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Association of self-directed walking with toxicity moderation during chemotherapy for the treatment of early breast cancer

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Received: 7 June 2023 / Accepted: 18 December 2023 © The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2023

Abstract

Background In the field of exercise oncology, there is a need to quantify the potential benefits of moderate, self-directed physical activity during active treatment. In a pooled analysis of three identical single-arm intervention studies, we investigate the association of activity tracker steps with patient-reported toxicities during chemotherapy.

Methods Women with early breast cancer who were enrolled in the intervention studies reported their symptom severity every 2–3 weeks throughout chemotherapy, and daily steps were documented through a Fitbit activity tracker. Relative risks (RR) and 95% confidence intervals (CI) were calculated using Poisson regression models with robust variance. For outcomes significant in unadjusted models, adjusted RRs were calculated controlling for race, age, and education level. Tracker step cut point (high step, low step) was determined by the means. Cumulative incidence functions of moderate, severe, and very severe (MSVS) symptoms were estimated using the Kaplan-Meier method and compared using a Cox proportional hazard model. **Results** In a sample of 283 women, mean age was 56 years and 76% were White. Mean tracker-documented steps/week were 29,625, with 55% walking below the mean (low step) and 45% above (high step). In multivariable analysis, high step patients had lower risk for fatigue [RR 0.83 (0.70, 0.99)] (p = 0.04), anxiety [RR 0.59 (0.42, 0.84)] (p = 0.003), nausea [RR 0.66 (0.46, 0.96)] (p = 0.03), depression [RR 0.59 (0.37, 0.03)] (p = 0.02), and ≥ 6 MSVS symptoms [RR 0.73 (0.54, 1.00)] (p = 0.05) and had 36% lower risk for dose reductions [RR 0.64 (95% CI 0.43, 0.97)] (p = 0.03).

Conclusion Self-directed walking at a rate of at least 30,000 steps/week may moderate the severity of treatment side effects during chemotherapy for early breast cancer.

Trial numbers NCT02167932, NCT02328313, NCT03761706.

Keywords Breast cancer · Chemotherapy · Physical activity · Symptoms

Introduction

American Society of Clinical Oncology (ASCO) guidelines pertaining to exercise, diet, and weight management during cancer treatment [1] endorse physical activity (PA) to "reduce fatigue, preserve cardiorespiratory fitness,

Lay summary:

physical functioning and strength, and in some populations to improve QoL and reduce anxiety and depression." These guidelines were derived from decades of observational and exercise intervention studies in adults with cancer [2-4]. Most of the intervention studies have focused on PA and the management of fatigue [5-11] and to a lesser extent on physical function, mental health, and quality of life [12–14] The ASCO guideline is "strongly" recommended, but it is also noted in the guideline that the quality of supporting evidence is moderate to low. Numerous research questions remain regarding how and to what extent exercise is beneficial for adults with cancer, especially during active treatment [15]. One research question identified by Courneya et al. pertains to which specific cancer symptoms can be managed by physical activity, especially the array of toxicities that arise during chemotherapy.

[•] This study explores whether home-based, self-directed walking throughout chemotherapy for early breast cancer can moderate the severity of treatment-related side effects (symptoms).

[•] Study participants whose tracker steps were above the mean for the full sample (high step) reported fewer instances of moderate, severe, or very severe symptoms for 11 commonly reported chemotherapy toxicities as compared to participants who walked below the mean (low step).

Extended author information available on the last page of the article

Hence, our study aimed to address two research questions. The first is whether home-based, minimally directed PA during chemotherapy is associated with completion of the chemotherapy regimen as planned. Suboptimal treatment completion is particularly problematic in patients receiving chemotherapy regimens that are especially toxic [16, 17]. Evidence from prior studies related to the impact of PA on treatment completion is minimal, with most studies pertaining to the impact of pre-chemotherapy PA history [18–20] and to a lesser extent to PA during chemotherapy [21]. One study by Van Waart et al. entailed a home-based PA regimen that was individualized to each study participant, including supervised moderate-to-high intensity resistance and aerobic training, and showed significantly lower chemotherapy adjustment rate between usual care (25%) and intervention (10%) (p = 0.014) [21].

