J Cancer Surviv (2007) 1:116–128
DOI 10.1007/s11764-007-0014-1

Physical activity, long-term symptoms, and physical health-related quality of life among breast cancer survivors: A prospective analysis

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Published online: 5 April 2007

Abstract
Introduction Many breast cancer survivors experience persistent physical symptoms of cancer and treatment that can decrease health-related quality of life (HRQOL). This prospective study investigated physical activity (PA), occurrence of physical symptoms, and HRQOL in a large, ethnically-diverse cohort of breast cancer survivors.
Materials and methods Survivors (n=545), on average 6 months post-diagnosis, were assessed in person or by mail at baseline (retrospective reports of pre-diagnosis PA), at 29 months post-diagnosis (post-diagnosis PA), and at 39 months post-diagnosis (pain, hormone symptoms, sexual interest/dysfunction, fatigue, physical subscales of HRQOL). Linear regression and analysis of covariance assessed the relationships between pre- and post-diagnosis PA and PA change after cancer with symptoms and HRQOL.
Results Greater pre-diagnosis PA was associated with better physical functioning at 39 months (βs 1.1–2.3; all $p<0.01$) but was generally unrelated to symptoms. Greater post-diagnosis sports/recreational PA was related to less fatigue and better physical functioning (βs −0.146, 2.21; both $p<0.01$). Increased PA after cancer was related to less fatigue and pain and better physical functioning (all $p<0.01$). Significant positive associations were found for moderate to vigorous and vigorous sports/recreation PA, not household activity. Results were similar for Hispanic and non-Hispanic White women.
Discussion/conclusions Increased PA, especially after cancer, was consistently related to better physical functioning and

This research was supported by contracts from the National Cancer Institute (N01-CN-75036-20, N01-CN-05228, N01-PC-67010). Part of Dr. Alfano's effort was conducted at the Fred Hutchinson Cancer Research Center, funded by a training grant from the National Cancer Institute (CA92408). Some material presented in this manuscript was presented at the 2004 meeting of the Society of Behavioral Medicine.

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to reduced fatigue and bodily pain, underscoring the need for PA promotion among survivors.

Implications for cancer survivors Survivors may be able to decrease fatigue and bodily pain and be better able to pursue daily activities through increasing recreational PA after cancer.

Keywords Physical activity · Breast cancer · Survivors · Long-term effects · Quality of life

Introduction

The National Cancer Institute estimates that there are at least 2.3 million female breast cancer survivors in the United States, and this number will continue to grow [37]. Evidence is accumulating that the multifaceted sequelae of breast cancer do not cease with the conclusion of treatment. Two recent reports make clear that the period after completion of active treatment brings its own set of unique, and in some cases, still poorly understood challenges [22, 36]. Many breast cancer survivors experience persistent physical symptoms of cancer and treatment including fatigue [5, 9, 28], pain or sensations in the arm or breast [16], hormone-related symptoms [10, 19, 20], and sexual dysfunction [19, 26].

The prevalence of these long-term physical symptoms is not trivial. Fatigue may continue to be problematic 5–7 years into survivorship for as many as a third of breast cancer survivors [9]. Post-surgery pain and troublesome physical sensations (e.g., numbness, pins and needles) in the arm or breast or chest wall have been shown to be problematic for a third of long-term survivors of breast cancer [26]. Hormone-related symptoms including vasomotor symptoms (hot flashes, sweats, palpitations), urinary incontinence, vaginal dryness, and cognitive and mood changes are common in breast cancer survivors [10] and occur at higher rates than in age-matched healthy peers [20]. Approximately 20–30% of breast cancer survivors experience sexual problems including general sexual disruption, decreased frequency of intercourse, and difficulties reaching orgasm that may persist 20 years post-treatment [26].

These physical symptoms can inhibit psychosocial adaptation, disrupt the ability to perform normal life roles, and decrease health-related quality of life (HRQOL) for years after the conclusion of primary treatment [10, 31, 38]. Persistent physical symptoms can also serve as a continuous reminder of cancer and result in significant psychological morbidity including anxiety, depression, problematic levels of fear of recurrence [15, 23, 31], and symptoms of post-traumatic stress disorder as much as 20 years after treatment [26].

Physical activity is one factor that may modify risk of these problematic long-term physical symptoms. Physical activity among healthy people has been linked to improvements in many of the same physical and psychological symptoms that are problematic among cancer survivors [7, 44]. Further, according to the " buffering model," physical activity before diagnosis can "build up" a patient's physical status to begin cancer treatment in the best possible condition which should minimize problematic symptoms [14]. Despite this, the pre-diagnosis level of physical activity as a prognostic factor for subsequent levels of symptoms or physical aspects of HRQOL during or after treatment has received little research attention [14].

Further support for a protective role of physical activity comes from the growing number of intervention studies investigating the effect of physical activity during and after cancer treatment on symptoms and physical aspects of HRQOL. Several recent reviews on the impact of physical activity interventions in cancer survivors both on- and off-treatment show that physical activity can have positive effects on physical symptoms such as fatigue, pain, cognition, and sleep, on fitness measures, body composition, and biological changes such as immune functioning, and on psychosocial measures including depression, anxiety, self-esteem, and multiple aspects of QOL, including HRQOL [24, 29, 30, 32, 34, 42, 43].

Finally, it may be that the overall pattern of physical activity maintenance or change over the course of cancer treatment is related to subsequent symptoms and HRQOL. In one study of survivors of several common cancers (breast, colorectal, lung, prostate, non-Hodgkin's lymphoma) on average 2.2 years post-diagnosis, consistency of maintaining physical activity levels after cancer treatment was a more important predictor of QOL than the absolute amount of activity [6]. There is some evidence that breast cancer survivors who were active before diagnosis and then failed to resume exercise are at elevated risk for poor QOL after treatment compared to those who maintained or increased their activity levels [12]. This finding has also been seen in colorectal cancer survivors [13]. Increasing activity in the years after diagnosis has been related to greater physical HRQOL in long-term breast cancer survivors [25]. However, it is not known whether activity patterns are similarly related to persistent physical symptoms.

