Physical Activity and Cardiac Function in Long-Term Breast Cancer Survivors

Naaktgeboren, Willeke R.; Groen, Wim G.; Jacobse, Judy N.; Steggink, Lars C.; Walenkamp-Hageman, Annemiek M.E.; van Harten, Wim H.; Stuiver, Martijn M.; Aaronson, Neil K.; Aleman, Berthe M.P.; van der Meer, Peter

Published in:
Jacc: cardiooncology

DOI:
10.1016/j.jaccao.2022.02.007

Publication date:
2022

JACC: CARDIOONCOLOGY VOL. ■, NO. ■, 2022

ORIGINAL RESEARCH

Physical Activity and Cardiac Function in Long-Term Breast Cancer Survivors

A Cross-Sectional Study

Willeke R. Naaktgeboren, MD,[a,b] Wim G. Groen, PhD,[a] Judy N. Jacobse, MD, PhD,[a] Lars C. Steggink, MD, PhD,[c] Annemiek M.E. Walenkamp, MD, PhD,[c] Wim H. van Harten, MD, PhD,[a,d,e] Martijn M. Stuiver, PhD,[a,f,g] Neil K. Aaronson, PhD,[a] Berthe M.P. Aleman, MD, PhD,[h] Peter van der Meer, MD, PhD,[i] Michael Schaapveld, PhD,[a] Gabe S. Sonke, MD, PhD,[j] Jourik A. Gietema, MD, PhD,[c] Flora E. van Leeuwen, PhD,[a] Anne M. May, PhD[b]

ABSTRACT

BACKGROUND Higher levels of physical activity are associated with a lower risk of cardiovascular disease in the general population. Whether the same holds for women who underwent treatment for breast cancer is unclear.

OBJECTIVE The aim of this study was to evaluate the association between physical activity in a typical week in the past 12 months and cardiac dysfunction in breast cancer survivors.

METHODS We used data from a cohort of breast cancer survivors who were treated at ages 40 to 50 years (N = 559). The association between physical activity and global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF) was evaluated using both linear and modified Poisson regression analyses adjusted for relevant confounders.

RESULTS In total, 559 breast cancer survivors were included, with median age of 55.5 years and a median time since treatment of 10.2 years. GLS was less favorable in inactive survivors (−17.1%) than in moderately inactive (−18.4%), moderately active (−18.2%), and active survivors (−18.5%), with an adjusted significant difference for active versus inactive survivors (β = −1.31; 95% CI: −2.55 to −0.06)). Moderately active (n = 57/130) and active survivors (n = 87/124) had significantly lower risks of abnormal GLS (defined as >−18%) compared with inactive survivors (n = 17/26) (RR: 0.65 [95% CI: 0.45-0.94] and RR: 0.61 [95% CI: 0.43-0.87], respectively). LVEF, in normal ranges in all activity categories, was not associated with physical activity.

CONCLUSION In long-term breast cancer survivors, higher physical activity levels were associated with improved GLS but not LVEF, with the relatively largest benefit for doing any activity versus none. This finding suggests that increasing physical activity may contribute to cardiovascular health benefits, especially in inactive survivors. (J Am Coll Cardiol CardioOnc 2022;■:■-■) © 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/).

From [a]The Netherlands Cancer Institute, Division of Psychosocial Research and Epidemiology, Amsterdam, the Netherlands; [b]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [c]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [d]Rijnstate Hospital, Arnhem, the Netherlands; [e]Department of Health Technology and Services Research, University of Twente, Enschede, the Netherlands; [f]Center for Quality of Life, The Netherlands Cancer Institute, Amsterdam, the Netherlands; [g]Centre of Expertise Urban Vitality, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, the Netherlands; [h]Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands; [i]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; and the [j]Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.02.007

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

GLS = global longitudinal strain

LV = left ventricular

LVEF = left ventricular ejection fraction

UMCG = University Medical Center Groningen

The population of breast cancer survivors has grown substantially over the last decades because of, among other factors, improvements in early detection and anticancer regimens.[1] Advances in primary treatment and cures are expected to further increase the number of breast cancer survivors. Consequently, adequate evaluation of long-term side effects of breast cancer treatment is of increasing importance.

A significant, long-term side effect of breast cancer treatment is cardiovascular disease (CVD), which includes a variety of clinical manifestations including declines in left ventricular ejection fraction (LVEF).[2] Breast cancer survivors more than 7 years after treatment have an almost 2-fold increased risk of CVD-related mortality compared with age-matched women without cancer.[3] Among patients with pre-existent CVD who survived more than 5 years after treatment, cardiovascular death has even replaced breast cancer-related death as the leading cause of mortality.[4] The risk of developing CVD depends on the type of breast cancer treatment (and for anthracycline and radiotherapy, cumulative dose) as well as patient-related factors.[2,5] A linear relationship between the cumulative anthracycline dose and cardiac dysfunction has been demonstrated.[6] Radiation exposure of the heart may lead to an increased risk of coronary artery disease, valvular heart disease, and heart failure.[2] As for patient-related risk factors, women with an unfavorable cardiovascular risk profile (eg, elderly, presence of hypertension, diabetes mellitus, and obesity) have a higher risk of developing CVD.[5] Accordingly, strategies that aim to reduce CVD risk should preferably target both treatment- and patient-related factors.