Our second research question is whether PA during active treatment can moderate the severity of an array of common side effects of chemotherapy, beyond fatigue [17, 22]. Specifically, which side effects are amendable to modification through a clinic-based PA intervention with minimal intervention from research personnel and to what extent are these side effects modifiable? Within the literature pertaining to PA for symptom management during chemotherapy, the literature pertains primarily to fatigue [10, 23, 24]. We also investigate the related question of "causality"—did engagement in PA throughout chemotherapy lower symptom severity or did low symptom severity at baseline (pre-chemotherapy) enable engagement in higher levels of PA during chemotherapy that, in turn, modified symptom severity?

This study utilizes data from three single-arm studies of home-based, self-directed walking interventions that did not entail intense involvement of exercise trainers or supervision [17, 25]. Women with early breast cancer were recruited prior to their start of chemotherapy and were asked to wear a Fitbit activity tracker and self-report their symptom severity throughout treatment. We first explore associations between activity tracker steps and regimen modifications (dose delay, dose reduction, early treatment discontinuation) and hospitalization and then explore associations between walking steps and symptom severity for 11 common chemotoxicities. In light of differing toxicity profiles among chemotherapy regimens in current clinical practice [17, 22], we also compare the impact of walking under different chemotherapy regimens.

Methods

Study participants

This is a pooled analysis of data collected during three single-arm intervention studies of women engaged in

self-directed walking during chemotherapy for stage I-III breast cancer. The studies were identical with the exception of age criteria at breast cancer diagnosis-women aged 21 to 64 years (NCT02167932), aged 65 or older (NCT02328313), and aged 21 or older (NCT03761706). We pooled the data in order to include all age groups in the current analysis and to increase sample size and power. The enrollment period was between 2014 and 2022. The studies were approved by the University of North Carolina at Chapel Hill (UNC) Lineberger Comprehensive Cancer Center (LCCC) Protocol Review Committee and the Institutional Review Boards (IRB) of participating sites. Women scheduled to receive chemotherapy with curative intent were approached in-person or remotely and consented prior to chemotherapy initiation. Chemotherapy regimens were determined by treating oncologists in consultation with their patients depending on tumor stage and phenotype [26].

Intervention

Consented patients in all three studies agreed to participate in a home-based walking intervention; there was no random or other assignment to various levels of PA. Participants were encouraged to walk at least 150 min per week, at a place and pace they considered safe and sustainable throughout chemotherapy. They received a motivational booklet titled *Walk With Ease* [27] and were provided with an activity tracker that they were asked to wear during all waking hours. Study coordinators provided words of encouragement to walk when tracker data were uploaded into research computers during routine chemotherapy infusion visits. Further details regarding the intervention have been published previously [25].

In a prior analysis of participants in our walking studies [25], we reported that patients had great difficulty achieving the 150 min/week goal (an estimated 44,000 steps/week); only 19% were fully adherent in our "real world" intervention which entailed minimal PA encouragement and no adherence supervision from research personnel. We have also reported in our prior analysis that pre-chemotherapy (baseline) history of vigorous physical activity, higher walking minutes/week, and greater outcome expectations from exercise were associated with the achievement of higher number of Fitbit steps/week. In turn, lower achievement of Fitbit steps/week was associated with non-White race, high school education or less, and never/almost never drinking alcohol. In multivariable analysis, race and pre-chemotherapy walking minutes/ week remained independent predictors of steps/week during chemotherapy.

Measures of exercise

Activity tracker steps were uploaded into research computers by the study coordinator every 2 to 3 weeks depending on the patient's infusion schedule. For two studies (NCT02167932 and NCT02328313), the tracker was a Fitbit (Fitbit Inc., San Francisco CA) clip-on device. For the third study, the tracker was a Garmin Vivo (Garmin International Inc., Olathe KS) wristband device. Steps were tracked only during the chemotherapy portion of care; they were not tracked during anti-HER2 therapy that did not include a chemotherapy drug at the same time. In addition, participants were asked prechemotherapy about (1) self-reported walking minutes per week and (2) number of times per week they engaged in vigorous exercise.

