Short Communication

Cardiovascular Risk Profile of Patients with HER2/neu-Positive Breast Cancer Treated with Anthracycline-Taxane–Containing Adjuvant Chemotherapy and/or Trastuzumab

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Abstract

Purpose: **To evaluate the cardiovascular risk profile of a subset of patients with early-stage breast cancer treated with adjuvant taxane-anthracycline–containing chemotherapy and/or trastuzumab (Herceptin).**

Experimental Design: **Twenty-six patients with breast cancer (mean, 20 months postchemotherapy) and 10 healthy age-matched women were studied. We measured 14 metabolic and vascular established cardiovascular disease (CVD) risk factors, body mass index, cardiorespiratory fitness, and left ventricular systolic function. All assessments were done within a 14-day period.**

Results: **Cardiac abnormalities were suggested by left ventricular ejection fraction (LVEF) <50% in 8% of patients, LVEF remained >10% below pretreatment values in 38%, whereas 50% presented with resting sinus tachycardia. Brain natriuretic peptide was significantly elevated in 40% of patients and was correlated with LVEF ($r = -0.72$, $P = < 0.001$). For the majority of CVD risk factors, similar proportions of patients and controls (35-60%) were classified as ''undesirable.'' A significantly higher proportion of patients were classified with low cardiorespiratory fitness (46% versus 0%, $P < 0.01$), being overweight/obese (72% versus 50%, $P < 0.05$), and having resting sinus tachycardia (50% versus 0%, $P < 0.01$) compared with controls. Cardiorespiratory fitness and body mass index were correlated with CVD risk factors ($r = -0.64$ to 0.63, $P < 0.05$; $r = -0.63$ to 0.67, $P < 0.05$, respectively). Exploratory analyses revealed several differences between CVD risk factors based on chemotherapy regimen.**

Conclusion: **Breast cancer survivors treated with adjuvant chemotherapy are at a higher risk of developing late-occurring CVD than age-matched controls due to direct and indirect treatment-related toxicity.** (Cancer Epidemiol Biomarkers Prev 2007;16(5):1026–31)

Background

Breast cancer is the most commonly diagnosed malignancy in American women with ~178,000 new cases expected in 2007 (1). Improvements in early detection and treatment have resulted in significant survival gains with the current 5-year survival rate reported to be 88% (1). Moreover, seminal results from recent trials showing marked improvements in both disease-free (2-4) and overall survival (3) in patients with HER2/neu-positive early-stage breast cancer treated with trastuzumab (Herceptin), a humanized monoclonal antibody against HER2, during or after standard adjuvant chemotherapy, will further improve prognosis in this group.

With improving longevity, patients with early-stage breast cancer are becoming increasingly susceptible to the late-occurring toxic effects of cancer therapy. Breast cancer therapies, particularly anthracycline-trastuzumab–containing regimens, are associated with acute (5, 6) and long-term cardiac toxicity (4), as well as other negative side effects secondary to therapy such as physical inactivity (7) and weight gain (8). These clinical disorders substantially elevate the patient's risk of cardiovascular disease (CVD), which is becoming recognized as an increasingly important indicator of competing mortality in patients diagnosed with early-stage breast cancer (9).

Breast cancer clinical trials and day-to-day clinical practice rely solely on cardiac function evaluation via resting left ventricular ejection fraction (LVEF) to evaluate the cardiovascular safety of breast cancer therapeutics. Although the importance of symptomatic cardiac dysfunction as clinical end-points is clear, current monitoring techniques may not fully characterize the degree of adjuvant therapy–related global cardiovascular abnormalities that may precede the development of overt CVD. As such, we conducted a pilot study to comprehensively evaluate the cardiac and CVD risk

