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ORIGINAL RESEARCH

Self-Reported Physical Activity, QoL, Cardiac Function, and Cardiorespiratory Fitness in Women With HER2+ Breast Cancer

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ABSTRACT

BACKGROUND Women treated for breast cancer are at risk for worsening health-related quality of life (QoL), cardiac function, and cardiorespiratory fitness.

OBJECTIVES The aim of this study was to assess the associations of self-reported moderate to vigorous intensity physical activity (MVPA) during cancer treatment with concurrent measures of QoL and cardiac function and with post-treatment cardiorespiratory fitness in women with human epidermal growth factor receptor 2-positive breast cancer receiving sequential anthracyclines and trastuzumab.

METHODS EMBRACE-MRI 1 (Evaluation of Myocardial Changes During Breast Adenocarcinoma Therapy to Detect Cardiotoxicity Earlier With MRI) study participants who completed questionnaires for MVPA (modified Godin Leisure Time Physical Activity Questionnaire) and QoL (EQ-5D-3L, Minnesota Living With Heart Failure Questionnaire) and cardiac imaging every 3 months during treatment and post-treatment cardiopulmonary exercise testing were included. Participants engaging in ≥90 minutes of MVPA each week were labeled "active." Generalized estimation equations and linear regression analyses were used to assess concurrent and post-treatment associations with MVPA and activity status, respectively.

RESULTS Eighty-eight participants were included (mean age 51.4 ± 8.9 years). Mean MVPA minutes, QoL, and cardiac function (left ventricular ejection fraction, global longitudinal strain, E/A ratio, and E/e′ ratio) worsened by 6 months into trastuzumab therapy. Higher MVPA (per 30 minutes) during treatment was associated with better concurrent overall ($\beta = -0.42$) and physical ($\beta = -0.24$) Minnesota Living With Heart Failure Questionnaire scores, EQ-5D-3L index ($\beta = 0.003$), visual analogue scale score ($\beta = 0.43$), diastolic function (E/A ratio; $\beta = 0.01$), and global longitudinal strain ($\beta = 0.04$) at each time point ($P \leq 0.01$ for all). Greater cumulative MVPA over the treatment period was associated with higher post-treatment cardiorespiratory fitness (peak oxygen consumption; $\beta = 0.06$ per 30 minutes; $P < 0.001$).

CONCLUSIONS Higher self-reported MVPA during treatment for human epidermal growth factor receptor 2-positive breast cancer was associated with better QoL and diastolic and systolic left ventricular function measures during treatment and better post-treatment cardiorespiratory fitness. (J Am Coll Cardiol CardioOnc 2022;4:387–400) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CMR = cardiovascular magnetic resonance

CTRCD = cancer therapy-related cardiac dysfunction

GEE = generalized estimating equation

GLS = global longitudinal strain

HER2 = human epidermal growth factor receptor 2

LV = left ventricular

MLHFQ = Minnesota Living With Heart Failure Questionnaire

MVPA = moderate to vigorous physical activity

PA = physical activity

QoL = quality of life

VAS = visual analogue scale

Vo_{2peak} = peak oxygen consumption

Women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer are at risk for impaired quality of life (QoL),[1] cardiac function,[2] and cardiorespiratory fitness[3] during and following treatment. This risk is attributed to a combination of preexisting cardiovascular disease risk factors, exposure to cardiotoxic cancer therapies (eg, anthracyclines), and adverse lifestyle-related factors (eg, physical inactivity).[4] Emerging evidence suggests that low post-treatment cardiorespiratory fitness is associated with increased risk for all-cause, cancer-related, and cardiovascular disease-related mortality in cancer survivors[5] and that higher levels of physical activity (PA; ie, any bodily movement produced by major muscle groups that requires energy expenditure) engagement during and following treatment may help mitigate these risks in survivors of breast[6] and other[7] malignancies. Relatedly, exercise training has been shown to improve QoL,[8] cardiorespiratory fitness,[9] and cardiovascular disease risk scores[10] in patients with and survivors of breast cancer.

Health organizations such as the American College of Sports Medicine and the American Heart Association endorse regular engagement in self-directed moderate to vigorous PA (MVPA)[11] and supervised exercise-based interventions[12] for cancer survivors. Supervised training is optimal for delivering safe and effective doses of exercise (ie, regular bouts of PA specifically targeting improvements in physical fitness and health);[13,14] however, the availability of dedicated, supervised exercise support services and rehabilitation programs remains limited. Thus, there is a need to understand whether less resource-intensive approaches (eg, promoting higher levels of self-directed PA) are associated with better patient-reported QoL, cardiac function, and cardiorespiratory fitness in patients receiving cardiotoxic cancer therapies.

The purposes of this analysis of the EMBRACE-MRI 1 (Evaluation of Myocardial Changes During Breast Adenocarcinoma Therapy to Detect Cardiotoxicity Earlier With MRI) cohort (NCT02306538), a prospective cohort study of women with HER2+ breast cancer receiving anthracyclines followed by trastuzumab therapy, were to: 1) assess the concurrent associations between self-reported PA and measures of QoL and cardiac systolic and diastolic function during treatment; and 2) quantify the association between overall PA engagement during cancer treatment and post-treatment cardiorespiratory fitness.

METHODS

PARTICIPANTS. Women receiving sequential anthracycline and trastuzumab therapy for HER2+ breast cancer (stages I-III) enrolled in the EMBRACE-MRI 1 study were screened for eligibility. Methods for the EMBRACE-MRI 1 study were previously reported.[15] Clinical and imaging assessments and questionnaire administration occurred before anthracycline treatment (baseline; time 1), after anthracyclines but before trastuzumab (time 2), every 3 months during trastuzumab treatment (3, 6, and 9 months; times 3-5, respectively), and after trastuzumab completion (12 months; time 6). Participants were eligible if they had self-reported PA data collected at a minimum of 4 of 6 study visits. The EMBRACE-MRI 1 study was approved by the University Health Network ethics board. Written informed consent was obtained from all participants.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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PA ENGAGEMENT. The modified Godin Leisure Time Physical Activity Questionnaire[16] has been used in previous breast cancer research[17] and assesses self-reported PA engagement by asking participants to report the frequency and average duration of light-, moderate-, and vigorous-intensity PA performed during their free time over past 7 days. Total MVPA minutes were calculated as moderate intensity minutes plus 2 times vigorous intensity minutes.[18] At each study visit, participants were labeled active (ie, performing ≥90 minutes of MVPA per week) or inactive (ie, performing <90 minutes of MVPA per week) according to the cancer PA guidelines.[11] Participants were then classified according to their overall pattern of MVPA as inactive (ie, performing ≥90 minutes of MVPA per week at ≤1 visit), somewhat active (ie, performing ≥90 minutes of MVPA per week at 2-4 visits), or highly active (ie, performing ≥90 minutes of MVPA per week at 5 or 6 visits).