Patient-reported treatment toxicities and regimen modifications

Every 2–3 weeks throughout their chemotherapy, patients were asked to rate their symptom severity for 17 commonly observed side effects from chemotherapy, with the response options of none, mild, moderate, severe, or very severe (range 0 through 4). The symptoms were fatigue, insomnia, depression, anxiety, diarrhea, constipation, peripheral neuropathy, arthralgia, myalgia, pain (general), abdominal pain, nausea, vomiting, dyspnea, hot flashes, limb edema, and oral mucositis. For the current study, the focus is incidence and prevalence of symptoms-individual and total-rated moderate, severe, or very severe (MSVS) [28]. Symptom reporting was conducted online (patient responses were entered directly into a REDCap database via tablet provided during the chemotherapy infusion) and utilized the validated Patient-Report Symptom Monitor (PRSM, first two studies) [29] (Appendix 1) or the PRO-CTCAE (Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, most recent study) [30-32] when it became publicly available (Appendix 2), as described previously [17, 33-35].

Data regarding regimen modifications and hospitalizations during chemotherapy were extracted from the participants' electronic medical record (EMR). In light of known toxicity variations among different drug regimens [17, 22], events and MSVS symptom severity were analyzed for all participants combined and then separately for docetaxel versus paclitaxel/nab-paclitaxel regimens (most of which were sequential and included an anthracycline).

Pre-chemotherapy assessments and patient-reported outcome (PRO) measures

Prior to chemotherapy initiation, study participants were assessed by study coordinators and completed several PRO measures online. Ranges (continuous variables) and cut points (for dichotomized variables) are presented in Table 1. Assessed measures included Timed Up and Go (TUG) [36] and Short Physical Performance Battery (SPPB) [37]. PROs included Mental Health Index (MHI) to assess depression and/or anxiety [38], Instrumental Activities of Daily Living (IADL) [39], Functional Assessment of Cancer Therapy-General (FACT-G) to assess wellbeing in four domains (physical, social/family, emotional, functional) [40], and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [41].

Other measures

Participants self-reported their age, race, education, employment, marital status, and living alone. Body mass index (BMI) and comorbidities were extracted from the EMR, as were breast cancer diagnosis and treatment.

Statistical considerations

Descriptive statistics were calculated for the study variables. Kruskal-Wallis tests evaluated the association between continuous demographic and clinical characteristics with step count category, and Fisher's exact tests were used for categorical characteristics.

Relative risks (RR) and 95% confidence intervals (CI) were calculated using Poisson regression models with robust variance. RRs are reported for the entire sample, as well as subsets of patients based on chemotherapy regimen. For outcomes significant in the unadjusted models, adjusted RRs were calculated controlling for race (dichotomized as White and non-White), age (in 10-year increments), and education level, as these variables were significantly associated with step count category in univariate analysis (Table 1).

Cumulative incidence functions of MSVS symptoms were estimated using the Kaplan-Meier method and compared using a Cox proportional hazard model. Adjusted analyses were calculated using a Cox model, controlling for race, age, and education. A two-tailed p of <0.05 was considered significant. All analyses were performed with SAS statistical software (version 9.4; SAS, Cary, North Carolina).

Results

Study sample

The final sample included intervention study participants who had at least 5 weeks of activity tracker steps above 1000, the minimum that coauthors deemed necessary to indicate that the participant was wearing the activity tracker most of that week. These criteria resulted in the exclusion **Table 1** Study participants (N = 283)