The relative protective effects of pre- or post-diagnosis physical activity or of physical activity change on persistent physical symptoms and physical aspects of HRQOL remain unknown. Also unknown are the most beneficial type and amount of activity [4]. The objectives of this paper were to investigate whether physical activity amount and type in the year prior to diagnosis, within 2 years after diagnosis, and change in activity level during that time were associated with symptoms of pain and physical sensations, hormone-related symptoms, sexual interest/dysfunction, and fatigue in a large, ethnically diverse cohort of breast cancer survivors. The impact on

physical aspects of HRQOL was also investigated. It was hypothesized that higher pre-diagnosis activity, higher post-diagnosis activity, and maintenance or improvement of activity levels after diagnosis would be associated with fewer physical symptoms and higher levels of physical HRQOL. We also investigated whether all of these relationships were different for non-Hispanic White vs. Hispanic women.

Materials and methods

Study overview

Participants in this study are women enrolled in the Health, Eating, Activity, and Lifestyle (HEAL) Study, a multicenter, multiethnic, prospective study of women diagnosed with in situ or Stages I to IIIA breast cancer. HEAL study participants are being followed to determine the impact of weight, physical activity, diet, hormones, and other exposures on breast cancer prognosis. Written or documented verbal informed consent was obtained from each participant for participation in the original HEAL study and at each subsequent assessment. All study protocols were approved by the Institutional Review Boards of each participating center.

Eligibility and recruitment

Eligibility, recruitment, and retention of HEAL participants are described in detail elsewhere [8]. Briefly, 1,183 patients diagnosed with their first primary breast cancer were recruited from National Cancer Institute sponsored Surveillance Epidemiology and End Results (SEER) registries in three geographic regions of the United States; New Mexico (n=615), Western Washington (n=202), and Los Angeles County, California (n=366). Of those women who completed the baseline survey, 944 (80%) participated in the second assessment and 858 (73%) participated in the QOL follow-up. For analyses of QOL outcomes, we excluded 53 women diagnosed with recurrent breast cancer or a new primary breast cancer by the date of these analyses. This defined a QOL cohort of 805 women. For the analyses presented here, we required that participants have pre-diagnosis and post-diagnosis physical activity data using the Kriska questionnaire [27, 33], which excluded all participants (n=198) from the Los Angeles County site, where pre-diagnosis physical activity data were collected by another method that excluded household activity, and six women from the other two sites. We also required women to have complete data for the symptom and HRQOL variables and the covariates used in the analyses, which excluded an additional 56 participants. The final sample size for the current analysis was 545 women.

Data collection

Data for the current study derive from three data collection points; the baseline interview (on average 6 months following diagnosis), a second assessment called the 24-month assessment (on average 29 months after diagnosis), and a third assessment consisting of the QOL survey (on average 39 months after diagnosis). The average number of months since diagnosis at each data collection point differs by approximately 1 month from previous HEAL papers due to the inclusion of two out of the three study sites. The baseline and 24-month assessments were conducted via in-person interview or self-completed questionnaire at both sites and included information on demographic and clinical variables, as well as physical activity. The QOL survey assessed cancer-related symptoms and HRQOL and was administered by a combination of telephone interview and mailed questionnaire in both sites.

Measures

Independent variables

Both pre-diagnosis and post-diagnosis physical activity were collected using a questionnaire based on the Modifiable Activity Questionnaire developed by Kriska et al., which has been shown to be reliable and valid [27, 33]. The questionnaire administered at the baseline survey assessed the type, duration, and frequency of activities for the year prior to breast cancer diagnosis (retrospective reports of pre-diagnosis physical activity). The questionnaire administered at the 24-month assessment assessed similar information for the year prior to the interview (henceforth referred to as post-diagnosis activity). Data from the two timepoints were coded identically: Hours per week spent in each activity were estimated by multiplying the frequency by the duration reported. Each activity was converted to MET-hours based on the Compendium of Physical Activities [1]. Given the focus of this paper on type and amount of activity, physical activity data for each time point were coded into four variables for analysis. Two variables represented different activity intensities: (A) MET-hours/week of moderate to vigorous activity combined and (B) MET-hours/week of vigorous activity only; whereas, two variables represented mutually exclusive types of activities: (C) MET-hours/week of household/gardening activity and (D) MET-hours/week of sports/recreation activity. Analyses were also run for total MET-hours of activity (of any intensity); however, results were similar to moderate to vigorous activity and thus results are not included in this manuscript.

Dependent variables

Pain and physical sensations We used 14 items from a previous study of breast cancer survivors [40] assessing the frequency of pain and physical sensations (e.g., numbness, tenderness, pins and needles) during the last 3 months in the chest wall or breast (seven items) and in the arms (seven items). Factor analysis revealed the chest wall/breast and arm questions grouped into two separate scales with adequate internal consistency for each (Cronbach's alphas=0.81 and 0.88, respectively). For each body area, a mean score was calculated, ranging from 0 (never) to 4 (very often).

Hormone-related symptoms checklist We used a modified form of the Breast Cancer Prevention Trial hormone-related symptom checklist [17] to assess the severity of 16 symptoms. Responses ranged from 0 (not at all) to 4 (extremely). Previous psychometric work with this response scale using the HEAL cohort indicated five separate scales for vasomotor symptoms, urinary incontinence, cognitive/mood symptoms, vaginal symptoms, and weight gain/appearance concerns (Cronbach's alphas range from 0.60 to 0.88) [2].

Sexual interest/dysfunction We used the sexual summary scale from the Cancer Rehabilitation Evaluation System (CARES) [41], which includes the sexual interest and dysfunction subscales. The mean score is coded 0–3 where higher scores represent a more serious sexual problem. This scale was only computed for women who reported being sexually active in the last 6 months.

Fatigue We used the revised Piper Fatigue Scale which has been shown to be a reliable and valid measure of subjective fatigue [35]. The 22 items were coded into four scales (each coded 0–10) measuring the multidimensional aspects of fatigue: the observable behavioral changes in activities of daily living resulting from fatigue (behavioral/severity subscale), the emotional meaning attributed to fatigue (affective meaning subscale), the physical symptoms of fatigue (sensory subscale), and the mental and emotional symptoms related to fatigue (cognitive/mood subscale). We changed the response time frame to assess fatigue over the past month rather than the past week to minimize the effect of acute situational events and to enhance our assessment of the survivor's general state of fatigue. The scale's four factor structure was confirmed in the HEAL cohort (Cronbach's alphas for the subscales ranged from 0.92 to 0.97).