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Author contributions: L.W. Jones conceived the study, carried out the outcome assessments, conducted the statistical analysis, and drafted the manuscript. M. Haykowsky and C.J. Peddle carried out the cardiopulmonary exercise testing, the endothelial function testing and helped to draft the manuscript. E.N. Pituskin and L.M. Tkachuk assisted in the acquisition of participants and data. A.A. Joy helped monitor the cardiopulmonary exercise tests and draft the manuscript. K.S. Courneya and DJS helped draft the manuscript. J.R. Mackey conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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profile of a subset of HER2/neu-positive early-stage breast cancer patients enrolled in the Breast Cancer International Research Group (BCIRG) 006 clinical trial (4) using established and novel measures of metabolic and vascular CVD risk factors and body mass index, cardiorespiratory fitness, LVEF, and brain natriuretic peptide, an early indicator of asymptomatic left ventricular systolic dysfunction. We hypothesized that patients with breast cancer would have significantly worse cardiovascular risk profiles than healthy age-matched women.

Materials and Methods

Participants and Setting. Node-positive and high-risk node-negative patients with operable HER2/neu breast cancer who participated in BCIRG 006 at the Cross Cancer Institute, Edmonton, Canada were potentially eligible for this study. High-risk node-negative disease was defined as a patient with negative lymph node involvement, and at least one of the following factors: (*a*) tumor size >2 cm, (*b*) estrogen receptor and progesterone receptor status are both negative, (*c*) histologic and/or nuclear grade 2 to 3 disease, or (*d*) age <35 years. Additional eligibility criteria for the present study included: (*a*) no evidence of recurrent or progressive breast cancer, (*b*) ability to understand and read English, (*c*) no mental illness, (*d*) completion of adjuvant chemotherapy/trastuzumab, and (*e*) no contraindications to a cardiopulmonary exercise test.

Patients were randomly assigned to receive AC → T [four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by four cycles of docetaxel (100 mg/m^2)], AC → TH [four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by four cycles of docetaxel (100 mg/m^2) with concurrent trastuzumab for 1 year] or TCH [six cycles of concurrent docetaxel (75 mg/m^2) with platinum and concurrent trastuzumab for 1 year]. After completion of chemotherapy, postoperative radiation therapy was delivered according to local standard practice. Following the completion of adjuvant chemotherapy, all hormone receptor–positive patients were offered tamoxifen (20 mg/d) for 5 years.

Twenty-six BCIRG 006 study patients were enrolled in this study. In addition, 10 healthy, age-matched women were also recruited for comparison purposes. To be defined as ''healthy,'' women had to be free of documented CVD, cancer, or any other chronic health condition. The Alberta Cancer Board and the University of Alberta Institutional Review Boards approved the study. Written informed consent was obtained from all participants prior to initiation of study procedures.

Study Procedures. Using a cross-sectional design, potential participants were identified and contacted by the BCIRG 006 trial coordinator and asked if they would be willing to participate in the study. Interested participants were then scheduled for study assessments. Healthy control subjects were recruited from hospital staff via posted advertisements. For a given individual, all assessments were done at the Cross Cancer Institute or University of Alberta Hospital within a 14-day period.

Outcome Assessments. In order of presentation, participants completed the following assessments: (*a*) endothelial function, (*b*) blood collection, (*c*) body composition, (*d*) cardiopulmonary exercise test, and (*e*) left ventricular systolic function scan (breast cancer patients only) using standard procedures. Endothelial function and blood collection was done between 7:00 a.m. and 10:00 a.m. after a 12-hour, overnight, water-only fast; subsequent assessments were done after each participant had rested for at least 60 min and received a light breakfast.