Physical activity has been found to be associated with lower CVD risk in noncancer populations.[7] However, less evidence is available on whether physical activity can also decrease CVD risk in cancer patients and survivors given that CVD pathophysiology may be different in this population due to exposure to potential cardiotoxic treatment. Two observational studies reported that in breast cancer survivors with no prior history of CVD, higher levels of leisure-time physical activity were associated with a lower cumulative incidence of cardiovascular clinical end points, including myocardial infarction and heart failure, independent of the presence of other cardiovascular risk factors.[8,9] Cardiac dysfunction during and after cancer treatment is currently considered a gradual phenomenon in which progressive subclinical declines in parameters of cardiac function (ie, global longitudinal strain [GLS] and LVEF) can eventually lead to overt heart failure.[10] The association between physical activity and GLS and LVEF in breast cancer survivors is currently unknown. If such an association exists, this could prompt further research and ultimately have implications regarding physical activity recommendations for future breast cancer patients undergoing treatment with cardiotoxic regimens.

This study aimed to evaluate the association between current levels of physical activity and cardiac dysfunction in breast cancer survivors. We hypothesized that higher physical activity levels are associated with more favorable values of GLS and LVEF.

METHODS

SETTING AND PARTICIPANTS. Data from the HARBOR study (Identifying Subgroups With High Cardiovascular Risk in Breast Cancer Survivors) were used for the current analysis. The study design and results of this study have been published previously.[6] In brief, the HARBOR study was a cross-sectional investigation of long-term cardiac dysfunction in breast cancer survivors 5 to 7 or 10 to 12 years after treatment. Patients were treated between 2002 and 2007 and 2008 and 2012 for invasive breast cancer (TNM stage I-III) or ductal carcinoma in situ with or without anthracyclines (n = 306 [54.7%] and n = 253 [45.3%], respectively) at 40 to 50 years of age in either the Netherlands Cancer Institute/Antoni van Leeuwenhoek, Amsterdam, the Netherlands, or the University Medical Center Groningen (UMCG), Groningen, the Netherlands. The exclusion criteria were a history of radiotherapy or chemotherapy for other malignancies and a history of CVD before breast cancer diagnosis. A total of 569 women were enrolled in this study. The HARBOR study is registered with ClinicalTrials.gov (NCT02485626) and approved by the institutional review board of the Netherlands Cancer Institute/Antoni van Leeuwenhoek.

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.

Manuscript received January 30, 2022; accepted February 16, 2022.

CARDIOVASCULAR MEASUREMENTS. All women underwent cardiovascular assessment, including physical examination, blood and urine sampling, and a 2-dimensional echocardiogram. Physical examination included blood pressure measurement and evaluation of signs of heart failure (ie, pedal edema and pulmonary congestion). Echocardiograms were performed using the GE Vivid E9 machine and the Philips iE33 (Philips Healthcare) in the UMCG and Netherlands Cancer Institute, respectively. All echocardiographic measurements were analyzed centrally (UMCG). Consistent with current guidelines,[11] left ventricular (LV) volumes and ejection fraction were assessed via Simpson's biplane method on the apical 2- and 4-chamber views, and, in case of insufficient imaging quality (n = 89, 15.6%), a range was reported based on visual inspection. GLS was measured using apical 2-, 3-, and 4-chamber views with TomTec software (TomTec Imaging Software Systems). The imaging quality was insufficient for GLS analyses in 13.1% (n = 74) of the participants. The interobserver reliability (intraclass correlation coefficient) for the GLS analyses was 0.70 (95% CI: 0.59-0.70) in a random subset of 102 subjects.[6]

PHYSICAL ACTIVITY. All participants completed a questionnaire that contained questions on physical activity in the past 12 months, assessing both occupational and leisure activities, based on questions from the European Prospective Investigation into Cancer and Nutrition physical activity questionnaire[12] (Supplemental Material A). For occupational activities, participants reported their current employment status and the intensity of the activities carried out at work (ie, best described as "sedentary," "standing," "manual," or "heavy manual"). For recreational activities, the total hours per week spent on walking, cycling, sports, and gardening were recorded for summer and winter separately to limit seasonal influences.

To obtain a total physical activity score, we used the validated Cambridge physical activity index.[13] In a cohort of 1,941 healthy individuals from 10 European countries, the Cambridge index correlated strongest with physical activity energy expenditure and time spent in moderate and vigorous physical activity compared with other questionnaire-derived physical activity indices.[14] This categoric index, including "inactive," "moderately inactive," "moderately active," and "active," is derived by cross-tabulating the level of occupational activities with the combined hours per week spent on cycling and sports activity (**Table 1**). In calculating this index, all physical activity variables were scored as missing if none of the questions were answered, with the assumption being that these participants did not complete the questionnaire. All other variables were set to 0 if at least 1 question was completed, the assumption being that these participants completed the questionnaire but were not engaged in all activities.[15] The maximum hours per week spent on any given physical activity variable was set to 40 hours per week, and summer and winter scores were averaged to obtain an average score for the past year.

