Changes in physical activity behavior and C-reactive protein in breast cancer patients

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Abstract

Background C-reactive protein (CRP) concentrations are associated with morbidity and mortality in breast cancer patients and moderate-vigorous physical activity (MVPA) may help regulate CRP levels.

Purpose The purpose of this prospective study was to examine intraindividual and interindividual changes in MVPA on changes in CRP levels among early posttreatment breast cancer patients.

Methods During five data collections over the first year posttreatment for breast cancer, women ($N = 138$, $M_{age} = 55.3$, standard deviation = 11.1 years) completed a questionnaire, wore an accelerometer for seven consecutive days to measure MVPA, and provided blood samples to measure CRP concentrations. Intraindividual and interindividual associations between MVPA on CRP were tested using hierarchical linear modeling.

Results Based on the intraindividual associations, lower concentrations of CRP were evident when participants engaged in more, as compared to their average, MVPA ($\beta = -.02$, $p < .021$). In addition, interindividual analyses showed that women who engaged in more MVPA across the study period had lower concentrations of CRP compared to women who engaged in less MVPA ($\beta = -.24$, $p = .006$).

Conclusions MVPA in breast cancer patients is consistently associated with lower CRP concentrations over time.

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Interventions may target individual MVPA early after diagnosis to mitigate CRP levels in breast cancer patients.

Introduction

Low-grade inflammatory responses (i.e., C-reactive protein [CRP] concentrations) in women diagnosed with breast cancer are associated with all-cause mortality, breast cancer-related mortality, and additional breast cancer events [1, 2]. As such, strategies to decrease CRP concentrations in breast cancer patients are needed to improve prognosis and health outcomes. Increasing physical activity levels may be a cost-effective and non-pharmaceutical treatment that can mitigate CRP concentrations during cancer survivorship [3, 4]. Specifically, a recent systematic review and meta-analysis of physical activity interventions for breast cancer survivors noted that physical activity may significantly reduce CRP levels [5]. The combined effects of the four research papers showed the relationship between exercise and CRP levels was in the expected direction but did not reach statistical significance (i.e., weighted mean difference = −1.10 mg/l, 95% confidence interval [−2.39, 0.20], $p = .10$). The authors concluded that physical activity showed potentially meaningful results and called for additional research to test this contention [5]. Although moderate-vigorous physical activity (MVPA) has been found to decrease inflammatory cytokines such as CRP [3, 6], most of the evidence regarding the benefits of MVPA for breast cancer patients is based on cross-sectional, retrospective, or structured (e.g., controlled and supervised) laboratory-based interventions that fall short of describing naturally occurring developmental trends in MVPA and CRP over time (see Ballard-Barbash et al. [7], for a

review on physical activity and biomarkers in cancer survivors). Examining the association of changes in MVPA and CRP over time may result in a better understanding of mechanisms and inform intervention efforts to help improve survivorship for women diagnosed and treated for breast cancer. A specific understanding of the association between MVPA and inflammation during the first year posttreatment for breast cancer is needed to inform behavior modification strategies, and improve health and disease outcomes [8, 9].

Researchers targeting breast cancer survivors have predominantly used mean group-level analytical approaches (i.e., interindividual differences). These approaches, however, may mask reliable intraindividual changes in relevant predictor variables and thus may fail in providing potentially important information for patient-centered health care. Since treatment types, doses, and effects are unique to each patient, and each patient manages the effects of breast cancer differently, patient-centered approaches are necessary. This prospective study was designed to examine changes in MVPA and CRP concentrations in breast cancer patients at both the intraindividual (i.e., within-person changes) and interindividual (i.e., between-person changes) level over the first year posttreatment. It was hypothesized that assessment periods with comparatively higher levels of MVPA would be associated with improved immune processes indicated by reduced levels of CRP (in relation to assessments during which women had lower MVPA; within-person relations). At the interindividual level, it was hypothesized that women with generally higher than their average levels of MVPA over time would show lower CRP levels, relative to women with generally lower levels of MVPA (between-person relations). Furthermore, the potential interaction between intraindividual changes and interindividual levels of MVPA was tested to explore whether intraindividual changes in MVPA over time would be conducive to predicting lower CRP concentrations at generally high and/or lower than average levels of MVPA. Relevant covariates (i.e., age, education, weight status, breast cancer stage, time since diagnosis, treatment type, and medication use) were tested in the analyses.