OUTCOMES. Health-related QoL. The EQ-5D-3L, validated in oncology[19] and cardiac[20] populations, was used to assess 5 health-related QoL dimensions, including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression using a 3-point Likert-type scale (ie, no problems, some problems, extreme problems).[21] EQ-5D-3L index scores were calculated using a formula that weights each QoL dimension[22] and interpreted using normative EQ-5D-3L index score data for Canadians.[23] Participants rated their overall health using the EQ-5D-3L visual analogue scale (VAS), a self-rated vertical health scale from 0 (worst imaginable health) to 100 (best imaginable health).

Heart failure–specific QoL. The Minnesota Living With Heart Failure Questionnaire (MLHFQ)[24] was used to assess heart failure–specific QoL given that these patients may develop subclinical (eg, decreased global longitudinal strain [GLS]) or overt cancer therapy–related cardiac dysfunction (CTRCD) during and after treatment.[25] The MLHFQ rates 21 items on a 6-point Likert-type scale (from 0 [none] to 5 [very much]; the overall score ranges from 0 to 105 [best to worst]), has good psychometric properties,[26] and has been used in cardio-oncology research.[27] There is also a subscore for physical QoL (8 items; range 0-40) and emotional QoL (5 items; range 0-25).

Echocardiography. Participants underwent transthoracic echocardiography (E9, GE Healthcare) by study sonographers following American Society of Echocardiography guidelines.[28] A 3-dimensional full-volume (>20 volumes/s) dataset of the left ventricle was obtained. Semiautomated contours were used (4D Auto LVQ, EchoPAC Version 202, GE Healthcare) for measurement of 3-dimensional left ventricular (LV) ejection fraction. Contour adjustments were made as necessary, and images with poor quality or difficulty tracking despite contour adjustments were excluded.

GLS was measured via automated myocardial contours (EchoPAC version 202, Automated Function Imaging, GE Healthcare) from apical 4-, 3-, and 2-chamber images of the left ventricle for 3 cardiac cycles (40-80 frames/s). Contour adjustments were made as necessary, and poorly tracked segments were excluded after 3 attempts. An average of the remaining segments was recorded if individual segments were excluded. GLS is reported as absolute values.

Diastolic measures including early (E) and late diastolic (A) mitral inflow velocities, tissue Doppler imaging–based early diastolic mitral septal and lateral annular velocities (e′), left atrial volume, and tricuspid regurgitation velocity were measured. The E/e′ ratio was calculated using the average of the Doppler-defined septal and lateral annular velocities (e′) for left-sided filling pressures. Left atrial volume was calculated using the biplane method.[28] Diastolic dysfunction grade was determined per the American Society of Echocardiography guidelines.[29] All echocardiographic measurements were performed using deidentified images.

Cardiovascular magnetic resonance. Cardiovascular magnetic resonance (CMR) studies were performed using a 1.5-T scanner (Magnetom AvantoFit, Siemens Healthineers) and on the same day as echocardiography except for 9 months into trastuzumab. Balanced steady-state free precession cine sequences in a stack of short-axis and long-axis (2-, 3-, and 4-chamber) orientation were acquired for assessment of cardiac function. Analysis was performed using commercially available software (CVI42, Circle CVI) using deidentified images.

CMR was the reference standard for CTRCD, defined as a ≥10% reduction in LV ejection fraction compared with baseline (before anthracycline) without heart failure symptoms or ≥5% reduction, with symptoms, from baseline to <55% at each time point during follow-up.[30]

Cardiopulmonary exercise testing. At the completion of trastuzumab therapy (time 6), cardiorespiratory fitness (measured as peak oxygen consumption [Vo_{2peak}]) was assessed using a cardiopulmonary exercise test at 10 W/min,[31] performed on an upright electronically braked cycle ergometer (Lode Corival) with 12-lead electrocardiographic monitoring. Vo_{2peak}

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TABLE 1 Participant Characteristics at Baseline

Age, years	51.4 ± 8.9
Cancer side	
Left	55 (63)
Right	31 (35)
Bilateral	2 (2)
Disease stage	
I	8 (9)
II	54 (61)
III	26 (30)
IV[a]	1 (1)
Breast cancer treatment	
Cumulative epirubicin equivalent dose, mg/m^2	309.0 ± 21.7
Radiation	76 (86)
Heart radiation dose, cGy	187.0 ± 92.4
Cardiovascular risk factors	
Diabetes mellitus	4 (5)
Hypertension	11 (13)
Hyperlipidemia	8 (9)
Smoking history	23 (26)
Cardiac medications	
Beta-blockers	3 (3)
Angiotensin II receptor blockers	2 (2)
ACE inhibitors	3 (3)
Statins	4 (5)
Echocardiographic measures	
E velocity, cm/s	69.6 ± 15.8
A velocity, cm/s	62.2 ± 16.7
E/A ratio	1.2 ± 0.4
e′ lateral, cm/s	11.5 ± 3.2
e′ septal, cm/s	8.42 ± 2.4
E/e′ ratio (average)	7.2 ± 1.9
LAVi, mL/m^2	26.9 ± 5.9
TR velocity, m/s[b]	2.0 ± 0.3
LVMi, g/m^2	61.3 ± 14.0
3D LVEF, %	61.4 ± 3.3
GLS, %	20.4 ± 1.7
Diastolic dysfunction	6 (7)
Diastolic grade	
Grade 1	2 (2)
Grade 2	1 (1)
Grade 3	0 (0)
Indeterminate	3 (3)

Continued on the next page

was defined as the highest rate of oxygen consumption over a 15- to 20-second interval within the last 90 seconds of exercise.[32] The Medgraphics Ultima series was used for breath-by-breath respiratory gas analyses. The test was terminated for exhaustion, symptoms, or standard reasons for test discontinuation.[31] All tests were conducted by an exercise physiologist blinded to all unnecessary clinical and study-related information.

STATISTICAL ANALYSIS. The Shapiro-Wilk test was used to assess the normality of the data. Continuous variables are presented as mean ± SD or median (IQR). Categorical data are presented as counts with percentages. Between-group differences in continuous variables were assessed using 2-sample *t* tests. Between-group differences in categorical variables were compared using the chi-square or Fisher exact test. We first visualized profiles of MVPA, QoL, and cardiac function measures and their changes from baseline (current minus baseline) over the treatment period. The overall time profiles were estimated using generalized estimating equations (GEEs) with natural cubic splines with 4 degrees of freedom.

We separately quantified the concurrent associations of MVPA in minutes (continuous) or MVPA status (active vs inactive) with QoL and cardiac function measures. GEEs were applied to account for the longitudinal observations with an independent working correlation matrix. We used the identity link and logit function for continuous (eg, GLS) and binary (eg, CTRCD) outcomes, respectively. We adjusted for age, time, epirubicin equivalent dose, mean heart radiation dose (time-varying covariate), cardiac medication, and presence of ≥1 cardiovascular disease risk factor (ie, diabetes, hypertension, dyslipidemia, and smoking). We report the results of the GEE analysis in terms of regression coefficients (β) for continuous outcomes and odds ratios (ORs) for binary outcomes. The corresponding 95% confidence intervals (CIs) and *P* values were calculated using robust sandwich estimators.