Physical health-related quality of life We used the Medical Outcomes Study short form 36 (SF-36) to assess the physical aspects of HRQOL [21, 45]. The SF-36 includes 36 items, scored into eight subscales. A companion paper investigates the relationships between physical activity and psychosocial

Table 1 Demographic and clinical characteristics of HEAL participants with pre- and post-diagnosis physical activity data (*N*=545)

Characteristic	N	%	Mean±SD
Baseline characteristics			
Location			
New Mexico	383	70.3	
Western Washington	162	29.7	
Age (year)			
29–49	114	20.9	
50–59	213	39.1	
60–69	143	26.2	
70+	75	13.8	
			58.0±10.3
Education			
HS or less	113	20.7	
Some college	188	34.5	
College grad	123	22.6	
Grad school	121	22.2	
Race/ethnicity			
Non-Hispanic White	439	80.6	
Black	1	0.18	
Hispanic	82	15.1	
Other	23	4.22	
Stage at diagnosis			
in situ	128	23.5	
Local	321	58.9	
Regional	96	17.6	
Treatment type			
Surgery only	158	29.0	
Surgery/Radiation	233	42.8	
Surgery/Chemotherapy	38	7.0	
Surgery/Radiation/Chemotherapy	116	21.3	
Time since diagnosis			
Diagnosis to baseline (Measurement of pre-diagnosis physical activity)	545		6.15±1.84
Diagnosis to follow-up (Measurement of post-diagnosis physical activity)	545		29.35±2.73
Diagnosis to QOL questionnaire	545		39.47±6.31
24-Month Assessment Characteristics			
Menopausal status			
Pre	105	19.3	
Post	410	75.2	
Unclassifiable	30	5.50	
Tamoxifen			
Use between baseline and 24 months	251	46.1	
Use at or before baseline only	263	48.3	
No use during study period	247	45.3	
Cigarette smoking			
Current	61	11.2	
Past	220	40.4	
Never	264	48.4	
Comorbidity Index (Number conditions that limit activity)			
0	420	77.1	
1	90	16.5	
2+	35	6.42	
Body Mass Index	545		26.4±5.51
Pre-diagnosis physical activity			
Moderate to vigorous activity (met hours/week)	545		30.2±29.4
Vigorous activity (met hours/week)	545		5.20±12.3
Household activity (met hours/week)	545		39.7±36.7
Sport/recreational activity (met hours/week)	545		15.4±20.5

Table 1 (continued)

Characteristic	N	%	Mean±SD
Post-diagnosis physical activity			
Moderate to vigorous activity (met hours/week)	545		29.2±27.0
Vigorous activity (met hours/week)	545		4.51±11.7
Household activity (met hours/week)	545		47.9±38.4
Sport/recreational activity (met hours/week)	545		14.6±20.3
Physical activity change pre-post diagnosis			
Moderate to vigorous activity			
Decreased by >25%	190	35	
Maintained within +/−25%	143	26	
Increased by >25%	212	39	
Vigorous activity			
Decreased by >10%	321	59	
Maintained within +/−10%	90	16	
Increased by >10%	134	25	
Household activity			
Decreased by ≥1%	190	35	
Increased 0–100%	202	37	
Increased by >100%	153	28	
Sport/recreation activity			
Decreased by >25%	197	36	
Maintained within +/−25%	146	27	
Increased by >25%	202	37	

aspects of HRQOL in this cohort Smith et al. (unpublished data). Given the focus of the current analysis on physical symptoms and physical aspects of HRQOL, we used the four SF-36 physical health subscales: Physical Functioning, Role-Physical, Bodily Pain, and General Health. The SF-36 subscales ranged from 0–100 with increasing scores indicating better functioning, per standard coding protocol. Considerable psychometric analyses have been published on the SF-36, and our own analyses indicate high internal consistency among items in the subscales (Cronbach's alphas range from 0.78–0.91).

Covariates

Demographics included standard measures of age, education, and race/ethnicity (Black, non-Hispanic White, and Hispanic) collected at baseline. Stage of disease was based on SEER registry records. Breast cancer treatment data were obtained from medical record abstraction and SEER data and were coded as: surgery only; surgery with chemotherapy; surgery with radiation, or the combination of all three treatments. Use of tamoxifen was obtained from medical record abstraction and self-reported use at the baseline and 24-month assessments and coded as: use between baseline and 24-months, use at or before baseline only, and no use during the study period. Menopausal status was determined at the 24-month assessment using an algorithm (see [2]) that assigned women into pre, post, or unclassifiable menopausal status based on age, date of last menstruation, and hysterectomy and oophorectomy status. Smoking status (never, former, current) was assessed at the 24-month interview/assessment. Body mass index was calculated as weight in kilograms divided by height in meters squared, computed from clinic measures at baseline (height) and 24-months (weight). Comorbid medical conditions were assessed at the 24-month interview by asking participants to report which of 18 medical conditions plus other cancers had ever been diagnosed by a physician, and whether their current activities were limited by any of these conditions. A comorbidity summary score was generated based on the number of medical conditions that limited current activities, categorized as 0, 1, or ≥2 conditions.

Overview of analysis

We generated descriptive statistics to depict the demographic and clinical characteristics of the participants as well as the five categories of symptom and physical HRQOL outcome variables. The first research question tested whether the four pre-diagnosis physical activity variables were related to

Table 2 Symptoms and physical health-related quality of life outcomes reported by 545 breast cancer survivors

Outcome	N	Mean (SD)
Pain and physical sensations (Scored 0–4) [a]		
Arm pain	545	0.78 (0.84)
Breast pain	545	1.00 (0.81)
Hormone-related symptoms (Scored 0–4) [a]		
Vasomotor	545	1.65 (1.09)
Urinary incontinence	545	0.98 (1.04)
Cognitive/mood	545	1.12 (0.82)
Vaginal symptoms	545	0.56 (0.74)
Weight/appearance	545	1.54 (1.16)
Sexual interest/dysfunction (Scored 0–3) [a]	298[b]	0.94 (0.79)
Fatigue (Piper Fatigue Scale Subscales) (Scored 0–10) [a]		
Behavioral/severity	545	4.02 (2.31)
Affective meaning	545	5.41 (2.04)
Sensory	545	4.23 (2.26)
Cognitive/mood	545	3.85 (1.95)
Physical health-related QOL (SF-36 physical subscales) (Scored 0–100) [a]		
Physical functioning	545	77.2 (23.8)
Role-physical	545	65.5 (38.8)
Bodily pain	545	71.4 (24.0)
General health	545	71.2 (20.8)

[a] All scales were coded with increasing scores indicating more severe problems except for the SF-36 scales, where increasing scores indicate better functioning.