Methods

Participants and Procedures

University and hospital research ethics committees approved the study protocol, and all participants provided written informed consent prior to data collection. Based on inclusion criteria, participants ($N = 201$) were: (i) at least 18 years of age; (ii) 0–20 weeks post primary treatment (i.e., surgery, chemotherapy, radiation therapy) for stage I to III breast cancer; (iii) treated for a first cancer diagnosis; (iv) able to provide written informed consent in English or French; and (v) reporting no health concerns that prevented them from engaging in physical activity.

Participation in the study involved women completing a self-report questionnaire, wearing an accelerometer for seven consecutive days to measure MVPA, and providing a blood sample during five data collections (every three months). Because we were interested in the analysis of change, the current study includes 138 women who provided valid data on the outcome variable in at least two waves of data collection. These women did not significantly differ from the excluded women in baseline levels of age, education, smoking, body mass index (BMI), ethnicity, cancer stage, time since diagnosis, treatment type, inflammatory medication taken, or MVPA ($ps > .05$). However, a greater number of women excluded from the analysis reported receiving hormone therapy treatment (x^2 (1) 7.59, $p = .01$). There were no significant differences between women who adhered to wearing the accelerometer in at least two waves of the study and those who did not ($ps > .05$).

Sample Size Determination

The sample size was selected based on our primary research question regarding the changes in MVPA and CRP concentrations at both the intraindividual (i.e., within-person changes) and interindividual (i.e., between-person changes) level in breast cancer patients over the first year posttreatment. Based on Maas and Hox [10], our sample of 138 women at level two (with up to five data points each) was deemed sufficiently powered to detect estimated relations and variances.

Measures

Demographics

Self-report questionnaires included questions regarding age, education, ethnicity, breast cancer stage, time since diagnosis, cancer treatment(s) received, use of medication for inflammation, corticosteroids, statins, nonsteroidal anti-inflammatory drugs (no/yes), and smoking status. Baseline height and weight [used to calculate BMI as weight in kilograms divided by height in meters squared] were assessed by a trained technician in the lab.

Physical Activity

MVPA was assessed using a GT3X accelerometer (Actigraph, Pensacola, Florida). At each of the five time-points, women were asked to wear the accelerometer on their hip during waking hours for a 7-day period,

except for periods of bathing/showering or other water activities. Data were downloaded in 60-s epochs and established cut-points [11] were used to calculate daily minutes of moderate (1952–5724 counts•minute^{-1}) and vigorous (>5725 counts•minute^{-1}) physical activity, while controlling for the number of days and hours the accelerometer was worn. Data were included in the analyses if there were no extreme counts (>20,000) and if data were available for at least 600 min on four or more days [12, 13].

C-reactive Protein

Capillary whole blood was collected using a single-use lancet to deliver a uniform puncture to the index or middle finger. Drops of blood were collected on a Whatman protein saver card (VWR International, QC), which has a sample collection area of five 1.3-cm circles holding 75–80 μL of blood. The drops of blood were allowed to dry and then the card was stored at −80 degrees Fahrenheit. The samples were analyzed in the Laboratory for Human Biology Research at Northwestern University using a high-sensitive (i.e., low detection limit 0.1172 μg/mL) enzyme immunoassay protocol [14]. Validation studies measuring CRP concentrations from blood drops have shown high correlations with matched CRP samples from blood plasma, as well as good sensitivity and reliability [14]. The coefficient of variation in the current data ranged from 3.5% to 9.2%.

Data Analysis

Preliminary analyses were used to describe the sample (by calculating means, standard deviations [*SD*s], or percentages) and examine the general associations between MVPA and CRP concentrations across study waves using zero-order correlations. Next, the hypotheses of intraindividual and interindividual relationships of MVPA and CRP were tested by performing three sets of multilevel linear regression models using HLM 8.0. In the first analysis, a Level-1 model estimated variability in CRP levels across waves by an intercept, MVPA slope, Wave slope, and a residual term. MVPA and Wave were person-centered to allow for the interpretation of the intercept as average levels of CRP across waves. The slope coefficient for MVPA represented the hypothesis-relevant within-person association between MVPA and CRP. Wave (of data collection) was controlled at Level-1 to avoid potential confounds associated with time in study. Furthermore, the pattern of obtained significant effects did not change if wave was not included in the model.