Associations between post-treatment Vo_{2peak} and total cumulative MVPA (ie, sum of MVPA reported at each visit during treatment) were assessed via univariable and multivariable linear regression analyses. Variables considered in the univariable analysis were dichotomous parameters (ie, cardiovascular disease risk factors, new diastolic dysfunction or CTRCD during treatment) and continuous parameters (ie, age, CMR LV ejection fraction, 3-dimensional LV ejection fraction, E/A ratio, and E/e′ ratio post-treatment). Variables with *P* values <0.10 in the univariable analysis were included in the multivariable models. Our exploratory analysis assessed the association between overall activity levels (ie, inactive, somewhat active, highly active) and post-treatment Vo_{2peak} using univariable and multivariable linear regression analysis adjusting for the same variables. The results of the multivariable regression models are reported as regression coefficients (β) with their 95% CIs.

Very few participants had missing values, and missingness was at random. Thus, mean imputation was used for missing baseline variables, and the last observation carried forward approach was used for missing values at subsequent time points. Total imputed values were <5% of the data. We performed

TABLE 1 Continued

Cardiovascular magnetic resonance measures	
LVEF, %	63.3 ± 4.3
Quality of life (EQ-5D-3L; n = 79)	
EQ-5D-3L index score	0.8 ± 0.2
EQ-5D-3L VAS	71.6 ± 21.4
Quality of life (MLHFQ; n = 79)	
Overall HRQoL	15.0 ± 16.6
Physical HRQoL	5.0 ± 6.9
Emotional HRQoL	6.0 ± 5
Physical activity questionnaire (GLTEQ; n = 76)	
MVPA duration, min/wk	105 (0-360)
Meeting cancer PA guidelines[c]	42 (48)

Values are mean ± SD, n (%), or median (IQR). [a]1 patient had stage 3 disease at study enrollment but early during treatment was found to have solitary metastasis to the liver. She was kept in the study, as she followed the same cancer regimen. [b]Data were available for 46 of 88 patients. [c]Participating in ≥90 minutes of MVPA per week.

3D = 3-dimensional; ACE = angiotensin-converting enzyme; E/A = ratio of early to late mitral inflow diastolic velocities; E/e′ = ratio of mitral inflow early diastolic velocity and mean of the mitral annular medial and lateral velocities (used as marker of left ventricular filling pressures); GLS = global longitudinal strain; GLTEQ = Godin Leisure Time Exercise Questionnaire; HRQoL = health-related quality of life; LAVi = left atrial volume index; LVEF = left ventricular ejection fraction; LVMi = left ventricular mass index; MLHFQ = Minnesota Living With Heart Failure Questionnaire; MVPA = moderate to vigorous physical activity; TR = tricuspid regurgitation; VAS = visual analogue scale.

a sensitivity analysis using a subcohort with all MVPA data available for every time point (ie, complete case analysis). Statistical tests were 2 sided, and P values <0.05 were considered to indicate statistical significance. All statistical analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

PATIENTS. Of the 136 total participants in the EMRBACE-MRI 1 study, 88 (mean age 51.4 ± 8.9 years) with adequate PA data were included in this analysis. Clinical characteristics of the included participants are provided in Table 1. The primary reason for exclusion was the absence of PA data, which started being collected partway through the EMBRACE-MRI 1 study. There were no significant differences in measured baseline characteristics or cancer treatments between the included and excluded participants (Supplemental Table 1). The average total cumulative epirubicin equivalent dose was 309.0 ± 21.7 mg/m^2, and 76 of 88 participants (86%) received radiation therapy (63% left sided), with a mean heart radiation dose of 187.0 ± 92.4 cGy. During treatment, CTRCD occurred in 28 of 88 participants (32%), and new diastolic dysfunction occurred in 24 of 88 participants (27%) (17 [71%] grade I, 1 [4%] grade II, 0 [0%] grade III, and 6 [25%] indeterminate [ie, unable to determine grade]). None of the 6 participants with baseline diastolic dysfunction had worsening diastolic dysfunction grade during treatment. Baseline values for MVPA duration, QoL, and cardiac measures are provided in Table 1.

MVPA, QoL, AND CARDIAC FUNCTION DURING TREATMENT. There was an early decline in MVPA after treatment initiation (Central Illustration), with the nadir observed after anthracycline therapy (time 2) and at 3 months into trastuzumab therapy (time 3), with gradual return to baseline by 6 to 9 months (times 4 and 5) into trastuzumab therapy ($P < 0.001$) (Figure 1A). The proportion of patients classified as active at each visit followed a similar trend as MVPA engagement (Figure 2). There was a significant decrease across QoL measures ($P < 0.001$ for all) (Figures 1B to 1F) at times 2 and 3, with subsequent improvement by times 4 and 5. When we considered changes in MVPA and QoL measures from baseline, similar patterns were observed (Figure 3). Ejection fraction–defined and GLS-defined measures of cardiac function decreased over the treatment period ($P \leq 0.01$ for all) (Figure 4), with the lowest values seen at times 3 and 4. These measures remained below baseline (time 1) at the post-treatment time point (time 6). Markers of diastolic dysfunction gradually increased with the highest values seen at time 5 ($P \leq 0.01$ for all) (Figure 4).

ASSOCIATIONS AMONG MVPA, QoL, AND CARDIAC FUNCTION DURING TREATMENT. Every 30-minute increase in MVPA was associated with better QoL (measured as lower MLHFQ overall score by 0.42 points, lower MLHFQ physical score by 0.24 points, higher EQ-5D-3L VAS score by 0.43 points, and higher EQ-5D-3L index score by 0.003; $P \leq 0.011$ for all) and cardiac function (measured as higher E/A ratio by 0.01 and higher GLS by 0.04; $P \leq 0.001$ for all) in covariate-adjusted concurrent analyses (Table 2).

In the covariate-adjusted concurrent analysis, being labeled active at individual follow-up visits was associated with better MLHFQ overall score (7.8 points), MLHFQ physical score (4.4 points), EQ-5D-3L VAS score (7.7 points), and EQ-5D-3L index (0.05); higher E/A ratio (0.15) and GLS (0.49%); and lower E/e′ ratio (0.57) ($P \leq 0.029$ for all) at that visit (Table 2).