TABLE 1 Calculation of the Cambridge Physical Activity Index: A Cross-Tabulation of Occupational Activities With Recreational Activities

	Time Spent in Sports and Cycling (h/wk)			
	None	≤3.5	>3.5 to ≤7.0	>7.0
Sedentary	Inactive	Moderately inactive	Moderately active	Active
Standing	Moderately inactive	Moderately active	Active	Active
Manual	Moderately inactive	Active	Active	Active
Heavy manual	Active	Active	Active	Active
Unknown/missing	Inactive	Moderately inactive	Moderately active	Active

STATISTICAL ANALYSIS. Characteristics of the study participants were computed per Cambridge category and expressed as mean ± SD, median (25th and 75th percentiles [Q1-Q3]), or frequencies (percentages). Linear regression models were used with the Cambridge index as the independent variable and either GLS or LVEF as the dependent variable and results presented as the regression coefficient with 95% CI. GLS and LVEF were also dichotomized into impaired versus normal using clinically accepted cutoffs (ie, GLS >−18%/≤−18%[16] and LVEF <53%/≥53%[17]). The association between physical activity and dichotomized GLS or LVEF was investigated using modified Poisson regression with robust standard errors (sandwich estimator).[18] Results are presented as relative risk with 95% CI. We did not perform Poisson regression with dichotomized LVEF because only 34 patients had LVEF <53%, of whom only 1 participant was in the inactive reference group.

For sensitivity analyses, we repeated the analyses after excluding patients whose (level of) occupational activity data were missing (n = 88, 15.7%). Also, analyses were repeated with multiple imputations (n = 50) by a fully conditional specification for GLS because missing data on this variable exceeded 10% (MICE package, 2021[19]). Lastly, given that both GLS and LVEF are expressed as percentages bound between 0 and 100, we reanalyzed our data via a beta regression model.[20]

All models were adjusted for age, body mass index (BMI), radiotherapy (none vs right sided, left sided, or internal mammary chain), time since diagnosis (5-7 years or 10-12 years after treatment), and the

TABLE 2 Characteristics of Participants According to Cambridge Physical Activity Index Category

	Inactive (n = 28)	Moderately Inactive (n = 127)	Moderately Active (n = 154)	Active (n = 250)	Total (N = 559)
Age at diagnosis, y	46.8 (44.5-48.7)	46.4 (43.7-49.5)	46.3 (43.3-49.6)	47.1 (44.0-49.4)	46.9 (43.8-49.5)
Age at inclusion, y	55.2 (51.9-57.0)	56.0 (53.4-59.2)	55.1 (52.2-57.6)	55.4 (53.0-58.6)	55.5 (52.7-58.5)
Follow-up time, y	7.4 (6.9-11.1)	10.4 (6.8-11.6)	10.4 (6.9-11.6)	10.1 (6.7-11.6)	10.2 (6.8-11.6)
5-7 years	19 (67.9)	58 (45.7)	76 (49.4)	121 (48.4)	274 (49.0)
10-12 years	9 (32.1)	69 (54.3)	78 (50.6)	129 (51.6)	285 (51.0)
Cardiovascular risk factors[a]					
Hypertension	15 (53.6)	45 (35.4)	57 (37.5)	93 (37.2)	210 (37.7)
Hypercholesterolemia	9 (32.1)	43 (33.9)	45 (29.2)	79 (31.6)	176 (31.5)
Diabetes mellitus	4 (14.3)	8 (6.3)	9 (5.8)	17 (6.8)	38 (6.8)
Smoking					
Never	12 (42.9)	47 (37.0)	65 (42.2)	99 (39.6)	223 (39.9)
Former	10 (35.7)	55 (43.3)	65 (42.2)	123 (49.2)	253 (45.3)
Current	6 (21.4)	24 (18.9)	23 (14.9)	28 (11.2)	81 (14.5)
Unknown	0	1 (0.8)	1 (0.6)	0	2 (0.4)
Body mass index, mg/m^2	29.3 ± 6.0	26.2 ± 4.8	25.3 ± 4.1	25.7± 4	25.9± 4.4
Anthracyclines	15 (53.6)	66(52.0)	88 (57.1)	137 (54.8)	306 (54.7)
Cumulative doxorubicin equivalent dose,[b] mg/m^2	202.5 (191-243)	240.0 (203-242)	240.0 (203-300)	240.0 (203-300)	240.0 (203-293)
Radiotherapy field					
Left sided	15 (53.6)	52 (40.9)	57 (37.0)	114 (45.6)	238 (42.6)
Right sided	9 (32.1)	61 (48.0)	79 (51.3)	107 (42.8)	256 (45.8)
IMNs	3 (10.7)	9 (7.1)	7 (4.5)	18 (7.2)	37 (6.6)
None	1 (3.6)	5 (3.9)	11 (7.1)	11 (4.4)	28 (5.0)
Trastuzumab	2 (7.1)	12 (9.4)	16 (10.4)	19 (7.6)	49 (8.8)

Values are presented as median (Q1-Q3), n (%), or mean ± SD. [a]Cardiovascular risk factors are defined as follows: hypertension = having a blood pressure higher than 140 mm Hg (systolic) and 90 mm Hg (diastolic) or being treated with antihypertensive medication, hypercholesterolemia = having total cholesterol ≥6.5 mmol/L or being treated with statins, and diabetes mellitus = glucose ≥6.5 mmol/L or being treated with glucose-lowering medication. [b]These numbers are only applicable for those treated with anthracyclines (n = 306).