[b] Sexual function questions were only asked of those participants who reported being sexually active in the past 6 months.

subsequent symptom and physical HRQOL outcomes measured at approximately 39 months post-diagnosis. Separate linear regression models were run with each pre-diagnosis physical activity variable as the independent variable and each symptom/physical HRQOL variable evaluated as a dependent variable, adjusting for the set of covariates described above. Each model also tested an ethnicity by physical activity interaction term to test whether each relationship between physical activity and the symptom/physical HRQOL outcome differed for Hispanic vs. non-Hispanic White women.

The second research question evaluated whether post-diagnosis physical activity was related to subsequent symptom/physical HRQOL outcomes. The analytic strategy was identical to the pre-diagnosis activity analyses but all models also adjusted for the level of pre-diagnosis activity.

The third research question evaluated whether the change in each physical activity variable from pre- to post-diagnosis was related to subsequent symptom/physical HRQOL outcomes. Physical activity change variables were constructed as decreased activity by >25%, increased activity by >25% or stayed within +/−25% of their pre-diagnosis levels for moderate to vigorous activity and sports/recreation activity. A cutoff of 10% was used for vigorous activity analyses due to the restricted range of vigorous activity change. Since so many women reported increasing their household activity, household activity change was defined as decreased ≥1%, increased 0–100%, and increased >100%. Analysis of covariance (ANCOVA) models were run with each physical activity change variable as the independent variable represented by three levels and each symptom/physical HRQOL variable evaluated as a dependent variable, adjusting for the set of covariates described above.

We chose a more stringent criterion for statistical significance ($p<0.01$) to help control for the family-wise error rate stemming from the multiple statistical tests. To make the results more intuitive, beta coefficients (B) listed in the tables of results were calculated for a 10 MET-hour/week increase in the specified type of pre-diagnosis activity. Ten MET-hours is approximately equal to walking at a moderate pace for three hours per week [1]. All analyses were performed using SAS/STAT software, Version 9 of the SAS System for Windows [39].

Results

Participant characteristics

Table 1 presents the baseline and 24-month follow-up demographic and clinical characteristics of the 545 partic-

Table 3. Results of individual regression models testing the associations between *pre-diagnosis* physical activity with symptoms and physical health-related quality of life

Outcome	Moderate to vigorous activity B^a (SE)	Vigorous activity B^a (SE)	Household activity B^a (SE)	Sports/ recreational activity B^a (SE)
Pain and physical sensations				
Arm pain	0.011 (0.011)	−0.034 (0.028)	0.008 (0.009)	−0.013 (0.017)
Breast pain	0.038 (0.012)**	0.011 (0.029)	0.283 (0.010)**	0.027 (0.017)
Hormone-related symptoms				
Vasomotor	0.030 (0.015)	−0.002 (0.037)	0.011 (0.013)	0.048 (0.022)
Urinary Incontinence	−0.014 (0.015)	−0.051 (0.037)	0.003 (0.012)	−0.048 (0.022)
Cognitive/mood	0.001 (0.012)	−0.022 (0.029)	−0.003 (0.010)	0.234 (0.017)
Vaginal symptoms	−0.007 (0.011)	−0.006 (0.027)	0.003 (0.009)	0.001 (0.016)
Weight/appearance	0.007 (0.016)	0.012 (0.039)	0.013 (0.013)	0.018 (0.023)
Sexual interest/dysfunction	0.010 (0.015)	0.007 (0.039)	−0.004 (0.013)	−0.008 (0.022)
Fatigue				
Behavioral/severity	0.010 (0.046)	−0.028 (0.126)	0.013 (0.035)	0.061 (0.066)
Affective meaning	0.010 (0.041)	−0.016 (0.111)	−0.001 (0.031)	0.036 (0.058)
Sensory	−0.042 (0.033)	−0.164 (0.080)	0.008 (0.027)	−0.089 (0.048)
Cognitive/mood	0.015 (0.029)	−0.025 (0.069)	0.007 (0.023)	0.015 (0.042)
Physical health-related QOL				
Physical functioning	1.138 (0.315)***	2.306 (0.766)**	0.177 (0.258)	1.734 (0.456)***
Role-physical	0.449 (0.555)	1.676 (1.343)	−0.143 (0.449)	0.329 (0.804)
Bodily pain	−0.469 (0.349)	1.089 (0.844)	−0.432 (0.282)	−0.235 (0.506)
General health	0.105 (0.296)	1.137 (0.716)	0.098 (0.240)	0.266 (0.429)

[a] Beta coefficients are for an increase in 10 MET-hours/week of the specified physical activity. All models are adjusted for age, education, menopause status, treatment, stage of disease, tamoxifen use, smoking status, BMI, and race/ethnicity.

**$P<0.01$

***$P<0.001$

ipants. At baseline, participants ranged in age from 29–86 years with a mean of 58 years. The majority of women was non-Hispanic White (80%), had been diagnosed with localized breast cancer (59%), and was treated with a combination of surgery and radiation. At the 24-month follow-up, 75% of women were post-menopausal, 46% were taking tamoxifen, and 11% were current smokers. Over one-fifth of the participants reported at least one activity-limiting comorbid condition. The mean BMI was 26 kg/m^2, which is classified in the overweight range. There were no differences on demographic or medical variables between the 545 participants included in this analysis and the entire HEAL study QOL cohort (n=805), with the exception of variables related to the exclusion of the Los Angeles county site (e.g., all the participants from Los Angeles county were Black).

Physical activity levels pre- and post-diagnosis

Participants retrospectively reported a mean of 30 MET-hours per week of pre-diagnosis moderate to vigorous physical activity and 5 MET-hours per week of pre-diagnosis vigorous activity (see Table 1). Mean physical activity levels reported at 24-months post-diagnosis were only slightly lower. Most participants reported maintaining or decreasing their moderate to vigorous (61%) and their vigorous (75%) activity levels across the cancer experience. Women reported engaging in high levels of pre-diagnosis household activity (mean=39.7 MET-hours/week), and the mean level of household activity was even higher at the 24-month assessment (mean=47.9 MET-hours/week). Indeed, 65% of women reported increasing their household activity levels across the cancer experience. Participants reported a mean of 15 MET-hours per week of pre-diagnosis sports and recreation activity: the mean was lower at the 24-month follow-up assessment. Sixty-three percent of women reported maintaining or decreasing their sports and recreation activity across the cancer experience.