ASSOCIATIONS BETWEEN MVPA AND POST-TREATMENT CARDIORESPIRATORY FITNESS. Over the treatment period, every 30-minute increment of greater cumulative MVPA was associated with a +0.06-mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ higher Vo_{2peak} ($P < 0.001$) in the covariate-adjusted analysis (Table 3). Compared with inactive participants, participants who were

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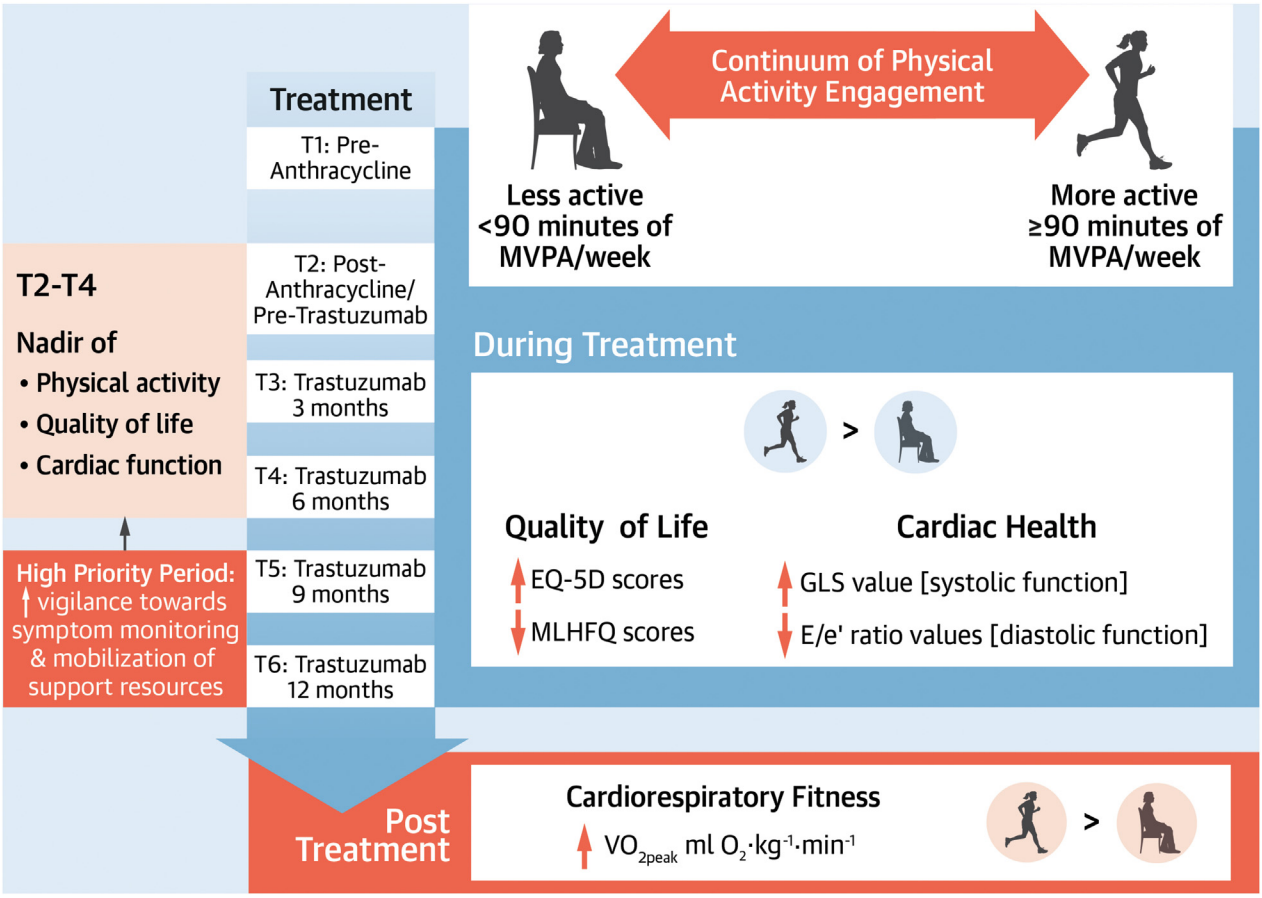
CENTRAL ILLUSTRATION **Physical Activity, QoL, and Cardiac Function with Anthracyclines & Trastuzumab**



The nadirs of moderate to vigorous physical activity (MVPA) level, quality of life (QoL), and cardiac function measures occurred either after anthracycline or within 6 months of trastuzumab therapy initiation. Higher self-reported MVPA was associated with better QoL and cardiac function measures during treatment and higher post-treatment cardiorespiratory fitness in participants with human epidermal growth factor receptor 2–positive breast cancer. Cardiopulmonary exercise testing was performed after trastuzumab therapy.

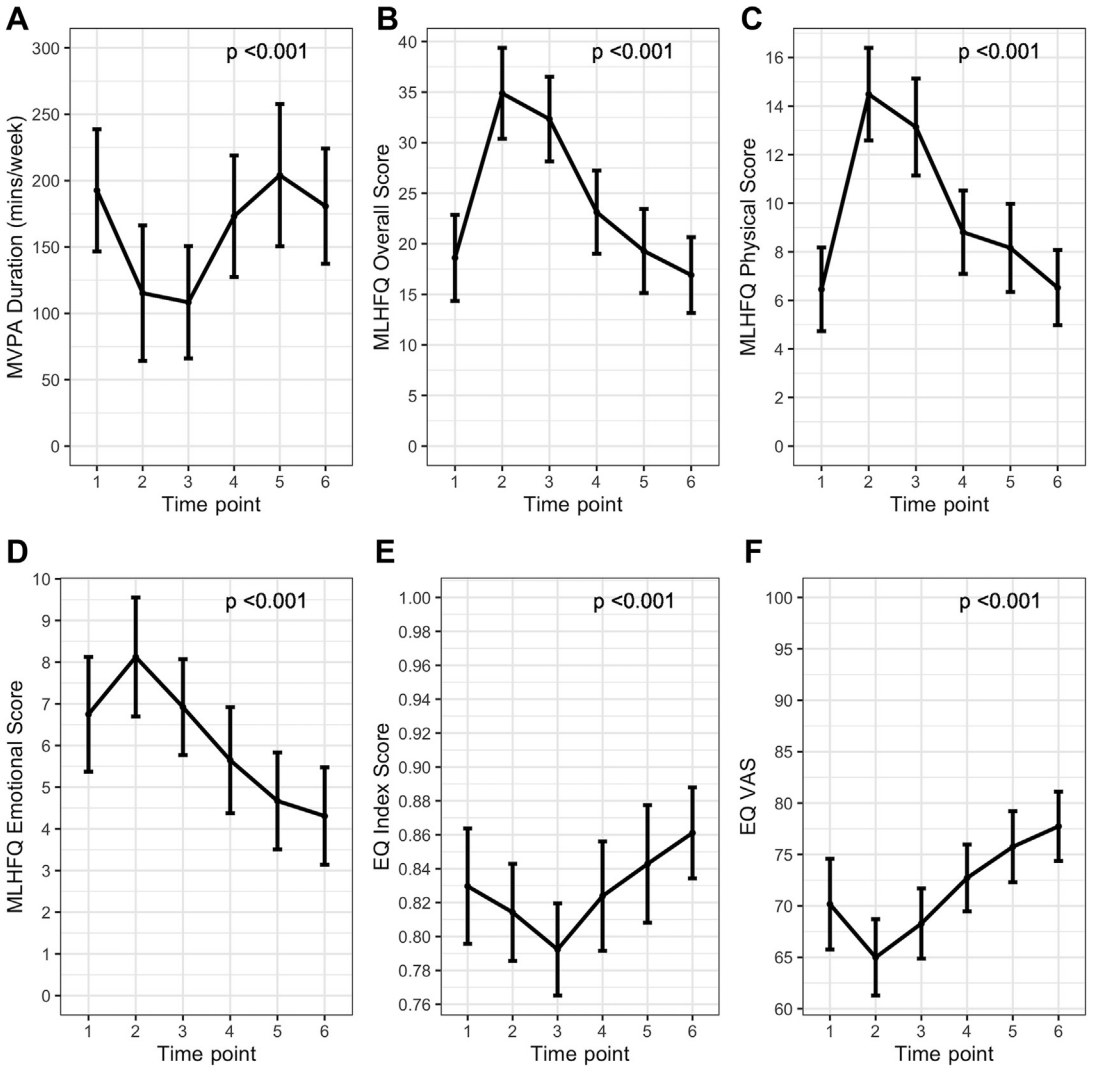
somewhat active and highly active had significantly higher post-treatment Vo_{2peak} values by 2.7 and 5.7 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in covariate-adjusted analysis, respectively ($P < 0.01$ for all) (**Table 4**). There were no statistically significant differences in baseline cardiovascular disease risk factors, cardiac medications, and QoL in the combined group of participants from the somewhat active and highly active groups compared with participants in the inactive group (Supplemental Table 2); however, the combined somewhat and highly active participants had higher e′ septal velocity ($P = 0.014$).

