2022

Changes in physical activity and relationships to submaximal exercise capacity and cardiac function during breast cancer therapy

Moriah P. Bellissimo
VCU

CHANGES IN PHYSICAL ACTIVITY AND RELATIONSHIPS TO SUBMAXIMAL EXERCISE CAPACITY AND CARDIAC FUNCTION DURING BREAST CANCER THERAPY

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

By
Moriah P. Bellissimo
B.S., Georgia Southern University, 2013
M.S., Georgia State University, 2015
Ph.D., Emory University, 2020

Advisor: W. Gregory Hundley, MD
Department of Internal Medicine

Virginia Commonwealth University School of Medicine
Richmond, Virginia
May 2022

ABSTRACT

Background: Breast cancer (BC) survivors are at high risk for cardiovascular diseases (CV) due to curative cancer therapies. In non-cancer populations, physical activity (PA) is a first line treatment for preventing CV disease. This study examined whether more PA was associated with better submaximal exercise capacity and cardiac function during the first three months of cancer therapy.

Methods: Participants included 223 women with stage I-III BC before therapy and after three months of undergoing treatment and 126 controls. Leisure time PA was reported using the Godin Sheppard leisure time PA questionnaire. Cardiac function was assessed by cardiac magnetic resonance, and submaximal exercise capacity was determined by 6-minute walk distance (6MWD).

Results: On average, women in the BC group were older (55.6 ± 10.9 y vs. 50.6 ± 14.1 y, $p<0.001$). The majority of women with BC were white (n=172, 77%) and had a mean body mass index of 29.4 ± 6.2, which was similar to the control group (28.4 ± 6.8, $p=0.19$). Women with BC reported similar PA scores at baseline (24.7 [95% CI: 21.7, 28.0]) relative to non-cancer controls (29.4 [95% CI: 25.0, 34.2]), which declined to 16.9 (95% CI: 14.4, 19.6) in the BC group at three months with 60% of women with BC reporting insufficient activity at three months. Among BC participants, higher PA during the study period was related to a higher submaximal exercise capacity (6.9 ± 1.6, $p<0.001$) and lower left ventricular (LV) strain (-0.16 ± 0.07, $p=0.03$). An increase in activity over the three months was also associated with decreased likelihood of having chemotherapy-related cardiac dysfunction (-0.02 ± 0.01, $p=0.03$) according to LV strain change >15%. Women categorized as active were protected from negative changes in exercise capacity, LV end systolic volume, LV ejection fraction, and LV strain.

Conclusions: PA declined in the first three months of receiving cancer therapy; however, maintaining PA during cancer therapy mitigated declines in exercise capacity and cardiac function that are often observed in this population.

INTRODUCTION

Substantial advancements in early detection and medical treatments for women diagnosed with breast cancer (BC) have increased the current 5-year cancer-related survival rate to 90% [1]. However, commonly used therapies to treat BC, such as anthracycline-based chemotherapy (anthra-bC) and chest radiotherapy, have known cardiotoxic side effects including injury to cardiac myocytes and other cells, increased oxidative stress, and reductions in left ventricular ejection fraction (LVEF), thereby accelerating the risk for cardiovascular (CV) disease in these patients, including the development of heart failure (HF) [2-5]. In fact, CV events are now the leading cause of morbidity and mortality among women diagnosed with stage I-III BC[6,7]. The improved survival rates of BC coupled with the growing number of women at increased risk CV, has motivated the investigation of factors impacting the onset and progression of CV complications to inform intervention strategies to reduce CV events in this population.

Physical activity (PA) participation may have utility to protect against CV complications in cancer populations. Strong evidence in non-cancer populations demonstrates higher levels of PA are associated with a reduction in the risk of CV disease and cancer incident[8,9]. In women with BC, higher levels of self-reported PA prior to initiating treatment, during treatment, and after completing treatment are related to lower risk of cancer and cardiovascular mortality[10]. There is a need to investigate if the cardioprotective benefits of PA may impact the onset and progression of CV complications in BC populations.

In women being treated for BC, often-observed decreases in exercise capacity and cardiac function may be key factors contributing to their increased risk for CV disease[2,11-13]. Evidence suggests PA participation may improve exercise capacity and cardiac function[14], yet the few studies investigating PA levels and cardiac function in cancer populations primarily take place after completion of cancer therapy[15,16]. One study reported modest but nonsignificant associations between higher amounts of self-reported PA and attenuated reductions of LVEF in

women after completion of BC therapy[16]. In a five-year prospective study, women who were more physically active had fewer symptoms of HF than physically inactive women following anthra-bC[15]. Preclinical work also demonstrates cardioprotective benefits of exercise in BC models[11]. Thus, PA participation may protect against CV complications, but there is a need to define longitudinal relationships between PA, exercise capacity, and cardiac function during BC treatment to inform intervention efforts.

The primary aims of this study were to describe levels of self-reported PA from baseline to three months after initiation of BC therapy and to test if these changes were related to submaximal exercise capacity and measures of cardiac function. As a variety of factors impact PA participation, a secondary aim was to assess if psychosocial and behavioral measures moderated the change in self-reported PA from baseline to three months of BC therapy.

METHODS

Population

Women enrolled in the UPBEAT (Understanding and Predicting Fatigue, Cardiovascular Decline, and Events After Breast Cancer) study were included in this secondary analysis (ClinicalTrials.gov Identifier NCT02791581). UPBEAT is a multi-center prospective cohort study enrolling women diagnosed with stage I to III BC. The study design and rationale along with detailed inclusion and exclusion criteria have been described previously[17]. In brief, inclusion criteria for both groups were age of 18 years or older with independent ambulatory status. Additional inclusion criteria for the BC group were a diagnosis of stage I to III BC, scheduled to receive chemotherapy, and having an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2. Exclusion criteria included contraindications for undergoing cardiovascular magnetic resonance (CMR) imaging, if previously-assessed, an LVEF <50%, current pregnancy or lactation, or uncontrolled metabolic or CV diseases. Women in the control group had no history of cancer or breast surgery and no previous chemotherapy. The current study includes data from baseline and the three month visits. In the BC group, visits were conducted before the initiation of therapy, and after the first three months of receiving treatment.

Clinical Data Collection

For the BC group, stage at diagnosis was determined according to the 8th edition of the American Joint Committee on Cancer Staging Manual[18], and medical treatment was retrieved from patients' medical records. Participant medical history was ascertained by medical chart review to document diagnosis of type 2 diabetes, hypertension, hyperlipidemia, and coronary artery disease.