Symptoms and physical HRQOL outcomes

Table 2 presents the mean scores for cancer-related symptoms and physical HRQOL domains reported by participants on average 39 months post-diagnosis. Mean scores for pain/physical sensations in the arm and the breast corresponded to experiencing these symptoms "rarely." Levels of hormone-related symptoms were also generally low with slightly higher scores for vasomotor symptoms and weight gain/appearance concern, which were between "slightly" and "moderately" bothersome. Problems with sexual interest or dysfunction were "a little problematic" among the 298

Table 4 Results of individual regression models testing the associations between *post-diagnosis* physical activity with symptoms and physical health-related quality of life

Outcome	Moderate to vigorous activity B^a (SE)	Vigorous activity B^a (SE)	Household activity B^a (SE)	Sports/ recreational activity B^a (SE)
Pain and physical sensations				
Arm pain	0.007 (0.013)	0.003 (0.029)	0.016 (0.009)	0.008 (0.017)
Breast pain	0.019 (0.013)	0.001 (0.030)	0.033 (0.009)***	0.012 (0.018)
Hormone-related symptoms				
Vasomotor	0.016 (0.017)	−0.027 (0.039)	0.005 (0.012)	0.027 (0.023)
Urinary incontinence	−0.012 (0.017)	−0.066 (0.038)	−0.002 (0.012)	−0.028 (0.023)
Cognitive/mood	0.003 (0.013)	−0.037 (0.030)	0.005 (0.009)	0.017 (0.018)
Vaginal symptoms	0.008 (0.012)	−0.005 (0.027)	0.008 (0.008)	0.001 (0.016)
Weight/appearance	0.017 (0.018)	−0.046 (0.040)	0.014 (0.012)	0.009 (0.024)
Sexual interest/dysfunction	−0.005 (0.017)	0.008 (0.034)	0.002 (0.013)	−0.010 (0.022)
Fatigue				
Behavioral/severity	−0.081 (0.059)	−0.379 (0.180)	0.014 (0.032)	−0.091 (0.083)
Affective meaning	−0.078 (0.052)	−0.034 (0.160)	−0.021 (0.028)	−0.011 (0.073)
Sensory	−0.117 (0.036)**	−0.245 (0.082)**	0.009 (0.026)	−0.146 (0.048)**
Cognitive/mood	−0.022 (0.032)	−0.048 (0.072)	0.011 (0.022)	0.006 (0.042)
Physical health-related QOL				
Physical functioning	1.726 (0.342)	2.515 (0.793)**	−0.164 (0.247)	2.211 (0.461)***
Role-physical	−0.074 (0.610)	1.131 (1.392)	−0.862 (0.428)	0.754 (0.819)
Bodily pain	0.057 (0.384)	1.247 (0.874)	−0.512 (0.269)	0.195 (0.516)
General health	0.389 (0.325)	1.570 (0.740)	−0.372 (0.229)	0.853 (0.436)

[a] Beta coefficients are for an increase in 10 MET-hours/week of the specified physical activity. All models are adjusted for age, education, menopause status, treatment, stage of disease, tamoxifen use, smoking status, BMI, race/ethnicity, and pre-diagnosis activity level.
**P<0.01
***P<0.001

Table 5 Adjusted mean symptom and physical health-related quality of life scores by change in physical activity from ANCOVA models