The second model sought to identify potential covariates (i.e., education, BMI, breast cancer stage, time since diagnosis, lumpectomy, lymph node dissection, single mastectomy, double mastectomy, chemotherapy, radiotherapy, reconstructive surgery, current hormone therapy, inflammation medication, ethnicity) that could explain significant variability in the Level-1 intercept (i.e., average levels of CRP). To explain significant variability in the Level-1 coefficients, variables identified as significant (*p*s < .05) were incorporated in the third model as Level-2 between-person predictor variables in addition to average MVPA across waves. All Level-2 predictor variables were standardized prior to conducting the analysis, and the reported relations are based on restricted maximum-likelihood estimation and robust standard errors (*SE*s).

The hypothesis-relevant coefficient of interest at Level-2 was the interindividual relations of average MVPA on the intercept, testing whether higher between-person levels of MVPA would be associated with lower levels of CRP concentrations. Results are reported from a parsimonious model, including Level-1 and Level-2 predictors, because this model provides information about whether the within-person relations of MVPA were independent of the between-person relations of MVPA in predicting CRP concentrations.

Results

Preliminary Analyses

Across waves, between 68.8% and 77.5% of participants had sufficient CRP data (Time 1 = 73.25%, Time 2 = 68.8%, Time 3 = 74.6%, Time 4 = 77.5%, Time 5 = 72.5%), and there was between 98.6% and 100.0% of usable accelerometer data (Time 1 = 98.6%, Time 2 = 100.0%, Time 3 = 99.3%, Time 4 = 98.6%, Time 5 = 99.3%). Of note, 10 accelerometer data points (0.01% of all accelerometer data) across the study waves were included for women who wore the accelerometer between 570 and 596 minutes per day. Since HLM is capable of handling missing data on Level-1, missing data for CRP and MVPA were not replaced. Missing data of Level-2 variables were replaced with the sample mean and did not exceed 5% [15] on any one of the variables (i.e., age = 0.7%, education = 0.0%, ethnicity = 0.0%, stage of cancer = 0.0%, months since diagnosis = 1.4%, BMI = 0.0%, smoking status = 2.2%, treatment type = 0.0%, medications = 0.0%).

Descriptive statistics of the study sample are reported in Table 1. Participants were between 28 and 79 years old, were predominantly well-educated, and had BMI values that are classified as overweight. Participants were enrolled in the study approximately 11 months past diagnosis and 3 months after primary treatment. The majority of participants were diagnosed with either Stage I or Stage II breast cancer. Across waves, mean accelerometer wear times were 821.8 (*SD* = 83.0) to

Table 1 Score ranges, means, standard deviations, and frequencies of main study variables ($N = 138$)

Variable	Score range	Mean (SD) or percentage[a]
Moderate-to-vigorous physical activity (min)		
Baseline	0–52	16.44 (12.08)
3 months	0–58	16.30 (12.62)
6 months	0–66	15.66 (13.15)
9 months	0–52	14.88 (11.51)
12 months	0–51	14.16 (11.55)
C-reactive protein (mg/L)		
Baseline	0–8	1.47 (1.70)
3 months	0–8	1.24 (1.39)
6 months	0–9	1.07 (1.31)
9 months	0–9	1.15 (1.36)
12 months	0–10	1.16 (1.61)
Age	28–79	55.28 (11.05)
Education (baseline)		
Did not complete high school (%)		4.3
High school diploma (%)		16.7
Post-secondary no diploma (%)		8.7
College/technical diploma (%)		20.3
Undergraduate degree (%)		27.5
Post-graduate degree (%)		22.5
Stage of cancer (baseline)	1–3	1.73 (0.72)
Stage I (%)		43.5
Stage II (%)		40.6
Stage III (%)		15.9
Months since diagnosis (baseline)	2–20	10.59 (3.41)
Body mass index (baseline)	18–50	26.44 (5.79)
Smoking status yes (%)		6.5
Anti-inflammatory medication use yes (%)		37.7
Current use of hormone therapy yes (%)		
Cancer treatment yes (baseline)		
Lumpectomy (%)		58.0
Lymph node dissection (%)		60.9
Single mastectomy (%)		26.1
Double mastectomy (%)		15.9
Chemotherapy (%)		64.5
Radiotherapy (%)		90.6
Reconstructive surgery		5.8
Hormone therapy (%)		57.2
Ethnicity, white (%)		84.8