Endothelial function was assessed via flow-mediated dilation of the brachial artery using high-resolution vascular ultrasound (Sonos 5500, Hewlett Packard) for imaging arterial diameter in response to endothelium-dependent (i.e., reactive hyperemia) and endothelium-independent stimuli (i.e., nitroglycerin) as described elsewhere (10). Left ventricular function was determined using Multiple Gated Acquisition scan to assess LVEF using standardized procedures. Resting blood pressure and heart rate were assessed according to the procedures recommended by the American Heart Association (11). Plasma concentration of brain natriuretic peptide was determined using a highly sensitive and specific immunoassay based on a double-antibody sandwich technique (12). Body composition was measured by body mass index, calculated as weight divided by height squared (kg/m^2). Weights and heights of all study participants were measured using

Table 1. Descriptive and between-group comparison on cardiovascular outcomes

Cardiovascular outcome	Breast cancer patients (n = 26)	Healthy controls (n = 10)	P
Cardiac function			
Baseline LVEF	64 ± 6	—	—
Postchemotherapy LVEF, 20 mo postchemotherapy (%)	59 ± 8	—	—
LVEF change, baseline to postchemotherapy (%)	−8 ± 11	—	—
Hemoglobin (g/L)	116 ± 10	—	—
Resting heart rate (bpm)	98 ± 18	82 ± 10	0.002
Resting systolic blood pressure (mm Hg)	120 ± 14	121 ± 14	0.755
Resting diastolic blood pressure (mm Hg)	81 ± 9	84 ± 7	0.489
Brain natriuretic peptide (pg/mL)	70.8 ± 85.7	45.3 ± 29.3	0.393
Body composition			
Body mass index (kg/m^2)	29 ± 6	27 ± 6	0.398
Cardiorespiratory fitness			
Peak oxygen consumption (mL/kg/min^{-1})	19.2 ± 4.6	26.1 ± 8.6	0.004
Peak oxygen consumption (L/min^{-1})	1.5 ± 0.3	1.9 ± 0.6	0.007
Peak workload (W)	104 ± 23	141 ± 49	0.005
Vascular risk factors			
Endothelial-dependent vasodilation (% change)	5.4 ± 4.1	8.4 ± 7.7	0.184
Endothelial-independent vasodilation (% change)	16.8 ± 6.6	18.0 ± 7.2	0.687
C-reactive protein (mmol/L)	2.5 ± 3.5	3.0 ± 3.4	0.715
Metabolic risk factors			
Total cholesterol (mmol/L)	5.2 ± 0.9	5.4 ± 1.0	0.507
Triglyceride (mmol/L)	1.9 ± 1.5	1.0 ± 0.7	0.020
High-density lipoprotein (mmol/L)	1.4 ± 0.3	1.6 ± 0.3	0.035
Low-density lipoprotein (mmol/L)	3.1 ± 1.0	3.3 ± 1.1	0.490
Fasting insulin (mU/L)	10.9 ± 7.3	6.7 ± 4.4	0.060
Fasting glucose (mmol/L)	4.9 ± 0.5	4.8 ± 0.4	0.542

Table 2. Between-group proportion comparison within normality values for cardiovascular outcomes