SENSITIVITY ANALYSIS. We performed complete case analysis in 68 participants without any missing MVPA data. The findings remained consistent with the primary analysis with significant concurrent association between MVPA and during treatment measures of QoL and cardiac function (Supplemental Table 3) and post-treatment cardiorespiratory fitness (Supplemental Table 4).

DISCUSSION

Our study characterized MVPA engagement, QoL, and cardiac systolic and diastolic function measures during cancer treatment and post-treatment cardiorespiratory fitness in women with HER2+ breast cancer. We found that: 1) there were concurrent declines in MVPA, QoL, and measures of cardiac systolic and diastolic function early during treatment (first

FIGURE 1 **Time Profiles of MVPA and QoL Over the Treatment Period**



Nadir values for **(A)** moderate to vigorous physical activity (MVPA) and **(B to F)** quality of life (QoL) measures occurred at time points 2 and 3. **Error bars** represent 95% CIs, on the basis of generalized estimation equation model with natural cubic splines. *P* values reflect changes over the entire observation period. MLHFQ = Minnesota Living With Heart Failure Questionnaire; VAS = visual analogue score.

6 months) with recovery in MVPA and QoL, but not cardiac systolic function measures, by treatment completion; 2) at each time point, both higher levels of MVPA (continuous measure) and meeting the cancer PA guidelines (binary measure) were associated with better QoL and cardiac systolic and diastolic function measures; and, 3) higher cumulative MVPA across the entire cancer treatment period or better overall PA classification (ie, somewhat active and highly active) was associated with higher cardiorespiratory fitness following treatment.

MVPA DURING TREATMENT. Our participants experienced significant decreases in MVPA during anthracycline treatment and 3 months into trastuzumab therapy (times 2 and 3); however, MVPA returned to, and remained near, baseline levels from 6 months into trastuzumab therapy (time 4) to its completion (time 6). This decline may have been attributable to physical treatment-related sequelae (eg, anthracycline-related nausea and fatigue, taxane-related neuropathies and musculoskeletal pain) and related psychosocial sequelae (eg,

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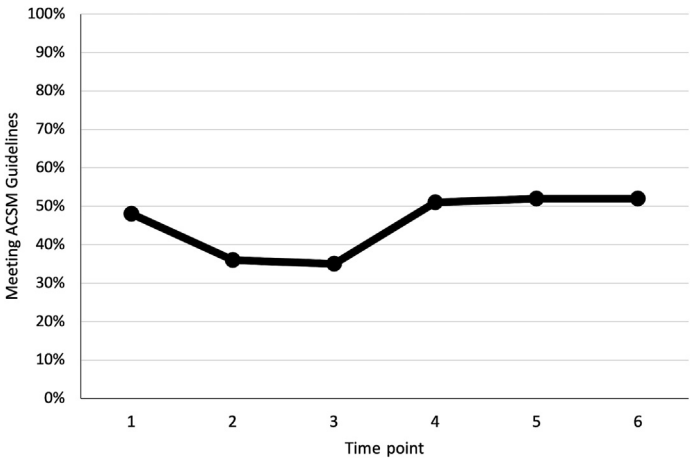
FIGURE 2 Proportion of Active Participants at Each Time Point During Treatment



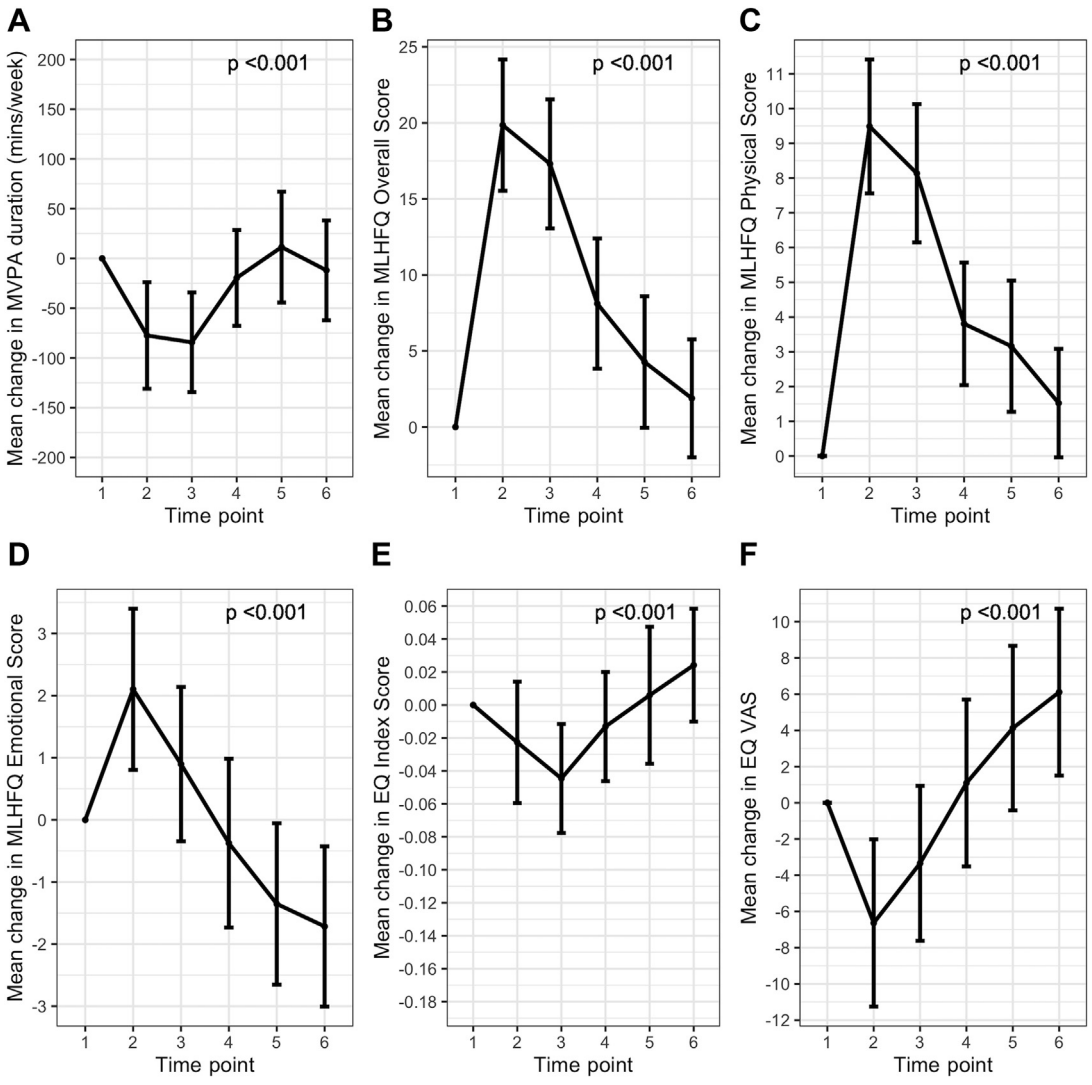
Active participants engaged in ≥90 minutes of moderate to vigorous physical activity. The proportion meeting this target was the lowest at time points 2 and 3.
ACSM = American College of Sports Medicine.