IMN = internal mammary nodes.

clinically documented cumulative dose of anthracyclines. The cumulative dose of epirubicin was translated into a doxorubicin-equivalent dose in a similar manner to the original HARBOR analyses.[6] In addition, we adjusted for the presence of CVD risk factors at the time of the study visit (hypertension, hypercholesterolemia, diabetes mellitus, smoking; none vs 1-2 or ≥3 risk factors) to the model. These risk factors were defined as follows: hypertension as having a blood pressure higher than 140 mm Hg (systolic) and 90 mm Hg (diastolic) or being treated with antihypertensive medication, hypercholesterolemia as having a total cholesterol ≥6.5 mmol/L or being treated with statins, and diabetes as having a fasting glucose ≥6.5mmol/L or being treated with glucose-lowering medication. Finally, we explored whether the treatment with anthracyclines modified the association between physical activity and cardiac dysfunction by adding an interaction term to the fully adjusted model. A P value <0.05 was considered significant, and all analyses were performed using R software (R version 4.0.3, The R Core Team).

RESULTS

In total, 569 breast cancer survivors participated in the HARBOR study, 10 (1.8%) of whom were excluded from the current analysis because of the absence of physical activity data. Characteristics of the study population (N = 559) are presented in Table 2. The median (Q1-Q3) age at diagnosis and at the time of study participation was 46.9 years (43.8-49.5 years) and 55.5 years (52.7-58.5 years), respectively.

Using the Cambridge index, 28 participants (5.0%) were classified as inactive, 127 (22.7%) as moderately inactive, 154 (27.5%) as moderately active, and 250 (44.7%) as active at the time of the study visit. Most breast cancer survivors reported a sedentary occupation, with very few describing their occupational activities as “manual” or “heavy manual.”

In the inactive category, the median (Q1-Q3) time since diagnosis was 7.4 years (6.9-11.1 years), with two-thirds of the survivors being between 5 to 7 years postdiagnosis. In the 3 other categories, the median time since diagnosis was more than 10 years. Cardiovascular risk factors were relatively common,

TABLE 3 Association Between the Cambridge Index and Cardiac Function

	Inactive (n = 28)	Moderately Inactive (n = 127)	Moderately Active (n = 154)	Active (n = 250)
GLS (%)[a]				
Mean GLS (%)	−17.1 ± 2.31	−18.4 ± 3.40	−18.2 ± 2.55	−18.5 ± 3.14
Unadjusted β (95% CI)	Ref	−1.31 (−2.59 to −0.02)[b]	−1.12 (−2.39 to 0.15)	−1.47 (−2.70 to −0.24)[b]
Partially adjusted β (95% CI)[c]	Ref	−1.14 (−2.43 to 0.15)	−0.87 (−2.16 to 0.42)	−1.29 (−2.54 to −0.05)[b]
Fully adjusted β (95% CI)[d]	Ref	−1.12 (−2.41 to 0.17)	−0.92 (−2.21 to 0.38)	−1.31 (−2.55 to −0.06)[b]
GLS (>-18%)[a]				
n/N at risk (%)	17/26 (65.4)	54/115 (47.0)	57/130 (43.8)	87/214 (40.7)
Unadjusted RR (95% CI)	Ref	0.72 (0.51-1.01)	0.67 (0.48-0.94)[b]	0.62 (0.45-0.86)[b]
Partially adjusted RR (95% CI)[a]	Ref	0.72 (0.50-1.03)	0.68 (0.47-0.98)[b]	0.61 (0.43-0.88)[b]
Fully adjusted RR (95% CI)[a]	Ref	0.71 (0.50-1.02)	0.65 (0.45-0.94)[b]	0.61 (0.43-0.87)[b]
LVEF (%)				
Mean LVEF (%)	58.7 ± 4.61	59.2 ± 3.97	58.9 ± 4.48	59.1 ± 5.00
Unadjusted β (95% CI)	Ref	0.49 (−1.40 to 2.38)	0.25 (−1.61 to 2.11)	0.40 (−1.40 to 2.21)
Partially adjusted β (95% CI)[a]	Ref	0.37 (−1.55 to 2.28)	0.28 (−1.62 to 2.18)	0.39 (−1.44 to 2.23)
Fully adjusted β (95% CI)[a]	Ref	0.27 (−1.64 to 2.18)	0.20 (−1.70 to 2.09)	0.35 (−1.48 to 2.18)
LVEF (<53%)				
n/N at risk (%)	1/27 (3.6)	5/127 (3.9)	10/163 (6.5)	18/249 (7.2)

Values are mean ± SD or n/N unless otherwise indicated. [a]GLS data were not available for n = 74 (13.2%). [b]These findings correspond with a *P* value <0.05. [c]Adjusted for age, body mass index, radiotherapy field, and cumulative doxorubicin (equivalent) dose. [d]Additionally adjusted for the presence of cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, and smoking).