Cardiovascular outcome	All patients (n = 26)	Healthy controls (n = 10)
	No. (%)	No. (%)
Cardiac function		
Postchemotherapy LVEF (20 months postchemotherapy)		
Undesirable, ≤50%	2 (8.0)	—
LVEF change (baseline to postchemotherapy)		
Grade 1, ≥−10%	10 (38.4)	—
Resting heart rate (bpm)*		
Sinus tachycardia, ≥110	13 (50.0)	0 (0)
Resting systolic blood pressure (mm Hg)		
Normal, >100 to ≤160	25 (96.2)	10 (100)
Hypertension, >160	1 (3.8)	0 (0)
Resting diastolic blood pressure (mm Hg)		
Normal, >60 to ≤80	11 (45.8)	4 (40)
Hypertension, >80	13 (54.2)	6 (60)
NH_2-terminal brain natriuretic peptide (pg/mL)		
Undesirable ≥64	10 (40.0)	3 (33.3)
Desirable <63	15 (60.0)	6 (67.7)
Body composition, body mass index (kg/m^2)*		
Normal, <24.9	7 (28.0)	5 (50.0)
Overweight, ≥25 to <29.9	9 (36.0)	2 (20.0)
Obese, ≥30	9 (36.0)	3 (30.0)
Cardiorespiratory fitness		
Peak oxygen consumption ($mL/kg/min^{-1}$)*		
Low fitness, ≤18.0	12 (46.2)	0 (0)
Moderate fitness, >18.0 to ≤28.0	13 (50.0)	7 (70.0)
High fitness, >28.0	1 (3.8)	3 (30.0)
Vascular risk factors		
Endothelial-dependent, hyperemia (% change)		
Undesirable, ≤5%	8 (42.1)	4 (40.0)
Desirable, >5%	11 (57.9)	6 (60.0)
Endothelial-independent, NTG (% change)		
Undesirable, ≤15%	7 (36.8)	4 (40.0)
Desirable, >15%	12 (64.7)	6 (60.0)
C-reactive protein (mmol/L)		
Undesirable, ≥3.5	5 (20.0)	3 (33.3)
Desirable, <3.5	20 (80.0)	6 (66.7)
Metabolic risk factors		
Total cholesterol (mmol/L)		
Undesirable, ≥5.3	11 (49.8)	5 (55.6)
Desirable, <5.3	12 (50.2)	4 (44.4)
Triglycerides (mmol/L)		
Undesirable, >2.3	3 (13.0)	1 (11.1)
Desirable, ≤2.3	20 (87.0)	8 (88.9)
High-density lipoprotein (mmol/L)		
Undesirable, <0.89	0 (0)	0 (0)
Desirable, ≥0.89	18 (100)	9 (100)
Low-density lipoprotein (mmol/L)		
Undesirable, >3.5	7 (32.8)	5 (50.0)
Desirable, ≤3.5	15 (67.2)	5 (50.0)
Fasting insulin (mU/L)		
Undesirable, <5.0 and >20.0	6 (26.1)	3 (30.3)
Desirable, 5.0-20.0	17 (73.9)	6 (66.7)
Fasting glucose (mmol/L)		
Undesirable, <3.3 and >6.0	1 (4.2)	0 (0)
Desirable, 3.3-5.9	23 (95.8)	10 (100)

*$P < 0.05$.

standard procedures prior to the cardiopulmonary exercise test. Cardiorespiratory fitness was determined using a maximal physician-supervised 12-lead ECG-graded exercise test with expired gas analysis according to American Heart Association guidelines (13). Metabolic risk factors included lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglyceride), plasma insulin, glucose, and C-reactive protein. All assays were done in one batch and in duplicate against known standards. All assessments were done by personnel blinded to treatment and study group.

Statistical Analysis. The initial analysis provided descriptive information on the demographic, clinical treatment characteristics and CVD risk profile of study participants. We also classified participants within established clinically predictive values for each CVD risk factor. To examine potential differences between patients with breast cancer and healthy controls on CVD risk factors, we used one-way ANOVA for mean comparisons and Pearson χ^2 for proportion comparisons. To determine the univariate association between CVD risk factors, we used linear regression analyses. To examine the independent predictors of LVEF, we used multiple linear regression analyses. Data are presented as mean ± SD. Statistical significance was set at $P < 0.05$ for all analyses.

Results

A total of 41 patients with HER2/neu-positive breast cancer were randomized to BCIRG 006 at the Cross Cancer Institute and approached for participation in this substudy. Of these, 36 met inclusion criteria and 26 agreed to participate in this ancillary study, a participation rate of 72% (26/36). Reasons for noneligibility were mental illness (n = 1),

pregnancy ($n = 1$), and progressive disease ($n = 3$). Reasons for nonparticipation were geographic location ($n = 2$) and lack of interest ($n = 8$). There were no differences between participants and nonparticipants on any demographic or clinical treatment characteristic.