Outcome	Moderate to vigorous activity Mean[a] (95% CI)	Vigorous activity Mean[a] (95% CI)	Household activity[b] Mean[a] (95% CI)	Sports/ recreational activity Mean[a] (95% CI)
Pain and physical sensations				
Arm pain				
Decreased physical activity	0.90 (0.73, 1.07)	0.82 (0.64, 0.99)	0.88 (0.71, 1.05)	0.86 (0.69, 1.03)
Maintained physical activity	0.84 (0.66, 1.02)	0.92 (0.76, 1.08)	0.86 (0.70, 1.03)	0.90 (0.73, 1.08)
Increased physical activity	0.94 (0.77, 1.10)	0.99 (0.80, 1.18)	0.98 (0.80, 1.16)	0.94 (0.77, 1.11)
Breast pain				
Decreased physical activity	1.12 (0.94, 1.29)	1.15 (0.96, 1.33)	1.08 (0.90, 1.25)	1.12 (0.95, 1.29)
Maintained physical activity	1.08 (0.90, 1.27)	1.04 (0.97, 1.21)	1.09 (0.92, 1.26)	1.08 (0.91, 1.27)
Increased physical activity	1.07 (0.90, 1.24)	1.11 (0.92, 1.30)	1.10 (0.92, 1.29)	1.05 (0.88, 1.23)
Hormone-related symptoms				
Vasomotor				
Decreased physical activity	1.65 (1.42, 1.88)	1.69 (1.46, 1.93)	1.72 (1.49, 1.94)	1.64 (1.42, 1.87)
Maintained physical activity	1.74 (1.50, 1.99)	1.57 (1.35, 1.79)	1.59 (1.36, 1.81)	1.65 (1.41, 1.88)
Increased physical activity	1.51 (1.29, 1.73)	1.61 (1.36, 1.87)	1.53 (1.29, 1.78)	1.57 (1.33, 1.80)
Urinary incontinence				
Decreased physical activity	1.12 (0.89, 1.35)	1.23 (0.99, 1.46)	1.29 (1.06, 1.51)	1.17 (0.95, 1.40)
Maintained physical activity	1.26 (1.02, 1.51)	1.10 (0.88, 1.32)	1.11 (0.89, 1.33)	1.19 (0.95, 1.43)
Increased physical activity	1.15 (0.93, 1.37)	1.24 (0.99, 1.49)	1.10 (0.86, 1.34)	1.14 (0.91, 1.37)
Cognitive/mood				
Decreased physical activity	1.22 (1.04, 1.40)	1.33 (1.15, 1.52)	1.30 (1.12, 1.47)	1.37 (1.19, 1.54)
Maintained physical activity	1.35 (1.16, 1.54)	1.24 (1.07, 1.41)	1.27 (1.10, 1.44)	1.20 (1.01, 1.38)
Increased physical activity	1.31 (1.14, 1.48)	1.33 (1.14, 1.53)	1.31 (1.13, 1.50)	1.29 (1.11, 1.47)
Vaginal symptoms				
Decreased physical activity	0.61 (0.44, 0.77)	0.75 (0.58, 0.91)	0.72 (0.56, 0.88)	0.69 (0.54, 0.85)
Maintained physical activity	0.75 (0.58, 0.93)	0.65 (0.49, 0.80)	0.68 (0.52, 0.84)	0.68 (0.51, 0.84)
Increased physical activity	0.74 (0.58, 0.89)	0.73 (0.55, 0.91)	0.69 (0.52, 0.86)	0.72 (0.56, 0.89)
Weight/appearance				
Decreased physical activity	1.58 (1.34, 1.82)	**1.84 (1.59, 2.08)[1]**	1.59 (1.35, 1.83)	1.69 (1.46, 1.93)
Maintained physical activity	1.65 (1.39, 1.90)	**1.50 (1.27, 1.72)[1]**	1.64 (1.41, 1.87)	1.55 (1.30, 1.80)
Increased physical activity	1.64 (1.41, 1.87)	1.56 (1.30, 1.82)	1.64 (1.39, 1.89)	1.61 (1.36, 1.85)
Sexual Interest/dysfunction				
Decreased physical activity	1.00 (0.74, 1.25)	1.04 (0.78, 1.30)	0.89 (0.64, 1.14)	1.04 (0.77, 1.30)
Maintained physical activity	1.00 (0.72, 1.27)	0.87 (0.62, 1.12)	1.01 (0.76, 1.27)	0.89 (0.62, 1.16)
Increased physical activity	0.91 (0.66, 1.15)	1.02 (0.75, 1.29)	0.99 (0.71, 1.26)	0.95 (0.70, 1.20)
Fatigue				
Behavioral/severity				
Decreased physical activity	4.49 (3.87, 5.11)	4.40 (3.74, 5.05)	4.15 (3.50, 4.79)	**4.85 (4.25, 5.45)[1, 2]**
Maintained physical activity	4.37 (3.70, 5.04)	4.16 (3.57, 4.76)	4.37 (3.78, 4.96)	**4.08 (3.43, 4.73)[1]**
Increased physical activity	3.89 (3.28, 4.50)	4.13 (3.44, 4.82)	4.06 (3.37, 4.75)	**3.64 (3.03, 4.25)[2]**
Affective meaning				
Decreased physical activity	5.87 (5.32, 6.42)	5.93 (5.35, 6.51)	5.62 (5.06, 6.18)	**6.07 (5.53, 6.61)[1]**
Maintained physical activity	**6.07 (5.49, 6.66)[1]**	5.62 (5.09, 6.14)	**6.00 (5.48, 6.52)[1]**	5.61 (5.03, 6.19)
Increased physical activity	**5.31 (4.78, 5.85)[1]**	5.62 (5.01, 6.23)	**5.27 (4.66, 5.87)[1]**	**5.41 (4.86, 5.95)[1]**
Sensory				
Decreased physical activity	5.01 (4.52, 5.50)	4.75 (4.25, 5.26)	4.81 (4.33, 5.30)	4.91 (4.43, 5.39)
Maintained physical activity	4.79 (4.27, 5.31)	4.99 (5.52, 5.46)	4.97 (4.50, 5.45)	5.02 (4.51, 5.52)
Increased physical activity	4.72 (4.25, 5.20)	4.63 (4.09, 5.16)	4.66 (4.17, 5.18)	4.56 (4.07, 5.06)
Cognitive/mood				
Decreased physical activity	4.42 (4.00, 4.85)	4.52 (4.08, 4.96)	4.31 (3.89, 4.73)	4.55 (4.13, 4.97)
Maintained physical activity	4.42 (3.97, 4.88)	4.32 (3.91, 4.72)	4.45 (4.04, 4.87)	4.29 (3.85, 4.73)
Increased physical activity	4.32 (3.91, 4.73)	4.31 (3.84, 4.77)	4.37 (3.92, 4.82)	4.27 (3.84, 4.70)
Physical health-related QOL				
Physical functioning				
Decreased physical activity	70.0 (65.3, 74.1)	73.9 (69.1, 78.8)	74.3 (69.6, 79.0)	72.8 (68.2, 77.5)
Maintained physical activity	75.5 (70.5, 80.5)	**71.2 (66.7, 75.7)[1]**	72.2 (67.6, 76.8)	72.3 (67.4, 77.2)
Increased physical activity	74.6 (70.1, 79.2)	**77.0 (71.9, 82.2)[1]**	73.6 (68.6, 78.6)	74.9 (70.1, 79.7)

Table 5 (continued)

Outcome	Moderate to vigorous activity Mean[a] (95% CI)	Vigorous activity Mean[a] (95% CI)	Household activity[b] Mean[a] (95% CI)	Sports/ recreational activity Mean[a] (95% CI)
Role-physical				
Decreased physical activity	61.6 (53.3, 69.9)	61.5 (52.9, 70.0)	64.0 (55.9, 72.2)	58.3 (50.2, 66.4)
Maintained physical activity	62.8 (53.9, 71.6)	60.6 (52.8, 68.5)	58.4 (50.4, 66.4)	65.4 (56.9, 73.9)
Increased physical activity	58.2 (50.2, 66.2)	58.7 (49.7, 67.8)	58.9 (50.1, 67.6)	58.3 (50.0, 66.6)
Bodily pain				
Decreased physical activity	64.0 (58.9, 69.2)	64.2 (58.9, 69.6)	65.6 (60.5, 70.8)	**62.0 (57.0, 67.1)[1]**
Maintained physical activity	63.6 (58.1, 69.1)	65.7 (60.8, 70.6)	63.2 (58.2, 68.2)	67.8 (62.5, 73.2)
Increased physical activity	67.6 (62.6, 72.6)	66.4 (60.7 , 72.0)	68.3 (62.8, 73.8)	**66.9 (61.7, 72.1)[1]**
General health				
Decreased physical activity	66.1 (61.7, 70.5)	66.7 (62.2, 71.3)	67.4 (63.0, 71.7)	66.6 (62.3, 71.0)
Maintained physical activity	65.6 (60.9, 70.3)	67.1 (62.9, 71.3)	67.0 (62.7, 71.3)	66.7 (62.2, 71.3)
Increased physical activity	68.5 (64.3, 72.8)	67.0 (62.2, 71.8)	66.3 (61.7, 71.0)	67.6 (63.2, 72.1)

[a] All mean symptom and HRQOL scores are adjusted for age, education, menopause status, treatment, stage of disease, tamoxifen use, smoking status, BMI, and race/ethnicity.