Physical Activity Assessment

The Godin Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ) was used to measure self-reported PA participation[19]. This survey is frequently used in oncology research to assess leisure time PA[20]. Participants report weekly participation in mild, moderate, and strenuous activities. Data for each activity is then multiplied by respective metabolic equivalents of task (METs) values and summed to calculate a total weekly leisure score index. Using data from the moderate and strenuous activity responses, participants were also categorized as being active (≥24 units), moderately active (14-23 units), or insufficiently active (<14 units)[19]. The active category is in line with meeting weekly PA recommendations, which are associated with substantial health benefits[20].

Submaximal Exercise Capacity Assessment

Participants' submaximal exercise capacity was determined by completing a 6-minute walk test according to established guidelines[21] and measuring the 6-minute walk distance (6MWD). The 6MWD test took place on an indoor track or open corridor with no obstructions, and participants were instructed to cover as much distance as they could within six minutes at their own pace. All tests were observed and distances recorded in meters (m) by a trained study coordinator.

Psychosocial and Behavioral Measures

The Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-fatigue) questionnaire was used to assess fatigue. This questionnaire was self-administered or administered by a trained interviewer. The survey includes 13 items, and higher total scores indicate lower levels of fatigue (range 0-52). The Sleep Disturbance (PROMIS SF-8a) questionnaire was also completed by participants to self-report sleep disturbances. This 8-item survey is scored by summing each of the items and higher scores indicate greater sleep disturbance. Depression was assessed by the Center for Epidemiological Studies Depression Scale (CESD-10). Perceived stress was evaluated by Cohen's Perceived Stress Scale (PSS),

and social support was measured using the Medical Outcomes Study (MOS) Social Support survey.

Assessment of Cardiac Function

The primary measures of cardiac function included LVEF (%), LV end systolic volume (ESV, mL), LV end diastolic volume (EDV, mL), and LV mean myocardial circumferential strain (LV strain). Participants underwent a non-contrast 10-15 minute rapid CMR examination at baseline and three months. Each CMR assessment was analyzed by a core laboratory and CMR analysts were blinded to patient identifiers, the exam number, and prior CMR exams of the same measure. A double reading was performed on 15% of the CMR data for quality control. Participants were also categorized as having chemotherapy-related cardiac dysfunction (CTRCD) if they exhibited a decline in LVEF by at least 10 points from baseline to three months, or if the three month LVEF declined below normal (i.e., 50%). Study participants were also categorized as having cancer treatment-related cardiac dysfunction according to changes in LV strain if they exhibited a 15% increase in LV strain over the study period.

Statistical Analyses

Descriptive statistics were performed for all variables and summarized as mean ± standard deviation for continuous variables or count and % for categorical variables. The primary measures of leisure score index (i.e., total weekly PA), exercise capacity, and cardiac function measures were modeled as continuous outcomes. To account for a non-normal distribution, leisure score index was square root transformed. Where indicated, self-reported PA was also categorized as active, moderately active, or insufficiently active. To assess total weekly PA at baseline and three months in the study groups, a longitudinal linear mixed model was used with leisure score index as the outcome. Cancer status, age, body mass index (BMI), and visit were included as main effects, and an interaction term between cancer status and visit tested for a

difference in change over time between the groups. A patient level random effect was also included in the model. To examine if psychosocial or behavioral measures moderated the relationships in PA from baseline to three months, interaction terms between each psychosocial/behavioral measure and study visit were included in separate models. Differences in proportions of activity groups by visit were examined by chi square tests. Among healthy controls, no changes are expected within a three month timeframe for exercise capacity or cardiac function without receiving an intervention. Thus, analyses of relationships between PA, exercise capacity, and cardiac function were only conducted in BC participants. To test for relationships among BC participants between PA at baseline and three months to measures of submaximal exercise capacity (6MWD) and cardiac function measures (LV-ESV, LV-EDV, LVEF, and LV strain), separate longitudinal linear mixed effects models were used. For each model, cancer stage, age, BMI, anthra-bC receipt (yes/no), and visit were included as main effects, and a patient level random effect was also included. Interaction terms between PA and visit were used to test if change in total PA over time was related to submaximal exercise capacity or cardiac function. Interaction terms between cancer stage and visit and anthracycline treatment and visit were also tested. Lastly, multiple logistic regression was used to test if change in total PA was related to CTRCD, adjusting for age, BMI, cancer stage, anthracycline treatment, and baseline LVEF/LV strain. Statistical significance for all main effects was based on a significance level of 0.05, and interaction effects were deemed significant and left in the model at a significance level of 0.10.

RESULTS

Baseline demographic and clinical characteristics of both study groups are presented in **Table 1**. The BC group had a higher average age than the control group ($p<0.001$). Race/ethnicity between groups was similar ($p=0.80$) with White women constituting the majority of the cohort for the BC (77%) and control groups (80%). The average BMI for both groups was within the overweight category (29.4 ± 6.2 kg/m^2 for the BC group and 28.5 ± 6.9 kg/m^2 for the control group, $p=0.19$). Most women in the BC group were diagnosed with stage II BC (n=115, 52%), followed by stage I (n=85, 38%), and stage III (n=23, 10%). Of 223 women in the BC group, 109 (49%) received anthra-bC. Among comorbidities, there were no differences in prevalence of chronic disease between groups (all, $p>0.05$).

Comparisons of baseline and three-month PA between BC and control groups

Baseline and three month data for PA are shown in **Figure 1**. There was a significant change in activity score over time by study group (-0.25 ± 0.1, $p<0.001$). At baseline, the BC and control groups reported similar activity scores (24.7 [95% confidence interval, CI: 21.7, 28.0] versus 29.4 [95% CI: 25.0, 34.2], $p>0.05$), but activity scores declined to 16.9 (95% CI: 14.4, 19.6) in the BC group at three months (**Figure 1A**). BC participants reported a lower amount of moderate to strenuous activity at baseline compared to the control group (19.0 [95% CI: 16.5, 21.5] versus 24.8 [95% CI: 21.5, 28.1]), which significantly declined to 12.9 (95% CI: 10.4, 15.4) at three months. This was due to declines in both strenuous and moderate activity levels over the study period (**Figure 1B**).

PA was also described as a categorical outcome and reported as active, moderately active, and insufficiently active. There was a difference in proportion of activity groups at baseline ($p=0.02$) and three months ($p<0.001$) between cancer and control participants. At baseline among BC participants, 76 (34%) were considered active, 50 (22%) moderately active, and 97 (44%) insufficiently active while control participants had 61 (48%) categorized as active,

17 (25%) as moderately active, and 48 (38%) as insufficiently active. By three months, the proportions of activity groups among BC participants changed (p=0.002) with 49 (22%) considered active, 40 (18%) moderately active, and 134 (60%) insufficiently active compared to 66 (52%) as active, 26 (21%) as moderately active, and 34 (27%) as insufficiently active in the control group.