increased stress or anxiety). Indeed, in our sample, anthracycline and taxane therapies were complete by times 2 and 3, respectively, potentially explaining the improvement in MVPA by time 4 (6 months into trastuzumab therapy). However, we acknowledge the possibility of a reverse relationship with reduced PA engagement potentially having contributed to these symptoms.[33] Our results are consistent with findings from other studies that similarly observed decreased MVPA during anthracycline treatment with partial or complete recovery at 1- year postdiagnosis and beyond.[34] However, these prior findings may not have been generalizable to our sample, because they did not assess the relationship between MVPA and other outcomes and together had only 35 participants with HER2+ breast cancer.[34] Moreover, our participants received prolonged cancer treatment (~15 months) and were at higher risk for CTRCD. Thus, our study adds to the available research by comprehensively assessing the trajectory of MVPA throughout treatment and its associations with key measures of cardiac function and psychosocial outcomes in women with HER2+ breast cancer.

MVPA AND QoL DURING TREATMENT. The causes of worsening QoL in breast cancer survivors are likely multifactorial and at least partially overlap with those limiting PA engagement, as suggested by the similar trajectories of MVPA and QoL in our study. The improvement in EQ-5D-3L index, EQ-5D-3L VAS, and MLHFQ emotional scores at post-treatment may be related to the overall increase in MVPA (via favorable effects on physical functioning, mental health, and positive social engagement)[35] or may simply reflect the spontaneous improvement in participants' outlook following treatment relative to at diagnosis. Conversely, the persistent reduction in overall and physical MLHFQ scores suggests that survivors experience ongoing physical limitations despite the normalization of MVPA levels. The nature of these residual limitations remains unclear and should be the target of future research. The consistency in associations between MVPA and QoL measures in our study reinforces the interrelatedness of these outcomes, as previously reported;[36] however, causal relationships cannot be confirmed given our observational design. Notwithstanding the design limitations, randomized trial data indicate that exercise training improves QoL, and many of its determinants (eg, fatigue, symptom burden), within breast cancer survivors.[8]

MVPA AND CARDIAC FUNCTION DURING TREATMENT. Currently, there are limited strategies to reduce the risk for CTRCD (systolic or diastolic dysfunction) without adversely affecting cancer outcomes among women with HER2+ breast cancer. The prophylactic use of neurohormonal blockade has been evaluated; however, study results have been heterogenous[37] and the vasoactive effects of these drugs may negatively affect patients' QoL. Our results support the need for future studies that test whether increasing MVPA engagement during treatment reduces the incidence and severity of myocardial dysfunction. The positive association between MVPA and GLS reported here supports previous findings from a study of women with HER2-negative breast cancer demonstrating that moderate- to vigorous-intensity aerobic and resistance exercise during anthracycline treatment was associated with better GLS assessed via CMR following treatment.[38] Moreover, our diastolic function findings are aligned with that of a study in women with anthracycline-treated HER2-negative breast cancer wherein greater patient-reported PA levels were associated with a delay in the worsening of diastolic function.[39] As in previous studies, the observational nature of our design makes it difficult to determine whether increased MVPA levels may have caused, or resulted from, better cardiac function in this patient group. However, strategies to preserve systolic and diastolic function in these patients are important as changes in both GLS[40] and diastolic function measures[41] are prognostic of future

FIGURE 3 **Mean Changes From Baseline for MVPA and QoL**



Largest changes in **(A)** MVPA and **(B to F)** QoL measures occurred at time points 2 and 3. **Error bars** represent 95% CIs, on the basis of a generalized estimating equations model with natural cubic splines. *P* values reflect changes over the entire observation period. Abbreviations as in Figure 1.

CTRCD. MVPA has many established cardiovascular benefits, including physiological cardiac and vascular remodeling, improved antioxidant defenses and endothelial function, supporting favorable hormonal and growth factor profiles, and preventing and treating cardiovascular disease risk factors;[42] however, the specific mechanisms through which MVPA may mitigate CTRCD have been proposed[43] but not confirmed in humans and should be considered in future investigations.

MVPA DURING TREATMENT AND POST-TREATMENT CARDIORESPIRATORY FITNESS. Reductions in cardiorespiratory fitness have been frequently reported in breast cancer patients and survivors.[3] Up to 26% of breast cancer survivors have cardiorespiratory fitness below the threshold for functional independence,[44] and lower cardiorespiratory fitness in survivors is associated with worse cardiovascular disease, cancer, and overall mortality.[5] Therefore, strategies to maintain and improve cardiorespiratory