GLS = global longitudinal strain; LVEF = left ventricular ejection fraction.

especially in inactive survivors. For example, hypertension was prevalent in 53.6% (n = 15/28), 35.4% (n = 45/127), 37.5% (n = 57/154), and 37.2% (n = 93/250) in participants in the inactive, moderately inactive, moderately active, and active categories, respectively.

Approximately half of the survivors were treated with anthracycline-based chemotherapy regimens in all activity categories. The median (Q1-Q3) cumulative doxorubicin (equivalent) dose was 202 mg/m^2 (191-243 mg/m^2) (inactive category), 240 mg/m^2 (203-242 mg/m^2) (moderately inactive category), and 240 mg/m^2 (203-300 mg/m^2) (both moderately active and active category). The vast majority (>90%) of the participants received breast/chest wall irradiation. Relatively few participants received additional treatment with the potentially cardiotoxic anti-HER2 drug trastuzumab (n = 2 [7.1%], n = 12 [9.4%], n = 16 [10.4%], and n = 19 [7.6%] for survivors in the inactive, moderately inactive, moderately active, and active category, respectively).

ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND CARDIAC DYSFUNCTION. GLS was least favorable (−17.1%) in inactive survivors and improved in moderately inactive (−18.4%), moderately active (−18.2%), and active survivors (−18.5%) (Table 3). Corresponding adjusted β coefficients, compared with inactive survivors, were −1.12 (95% CI: −2.41 to 0.17), −0.92 (95% CI: −2.21 to 0.38), and −1.31 (95% CI: −2.55 to −0.06), respectively. Similarly, higher physical activity was associated with a lower risk of impaired GLS for moderately inactive (RR: 0.71; 95% CI: 0.50-1.02), moderately active (RR: 0.65; 95% CI: 0.45-0.94), and most active (RR: 0.61; 95% CI: 0.43-0.87) compared with inactive survivors (Central Illustration).

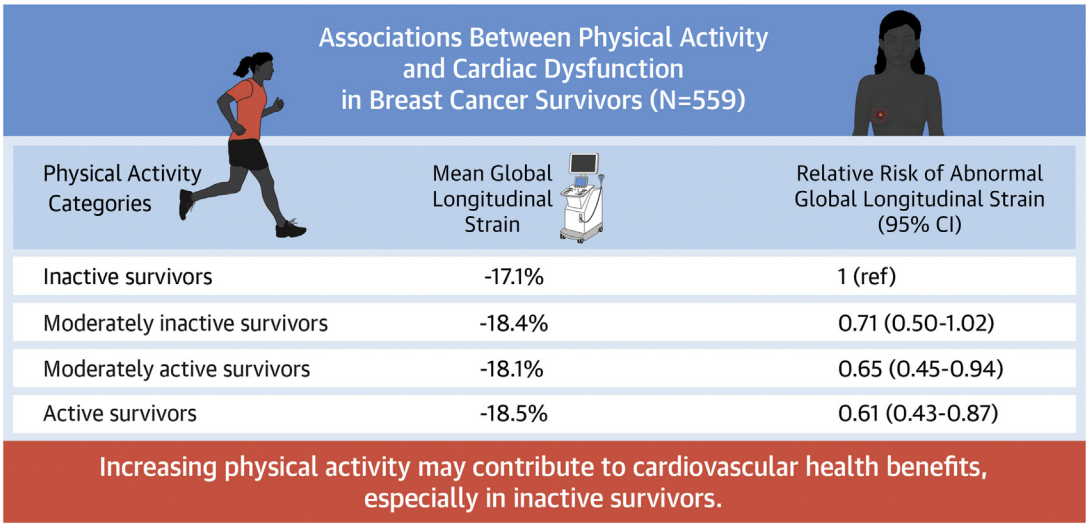
For LVEF, mean values did not differ and were within normal ranges in all 4 physical activity categories. Compared with inactive survivors, adjusted β coefficients for moderately inactive, moderately active, and active were 0.27 (95% CI: −1.64 to 2.18), 0.20 (95% CI: −1.70 to 2.09), and 0.35 (95% CI: −1.48 to 2.18), respectively. All interaction terms were nonsignificant ($P > 0.10$).

All sensitivity analyses (ie, exclusion of participants for whom [levels of] occupational activities were not recorded [n = 88, 15.7%]) using imputed data for GLS (missing in n = 74, 13.2%) and the use of a beta regression model for continuous outcomes yielded comparable results and did not change the conclusions (data not shown).

DISCUSSION

In this cross-sectional study of breast cancer survivors, we found that higher levels of self-reported physical activity were associated with more favorable GLS values but not with LVEF. This was after accounting for treatment-related risk

CENTRAL ILLUSTRATION **Physical Activity and Cardiac Function in Long-Term Breast Cancer Survivors**



Naaktgeboren WR, et al. J Am Coll Cardiol CardioOnc. 2022;■(■):■-■.