Variables	Full sample $N = 283$	Tracker steps below the mean (low) N = 156 (55%)	Tracker steps above the mean (high) N = 127 (45%)	<i>p</i> value	
Activity tracker steps during chemotherapy					
Activity tracker steps during chemotherapy—per week	29,625 (SD 18,118) (range 2107–97,920)	16,361 (SD 7451.7) (range 2107–29,652)	45,917 (SD 13,454) (range 29,934–97,920)	<0.0001	
Demographics at baseline (pre- chemotherapy)					
Age, mean (SD)	56.5 years (SD 12.2) (range 24–83)	58.9 years (SD 12.8) (range 24–82)	53.5 years (SD 10.8) (range 31–83)	<0.0001	
Race					
White	214 (76%)	107 (69%)	107 (84%)	0.0005	
Black	52 (18%)	41 (26%)	11 (9%)		
Other	17 (6%)	8 (5%)	9 (7%)		
Education					
High school or less	35 (13%)	30 (20%)	5 (4%)	0.0002	
More than high school	227 (87%)	119 (80%)	108 (96%)		
Employed more than 32 h/week					
No	165 (64%)	104 (70%)	61 (55%)	0.02	
Yes	93 (36%)	44 (30%)	49 (45%)		
Married	× ,				
No	127 (45%)	78 (50%)	49 (39%)	0.07	
Yes	153 (55%)	77 (50%)	76 (61%)		
Living alone					
No	201 (79%)	111 (76%)	90 (83%)	0.16	
Yes	53 (21%)	35 (24%)	18 (17%)		
Breast cancer diagnosis					
Breast cancer stage					
1	89 (31%)	47 (30%)	42 (33%)	0.64	
2	131 (46%)	71 (46%)	60 (47%)		
3	63 (22%)	38 (24%)	25 (20%)		
Phenotype	× ,				
HR–/HER2–	70 (25%)	51 (33%)	19 (15%)	0.0002	
HR-/HER2+	34 (12%)	24 (16%)	10 (8%)		
HR+/HER2-	125 (44%)	56 (36%)	69 (54%)		
HR+/HER2+	53 (19%)	24 (16%)	29 (23%)		
Breast cancer treatment					
Chemotherapy drug—taxane					
None	5 (2%)	2 (1%)	3 (2%)		
Paclitaxel/nab-paclitaxel	137 (49%)	75 (49%)	62 (49%)	0.93	
Docetaxel	135 (48%)	75 (49%)	60 (47%)		
Both	4 (1%)	2 (1%)	2 (2%)		
Chemotherapy regimen					
Doxorubicin/cyclophos- phamide before/after pacli- taxel (AC-T or T-AC)	81 (29%)	42 (27%)	39 (31%)	0.31	
Doxorubicin/cyclo- phosphamide before/after paclitaxel/carboplatin (AC-TC or TC-AC)	20 (7%)	14 (9%)	6 (5%)		
Docetaxel/cyclophospha- mide (± anti-HER2) (TC)	79 (28%)	39 (25%)	40 (32%)		

Table 1 (continued)