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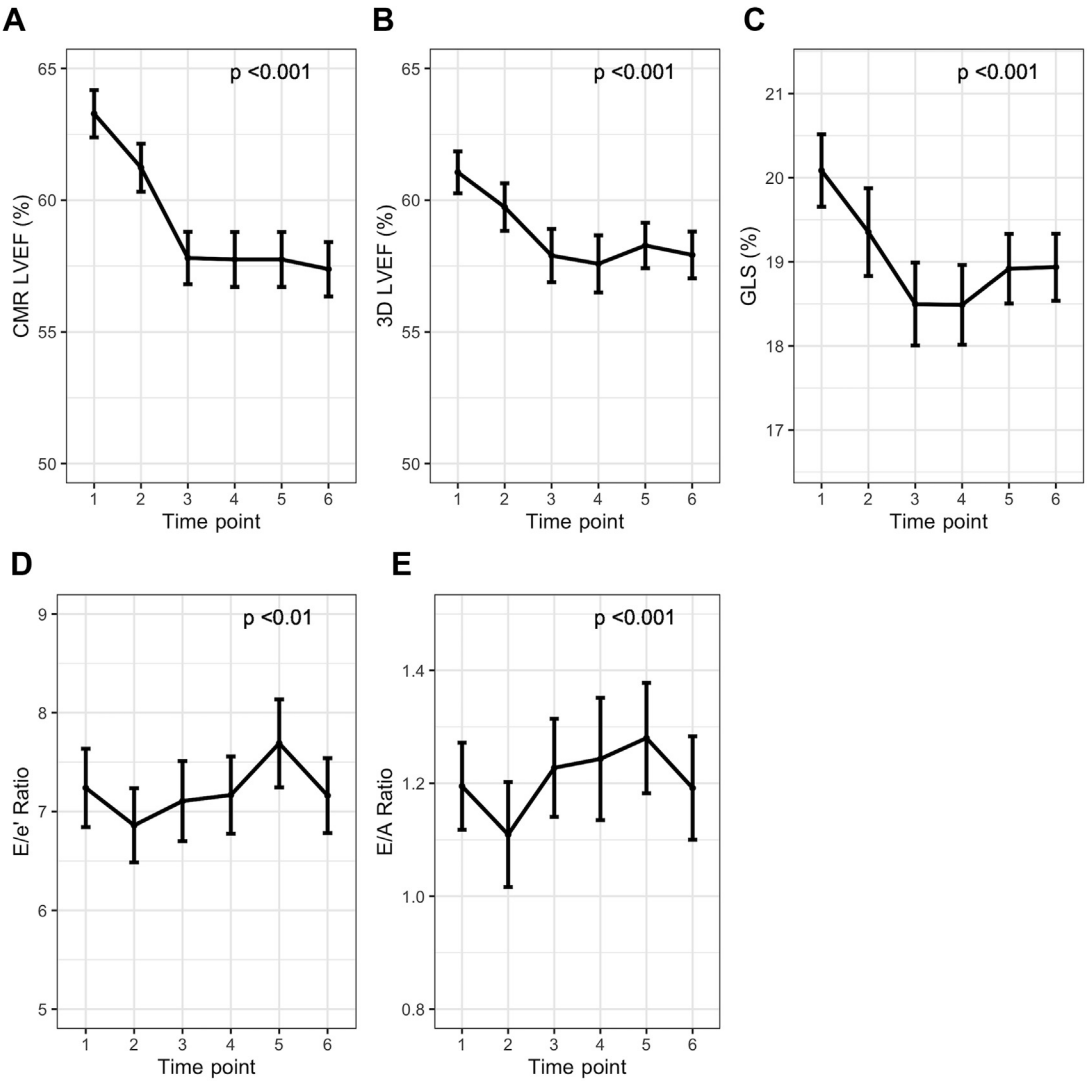
FIGURE 4 **CMR LVEF and Echocardiographic Measures During Treatment**



Nadir values for **(A)** cardiac magnetic resonance (CMR), **(B)** 3 dimensional (3D) left ventricular ejection fraction (LVEF), and **(C)** global longitudinal strain (GLS) (absolute values) occurred at time points 3 and 4. Peak values of **(D)** E/e' ratio and **(E)** E/A ratio occurred at time point 5. **Error bars** represent 95% CIs, on the basis of a generalized estimating equations model with natural cubic splines. *P* values reflect changes over the entire observation period. E/A = ratio of early to late mitral inflow diastolic velocities; E/e′ = ratio of mitral inflow early diastolic velocity and mean of the mitral annular medial and lateral velocities (used as marker of left ventricular filling pressures).

fitness are likely important. In our study, participants reporting greater MVPA during cancer treatment had better cardiorespiratory fitness following the completion of trastuzumab therapy. In our exploratory analysis, participants who were classified as being highly active throughout treatment had a 5.74 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ higher $V_{O_{2peak}}$ compared with those classified as inactive. We recognize the possibility of reverse causation; however, these findings are consistent with meta-analytical data[9] from randomized trials demonstrating that exercise training improves cardiorespiratory fitness irrespective of cancer type and treatment phase.

CLINICAL IMPLICATIONS. If confirmed by others, our findings have important clinical implications. Patients with cancer experience concurrent adverse physical and psychosocial sequelae that may be preventable by initiating regular exercise training

TABLE 2 Concurrent Associations Between MVPA Levels and Outcome Measures During Cancer Treatment

	MVPA Continuous		Meeting Cancer PA Criteria	
	Adjusted Coefficient (95% CI)[a]	*P* Value	Adjusted Coefficient (95% CI)[a]	*P* Value
CMR LVEF	0.02 (−0.06 to 0.09)	0.66	−0.38 (−1.42 to 0.65)	0.47
3D LVEF	0.06 (−0.01 to 0.13)	0.073	0.23 (−0.67 to 1.18)	0.62
GLS	0.04 (0.02 to 0.06)	<0.001	0.49 (0.05 to 0.93)	0.029
MLHFQ overall	−0.42 (−0.75 to −0.10)	0.011	−8.33 (−12.34 to −3.31)	<0.001
MLHFQ physical	−0.24 (−0.38 to −0.11)	<0.001	−4.70 (−6.37 to −3.04)	<0.001
MLHFQ emotional	−0.05 (−0.14 to 0.04)	0.24	−0.84 (−2.01 to 0.41)	0.19
EQ-5D-3L VAS	0.43 (0.15 to 0.71)	0.003	8.22 (4.53 to 11.91)	<0.001
EQ-5D-3L index score	0.003 (0.001 to 0.005)	0.008	0.053 (0.020 to 0.085)	0.001
E/A ratio	0.01 (0.01 to 0.02)	<0.001	0.14 (0.04 to 0.24)	0.007
E/e′ ratio	−0.02 (−0.05 to 0.01)	0.10	−0.53 (−0.96 to −0.11)	0.014
Diastolic dysfunction[b]	0.99 (0.94 to 1.04)[c]	0.58	0.91 (0.47 to 1.76)[c]	0.78
CTRCD	0.97 (0.91 to 1.04)[c]	0.34	0.81 (0.35 to 1.89)[c]	0.63

MVPA is the independent variable, and quality-of-life and cardiac function measures are the dependent variables. MVPA was considered a continuous measure (coefficient per 30 minutes) and PA status a binary measure (performing ≥90 minutes vs performing <90 minutes of MVPA per week). [a]Adjusted coefficients based on generalized estimating equations adjusted for age at baseline, presence ≥1 cardiovascular disease risk factor, cardiac medication, epirubicin equivalent dose, and radiation dose (time varying). [b]Development of new diastolic dysfunction in patients who had normal or indeterminate diastolic function at baseline or worsening diastolic function grade compared to baseline. [c]Reported as OR (95% CI).