Changes in activity by BC stage and treatment receipt were also examined. There was a significant interaction by stage at diagnosis and activity over time. Relative to women diagnosed with stage I BC, control participants had higher activity (0.34 ± 0.11, p=0.002) over the study period while women diagnosed with stage II BC had greater declines in activity (-0.35 ± 0.11, p=0.002). By treatment, there was a significant change in total PA from baseline to visit two only between the control group relative to women who received anthracycline (0.34 ± 0.09, p<0.001) while women who did not receive anthracyclines exhibited similar change in activity over time to women who did receive anthracycline treatment (0.04 ± 0.09, p=0.66).

Upon examining relationships between psychosocial and behavioral variables and the change in PA over the study period, only fatigue attenuated the significant decrease in PA over the study period. Fatigue by study visit was not significantly related to total PA (0.12 ± 0.01, p=0.13); however, the change in PA was no longer significant after accounting for fatigue (0.09 ±0.08, p=0.24). Other measures including perceived stress, social support, depression, and sleep disturbances did not moderate the change in in PA from baseline to three months.

Relationships between PA from baseline to three months and submaximal exercise capacity

Results of the mixed effects model comparing total weekly PA to exercise capacity in BC participants are shown in **Table 2**. The relationship between total activity and time was not significant and was removed from the model (-2.2 ± 1.3 [95% CI: -4.7, 0.3]). Exercise capacity declined over the study period from 473 m at baseline (**Table 3**, 95% CI: 459, 486) to 454 m at three months (95% CI: 441, 468). Greater PA levels were associated with higher submaximal

exercise capacity (6.9 ± 1.6 m, p<0.001). The relationship between activity and exercise capacity remained significant (4.3 ± 1.4 m, p=0.002) following additional adjustment for fatigue (1.1 ± 0.4, p=0.002).

Analyses comparing relationships between activity groups and exercise capacity are shown in **Table 4. Figure 2** presents adjusted mean and standard error for each activity group, and group mean differences from baseline to three months are shown in **Table 5**. The relationships between the activity group did not depend on study visit; however, the active group did maintain a significantly higher exercise capacity relative to the insufficiently active group (20.6 ± 5.8 m, p<0.001) at three months. The insufficiently active group was the only group to exhibit a significant decline in exercise capacity from baseline to three months (p=0.03).

Relationships between PA from baseline to three months and cardiac function

Relationships between total weekly PA and cardiac function among BC participants are shown in Table 2. The were no significant relationships between total PA and time for models with LV-EDV, LV-ESV, and LVEF as the outcomes, so the interaction term was removed from each model. LV-EDV increased from baseline to three months (2.1 ± 0.8 mL, p=0.01), with an average increase of 0.7%. Higher PA over the study period (1.2 ± 0.4 mL, p=0.003) was related to a higher LV-EDV. LV-ESV increased significantly over the study period (2.6 ± 0.5, p<0.001) from 47.3 mL (95% CI: 45.2, 49.3, Table 3) at baseline to 52.5 mL (95% CI: 50.4, 54.7) at three months for an average increase of 8.7%. PA from baseline to three months was not significantly related to LV-ESV (0.3 ± 0.2 mL, p=0.18). LVEF among BC participants was (61.0% [95% CI: 59.9, 62.1]) at baseline, but LVEF declined significantly (-1.4 ± 0.3%, <0.001) by three months to 58.2% (95% CI: 57.1, 59.3). LVEF was not related to total activity over the study period (0.1 ± 0.1%, p=0.26). Baseline LV strain among BC participants was -20.1% (95% CI: -20.8, -19.4) and increased (i.e., worsened) to -17.8% (95% CI: -18.5, -17.1) at three months. Women who did not receive anthracyclines experienced less deteriorations in LV strain (-0.62 ± 0.17%,

p<0.001) relative to women who received anthra-bC. There was a significant relationship with total PA over time (-0.16 ± 0.07, p=0.03) such that women who were more active experienced a preserved LV strain over the study period. All results with cardiac function measures remained following additional adjustment for fatigue.

Results of comparisons between activity groups and cardiac function measures are shown in Table 4 with group means presented in Figure 2, and mean differences for each activity group are shown in Table 5. For the outcomes LV-ESV, LV-EDV, and LVEF, relationships with the activity groups by time was not significant, and the interaction terms were removed from each model. There were no significant increases in LV-EDV by activity groups, but the active group exhibited the smallest absolute mean change (Table 5). Only the active group maintained similar LV-ESV values at baseline and three months while both the moderately active (p=0.03) and insufficiently active groups (p<0.001) had significant increases in LV-ESV. Regarding LVEF findings, only the insufficiently active group experienced a significant decline in LVEF from baseline to three months (p=0.002). The relationship between activity groups and LV strain varied by time (-0.53 ± 0.28, p=0.058). Both the moderately active (p=0.008) and insufficiently active groups (p<0.001) had significant changes in LV strain (Table 5), while the active group maintained a similar LV strain from baseline to three months.

PA and chemotherapy-related cardiac dysfunction

Of 185 BC participants with CMR data at baseline and three months, 34 (18%) met clinical criteria for CTRCD according to LVEF, including 19 participants with a decrease in LVEF below 50% and 26 participants with a decrease in LVEF of at least 10 percentage points. Women who met criteria for CTRCD reported a lower PA score at baseline (22.8 ± 18.9 vs. 33.0 ± 26.3, p=0.009) and (15.0 vs. 24.5, p=0.006) at three months compared to women with normal EF. Change in total PA levels over the study period was not related to likelihood of meeting cardiac dysfunction criteria by LVEF (0.004 ± 0.009, p=0.65). Nine women had LVEF baseline

values below 50% and were excluded from the analysis. There was no difference in activity categories by cardiotoxicity groups at baseline (p=0.6) or three months (p=0.16).

According to CTRCD classifications made by percent change in LV strain, 63 (37%) BC participants exhibited deteriorations in LV strain of 15% or greater. Women who met criteria for cardiac dysfunction reported slightly lower PA at baseline (20.3 [95% CI: 15.0, 26.4]) compared to women who did not meet criteria (27.7 [95% CI: 22.3, 33.6], p=0.05) but similar levels of activity at three months (16.8 [95% CI: 11.6, 23.1] versus 16.5 [95% CI: 12.0, 21.6], p=0.91). A difference in distribution of activity groups was also found at baseline with fewer active women categorized as meeting CTRCD criteria (41% versus 22%, p=0.02). Activity group distribution at three months was similar (p=0.78). Change in activity over the study period was significantly related to likelihood of being classified as having CTRCD according to LV strain deteriorations (-0.02 ± 0.01, p=0.03), suggesting that for every unit increase in activity over the study period, the likelihood of meeting CTRCD criteria decreased by 2% (odds ratio 0.98, 95% CI: 0.97, 0.998).