In the cross-sectional analysis of a cohort of long-term breast cancer survivors (N = 559), we evaluated the association between global longitudinal strain and physical activity. Compared with inactive survivors, moderately active and active survivors had significantly lower risks of abnormal global longitudinal strain, with the relatively largest benefit for doing any activity versus none. This finding suggests that increasing physical activity may contribute to cardiovascular health benefits, especially in inactive survivors.

factors (ie, cumulative dosages of anthracyclines and thoracic irradiation) as well as patient-related risk factors (ie, age, BMI, and cardiovascular risk factors). Considering that subclinical cardiac dysfunction (ie, impaired GLS) may precede adverse cardiovascular events, these results suggest that efforts to increase physical activity levels by, for example, offering a physical activity program may contribute to reducing cardiovascular morbidity in breast cancer survivors.

Previous studies have extensively documented the association between physical activity and CVD risk in noncancer populations.[7] Increased physical activity has been linked to a lower incidence of various CVDs, including coronary artery disease and heart failure. Conversely, having a largely sedentary lifestyle, reflected by low levels of physical activity, is hypothesized to be a main predisposing factor for the development and progression of CVD.[21] A meta-analysis of 38 prospective cohort studies (including approximately 271,000 participants) and an individual patient data meta-analysis (8 studies, N = 36,383) both described a nonlinear dose-response relationship between higher self-reported leisure physical activities and a lower risk of all-cause mortality over a follow-up period with a median of 12 years (range: 4-40 years) and 5.8 years (range: 3-15 years), respectively.[22,23] Both studies reported that the most substantial reduction of risk was observed among moderately inactive patients compared with those who are not active, with relatively little additional risk reduction for the more active categories.[22,23] For cancer patients and survivors, less evidence on the relationship between physical activity and CVD is available. The pathogenesis of CVD in this population is likely different given that patients might be treated with cardiotoxic regimens. Anthracyclines may inhibit topoisomerase IIβ, thereby causing double-strand DNA breaks, which eventually may lead to irreversible loss of functional cardiomyocytes and fibrosis.[24] Pathogenesis of radiation-induced coronary artery disease is presumably a multifactorial process with key roles for endothelial injury and inflammation.[25] As a result, cancer patients may present with CVD, sometimes even in the absence of traditional cardiovascular risk factors. Therefore, evidence of physical activity-based interventions on noncancer populations may not necessarily generalize to cancer patients and survivors. Two previous studies among breast cancer survivors demonstrated that leisure-time physical activity after treatment was associated with a graded decrease of CVD.[8,9] Our

observation of a reduction in subclinical cardiac dysfunction (GLS) with increased physical activity is in line with these studies. The reduction was most apparent for inactive versus noninactive survivors, and differences in the magnitude of the association were relatively small among breast cancer survivors categorized as moderately inactive, moderately active, or active. Similarly, we also observed a higher burden of cardiovascular risk factors among inactive patients. These findings must be interpreted with caution given the small numbers in the inactive category. However, our data support the proposition that even a relatively modest increase in daily physical activity may be valuable.

We observed a significant association between physical activity and subclinical cardiac dysfunction (ie, impaired GLS) but not LVEF. GLS abnormalities were common (44%). In contrast, LVEF was within the normal range in nearly all patients (94%), which may have resulted in the lack of association between abnormal LVEF and physical activity. The higher prevalence of impaired GLS compared with decreased LVEF may be explained by the prevailing hypothesis that considers cancer therapy-related cardiac dysfunction as a continuous phenomenon in which GLS is thought to be an earlier marker of cardiotoxicity than decreased LVEF.[10] Previous studies have shown that abnormalities in GLS can be detected during or shortly after the course of cancer therapy.[26-28] On the other hand, a decline in LVEF is proposed as a "late" parameter of cardiotoxicity, occurring after cardiac compensatory mechanisms fail. An exception to this is a decline in LVEF during trastuzumab treatment, which occurs in approximately 10% of all patients and is mostly reversible upon cessation of treatment.[29,30] In contrast to GLS, LVEF is a volume-derived index that is, on echocardiography, indirectly measured from estimations of LV volumes in systole and at the end of diastole.[31] Therefore, LVEF is highly dependent on the pre- and afterload.[32] As such, LVEF is not only a parameter of myocardial contractility but also of LV remodeling. On the other hand, GLS tracks the myocardium directly and quantifies changes in longitudinal lengthening per cardiac segment throughout the cardiac cycle.[31] As a result, although GLS is still load dependent, it is less so and may be more suitable to detect regional myocardial changes, including tissue composition (eg, interstitial fibrosis),[33] compared with LVEF. GLS may be a better parameter for the assessment of cardiac function. This is further supported by evidence from studies demonstrating that GLS is a better predictor of all-cause mortality than LVEF.[34,35] Nevertheless, because the first trial among cancer patients undergoing anthracycline-based chemotherapy (N = 307) failed to demonstrate the benefit of the GLS-guided versus LVEF-guided approach for cardioprotection,[36] future studies are needed to document the prognostic value of GLS in cancer patients in terms of clinical outcomes.