[b] For household activity, the activity change categories were: decreased ≥1%, increased 0–100%, and increased >100%

All symptoms scales coded with higher scores indicating greater symptoms except health-related QOL where higher scores indicated greater health-related QOL in that domain.

[1–2] Pairwise comparisons of means that share a common superscript letter are those that differ significantly from each other: $p<0.01$. Results significant at this level are in bold-face type for emphasis.

participants who reported sexual activity. Participants reported some mild to moderate problems with fatigue, especially for the affective meaning (mean=5.41) and sensory (mean=4.23) subscales. Physical HRQOL domains on the SF-36 ranged from a low of 65.5 (role-physical subscale) to a high of 77.2 (physical functioning subscale).

Pre-diagnosis physical activity: Relationships with symptoms and physical HRQOL

Table 3 presents the results of linear regression models predicting symptoms and physical HRQOL scores on average 39 months post-diagnosis from pre-diagnosis physical activity levels. Greater levels of pre-diagnosis moderate to vigorous and household activity were associated with slightly higher breast pain/sensation scores (B= 0.04, 0.28 respectively; $p<0.01$) but not with arm pain/sensation. Greater pre-diagnosis moderate-vigorous, vigorous, and sports/recreation physical activity levels were associated with greater physical HRQOL scores, specifically in the physical functioning domain (B=1.14, 2.30, 1.73 respectively; all $p<0.01$). There were no associations between pre-diagnosis physical activity and other domains of physical HRQOL, hormone-related symptoms, sexual interest/dysfunction, or fatigue. There were no consistent significant ethnicity by physical activity interactions for pre-diagnosis activity, or in any of the other analyses, and so these results are not presented in this manuscript.

Post-diagnosis physical activity: Relationships with symptoms and physical HRQOL

Table 4 presents the results of linear regression models predicting symptoms and physical HRQOL scores on average 39 months post-diagnosis from post-diagnosis physical activity levels. Greater levels of post-diagnosis household physical activity were associated with slightly increased breast pain/sensation scores at 39 months post-diagnosis (B=0.03; $p<0.001$) but not with arm pain/sensations. Greater post-diagnosis moderate to vigorous, vigorous, and sports/recreational activity levels were associated with lower sensory fatigue scores (B=−0.11, −0.25, −0.15 respectively; all $p<0.01$). Greater levels of post-diagnosis vigorous and sports/recreational activity were associated with higher physical functioning aspects of physical HRQOL (B=2.52, 2.21 respectively; both $p<0.01$). No significant relationship was found between post-diagnosis physical activity and hormone-related symptoms or sexual interest/dysfunction.

Physical activity change from pre- to post-diagnosis: Relationships with symptoms and physical HRQOL

The third research question evaluated whether change in physical activity from pre- to post-diagnosis was related to symptom/physical HRQOL outcomes at 39 months post-diagnosis (Table 5). Analyses of covariance testing the differences in mean symptom and physical HRQOL scores for the three physical activity change categories found

significant results for weight gain/appearance concern, fatigue, and physical HRQOL, but not for pain/sensation, other hormone-related symptoms, or sexual activity/dysfunction.

Survivors who maintained their vigorous activity levels reported lower weight gain/appearance concern scores compared to those who decreased their vigorous activity levels (1.50 vs. 1.84; $p<0.001$). A similar trend was evident among those who increased vs. decreased their vigorous activity as well; however, this was not statistically significant under our criterion ($p=0.04$).

Survivors who increased or maintained their sports/recreation activity had lower behavioral/sensory aspects of fatigue than those who decreased their sports/recreational activity levels (3.64, 4.08 respectively, vs. 4.85; both $p<0.01$). Survivors who increased their moderate to vigorous activity reported lower affective meaning fatigues scores compared to those who maintained their activity levels (5.31 vs. 6.07; $p<0.001$). There was a similar trend for those who increased vs. decreased their moderate to vigorous activity; however, this was not statistically significant under our criterion ($p=0.03$). Survivors who increased their sports/recreational activity levels reported lower affective meaning fatigue scores compared to those who or decreased their activity (5.41 vs. 6.07; $p<0.01$). Those who greatly increased their household activity level (i.e., by >100%) also reported lower affective meaning fatigue scores compared to those who increased their activity levels by a smaller amount (5.27 vs. 6.00; $p<0.01$).

Physical activity change was also related to physical HRQOL. Survivors who increased their vigorous activity levels reported higher physical functioning than those who maintained their vigorous activity levels (77.0 vs. 71.2; $p<0.01$). Survivors who increased their sports-recreational activity levels reported lower body pain than those who decreased their sports/recreational activity (66.9 vs. 62.0; $p<0.001$). A similar trend was evident in those who maintained vs. decreased their sports/recreational activity; however, this was not statistically significant under our criterion ($p=0.02$).

Discussion

This study sought to determine whether pre- or post-diagnosis physical activity levels or change in physical activity after cancer were related to physical symptoms and physical aspects of HRQOL in a large, ethnically-diverse cohort of breast cancer survivors. Other aims were to evaluate the most protective type and amount of physical activity and whether these relationships were different for non-Hispanic White vs. Hispanic women. Overall, our study hypotheses were partially met. As hypothesized, higher pre-diagnosis activity, higher post-diagnosis activity, and maintenance or improvement of activity levels after diagnosis subsequently were associated with less problematic physical symptoms and higher levels of physical HRQOL. However, these relationships were not entirely consistent, and occasionally, results were counter to expectations.

Pre-diagnosis physical activity: Relationships with symptoms and physical HRQOL

We did not find significant inverse relationships between pre-diagnosis activity levels and symptoms at 39 months post-diagnosis in these breast cancer survivors. Greater pre-diagnosis activity was actually related to greater breast pain; however, the small magnitude of the coefficients indicate that these results are not likely clinically meaningful. We know of no studies that have specifically looked at pre-diagnosis activity in relation to subsequent symptoms in breast cancer survivors. We might expect a history of physical activity to be associated with reduced severity of cancer-related symptoms (e.g., fatigue) because physical activity in non-cancer samples is associated with reduced severity of similar symptoms [7]. It may be that our measures of pre-diagnosis activity, recalled for the year prior to diagnosis, do not accurately reflect a woman's physical activity. However, we did find a more consistent relationship between pre-diagnosis activity and higher physical HRQOL, specifically the physical functioning subscale. Our results suggest that women with higher levels of pre-diagnosis sports/recreation activity, especially vigorous activity, may be better able to be physically active in their daily lives (e.g., climb stairs, walk several blocks) after breast cancer treatment.