DISCUSSION

Women who receive treatment for BC are at increased risk for CV disease. PA participation decreases the risk for CV disease in non-cancer populations and cancer survivors post-treatment, however, there is a lack of evidence investigating the relationships between PA and factors that influence CV disease risk such as exercise capacity and cardiac function in a cancer population actively receiving treatment. This study reports PA levels before initiation and through the first three months of cancer therapy and compared longitudinal relationships between PA and submaximal exercise capacity and cardiac function. Study groups reported similar levels of PA between control and BC participants at baseline, but PA significantly declined in the first three months of receiving curative treatment for BC, with 60% of the BC group reporting insufficient levels of PA. The evidence presented here also suggests a dose-response relationship of maintaining greater PA participation linked to preserved exercise capacity and measures of cardiac function including LV-ESV, LVEF, and LV strain, thereby providing evidence that PA participation during cancer therapy may reduce CV complications and disease risk.

In line with others who report decreased PA following a BC diagnosis, we report a decline in PA from pre-treatment through the first three months of treatment initiation[16,20,22,23]. BC participants reported an average activity score of 24.8 at baseline, which was higher than a recently reported pre-treatment median of 9.0 from a cohort of women with BC treated with trastuzumab and/or doxorubicin[16]. Total PA decreased to 16.9 at three months, which was attributed to a decrease in moderate and strenuous activity participation. Of the women in the BC group, 34% were categorized as sufficiently active at baseline, which declined to 22% at three months, and 60% of BC participants were insufficiently active at three months. Fatigue was a predictor of activity participation and accounting for fatigue attenuated the significant decline in PA reported over the study period. Given the strong evidence of the beneficial effects of PA to improve fatigue, physical function, and CV and cancer outcomes[10,24], increasing PA in

this population represents an important target for primary and secondary prevention of CV disease and recurrent malignancies. These findings suggest that interventions targeting increased PA levels should also consider targeting fatigue in this population.

Higher PA levels from baseline to three months were related to a greater exercise capacity, and women who were active at three months had significantly greater exercise capacity relative to insufficiently active women. Baseline 6MWD values were similar to the average of BC survivors in a recently published meta-analysis[25]. A cross-sectional study of women across the BC treatment and survivorship continuum detailed that women with BC often exhibit a lower exercise capacity than control participants and experience significant declines during cancer treatment[11,26]. Prospective data presented here suggests a dose-response relationship with PA levels to preserve exercise capacity during cancer treatment. On average, 6MWD declined by 22.5 meters among BC participants, which is considered a major decline in patients with heart failure[27] and meets criteria for a clinically meaningful change in exercise capacity[28]. However, women in the highest level of PA participation did not exhibit declines in exercise capacity. As exercise capacity is a function of cardiac output and oxygen delivery and uptake[29], these findings suggest that PA participation is acting on one of these elements to preserve exercise capacity. Declines in exercise capacity are common during BC therapy[11], and one intervention has shown that targeting increased PA in BC patients receiving treatment led to improvements in exercise capacity measured by 6MWD[30]. Together with previous work demonstrating positive effects of PA on physical functioning[24], psychosocial measures[31], and physical fitness[30], findings here contribute evidence that maintaining PA levels during cancer therapy helps to retain exercise capacity, an independent predictor of mortality[32].

In line with other studies detailing acute changes in cardiac function with BC therapy[33-38], findings reported here demonstrate significant declines in LV systolic function within the first three months of receiving cancer therapy. LVEF decreased significantly due to increases in LV-ESV with concomitant increases in LV-EDV. These changes are in line with work from our group

and others showing early deteriorations in cardiac function with administration of cancer therapies[33-38]. Total PA was not related to LVEF or LV-ESV; however, differences were observed by level of activity. Women who reported meeting moderate and strenuous PA guidelines experienced the greatest benefits for mitigating declines in cardiac function. Women in the active category were the only group to maintain LV-ESV from baseline to three months and did not exhibit significant declines in LVEF during the study period. These findings suggest that greater moderate and strenuous PA participation helps to retain cardiac function, which is an important factor determining exercise capacity.

Results reported here also demonstrated that individuals who continued PA participation throughout the first three months of receiving cancer therapy experienced an attenuated deterioration in LV strain. Women in the active category were the only activity group to preserve similar LV strain values from baseline to three months. Further, individuals who maintained activity over the study period were less likely to meet LV strain criteria for CTRCD. LV strain is a sensitive indicator of subclinical LV dysfunction and may increase secondary to increased LV-ESV or decreased LV-EDV[33,39]. LV strain may provide earlier detection of LV dysfunction relative to evaluations of LVEF, which has important implications for guiding clinical decision making for administering cancer and cardioprotective therapies[40]. In line with this, compared to 18% of BC participants who met CTRCD criteria by LVEF, CTRCD based on changes in LV strain identified 37% of women with BC who met criteria. Findings reported here support that greater total PA participation and meeting moderate and strenuous PA recommendations may help to preserve LV function via protection of LV strain during the first three months of cancer therapy.

Findings regarding LV strain, LVEF, and LV-ESV are some of the first in a human population actively receiving cancer treatment to support previous preclinical work demonstrating a cardioprotective effect of exercise in the context of receiving cancer treatment[11]. These preclinical studies, which used an anthracycline-induced model of

cardiomyopathy, have demonstrated cardioprotective benefits of exercise such as improvements in LV function [11]. However, less evidence is available in humans. One prospective study linked higher baseline PA to a positive change in LVEF over cancer treatment[16]. An intervention in women undergoing trastuzumab treatment for BC reported a decline in LVEF despite participation in aerobic training in the first four months of receiving trastuzumab[41]. Two recent pilot randomized controlled trials reported attenuated decline in cardiac function with a bout of exercise performed prior to receiving doxorubicin[42], and improved LVEF in the exercising group relative to controls[43]. In total, preclinical and limited clinical work suggests that exercise may be an effective strategy to prevent or mitigate the adverse effects of cancer treatment on cardiac function, and findings reported here corroborate this evidence.

Strengths of this study include the prospective design, which allows for establishing temporality between exposures and outcomes. This study also used cardiac function assessed by CMR, a gold standard technique due to its high spatial and temporal resolution, noninvasive nature, and lack of ionizing radiation. Limitations of the study include the use of self-reported PA data. Despite the survey being validated in BC populations against accelerometers[44], overestimation of PA participation may have occurred and use of accelerometry data would provide an objective and accurate measure of PA dose and frequency. Women in this study were enrolled shortly after receiving a BC diagnosis. This may result in selection bias of healthier women being more compelled to enroll and may not be reflective of the entire BC population.