Given the cross-sectional design of our study, we cannot establish the direction of the association observed with certainty. It is theoretically possible that impaired cardiac function has led to lower physical activity levels (reverse causation). Nonetheless, we speculate that the opposite (ie, higher levels of physical activity have led to less cardiac dysfunction) is more likely to underlie the association observed.[37,38] First, from a biological standpoint, a protective effect of physical activity on subclinical cardiac dysfunction is plausible given that preclinical studies describe various pathways via which physical exercise can yield cardioprotection during and after treatment, including less chemotherapy accumulation in the myocardium following physical exercise.[39] Second, it seems less likely that subclinical cardiac dysfunction results in lower physical activity levels because patients are unlikely to experience symptoms solely from impaired GLS with LVEF in normal ranges. Third, the observed effect of physical activity on cardiac dysfunction is consistent with previous evidence from randomized studies in noncancer populations, documenting beneficial effects of physical exercise on cardiac function, including LVEF.[40,41] The limited evidence from studies in cancer patients also points toward the hypothesis of exercise-mediated cardioprotection, although no clear, consistent benefit has been demonstrated thus far on LVEF or GLS.[42-45] Finally, analyses were adjusted for relevant confounders, including cardiovascular risk factors.

STUDY LIMITATIONS. Important strengths of our study include the use of 2 valid markers of cardiac dysfunction, the large study population, and the availability of accurate data on potential confounders. However, several limitations should also be considered when interpreting our results. First, not all types of physical activity were recorded in the questionnaire, including light to moderate activities. Hence, we were unable to calculate the total energy expenditure per day. However, the Cambridge index is a validated index that compared with other European Prospective Investigation into Cancer and Nutrition-derived indices has the highest correlation with objectively measured physical activity.[14] Second, physical activities were self-reported and therefore vulnerable to misclassification. This would, on average, most likely have led to over-reporting of the amount of physical activity. Although GLS was

unknown to the participants and very few participants had cardiovascular symptoms,[6] misclassification of the physical activity category could have underestimated our association because those with an inactive lifestyle would be more likely to overreport their activities. Third, additional subgroup analyses (ie, in patients treated with anthracyclines and with and without trastuzumab) were deemed inappropriate because only a small number of patients received sequential treatment with trastuzumab (n = 46/316). Lastly, GLS was missing in 74 (13.2%) women. This was unrelated to physical activity (data not shown), but participants with missing GLS were more likely to have been treated with higher cumulative doxorubicin (equivalent) dosages (150.8 vs 121.5 mg/m^2, $P = 0.82$) and had a higher mean BMI (26.9 vs 25.7 kg/m^2, $P = 0.037$). This may have led to underestimating the association between physical activity level and GLS, although multiple imputations did not result in any relevant difference in our inferences.

CONCLUSIONS

In conclusion, we found that higher physical activity levels are associated with less cardiac dysfunction as quantified by GLS but not LVEF independent of cardiovascular risk factors and potential cardiotoxic breast cancer treatment. A relatively large risk reduction was observed for moderately inactive survivors compared with inactive breast cancer survivors. This suggests that physical activity programs may contribute to reducing cardiovascular morbidity in breast cancer survivors, particularly among those who are physically inactive. Future, prospective randomized studies are needed to determine whether cardiac dysfunction following breast cancer treatment can be reduced by physical activity programs.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was financially supported by Pink Ribbon/Dutch Cancer Society (grant 2012.WO39.C143). Dr Sonke reports institutional research support from AstraZeneca, Merck, Novarits, Roche, and Seagen; and is a consultant for Biovica. Dr Gietema reports Roche, Siemens, and Abbvie grant paid to the institution. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Anne M. May, STR 6.131, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands. E-mail: a.m.may@umcutrecht.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In long-term breast cancer survivors, higher levels of physical activity are associated with less cardiac dysfunction quantified by global longitudinal strain independent of cardiovascular risk factors and potential cardiotoxic treatment.

TRANSLATIONAL OUTLOOK: Furthermore, prospective randomized studies are needed to determine whether cardiac dysfunction after breast cancer treatment can be reduced by physical activity programs.

REFERENCES

1. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66:271-289.

2. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology. *Eur Heart J*. 2016;37:2768-2801.

3. Bradshaw PT, Stevens J, Khankari N, Teitelbaum SL, Neugut AI, Gammon MD. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology*. 2016;27:6-13.

4. Abdel-Qadir H, Austin PC, Lee DS, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. *JAMA Cardiol*. 2017;2:88-93.

5. Lotrionte M, Biondi-Zoccai G, Abbate A, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Cardiol*. 2013;112:1980-1984.

6. Jacobse JN, Steggink LC, Sonke GS, et al. Myocardial dysfunction in long-term breast cancer survivors treated at ages 40-50 years. *Eur J Heart Fail*. 2020;22:338-346.

7. Wang G, Pratt M, Macera CA, Zheng Z-J, Heath G. Physical activity, cardiovascular disease, and medical expenditures in U.S. adults. *Ann Behav Med*. 2004;28:88-94.

8. Jones LW, Habel LA, Weltzien E, et al. Exercise and risk of cardiovascular events in women with nonmetastatic breast cancer. *J Clin Oncol*. 2016;34:2743-2749.