Variables	Full sample $N = 283$	Tracker steps below the mean (low) N = 156 (55%)	Tracker steps above the mean (high) N = 127 (45%)	p value	
Docetaxel/carboplatin/anti- HER2 (TCH)	50 (18%)	32 (21%)	18 (14%)		
Other	51 (18%)	27 (18%)	24 (19%)		
General health at baseline					
Self-reported walking minutes/ week pre-chemotherapy	139 (SD 165.25) (range 0–1285)	95.0 (SD 96.7) (range 0-600)	198.2 (SD 212.9) (range 0–1285)	<0.0001	
Self-reported vigorous exercise pre-chemotherapy					
Never, few times/month	122 (48.4)	88 (62%)	34 (31%)	<0.0001	
1 or more times a week	130 (52%)	53 (38%)	77 (69%)		
Body mass index/BMI, mean (SD), range (kg/m ²)	30 (SD 6.8) (range 16.8–64.9)	31 (SD 7.2) (range 17–65)	27 (SD 5.7) (range 26–43)	<0.0001	
Number of comorbidities, mean (SD), range	0.99 (SD 1.2) (range 0-6)	1.3 (SD 1.2) (range 0–5)	0.6 (SD .97) (range 0–6)	<0.0001	
Assessments at baseline					
Timed Up and Go (TUG)					
12 s or less	178 (93%)	103 (90%)	75 (96%)	0.16	
Greater than 12 s	14 (7%)	11 (10%)	3 (4%)		
Short Physical Performance Battery (SPPB), mean (SD); range 0 = worst to 12 = best performance	10.6 (SD 1.8) (range 3–12)	10.1 (SD 2.0) (range 3-12)	11.3 (SD 1.2) (range 6–12)	<0.0001	
Questionnaires at baseline					
Mental Health Index (MHI), range $0-43$ (depressed score > = 12)					
Not depressed	187 (76%)	98 (70%)	89 (85%)	0.006	
Depressed	59 (24%)	43 (30%)	16 (15%)		
Mental Health Index (MHI) range 0–20 (anxious score > = 6)					
Not anxious	147 (58%)	75 (53%)	72 (65%)	0.06	
Anxious	106 (42%)	67 (47%)	39 (35%)		
Instrumental Activities of Daily Living (IADL)					
<14 = limitations	58 (21%)	33 (22%)	25 (20%)	0.88	
14 = no limitations	222 (79%)	122 (79%)	100 (80%)		
Functional Assessment of Can- cer Therapy (FACT)-General (higher score = higher wellbe- ing)—mean					
Physical wellbeing (range 0–28)	24.8 (SD 3.7) (range 8–28)	24.3 (SD 4.0) (range 8–28)	25.5 (SD 3.3) (range 9–28)	0.008	
Social/family wellbeing (range 0–28)	24.7 (SD 4.6) (range 2–28)	24.4 (SD 5.0) (range 2–28)	25.0 (SD 4.2) (range 6–28)	0.30	
Emotional wellbeing (range 0–24)	19.2 (SD 3.6) (range 1–24)	19.3 (SD 3.8) (range 1–24)	19.2 (SD 3.4) (range 4–24)	0.53	
Functional wellbeing (range 0–28)	20.9 (SD 5.6) (range 0-28)	20.3 (SD 5.9) (range 0–28)	21.7 (SD 5.1) (range 6–28)	0.08	

Table 1 (continued)

severe (MSVS); mean

Patient-reported symptoms

during chemotherapy—rated moderate, severe, or very severe (MSVS); mean

Variables	Full sample $N = 283$	Tracker steps below the mean (low) N = 156 (55%)	Tracker steps above the mean (high) N = 127 (45%)	<i>p</i> value				
Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Subscale (reverse scored so that higher score = less fatigue) (range 0–52)—higher score = less fatigue	43.2 (SD 8.7) (range 5–52)	41.5 (SD 9.5) (range 5–52)	45.2 (SD 7.1) (range 18–52)					
Patient-reported symptoms prior to chemotherapy—rated moderate, severe, or very	1.5 (SD 2.1) (range 0-11)	1.6 (2.2) (range 0–11)	1.5 (SD 2.0) (range 0–11)	0.80				

6.7 (SD 4.0) (range 0–17)

Bold print denotes statistical significance

of 66 participants (19% of 349 enrolled in the three studies). The excluded group is slightly older and has a higher proportion of Black patients, but otherwise, there were no significant differences between the included and excluded groups with regard to chemotherapy regimens (Appendix 3).

6.1 (SD 3.9) (range 0-17)

Activity tracker steps during chemotherapy

Only 20% achieved the goal of 44,000 steps/week and was considered too small a sample for dichotomization at that cut point. Average tracker steps for the full sample were 29,625 steps/week, with 55% below this mean (low step) and 45% above (high step) (Table 1). The resulting dichotomized variable-high step vs low step-is the primary measure of PA for all subsequent analyses. Low step participants had weekly steps ranging from 2107 to 29,652 and high step from 29,934 to 97,920 (*p* < 0.0001).

Sample characteristics

Table 1 presents a descriptive overview of the final sample of 283 patients. The mean age at study enrollment was 56 years (range 24-83), 18% were Black and 6% other than White or Black, 87% had more than a high school education, 64% were employed less than 32 h/week, and 79% were not living alone. Low step participants were on average older, Black, high school education or less, and employed less than 32 h/week.