CMR = cardiac magnetic resonance; CTRCD = cancer therapy-related cardiac dysfunction; PA = physical activity; other abbreviations as in Table 1.

early into their cancer treatment. However, most medical oncology and cardio-oncology programs do not have access to exercise support services. At a minimum, clinicians should encourage patients to meet the recommended ≥90 minutes per week of MVPA at every clinical contact. This may be particularly relevant for inactive patients at baseline. MVPA has established physical and psychosocial benefits and these factors are known to reciprocally influence each other. Therefore, the simple act of primary healthcare team members endorsing regular MVPA engagement in patients and referring them to available support services may initiate a positive cascade of health benefits and behaviors for patients during and following treatment.

STUDY LIMITATIONS. This was a single-center study with a modest sample size, and we did not assess cardiorespiratory fitness at baseline. However, we had follow-up data at 528 total time points, used the more precise CMR to define CTRCD, and had

TABLE 3 Associations Between End of Treatment Clinical, Imaging, and MVPA and End of Treatment Cardiorespiratory Fitness

	Univariable Analysis		Multivariable Analysis	
	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Age	−0.16 (−0.27 to −0.04)	0.009	−0.03 (−0.14 to 0.08)	0.58
Diabetes mellitus	−3.45 (−8.52 to 1.62)	0.18		
Hypertension	−3.153 (−6.308 to 0.001)	0.050	−0.49 (−3.20 to 2.23)	0.72
Hyperlipidemia	−3.45 (−7.09 to 0.18)	0.062	−0.51 (−3.50 to 2.49)	0.74
Smoking history	−1.11 (−3.53 to 1.30)	0.36		
CMR LVEF	−0.09 (−0.31 to 0.12)	0.39		
3D LVEF	0.05 (−0.21 to 0.30)	0.72		
E/e′ ratio	−1.00 (−1.54 to −0.45)	<0.001	−0.65 (−1.13 to −0.16)	0.009
E/A ratio	5.51 (3.34 to 7.68)	<0.001	2.89 (0.64 to 5.13)	0.012
Diastolic dysfunction[a]	−1.92 (−4.28 to 0.44)	0.11		
CTRCD[a]	−1.57 (−3.84 to 0.69)	0.17		
Cumulative MVPA[b]	0.08 (0.05 to 0.11)	<0.001	0.06 (0.03 to 0.09)	<0.001

Clinical and imaging measures and MVPA are the independent variables, and cardiorespiratory fitness is the dependent variable. MVPA levels were considered as total cumulative MVPA over treatment period (continuous measure). Coefficients for all other measures are per unit change of each measure. For binary variables, the comparator is the absence of each measure (eg, hypertension). Variables included in the multivariable analysis were chosen on the basis of variables with *P* values < 0.10 on univariable analysis. [a]Diastolic dysfunction is defined as the development of new diastolic dysfunction in patients who had normal or indeterminate diastolic function at baseline or worsening diastolic function grade at any point during treatment compared to baseline. CTRCD is defined as the development of CTRCD at any time point during study follow-up. [b]Cumulative MVPA was the sum of MVPA reported at each visit (coefficient per 30 minutes).

Abbreviations as in Tables 1 and 2.

TABLE 4 Association Between Overall Physical Activity Status During Cancer Treatment and Post-Treatment Cardiorespiratory Fitness

Overall PA Status	n	Active at Baseline[a]	Active ≥1 Visit Between Time Points 2 and 4[b]	Mean Vo_{2peak} (mL O_2/kg/min)	Univariable Association, Coefficient (95% CI)	*P* Value	Multivariable Association, Coefficient [95% CI][c]	*P* Value
Inactive	27	6 (22%)	3 (11%)	16.2	—	—	—	—
Somewhat active	35	22 (63%)	31 (89%)	19.1	2.82 (0.72 to 4.92)	0.009	2.66 (0.69 to 4.63)	0.009
Highly active	26	26 (100%)	26 (100%)	23.6	7.39 (5.14 to 9.64)	<0.001	5.74 (3.51 to 7.96)	<0.001

Values are n (%) unless otherwise indicated. Overall physical activity status is the predictor, and cardiorespiratory fitness is the outcome (Vo_{2peak}). Overall physical activity status is defined as inactive (active at 0 or 1 visit), somewhat active (active at 2-4 visits), and highly active (active at 5 or 6 visits). [a]Number of participants in each activity group who reported as meeting cancer PA guidelines level of activity at baseline visit. [b]The respective numbers of patients in each of the activity categories who were deemed active at ≥2 visits between visits 2 and 4 were 0 (0%), 7 (20%), and 26 (100%), respectively. This information is provided to demonstrate that patients who were somewhat active or highly active were in fact active at the time when cardiac function and quality of life measures were the lowest for the entire cohort. [c]Adjusted for the same variables as in Table 3 that were found to have univariable associations with Vo_{2peak} with a p-value< 0.1.

PA = physical activity; Vo_{2peak} = peak oxygen consumption.

comprehensive echocardiographic assessment at each time point. The incompleteness of PA and QoL data in all EMBRACE-MRI 1 participants was due primarily to the delayed addition of these outcomes to the study. However, there were no systematic differences between included and excluded participants. MVPA was quantified via self-report and not objectively via digital activity trackers. However, prior studies have demonstrated moderate to good associations between patient-reported MVPA using the Godin Leisure Time Physical Activity Questionnaire and objectively quantified MVPA.[17]

CONCLUSIONS

Women with HER2+ breast cancer receiving anthracyclines and trastuzumab experienced concurrent declines in MVPA, QoL, and cardiac function early into treatment. Greater MVPA engagement during cancer treatment was associated with better QoL, diastolic and systolic cardiac function measures, and post-treatment cardiorespiratory fitness. Randomized controlled trials are required to evaluate the impact of regular MVPA engagement on cardiac and QoL outcomes in women with HER2+ breast cancer and whether MVPA should become a standard adjunct or supportive intervention in this group.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients undergoing treatment for HER2+ breast cancer experience concurrent declines in MVPA, QoL, and cardiac systolic and diastolic function that are most pronounced within the first 6 months of sequential cancer treatment with anthracyclines and trastuzumab.

We found significant associations among MVPA engagement, QoL, and cardiac function measures during treatment and post-treatment cardiorespiratory fitness. If found to be causal in future studies, these findings suggest that clinicians caring for women with HER2+ breast cancer should consider promoting regular MVPA engagement during each clinical contact, as it may lead to improved physical, psychosocial, and cardiovascular outcomes in this population.

TRANSLATIONAL OUTLOOK: Further research is needed to establish whether the higher levels of patient-reported MVPA are the cause, or a marker, of better QoL and cardiac function during treatment and better cardiorespiratory fitness following treatment for HER2+ breast cancer. Additional research to identify the optimal amount of MVPA to improve these outcomes would be warranted if a causal relationship between MVPA and these outcomes is established.

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KEY WORDS **anthracycline, cardiorespiratory fitness, echocardiography, physical activity, quality of life, trastuzumab**

APPENDIX **For supplemental tables, please see the online version of this paper.**