Participant Characteristics. Patients' mean age was 48.0 ± 8.5 years (range, 31-62 years), mean months since diagnosis and chemotherapy completion was 30 ± 10 and 20 ± 10, respectively. Clinical treatment characteristics indicated that 65% ($n = 17$) of patients were diagnosed with stage I or II disease, 42% ($n = 11$), 31% ($n = 8$), and 27% ($n = 7$) received TCH, AC → TH, or AC → T, respectively. Sixty-five percent received radiation therapy, 52% underwent a mastectomy, and 62% received tamoxifen. Healthy control subjects mean age was 45.2 ± 8.3 years (range, 34-58 years). All subjects were free of recurrent or progressive breast cancer and symptomatic cardiac dysfunction at study entry.

Overall Cardiovascular Risk Factor Characteristics. Overall, CVD risk factors were consistently higher in patients compared with healthy controls, with several individual CVD risk factors reaching statistical significance (see Table 1). Resting heart rate and triglyceride levels were significantly higher in patients compared with control subjects, whereas cardiorespiratory fitness, peak workload, and high-density lipoprotein levels were significantly lower in patients than controls ($P < 0.05$). Group comparisons according to known standards for CVD risk factors are presented in Table 2. Ten percent of patients presented with a LVEF <50%. A decline in LVEF of ≥10% was indicated in 38% and sinus tachycardia in 50% of the patients. Similar proportions of patients with breast cancer and healthy controls (35-60%) were classified as ''undesirable'' for the majority of CVD risk outcomes. However, a significantly higher proportion of patients were classified with low cardiorespiratory fitness, ≤18.0 mL/kg/min^{-1}, (46.2% versus 0%, $P < 0.01$), being overweight or obese, body mass index ≥25 kg/m^2 (72% versus 50%, $P < 0.05$), and having sinus tachycardia, resting heart rate ≥100 bpm (50% versus 0%, $P < 0.01$) compared with healthy subjects.

Associations between LVEF, VO_{2peak}, Body Mass Index, and CVD Risk Factors. Given the propensity of oncologists to solely rely on LVEF to assess cardiovascular function, and the comparably higher proportion of unfit and overweight patients with breast cancer, we examined the univariate associations between LVEF, cardiorespiratory fitness, body mass index, and CVD risk factors (see Table 3). Regarding LVEF, there were several significant moderate (>0.40) to large (>0.60) univariate associations. Independent predictors of LVEF were brain natriuretic peptide (−0.41) and cardiorespiratory fitness (0.42). Cardiorespiratory fitness and body mass index were consistently correlated with the majority of individual CVD risk factors ($r = -0.64$ to 0.63, $P < 0.05$; $r = -0.63$ to 0.67, $P < 0.05$, respectively).

Comparisons between Chemotherapy Regimen and CVD Risk Factors. Finally, given the interest in the potential differential clinical cardiac tolerability of anthracycline-trastuzumab therapy combinations, we also explored potential differences between chemotherapy regimen and CVD risk factors (presented in Table 4). In general, although AC → TH was associated with a more unfavorable CVD profile in comparison with either AC → T or TCH, there were no statistically significant differences between chemotherapy regimens for any CVD outcome ($P > 0.05$).

Discussion

The results of this pilot study support numerous prior epidemiologic reports indicating that a considerable proportion of middle-aged women are at a high risk for CVD independent of prior history of breast cancer treatment (14-18); however, patients with early-stage HER2/neu-positive breast cancer seem to be at an even greater risk of CVD than these women due to the direct and indirect toxic effects of adjuvant breast cancer therapy.

In the present study, we reported that 10 patients (38.4%) had a decline in LVEF of 10 percentage points or greater from baseline to entry into our study (~20 months postchemotherapy). In the recently reported HERA trial (2), 7.1% of patients treated with trastuzumab for 12 months had a decrease in

Table 3. Univariate associations between LVEF, peak oxygen consumption, body mass index, and cardiovascular risk factors ($n = 26$)