Low step participants included a higher proportion with hormone receptor-negative tumors (p = 0.0002). There were no significant differences in chemotherapy regimens between the two groups (p = 0.31). For the entire sample, chemotherapy regimens were 29% doxorubicin/cyclophosphamide before/after paclitaxel (AC-T or T-AC), 7% doxorubicin/ cyclophosphamide before/after paclitaxel/carboplatin (AC-TC or TC-AC), 28% docetaxel/cyclophosphamide (± anti-HER2) (TC), 18% docetaxel/carboplatin/anti-HER2 (TCH), and 18% other.

5.4 (SD 3.7) (range 0-15)

0.002

Low step participants had baseline (pre-chemotherapy) fewer self-reported walking minutes/week, were less likely to have engaged in vigorous exercise, had higher body mass index/BMI, and had higher number of comorbidities. Low step participants included a higher proportion rated depressed and scoring slightly worse on the SPPB test, FACT-G physical wellbeing, and FACIT-Fatigue.

At baseline (pre-chemotherapy), the average number of symptoms rated moderate, severe, or very severe (MSVS) was 1.5 (range 0-11) with no significant difference between high and low step groups. During chemotherapy, low step participants averaged 6.7 MSVS symptoms (range 0-17) compared to 5.4 symptoms (range 0-15) for high step participants (p < 0.0001). In Fig. 1, the percentage reporting MSVS severity is shown for 17 symptoms pre-chemotherapy as compared to during chemotherapy for the full sample.

Regimen modifications and associations with activity tracker steps

One or more dose delays during chemotherapy infusion were experienced by 16% of study subjects (N = 44), 35% had at least one dose reduction (N = 98), 12% had early treatment discontinuation (N = 34), and 14% were hospitalized (N =38) during their chemotherapy (Appendix 4). In multivariable (MV) analysis adjusted for race, age, and education (significant in univariate analysis of associations with tracker steps), high step participants had 36% lower risk for dose



Fig. 1 Patient-reported symptoms-moderate, severe, or very severe (%)

reduction [RR 0.64 (95% CI 0.43, 0.97)] (p = 0.03). There were no other significant differences between high and low step participants for dose delay (p = 0.64), early treatment discontinuation (p = 0.54), or hospitalization (p = 0.94).

Primary reasons for regimen modifications, as recorded in clinician notes, are listed in Appendix 4. Neuropathy is noted for 17% of dose delays, 36% of dose reductions, and 27% of early treatment discontinuations. Fatigue is the cited reason for 6% of dose reductions and 9% of early treatment discontinuations. Nausea and/or vomiting accounted for 5% of dose reductions. Otherwise, reasons listed by clinicians pertained primarily to hematological and other clinical factors such as neutropenia, anemia, thrombocytopenia, neutropenic fever, and port complications.

Symptom severity and associations with activity tracker steps

In Table 2, we present univariate associations between activity tracker steps and risk for moderate, severe, or very severe scores (as compared to none or mild) for 11 symptoms with the highest proportion rated MSVS (see Fig. 1) and mean number of toxicities ≥ 6 rated MSVS. The associations are presented as relative risk (RR with 95% confidence interval) for participants with high steps (low steps is the referent). In univariate analysis, high steps were associated with lower risk for MSVS fatigue, anxiety, nausea, peripheral neuropathy, depression, and ≥ 6 of symptoms. In MV analysis, all associations between high steps and toxicities remained significant, except peripheral neuropathy: fatigue [RR 0.83 (0.70, 0.99)] (p = 0.04), anxiety [RR 0.59 (0.42, 0.84)] (p = 0.003), nausea [RR 0.66 (0.46, 0.96)] (p = 0.03), depression [RR 0.59 (0.37, 0.03)] (p = 0.02), and ≥ 6 MSVS symptoms [RR 0.73 (0.54, 1.00)] (p = 0.05).

