity across the pre- to post-intervention period predicted less interference in daily life as a result of fatigue. This finding is largely congruent with conclusions from meta-analyses that physical activity during treatment mitigates fatigue [39,40]. While most research focuses on fatigue intensity [41–43], the present study is novel in its investigation of the unique role FRDI may play in the effects of physical activity on psychosocial functioning during breast cancer treatment.

In line with previous work and our hypotheses, women who reported reductions in FRDI had reduced clinician- and self-rated depressive symptoms and improved functional QoL [44,45], suggesting that changes in whether a woman perceives fatigue to disrupt her life is relevant to her emotional well-being and overall functioning. Moreover, consistent with cross-sectional research [9] these longitudinal findings suggest that change in FRDI may mediate the relationship between increased physical activity and decreased depressed mood and improved functional QoL during breast cancer treatment. These findings add to a growing body of research clarifying the relationship between physical activity and psychosocial functioning via a novel mechanism involving FRDI, rather than fatigue intensity.

Particularly noteworthy is our finding that increases in physical activity during primary treatment is significantly related to decreased FRDI, above and beyond the effect of an intervention known to decrease FRDI [16]. This finding expands upon prior research by suggesting that women can benefit from both physical activity and CBSM intervention. Interest in the effects of combined physical activity and psychosocial interventions for cancer populations is growing, with some findings suggesting the efficacy of such integrated protocols for cancer survivors [18], although a lack of clarity remains about applying these interventions in the active treatment phase. Our results provide preliminary support for the notion that combining both physical activity and cognitive behavioral interventions may be advantageous for patients during breast cancer treatment.

Several mechanisms have been proposed to explain how physical activity may influence fatigue, including self-efficacy [46], coping capacity [47], sleep quality [48], and reduced inflammation [49]. Heightened self-efficacy and augmented coping abilities may lead to increased participation in life activities and a lower appraisal of fatigue interference. Physical activity may also increase a woman’s sense of confidence in functional capacity and similarly reduce perceived fatigue interference. Women who experience less FRDI are able to participate in more social and work activities, which may provide meaning, purpose, and social support, resulting in fewer depressive symptoms and better QoL. It is likely that common mechanisms of CBSM and physical activity that reduce fatigue interference overlap. For example, prior work suggests that CBSM may partially reduce FRDI by improving sleep quality and attenuating cognitive distortions related to perceptions of fatigue and its interference to daily activities [16]. CBSM has also been shown to maintain social support networks [19], decrease inflammation [50], and improve immune function [51]; while not yet tested, such factors may contribute to reductions in FRDI. However, some mechanisms may be distinct and help to explain the independent effects of physical activity and CBSM on FRDI. Further work is needed to compose a more comprehensive explanatory model for fatigue in breast cancer patients.

These findings should be considered in light of several limitations. First, this was an observational post-hoc secondary analysis utilizing data from an intervention trial with a primary aim of testing the effects of a CBSM intervention. Despite the use of robust statistical methodology, our analyses did not control for body mass index (BMI) or general medical comorbidities, which may have influenced outcome variables of interest. Unfortunately, these data were not collected consistently at either assessment. Primary use of self-report measures may limit the reliability of these findings. Future research should include additional objective measures (e.g., pedometers, actigraphs, Fitbits, etc.) to quantify physical activity. Additionally, one item of the Hamilton Rating Scale for Depression concerns somatic manifestations of depressed mood, including fatigue. This item was retained in the scale score for analysis because it references musculoskeletal complaints and headaches in addition to fatigue; however, it should be noted that this item potentially overlaps with our measure of FRDI. Finally, these data were collected in a university-based study comprised of white, highly-motivated, and well-educated middle-class women in Miami, Florida, and results may not generalize to other samples.

4.1. Clinical implications and future directions

Multiple factors have been linked to fatigue, but research has yet to provide a complete model of fatigue in breast cancer [52]. The current findings provide novel insight and expand upon previous knowledge regarding the role of physical activity in ameliorating physical and psychological sequelae throughout adjuvant breast cancer treatment. Most patients with breast cancer will experience fatigue during treatment, and some studies have found that fatigue has the largest negative impact on QoL compared to other cancer-related symptoms [53,54]. As such, fatigue and its treatment are of high clinical importance. Evidence that reduced perceived fatigue interference is a pathway by which physical activity improves overall functioning and emotional well-being is informative for intervention development and implementation, especially as efficacious interventions for fatigue are lacking in breast cancer populations. These findings provide further evidence of the efficacy of physical activity for fatigue management during breast cancer treatment. It is important, however, to evaluate benefits and feasibility of a physical activity regimen, as not all patients will be able to engage in physical activity at points during treatment. Additional research investigating demographic and medical variables that relate to stagnant or reduced physical activity among breast cancer patients is warranted, as this information will likely facilitate the dissemination and implementation of physical activity interventions.

Moreover, observations that physical activity and CBSM are both beneficial provides further reason to study the benefit of physical activity independently and in addition to psychosocial interventions. More work is needed to elucidate whether physical activity and CBSM are functioning via similar or distinct mechanisms.

4.2. Conclusions

Maintaining moderate to vigorous physical activity is important for optimizing physical and psychological functioning throughout primary treatment for non-metastatic breast cancer. Findings of this study suggest that increased physical activity in the initial months of treatment may independently improve FRDI, beyond what follows in a psychosocial intervention. Hybrid approaches combining physical activity and cognitive-behavioral techniques should be evaluated in randomized trials in breast cancer patients undergoing primary treatment to enhance our understanding of how best to integrate efficacious psychotherapy and exercise components to more comprehensively address physical and psychological concerns related to breast cancer treatment.

Disclosures

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References

[1] Thornton LM, Andersen BL, Blakely WP. The pain, depression, and fatigue symptom