SD standard deviation.

[a] Mean and SD are presented for continuous variables.

899.4 ($SD = 90.2$) minutes per day, median number of days worn per week was seven, and participants engaged in approximately 14 to 17 minutes of daily MVPA on average. Average levels of CRP concentrations across waves were between 1.0 and 1.5 mg/L.

The zero-order correlations between MVPA and CRP concentrations across waves are reported in Table 2. The observed pattern of significant findings indicates positive associations over time for both MVPA (rs = .58 to .80; ps < .01) and CRP (rs = .26 to .79, ps < .05), suggesting some stability in these variables. In addition, the results document a considerable number of significant associations between MVPA and CRP concentrations over time, indicating that higher levels of MVPA were generally associated with lower levels of CRP concentrations (17 of possible 25 correlation coefficients were significant at $p < .05$, $range = -.20$ to $-.33$).

Main Analyses

The results of the main analysis are presented in three different models, representing Level-1 results only (model 1), the identification of potential covariates (model 2), and a final model incorporating Level-1 and Level-2 predictors (model 3). In the first model, the Level-1 results showed a significant intercept ($B = 1.207$, $SE = 0.10$, $p \leq .001$), indicating that average levels of CRP across waves were significantly different from zero. In support of the hypotheses, the Level-1 results further demonstrated a significant slope effect for within-person variation in MVPA ($B = -0.025$, $SE = 0.01$, $p < .001$). Levels of CRP did not significantly change across time ($B = -0.019$, $SE = 0.01$, $p = .13$).

In the second model, all potential personal and cancer-specific descriptive information was added as potential Level-2 covariates. Of the potential covariates, only BMI, stage of cancer, and time since diagnosis (Bs ≥ |0.27|, SEs < 0.13, ps < .003), exerted unique significant effects on average levels of CRP concentrations. Lumpectomy, lymph node dissection, single mastectomy, double mastectomy, chemotherapy, radiotherapy, reconstructive surgery, current hormone therapy, inflammation medication, and ethnicity were not significantly associated with levels of CRP (all Bs < 0.24, SEs > .40 0.13, ps < .14). To maintain parsimony in the analyses, the final presented model is restricted to include only these covariates as Level-2 predictors that were significantly associated with CRP levels.

The final model included both Level-1 and Level-2 predictors and showed that Level-1 results were highly similar to the first model. Average levels of CRP across waves were significantly different from zero (i.e., intercept; $B = 1.202$, $SE = 0.09$, $p \leq .001$), CRP did not significantly change over time (i.e., wave slope; $B = -0.019$, $SE = 0.01$, $p = .13$), and within-person changes in MVPA significantly predicted CRP concentrations (i.e., MVPA slope; $B = -0.02$, $SE = 0.01$, $p = .02$). As illustrated in Fig. 1 (left panel), participants exhibited lower levels of

CRP in waves in which they engaged in more, as compared to less, MVPA.

Consistent with the second model, the analysis further showed that the included Level-2 covariates were meaningfully associated with average levels of CRP across waves. In particular, a higher BMI ($B = 0.452$, $SE = 0.12$, $p < .001$), a higher breast cancer stage ($B = 0.319$, $SE = 0.12$, $p = .01$), and a more recent diagnosis ($B = -0.272$, $SE = 0.08$, $p = .002$) predicted higher average levels of CRP across waves. The Level-2 results demonstrated a significant between-person effect of average levels of MVPA on average levels of CRP across waves ($B = -0.242$, $SE = 0.09$, $p = .006$). In support of our hypotheses, Fig. 1 (right panel) demonstrates that participants who generally engaged in more MVPA across the study period reported lower overall levels of CRP than their counterparts who engaged in less MVPA. In addition, supplemental analyses showed that the effect of MVPA remained significant if the covariates that were excluded on an empirical basis were separately incorporated.