Conclusions

The findings of this project may have important clinical implications providing evidence that PA may preserve exercise capacity and reduce cardiac dysfunction and cardiotoxicity among women undergoing treatment for BC. On average, self-reported PA declined from pre-treatment through the first three months of treatment; however, higher PA levels throughout the

study period were associated with greater exercise capacity and attenuated reductions in cardiac function in the first three months of receiving treatment for stage I-III BC. Continued study will determine if these relationships persist throughout the entirety of receiving treatment for BC.

Funding: Data collection was funded by the Wake Forest NCORP Research Base grant 2UG1CA189824 with support of the NCI Community Oncology Research Program (NCORP). Additional funding for this study was provided by grants from the National Institutes of Health, National Cancer Institute (R01CA199167 and T32CA093423).

Clinical Trial ID: NCT02791581 for WF97415 UPBEAT

Table 1. Baseline demographic and clinical characteristics			
	Breast Cancer N=223	**Control N=126**	**p-value**
Age at baseline, years	**55.6 ± 10.9**	**50.6 ± 14.1**	**<0.001**
Race			0.73
White	172 (77)	101 (80)	
Black	38 (17)	18 (14)	
Other (Asian, Native Hawaiian, or not reported)	13 (6)	7 (6)	
Ethnicity			0.80
Hispanic or Latino	2 (1)	2 (2)	
Stage at diagnosis			
I	85 (38)		
II	115 (52)		
III	23 (10)		
Anthracycline receipt	109 (49)		
BMI (kg/m^2)	29.4 ± 6.2	28.4 ± 6.8	0.19
History of hypertension	61 (31)	18 (21)	0.13
History of hyperlipidemia	66 (33)	27 (31)	0.57
History of coronary artery disease	1 (1)	1 (1)	0.67
History of diabetes	16 (8)	5 (6)	0.63
Data are presented as unadjusted means ± SD or n (%). Medical history included 199 participants in the breast cancer group and 88 participants in the control group Abbreviation: BMI, body mass index			

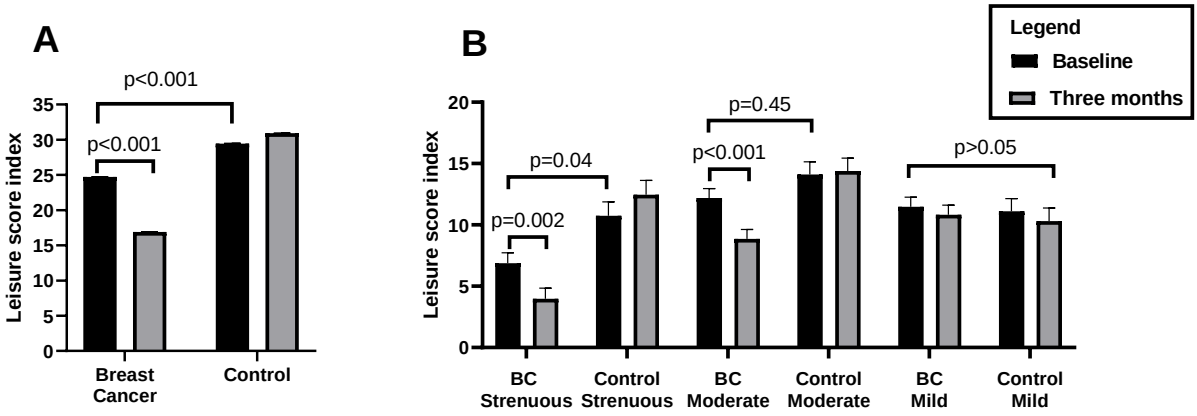

Figure 1. A) Total weekly physical activity at baseline and three months for breast cancer and control participants. B) Total weekly strenuous, moderate, and mild physical activity at baseline and three months for breast cancer (BC) and control participants.

Table 2. Physical activity (leisure score index[+]) from baseline to three-months related to measures of exercise capacity and cardiac function in breast cancer participants

Predictor	Exercise capacity		LV end diastolic volume		LV end systolic volume		LV ejection fraction		LV strain	
	Beta ± SE	**(95% CI)**	**Beta ± SE**	**(95% CI)**	**Beta ± SE**	**(95% CI)**	**Beta ± SE**	**(95% CI)**	**Beta ± SE**	**(95% CI)**
Visit	-9.1 ± 3.5	(-16, -2.2)**	2.2 ± 0.8	(0.5, 3.8)*	2.6 ± 0.5	(1.7, 3.6)***	-1.38 ± 0.3	(-2.0, -0.8)***	1.2 ± 0.2	(0.8, 1.6)***
Stage 3	14.3 ± 10.1	(-5.6, 34.2)	5.7 ± 2.9	(-0.1, 11.4)	2.0 ± 1.7	(-1.3, 5.3)	0.4 ± 0.8	(-1.2, 2.0)	-0.39 ± 0.49	(-1.36, 0.58)
Stage 2	-8.8 ± 7.0	(-22.7, 5.0)	-6.1 ± 2	(-10, -2.1)**	-2.4 ± 1.2	(-4.6, -0.1)*	-0.2 ± 0.6	(-1.3, 0.9)	0.32 ± 0.35	(-0.36, 1.0)
Visit * Stage 3	-5.5 ± 6.0	(-17.3, 6.4)	3.6 ± 1.4	(0.8, 6.4)*	2.6 ± 0.8	(1.0, 4.3)**	-1.0 ± 0.5	(-2.0, 0.1)	0.57 ± 0.35	(-0.12, 1.25)
Visit * Stage 2	-7.3 ± 4.1	(-15.4, 0.8)	-3.1 ± 1	(-5.0, -1.1)**	-1.0 ± 0.6	(-2.1, 0.2)	-0.3 ± 0.4	(-1.0, 0.4)	0.003 ± 0.24	(-0.48, 0.48)
Age	-2.3 ± 0.4	(-3.2, -1.5)***	-0.7 ± 0.1	(-0.9, -0.4)***	-0.4 ± 0.1	(-0.6, -0.3)***	0.1 ± 0.04	(0.1, 0.2)***	-0.07 ± 0.02	(-0.11, -0.03)**
Body mass index	-3.9 ± 0.7	(-5.3, -2.4)***	1.3 ± 0.2	(0.9, 1.7)***	0.4 ± 0.1	(0.2, 0.7)***	0.1 ± 0.1	(-0.1, 0.2)	0.05 ± 0.04	(-0.02, 0.12)
Leisure score index+	**7.1 ± 1.6**	**(4.0, 10.1)*** **	**1.2 ± 0.4**	**(0.4, 2.0)** **	0.3 ± 0.2	(-0.2, 0.7)	0.2 ± 0.1	(-0.1, 0.4)	0.05 ± 0.08	(-0.12, 0.21)
Leisure score index[+] * Visit	-	-	-	-	-	-	-	-	**-0.16 ± 0.07**	**(-0.29, -0.02)***
Anthracycline	-0.02 ± 5.1	(-10.0, 10.0)	-1.3 ± 1.5	(-4.1, 1.6)	-0.7 ± 0.8	(-2.4, 0.9)	0.2 ± 0.4	(-0.6, 1.0)	0.44 ± 0.25	(-0.05, 0.92)
Anthracycline * Visit	-	-	-	-	-	-	-	-	-0.62 ± 0.17	(-0.96, -0.28)***