Post-diagnosis physical activity: Relationships with symptoms and physical HRQOL

Numerous intervention studies and several reviews suggest that physical activity after diagnosis can be helpful in reducing cancer-related symptoms and improving HRQOL [24, 29, 30, 32, 34, 42, 43]. Our results were consistent with this emerging literature. Higher post-diagnosis sports/recreational activity, but not household activity, was consistently related to less severe reports of the physical symptoms of fatigue. The reduction in fatigue was stronger for vigorous activity compared to moderate to vigorous activity, suggesting a dose-response effect. Breast cancer survivors who reported greater vigorous sports/recreational activity post-diagnosis also reported greater physical HRQOL, specifically in the ability to be physically active in their daily lives. The most beneficial types and amount of post-diagnosis activity are not known [4]. That these relationships were not significant for household activity and were not significant or weaker for moderate to vigorous activity suggests that engaging in

vigorous sports/recreational activity after diagnosis may be needed to produce significant decreases in activity-limiting fatigue and improvements in physical functioning.

An important caveat to these results is that our study design does not permit us to know whether women who reported symptoms (e.g., fatigue) at 39 months also were experiencing those symptoms when post-diagnosis activity was measured. For example, if women were experiencing fatigue at the time physical activity was measured that limited their ability to participate in physical activity, then that could account for the significant results between physical activity and fatigue at 39 months.

This study found increased post-diagnosis household physical activity was associated with increased breast pain scores. As in the pre-diagnosis results, the small magnitude of the coefficient likely means that these results are not clinically meaningful. However, if future studies replicate associations between physical activity and pain, this would point to the need for physical therapists to assist survivors in increasing their activity after cancer treatment in a well-paced and safe manner.

Physical activity change from pre- to post-diagnosis: Relationships with symptoms and physical HRQOL

Evidence is accumulating that the overall pattern of physical activity change in the initial years after cancer treatment is related to subsequent HRQOL [6, 12, 13, 25]. Our study found that survivors who increased their activity over the cancer experience were better able to be physically active in their daily lives (e.g., climb stairs, walk several blocks) and reported lower body pain. Thus, our results confirm the physical HRQOL results of previous studies but further suggest that the pattern of physical activity change may also be related to symptoms, especially to fatigue. Survivors who increased their sports/recreational activity over the cancer experience reported having to make fewer behavioral changes in their daily activities due to fatigue and reported lower emotional meaning of fatigue compared to those who decreased their activity. Maintaining the level of activity was sometimes, but not always, associated with a better fatigue profile compared to decreasing activity levels. However, again, these results may be an artifact of decreased physical activity in survivors who had activity-limiting fatigue at the time post-diagnosis activity was measured, as discussed above. It is not known whether reduction in activity was a cause or a consequence of fatigue.

The results of this study suggest that the potential impact of physical activity change on hormone-related symptoms is questionable. However, one intriguing finding is that survivors who maintained their vigorous activity levels over the course of the cancer experience reported less weight gain and concern with their appearance than those who decreased their activity. Physical activity may be an important way to avert the weight gain typically seen in breast cancer survivors after treatment which is important since excess body weight has been associated with increased breast cancer recurrence and lower survival rates [11].

Finally, it is noteworthy that in these analyses of physical activity change, as well as in the pre- and post-diagnosis activity analyses, activity was never related to sexual dysfunction. This null result makes sense given the conclusions from other studies finding that although breast cancer treatments may effect physical aspects of sexual functioning, the key predictors of sexual health in breast cancer survivors are similar to those in healthy women: sexual self-image [3], emotional well-being, body image, the quality of the partnered relationship, vaginal dryness, and whether the woman's partner has sexual problems [18].

The results of this study extend the literature on the potential role of physical activity in improving symptom management and physical HRQOL for breast cancer survivors by investigating activity type, intensity, and pattern over the cancer experience in a large diverse cohort of women. Since physical activity may have differential effects on symptoms not reflected in general measures of HRQOL, these results also underscore the need for future studies to investigate the effects of physical activity programs on symptoms as well as on HRQOL. The fact that we did not find differences in the potential role of physical activity for non-Hispanic White vs. Hispanic survivors is encouraging in that physical activity has the potential to benefit both ethnic groups. However, the small number of Hispanic women likely limited our ability to detect ethnic differences.

Key strengths of this study included a large, diverse group of survivors recruited through registries, multiple measures of physical activity using a well-validated instrument assessing frequency, intensity, duration and type of activity, and a prospective study design assessing symptoms and physical HRQOL with several years of follow-up time.

The results of this study were limited by several factors. Symptoms were measured approximately 39 months post-diagnosis. If symptoms have become long-established problems by this point in survivorship, physical activity might not have as much of a role to play in symptom management compared to during treatment. Alternatively, survivors reported low levels of symptoms, potentially creating a floor effect for demonstrating symptom improvement. Symptoms were only measured once, limiting our ability to discern whether activity changes were a cause or consequence of problematic symptoms such as fatigue. Even with our more stringent criterion for statistical significance, the large number of statistical tests performed in this analysis might have resulted in some spurious positive findings.

Further bias may arise from the correlations among some of the outcome variables (e.g., correlation among SF-36 subscales that all came from the same instrument). Finally, the positive associations between physical activity and symptoms and physical HRQOL in this study were small in magnitude. Though consistent with other literature [42], it is not known whether the positive relationships would be greater without the limitations cited above.

Despite these limitations, the results of this study suggest that physical activity plays a role in the rehabilitation of cancer survivors. Increased physical activity, especially after cancer, was consistently related to better physical functioning and to reduced fatigue and bodily pain, underscoring the need for promoting physical activity among survivors. Future studies that address these limitations are needed to solidify the protective role of increases in physical activity after cancer for ameliorating persistent physical symptoms and improving HRQOL in breast cancer survivors. Future studies should also aim to determine the most beneficial type and amount of physical activity and the mechanisms by which physical activity can improve symptoms and HRQOL.

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