Note that the intraindividual association between MVPA and CRP concentrations was significant above and beyond the covariates and average MVPA across waves, which were included in Level-2 of the analysis. In addition, the Level-2 covariates and average MVPA across waves did not show additional cross-level interaction effects on either the intraindividual association between MVPA and CRP concentrations ($B_{BMI} = 0.003$, $SE = 0.01$, $p = .77$; $B_{\text{breast cancer stage}} = -0.017$, $SE = 0.01$, $p = .07$; $B_{\text{time since diagnosis}} = 0.009$, $SE = 0.01$, $p = .10$; $B_{\text{average levels of MVPA}} = -0.004$, $SE = 0.01$, $p = .67$) or the association between time in study and CRP levels ($B_{BMI} = 0.003$, $SE = 0.01$, $p = .84$; $B_{\text{breast cancer stage}} = 0.029$, $SE = 0.02$, $p = .06$; $B_{\text{time since diagnosis}} = 0.007$, $SE = 0.01$, $p = .48$; $B_{\text{average levels of MVPA}} = 0.012$, $SE = 0.01$, $p = .24$). These results indicate that within-person associations between MVPA and CRP did not depend

on participants' average levels of MVPA or the selected covariates. In supplemental analyses, a similar pattern of findings was observed for the three sets of multilevel linear regression models when moderate and vigorous intensities were analyzed separately. However, the between-person effect of average levels of vigorous physical activity on average levels of CRP across waves was not significant at Level-2 of the final model ($B = -0.009$, $SE = 0.03$, $p = .725$).

Discussion

The purpose of this prospective study was to examine intraindividual and interindividual variability in MVPA on CRP levels among early posttreatment breast cancer patients. Changes in MVPA over time were inversely related to CRP levels. Changes in individual's MVPA levels (i.e., relative to their own typical amounts; within-in-person or intraindividual relations) were negatively associated with changes in their CRP concentrations. Furthermore, participants who generally engaged in more, as compared to less MVPA (i.e., between-person or interindividual relationships), had overall lower levels of CRP concentrations.

Women who engage in physical activity after a breast cancer diagnosis have reduced overall morbidity and mortality [1]. CRP is an important biomarker of chronic inflammatory processes that may explain health challenges among women following breast cancer diagnosis. For example, higher CRP levels have been implicated in reduced disease-free survival and higher risk of mortality among breast cancer patients [2, 16, 17]. Physical activity has been inversely associated with CRP [3, 6, 7], and thus, may represent a mechanism that protects breast cancer patients from the deleterious effects of chronic inflammatory processes. In the current longitudinal study,

Table 2 Zero-order correlations between moderate-to-vigorous physical activity (MVPA) and C-reactive protein (CRP) across five data collections

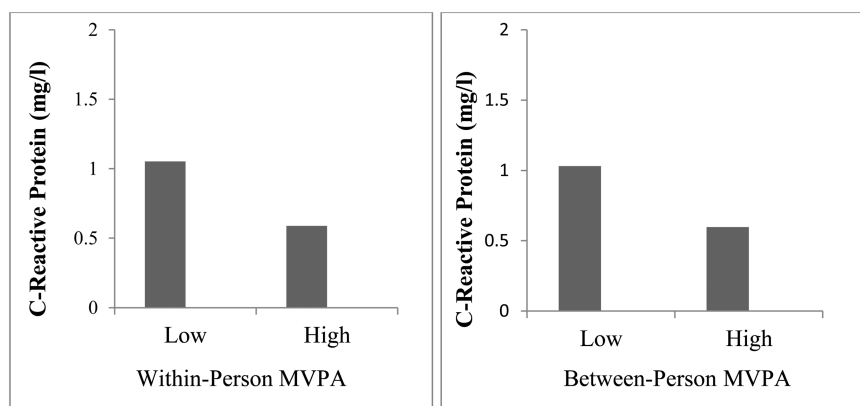|	1	2	3	4	5	6	7	8	9
1. MVPA (baseline)									
2. MVPA (3 months)	.76**								
3. MVPA (6 months)	.70**	.76**							
4. MVPA (9 months)	.65**	.75**	.76**						
5. MVPA (12 months)	.58**	.72**	.67**	.80**					
6. CRP (baseline)	−.23*	−.16	−.20*	−.18	−.22*				
7. CRP (3 months)	−.26**	−.24*	−.28**	−.18	−.24*	.37**			
8. CRP (6 months)	−.28**	−.32**	−.34**	−.33**	−.33**	.58**	.58**		
9. CRP (9 months)	−.19*	−.27**	−.21*	−.27**	−.23*	.55**	.51**	.79**	
10. CRP (12 months)	−.13	−.13	−.17	−.03	−.15	.26*	.63**	.36**	.61**