*p<0.05; **p<0.01; ***p<0.001

Visit variable compares visit 2 (three months) to visit 1 (baseline). Anthracycline variable compares no anthracycline treatment to receiving anthracycline treatment.

[+] square root transformed

Abbreviations: SE, standard error; CI, confidence interval; LV, left ventricular

All models include a patient level random effect

Table 3. Exercise capacity and cardiac function measures at baseline and three months in breast cancer participants

	Breast Cancer Group Baseline Mean (95% CI) N=223	**Breast Cancer Group Three months Mean (95% CI) N=223**
Exercise capacity (meters)	473 (459, 486)	454 (441, 468)
LV end diastolic volume (mL)	120.7 (117.1, 124.3)	125.1 (121.4, 128.8)
LV end systolic volume (mL)	47.3 (45.2, 49.3)	52.5 (50.4, 54.7)
LV ejection fraction (%)	61.0 (59.9, 62.1)	58.2 (57.1, 59.3)
LV strain (%)	-20.1 (-20.8, -19.4)	-17.8 (-18.5, -17.1)

Data are presented as adjusted means and 95% confidence intervals or n (%). All data are adjusted according to the full models presented in Table 3.
Abbreviations: CI, confidence interval; LV, left ventricular

Table 4. Activity groups from baseline to three-months related to measures of exercise capacity and cardiac function in breast cancer participants

Predictor	Exercise capacity		LV end diastolic volume		LV end systolic volume		LV ejection fraction		LV strain	
	Beta ± SE	**(95% CI)**	**Beta ± SE**	**(95% CI)**	**Beta ± SE**	**(95% CI)**	**Beta ± SE**	**(95% CI)**	**Beta ± SE**	**(95% CI)**
Visit	-8.9 ± 3.5	(-15.9, -2.0)*	2.1 ± 0.8	(0.5, 3.8)*	2.6 ± 0.5	(1.7, 3.6)	-1.4 ± 0.3	(-2.0, -0.8)***	1.1 ± 0.2	(0.7, 1.5)
Stage 3	14.9 ± 10.2	(-5.2, 34.9)	5.5 ± 2.9	(-0.3, 11.3)	2.0 ± 1.7	(-1.3, 5.2)	0.37 ± 0.81	(-1.22, 1.97)	-0.4 ± 0.5	(-1.4, 0.6)
Stage 2	-8.4 ± 7.1	(-22.3, 5.5)	-6.0 ± 2.0	(-10.1, -2)**	-2.4 ± 1.2	(-4.6, -0.1)	-0.17 ± 0.57	(-1.28, 0.95)	0.3 ± 0.3	(-0.4, 1.0)
Visit * Stage 3	-5.6 ± 6.0	(-17.5, 6.3)	3.8 ± 1.4	(1.0, 6.6)**	2.7 ± 0.8	(1.0, 4.3)	-0.93 ± 0.52	(-1.95, 0.09)	0.5 ± 0.3	(-0.1, 1.2)
Visit * Stage 2	-8.3 ± 4.1	(-16.5, -0.2)*	-3.2 ± 1	(-5.1, -1.2)**	-1.0 ± 0.6	(-2.1, 0.2)	-0.35 ± 0.36	(-1.06, 0.35)	0.1 ± 0.2	(-0.4, 0.5)
Age	-2.3 ± 0.4	(-3.2, -1.4)***	-0.7 ± 0.1	(-0.9, -0.4)***	-0.4 ± 0.1	(-0.6, -0.3)	0.13 ± 0.04	(0.05, 0.2)***	-0.07 ± 0.02	(-0.12, -0.03)
Body mass index	-3.7 ± 0.7	(-5.1, -2.3)***	1.1 ± 0.2	(0.8, 1.5)***	0.4 ± 0.1	(0.2, 0.7)	0.02 ± 0.06	(-0.1, 0.13)	0.05 ± 0.04	(-0.02, 0.12)
Active group	**20.6 ± 5.8**	**(9.2, 32)*** **	2.6 ± 1.5	(-0.4, 5.6)	1.0 ± 0.9	(-0.7, 2.8)	0.05 ± 0.5	(-0.93, 1.03)	0.3 ± 0.3	(-0.3, 1.0)
Moderately active group	-1.8 ± 6	(-13.5, 9.9)	1.6 ± 1.5	(-1.5, 4.6)	0.1 ± 0.9	(-1.6, 1.9)	0.32 ± 0.51	(-0.69, 1.33)	-0.4 ± 0.3	(-1.1, 0.2)
Active group * Visit	-	-	-	-	-	-	-	-	-0.5 ± 0.3	(-1.1, 0.02)
Moderately active group * Visit	-	-	-	-	-	-	-	-	0.4 ± 0.3	(-0.2, 1)
Anthracycline	0.5 ± 5.1	(-9.6, 10.5)	-1.6 ± 1.5	(-4.5, 1.4)	-0.8 ± 0.8	(-2.4, 0.8)	0.18 ± 0.41	(-0.63, 0.98)	0.4 ± 0.2	(-0.1, 0.9)
Anthracycline * Visit	-	-	-	-	-	-	-	-	-0.6 ± 0.2	(-0.9, -0.3)***

*p<0.05; **p<0.01; ***p<0.001

Visit variable compares visit 2 (three months) to visit 1 (baseline). Anthracycline variable compares no anthracycline treatment to receiving anthracycline treatment.