Cumulative symptom incidence by tracker steps category

Figure 2 presents cumulative incidence curves for MSVS severity for four symptoms over 150 days (presented in 30-day increments), comparing study subjects who walked above average (high step) with those who walked below average (low step). In MV analysis adjusted for race, age, and education, high step participants had significantly lower fatigue (p = 0.006), anxiety (p = 0.008), depression (p = 0.04), and nausea (not shown in Fig. 2, p = 0.023). There was no significant difference in MSVS CIPN (p = 0.08).

In univariate analysis (Table 1), high step subjects had significantly lower FACIT-F Fatigue score, indicating less fatigue at baseline, and lower frequency of MHI depression.

Table 2	Univariate associa	tions of "hig	gh step" w	valking wi	th individual	symptoms rate	d moderate	, severe,	or very	severe ((MSVS)) during	chemo
therapy-	-relative risk (RR)) with 95% c	confidence	e interval									

Chemotherapy	Fatigue	Insomnia	Arthralgia	Anxiety	Constipation	Myalgia
All participants	0.85 (0.73, 0.98)*	0.89 (0.73, 1.08)	0.76 (0.56, 1.03)	0.64 (0.47, 0.87)**	0.75 (0.53, 1.04)	0.76 (0.56, 1.03)
Taxane						
Paclitaxel/nab- paclitaxel	0.92 (0.78, 1.09)	0.89 (0.68, 1.16)	0.82 (0.56, 1.20)	0.76 (0.50, 1.15) 0.46 (0.28,	0.92 (0.62, 1.36) 0.50 (0.26,	0.82 (0.56, 1.20) 0.65 (0.38, 1.09)
Docetaxel	0.71 (0.54, 0.94)*	0.80 (0.59, 1.09)	0.58 (0.34, 1.00)*	0.77)**	0.96)*	
Chemotherapy	Pain (general)	Nausea	Hot flashes	Peripheral neuropa- thy	Depression	Mean number of toxicities ≥ 6 rated MSVS
All participants	1.09 (0.83, 1.44)	0.71 (0.51, 0.99)*	1.16 (0.86, 1.57)	0.65 (0.47, 0.91)*	0.65 (0.44, 00.95)*	0.67 (0.51, 0.88)**
Taxane						
Paclitaxel/nab- paclitaxel	0.97 (0.67, 1.40)	0.78 (0.53, 1.16)	0.98 (0.66, 1.46)	0.71 (0.48, 1.05) 0.52 (0.27,	0.81 (0.49, 1.32) 0.47 (0.22,	0.67 (0.48, 0.93)*
Docetaxel	1.25 (0.82, 1.91)	0.53 (0.29, 0.98)*	1.31 (0.80, 2.14)	1.00)*	0.85)*	0.55 (0.33, 0.91)*

Bold print denotes statistical significance. $p \le 0.05$, $p \le 0.05$, $p \le 0.001$ —indicated in bold type

Referent is "low step" walking

Paclitaxel/nab-paclitaxel regimens generally included anthracycline

To reduce the effect of baseline symptoms on cumulative incidence, we ran hazard models for MSVS fatigue and depression *excluding* patients who reported MSVS fatigue or depression at baseline, respectively, as a sensitivity analysis. In these revised models (Fig. 3), high step participants continued to have significantly lower fatigue (p = 0.02) and lower depression (0.03).

Discussion

The objective of this study was to explore associations of self-directed walking with relative risk for regimen modifications and the occurrence of moderate, severe, or very severe (MSVS) symptom severity during commonly used chemotherapy regimens with differing toxicity profiles [17, 22]. All study participants were encouraged to walk at least 150 min/week, which equals about 44,000 steps per week [25]. Actual tracker steps achieved by our study participants were far below this goal, confirming previous observations that PA during chemotherapy for early breast cancer can be very challenging [25, 42]. But our data offered a wide range of engagement in walking, thereby allowing for meaningful two-group comparisons between participants who walked above (high step) versus below the mean (low step) of approximately 30,000 steps/week.