9. Kim KH, Choi S, Kim K, et al. Association between physical activity and subsequent cardiovascular disease among 5-year breast cancer survivors. *Breast Cancer Res Treat*. 2021;188:203-214.

10. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med*. 2020;7:26.

11. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:233-270.

12. Cust AE, Smith BJ, Chau J, et al. Validity and repeatability of the EPIC physical activity questionnaire: a validation study using accelerometers as an objective measure. *Int J Behav Nutr Phys Act*. 2008;5:33.

13. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived

from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Public Health Nutr*. 2003;6:407-413.

14. Peters T, Brage S, Westgate K, et al. Validity of a short questionnaire to assess physical activity in 10 European countries. *Eur J Epidemiol*. 2012;27:15-25.

15. Haftenberger M, Schuit AJ, Tormo MJ, et al. Physical activity of subjects aged 50-64 years involved in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr*. 2002;5:1163-1176.

16. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis. *JAMA Cardiol*. 2019;4:1007-1018.

17. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2014;15:1063-1093.

18. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159:702-706.

19. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J. Stat. Software; Vol 1, Issue 3 2011. https://www.jstatsoft.org/v045/i03

20. Ferrari S, Cribari-Neto F. Beta regression for modelling rates and proportions. *J Appl Stat*. 2004;31:799-815.

21. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. *Front Cardiovasc Med*. 2018;5:135.

22. Löllgen H, Böckenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. *Int J Sports Med*. 2009;30:213-224.

23. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ*. 2019;366:l4570.

24. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. *Heart*. 2018;104:971-977.

25. Belzile-Dugas E, Eisenberg MJ. Radiation-induced cardiovascular disease: review of an underrecognized pathology. *J Am Heart Assoc*. 2021;10:e021686.

26. Kang Y, Cheng L, Li L, et al. Early detection of anthracycline-induced cardiotoxicity using two-dimensional speckle tracking echocardiography. *Cardiol J*. 2013;20:592-599.

27. Florescu M, Magda LS, Enescu OA, Jinga D, Vinereanu D. Early detection of epirubicin-induced cardiotoxicity in patients with breast cancer. *J Am Soc Echocardiogr*. 2014;27:83-92.

28. Charbonnel C, Convers-Domart R, Rigaudeau S, et al. Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity. *Eur Heart J Cardiovasc Imaging*. 2017;18:392-401.

29. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. *ESMO Open*. 2016;1:e000073.

30. de Azambuja E, Ponde N, Procter M, et al. A pooled analysis of the cardiac events in the trastuzumab adjuvant trials. *Breast Cancer Res Treat*. 2020;179:161-171.

31. Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. *Eur Heart J*. 2016;37:1642-1650.

32. Kerkhof PLM, van de Ven PM, Yoo B, Peace RA, Heyndrickx GR, Handly N. Ejection fraction as related to basic components in the left and right ventricular volume domains. *Int J Cardiol*. 2018;255:105-110.

33. Park T-H, Nagueh SF, Khoury DS, et al. Impact of myocardial structure and function postinfarction on diastolic strain measurements: implications for assessment of myocardial viability. *Am J Physiol Heart Circ Physiol*. 2006;290:H724-H731.

34. Park JJ, Park J-B, Park J-H, Cho G-Y. Global longitudinal strain to predict mortality in patients with acute heart failure. *J Am Coll Cardiol*. 2018;71:1947-1957.

35. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging*. 2009;2:356-364.

36. Thavendiranathan P, Negishi T, Somerset E, et al. Strain-guided management of potentially cardiotoxic cancer therapy. *J Am Coll Cardiol*. 2021;77:392-401.

37. Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58:295-300.

38. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol*. 2015;12:14.

39. Naaktgeboren WR, Binyam D, Stuiver MM, et al. Efficacy of physical exercise to offset anthracycline-induced cardiotoxicity: a systematic review and meta-analysis of clinical and preclinical studies. *J Am Heart Assoc*. 2021;10:e021580.

40. Tucker WJ, Beaudry RI, Liang Y, et al. Meta-analysis of exercise training on left ventricular ejection fraction in heart failure with reduced ejection fraction: a 10-year update. *Prog Cardiovasc Dis*. 2019;62:163-171.

41. Martland R, Mondelli V, Gaughran F, Stubbs B. Can high-intensity interval training improve physical and mental health outcomes? A meta-review of 33 systematic reviews across the lifespan. *J Sports Sci*. 2020;38:430-469.

42. Kirkham AA, Eves ND, Shave RE, et al. The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: A. *Breast Cancer Res Treat*. 2018;167:719-729.

43. 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. *Int J Cardiol*. 2017;245:263-270.

44. Ma Z. Effect of anthracycline combined with aerobic exercise on the treatment of breast cancer. *Pak J Pharm Sci*. 2018;31:1125-1129.

45. Ansund J, Mijwel S, Bolam KA, et al. High intensity exercise during breast cancer chemotherapy - effects on long-term myocardial damage and physical capacity - data from the OptiTrain RCT. *Cardiooncology*. 2021;7:7.

KEY WORDS **breast cancer, echocardiography, heart failure, lifestyle risk factors**

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