Abbreviations: SE, standard error; CI, confidence interval; LV, left ventricular

Insufficiently active participants were the reference group in all models. All models include a patient level random effect

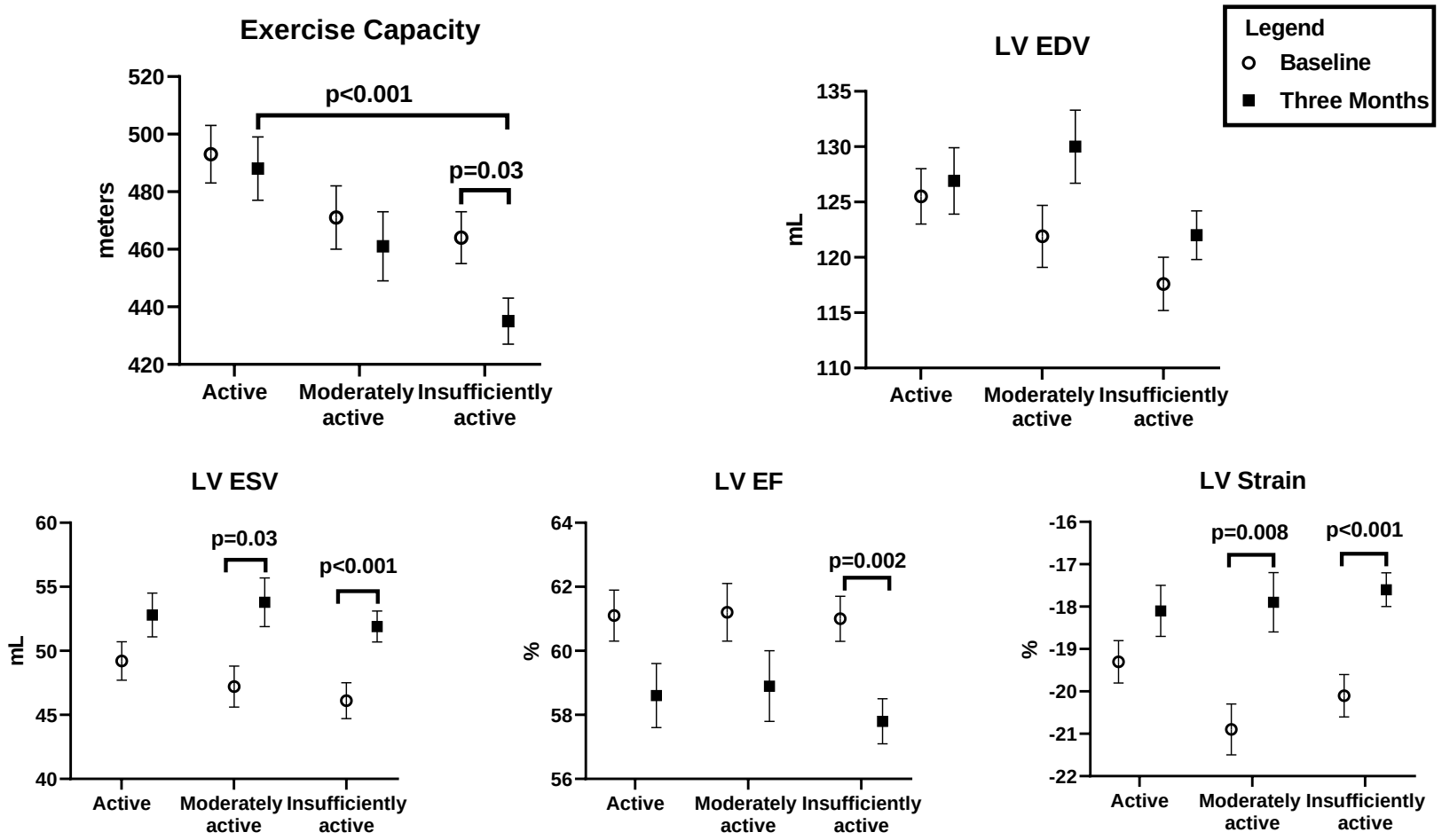

Figure 1. Measures of exercise capacity and cardiac function at baseline and three months among breast cancer participants categorized as active, moderately active, and insufficiently active. Adjusted mean and standard error are plotted for each graph. For each figure, baseline values are shown with an open circle, and three month values are shown with a solid square.

Table 5. Mean differences among physical activity groups from baseline to 3 months for exercise capacity and cardiac function

Activity group	**Exercise capacity**		**LV end diastolic volume**		**LV end systolic volume**		**LV ejection fraction**		**LV strain**	
	MD ± SE (m)	p-value	MD ± SE (mL)	p-value	MD ± SE (mL)	p-value	MD ± SE (%)	p-value	MD ± SE (%)	p-value
Active	-7 ± 12	0.99	2.3 ± 2.9	0.97	3.9 ± 1.7	0.23	-2.4 ± 1.0	0.2	1.2 ± 0.7	0.52
Moderately active	-10 ± 15	0.99	8.0 ± 3.4	0.23	**6.5 ± 2.1**	**0.03**	-2.3 ± 1.3	0.45	**3.0 ± 0.9**	**0.008**
Insufficiently active	**-29 ± 10**	**0.03**	4.4 ± 2.3	0.37	**5.8 ± 1.3**	**<0.001**	**-3.2 ± 0.8**	**0.002**	**2.5 ± 0.5**	**<0.001**

Abbreviations: MD, mean difference; SE, standard error; LV, left ventricular

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**(1): 7-30.
2. Narayan HK, Finkelman B, French B, et al. Detailed Echocardiographic Phenotyping in Breast Cancer Patients: Associations With Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up. *Circulation* 2017; **135**(15): 1397-412.
3. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007; **25**(25): 3808-15.
4. Saiki H, Petersen IA, Scott CG, et al. Risk of Heart Failure With Preserved Ejection Fraction in Older Women After Contemporary Radiotherapy for Breast Cancer. *Circulation* 2017; **135**(15): 1388-96.
5. Greenlee H, Iribarren C, Rana JS, et al. Risk of Cardiovascular Disease in Women With and Without Breast Cancer: The Pathways Heart Study. *J Clin Oncol* 2022: Jco2101736.
6. Armenian SH, Lacchetti C, Barac A, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2017; **35**(8): 893-911.
7. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular Disease Mortality Among Breast Cancer Survivors. *Epidemiology* 2016; **27**(1): 6-13.
8. Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet (London, England)* 2017; **390**(10113): 2643-54.
9. Eijsvogels TM, Molossi S, Lee DC, Emery MS, Thompson PD. Exercise at the Extremes: The Amount of Exercise to Reduce Cardiovascular Events. *Journal of the American College of Cardiology* 2016; **67**(3): 316-29.
10. Irwin ML, Smith AW, McTiernan A, et al. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *J Clin Oncol* 2008; **26**(24): 3958-64.
11. Yu AF, Jones LW. Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. *Cardiooncology* 2016; **2**.
12. Upshaw JN, Finkelman B, Hubbard RA, et al. Comprehensive Assessment of Changes in Left Ventricular Diastolic Function With Contemporary Breast Cancer Therapy. *JACC Cardiovasc Imaging* 2020; **13**(1 Pt 2): 198-210.
13. Jones LW, Habel LA, Weltzien E, et al. Exercise and Risk of Cardiovascular Events in Women With Nonmetastatic Breast Cancer. *J Clin Oncol* 2016; **34**(23): 2743-9.
14. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. *Jama* 2000; **283**(23): 3095-101.
15. Nagy AC, GulAcsi BP, CserEp Z, Hangody L, Forster T. Late cardiac effect of anthracycline therapy in physically active breast cancer survivors - a prospective study. *Neoplasma* 2017; **64**(1): 92-100.
16. Upshaw JN, Hubbard RA, Hu J, et al. Physical activity during and after breast cancer therapy and associations of baseline physical activity with changes in cardiac function by echocardiography. *Cancer Med* 2020; **9**(17): 6122-31.
17. Jordan JH, D'Agostino RB, Jr., Avis NE, et al. Fatigue, Cardiovascular Decline, and Events after Breast Cancer Treatment: Rationale and Design of UPBEAT Study. *JACC CardioOncol* 2020; **2**(1): 114-8.

18. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017; **67**(2): 93-9.
19. Godin G. The Godin-Shephard Leisure-Time Physical Activity Questionnaire. *Health Fit J Can* 2011; **4**(4): 18-22.
20. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. *BMC Med Res Methodol* 2015; **15**: 60.
21. ATS statement: guidelines for the six-minute walk test. *American journal of respiratory and critical care medicine* 2002; **166**(1): 111-7.
22. Milne HM, Gordon S, Guilfoyle A, Wallman KE, Courneya KS. Association between physical activity and quality of life among Western Australian breast cancer survivors. *Psychooncology* 2007; **16**(12): 1059-68.
23. Valenti M, Porzio G, Aielli F, et al. Physical exercise and quality of life in breast cancer survivors. *Int J Med Sci* 2008; **5**(1): 24-8.
24. Juvet LK, Thune I, Elvsaas I, et al. The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: A meta-analysis. *Breast* 2017; **33**: 166-77.
25. But-Hadzic J, Dervisevic M, Karpljuk D, et al. Six-Minute Walk Distance in Breast Cancer Survivors-A Systematic Review with Meta-Analysis. *International journal of environmental research and public health* 2021; **18**(5).
26. Jones LW, Courneya KS, Mackey JR, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012; **30**(20): 2530-7.
27. Jain SS, Cohen DJ, Zhang Z, et al. Defining a Clinically Important Change in 6-Minute Walk Distance in Patients With Heart Failure and Mitral Valve Disease. *Circ Heart Fail* 2021; **14**(3): e007564.
28. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017; **23**(2): 377-81.
29. Acierno LJ. Adolph Fick: mathematician, physicist, physiologist. *Clinical cardiology* 2000; **23**(5): 390-1.
30. Vincent F, Labourey JL, Leobon S, Antonini MT, Lavau-Denes S, Tubiana-Mathieu N. Effects of a home-based walking training program on cardiorespiratory fitness in breast cancer patients receiving adjuvant chemotherapy: a pilot study. *Eur J Phys Rehabil Med* 2013; **49**(3): 319-29.
31. Aguiñaga S, Ehlers DK, Cosman J, Severson J, Kramer AF, McAuley E. Effects of physical activity on psychological well-being outcomes in breast cancer survivors from prediagnosis to posttreatment survivorship. *Psychooncology* 2018; **27**(8): 1987-94.
32. Forman DE, Fleg JL, Kitzman DW, et al. 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. *Journal of the American College of Cardiology* 2012; **60**(25): 2653-61.
33. Drafts BC, Twomley KM, D'Agostino R, Jr., et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging* 2013; **6**(8): 877-85.
34. Haslbauer JD, Lindner S, Valbuena-Lopez S, et al. CMR imaging biosignature of cardiac involvement due to cancer-related treatment by T1 and T2 mapping. *International journal of cardiology* 2019; **275**: 179-86.
35. Jolly MP, Jordan JH, Meléndez GC, McNeal GR, D'Agostino RB, Jr., Hundley WG. Automated assessments of circumferential strain from cine CMR correlate with LVEF declines in cancer patients early after receipt of cardio-toxic chemotherapy. *J Cardiovasc Magn Reson* 2017; **19**(1): 59.

36. Jordan JH, Sukpraphrute B, Meléndez GC, Jolly MP, D'Agostino RB, Jr., Hundley WG. Early Myocardial Strain Changes During Potentially Cardiotoxic Chemotherapy May Occur as a Result of Reductions in Left Ventricular End-Diastolic Volume: The Need to Interpret Left Ventricular Strain With Volumes. *Circulation* 2017; **135**(25): 2575-7.
37. Nakano S, Takahashi M, Kimura F, et al. Cardiac magnetic resonance imaging-based myocardial strain study for evaluation of cardiotoxicity in breast cancer patients treated with trastuzumab: A pilot study to evaluate the feasibility of the method. *Cardiol J* 2016; **23**(3): 270-80.
38. Ong G, Brezden-Masley C, Dhir V, et al. Myocardial strain imaging by cardiac magnetic resonance for detection of subclinical myocardial dysfunction in breast cancer patients receiving trastuzumab and chemotherapy. *International journal of cardiology* 2018; **261**: 228-33.
39. Negishi T, Thavendiranathan P, Negishi K, Marwick TH. Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes: The SUCCOUR Trial. *JACC Cardiovasc Imaging* 2018; **11**(8): 1098-105.
40. Thavendiranathan P, Negishi T, Somerset E, et al. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. *Journal of the American College of Cardiology* 2021; **77**(4): 392-401.
41. Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DI. Adjuvant trastuzumab induces ventricular remodeling despite aerobic exercise training. *Clin Cancer Res* 2009; **15**(15): 4963-7.
42. Kirkham AA, Shave RE, Bland KA, et al. Protective effects of acute exercise prior to doxorubicin on cardiac function of breast cancer patients: A proof-of-concept RCT. *International journal of cardiology* 2017; **245**: 263-70.
43. Chung WP, Yang HL, Hsu YT, et al. Real-time exercise reduces impaired cardiac function in breast cancer patients undergoing chemotherapy: A randomized controlled trial. *Annals of physical and rehabilitation medicine* 2022; **65**(2): 101485.
44. Amireault S, Godin G, Lacombe J, Sabiston CM. Validation of the Godin-Shephard Leisure-Time Physical Activity Questionnaire classification coding system using accelerometer assessment among breast cancer survivors. *Journal of cancer survivorship : research and practice* 2015; **9**(3): 532-40.