$*p < .05$, $**p < .01$.

Fig. 1. Within-person (left panel) and between-person (right panel) effects of moderate-to-vigorous physical activity (MVPA) on C-reactive protein. Low versus high MVPA represent the lower versus upper averaged quartiles of the within-person and between-person distributions of MVPA.

we found consistent associations between MVPA and CRP in the first year posttreatment for breast cancer. These associations provide a clear public health message in that breast cancer patients had lower levels of CRP in waves when they engaged in more MVPA. These findings are particularly valuable because MVPA was measured objectively using accelerometers, which addresses limitations of previous research efforts linking biomarkers of physical health risks with self-reported physical activity. Furthermore, there were multiple assessments over the critical first year following treatment, which provided us with the opportunity to detect shorter term associations between changes in MVPA and CRP.

Consistent with previous research [3], we also found that interindividual levels of MVPA were associated with CRP. Furthermore, the associations between CRP and relevant covariates (e.g., BMI, breast cancer stage) are also aligned with previous findings [18, 19]. The current findings extend previous research [7] as we found intraindividual changes and interindividual levels of MVPA had independent relations and did not interact with each other in predicting patients' CRP levels. This result implies that engaging in more than usual levels of physical activity is associated with reduced levels of chronic inflammation independent of how physically active breast cancer patients were in general. Based on these findings, early after diagnosis, women with breast cancer may be encouraged to increase their engagement in regular MVPA. Furthermore, researchers should examine the extent to which interventions that increase MVPA in breast cancer survivors [20–23] may facilitate effective immune function.

The prospective longitudinal design including frequent data collections (every 3 months for five waves of data collection), objective assessments of MVPA, and the maintenance of a large proportion of the sample for analysis are important strengths of this study. Nonetheless, the study also incorporates a number of limitations. For example, the design of this study precludes inferences of causality and the sample limits generalizability of the findings. In addition, participants who were excluded from the analysis due to insufficient data for CRP levels were more likely to report receiving hormone therapy treatment than those who were included in the study. As such, caution is warranted in generalizing these findings to breast cancer survivors who receive hormone therapy treatment. Furthermore, CRP concentrations were assessed using dry blood rather than blood plasma collected via venipuncture, although evidence of validation of dry blood samples [14] supports this method of CRP analysis. Finally, CRP was the only marker of inflammatory processes measured in this study, and a variety of other inflammatory biomarkers (e.g., interleukins, tumor necrosis factor alpha) should be studied for a comprehensive approach to studying the association between physical activity and inflammation among breast cancer survivors. Also, it is important to note that the CRP levels in the current sample averaged to be in the range of healthy values that are not associated with known disease outcomes. However, the purpose of this study was not to examine thresholds of effects between MVPA and CRP and disease outcomes. Future work is needed to explore the effects of levels of CRP on disease outcomes in this target population.

In sum, this study demonstrated evidence of an inverse relationship between MVPA and CRP concentrations in both within- and between-person levels of analysis. Researchers and practitioners who seek to decrease CRP concentrations in breast cancer patients may be encouraged to target MVPA. Research efforts are needed to develop an understanding of how to best support MVPA in breast cancer patients to lower CRP concentrations and improve physical health outcomes.

Compliance With Ethical Standards

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