We observed demographic, exercise history, BMI, comorbidity, and baseline fatigue differences between the two walking groups, reflecting factors associated with higher versus lower levels of walking steps during chemotherapy for early breast cancer that we have reported in previously analyses [25]. Other studies have similarly noted lower exercise compliance among patients with obesity as compared to those with no obesity [43]. Importantly, in the current study, there were no significant intergroup differences in proportions receiving the four most common chemotherapy regimens, thereby eliminating potentially crucial confounders to our comparison of high vs low step walkers under differing treatment scenarios.

In our analysis of associations between tracker steps and regimen modifications during chemotherapy, a significant association was observed only for dose reductions, where there was a 36% lower risk among high step participants. Among the reasons listed in clinician notes for regimen changes, the most commonly noted reasons were hematological and other clinical toxicities, which are not likely to be modifiable through moderate PA. Prior studies have shown that peripheral neuropathy may be modifiable through PA at the start of chemotherapy [44, 45], but we did not observe this benefit in our sample. It is possible that higher intensity PA is required. There is growing evidence that PA is effective in managing fatigue during chemotherapy [10, 23, 24, 46], and our study provides further corroboration of this benefit. In multivariable analysis adjusted for age, race, and education, high step patients also had lower risk for anxiety, nausea, depression, and experiencing ≥ 6 MSVS symptoms.

The cumulative incidence plots shed some light on causality. Study subjects were mostly at the same severity level for all symptoms at week 0, with the exception of fatigue and depression. When we limited our analysis to participants who were not already reporting high levels of fatigue and depression prior to chemotherapy, we continued to observe significant benefits from walking in high versus low step participants. With roughly the same levels of fatigue at week



Fig. 2 Cumulative incidence curves (p value adjusted for race, age, and education)

0, high step walkers had significantly lower fatigue over the duration of their chemotherapy and similarly significantly less depression.

Our study has some limitations. Adherence to PA interventions during chemotherapy treatment can be challenging [25, 47] and most patients in our sample did not achieve the goal of 150 min/week of walking. This deserves further exploration through a more supervised exercise intervention to help improve adherence rates. Further, the generalizability of our findings is limited to the extent our study subjects agreed to participate in a PA intervention study and include a high proportion of women with more than a high school education, both of which are not necessarily representative of the general population of women with early breast cancer. A randomized controlled trial design of our home-based,

self-directed walking intervention may produce contradictory results or further strengthen our findings.

The strengths of our study include objective activity tracker data to measure PA and prospective patient-generated symptom reports throughout chemotherapy for a wide range of symptoms. We know only of the van Waart study that assesses PA impact on as many symptoms during chemotherapy [21]. Our dichotomization of walking steps as above-vs-below the mean—rather than adherence-vsnon-adherence to walking step targets—provided a valid and productive method for evaluating the impact of selfdirected walking on regimen modifications and treatment toxicities. And our prospective data on symptom severity over 150 days—showing a common starting point—provides insights into the causality, albeit not conclusive.



Fig. 3 Cumulative incidence curves of subjects who did not report moderate, severe, or very severe fatigue or depression prior to chemotherapy initiation (*p* values adjusted for race, age, and education)

Our findings suggest that self-directed walking may moderate the severity of common side effects of chemotherapy and contribute to the literature documenting to the benefits of exercise for women diagnosed with early breast cancer [48]. Regardless of symptom severity at week 0, many patients can experience the benefits of symptom modification even when they do not achieve guideline-recommended levels of activity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-023-08275-4.

Author contribution Kirsten A. Nyrop, Annie Page, Allison M. Deal, and Hyman B. Muss: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, and writing—review and editing. Chad Wagoner, Erin EA Kelly, Gretchen G. Kimmick, Anureet Copeland, JoEllen C. Speca, and William A Wood: writing—review and editing. All authors reviewed the manuscript.

Funding Breast Cancer Research Foundation (New York NY); Kay Yow Foundation (Raleigh NC); UNC Lineberger Comprehensive Cancer Center/University Cancer Research Fund (Chapel Hill NC).

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Boards of the University of North Carolina at Chapel Hill and Duke University.

Competing interests The authors declare no competing interests.

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