Cardiovascular outcome	Postchemotherapy LVEF (%)		Peak oxygen consumption (mL/kg/min^{-1})		Body mass index (kg/m^2)	
	Correlation coefficient	P	Correlation coefficient	P	Correlation coefficient	P
Cardiac function						
Postchemotherapy LVEF, 20 months postchemotherapy (%)	—	—	0.63	<0.001	−0.45	0.023
Resting heart rate (bpm)	−0.30	0.142	−0.25	0.224	0.34	0.086
Resting systolic blood pressure (mm Hg)	0.05	0.818	−0.20	0.329	0.53	0.007
Resting diastolic blood pressure (mm Hg)	0.04	0.854	0.40	0.050	0.67	0.001
Brain natriuretic peptide (pg/mL)	−0.72	<0.001	−0.53	0.006	0.45	0.023
Body composition						
Body mass index (kg/m^2)	−0.45	0.023	−0.63	<0.001	—	—
Cardiorespiratory fitness						
Peak oxygen consumption (mL/kg/min^{-1})	0.63	<0.001	—	—	−0.63	<0.001
Peak oxygen consumption (L/min^{-1})	0.30	0.149	0.54	0.003	0.16	0.448
Peak workload (W)	0.37	0.068	0.68	<0.001	−0.10	0.613
Vascular risk factors						
Brachial artery reactivity, RH (% change)	0.32	0.203	−0.05	0.823	−0.39	0.097
Brachial artery reactivity, NTG (% change)	0.48	0.045	0.15	0.534	−0.30	0.210
C-reactive protein	−0.24	0.083	−0.19	0.358	0.16	0.454
Metabolic risk factors						
Total cholesterol (mmol/L)	−0.31	0.144	−0.14	0.530	0.13	0.535
Triglycerides (mmol/L)	−0.17	0.198	−0.18	0.395	0.34	0.103
High-density lipoprotein (mmol/L)	0.32	0.144	0.53	0.007	−0.49	0.015
Low-density lipoprotein (mmol/L)	−0.29	0.198	−0.15	0.519	0.01	0.672
Fasting insulin (mU/L)	−0.08	0.741	−0.59	0.003	0.46	0.028
Fasting glucose (mmol/L)	−0.28	0.193	−0.64	0.001	0.48	0.017

Table 4. Descriptive and between-chemotherapy regimen group comparisons on cardiovascular outcomes

Cardiovascular outcome	TCH (n = 11)	AC → TH (n = 7)	AC → T (n = 8)
Cardiac function			
Baseline LVEF	64 ± 6	65 ± 6	63 ± 5
Postchemotherapy LVEF, 20 months postchemotherapy (%)	59 ± 6	58 ± 12	59 ± 6
LVEF change, baseline to postchemotherapy (%)	−7 ± 10	−11 ± 15	−5 ± 11
Hemoglobin (g/L)	132 ± 7	138 ± 14	134 ± 12
Resting heart rate (bpm)	94 ± 17	106 ± 17	98 ± 20
Resting systolic blood pressure (mm Hg)	124 ± 11	116 ± 14	114 ± 17
Resting diastolic blood pressure (mm Hg)	85 ± 7	81 ± 9	77 ± 11
NH_2-terminal brain natriuretic peptide (pg/mL)	53.1 ± 28.1	111.6 ± 156.0	57.2 ± 31.3
Body composition			
Body mass index (kg/m^2)	29 (6)	32 (8)	27 (5)
Cardiorespiratory fitness			
Peak oxygen consumption (mL/kg/min^{-1})	19.1 ± 4.1	18.3 ± 5.1	20.2 ± 5.1
Peak oxygen consumption (L/min^{-1})	1.5 ± 0.2	1.6 ± 0.3	1.5 ± 0.3
Peak workload (W)	100 ± 21	107 ± 19	106 ± 30
Vascular risk factors			
Endothelial-dependent (% change)	4.2 ± 3.4	3.2 ± 5.6	7.5 ± 3.9
Endothelial-independent (% change)	17.3 ± 6.1	14.7 ± 9.5	17.2 ± 6.8
C-reactive protein (mmol/L)	2.9 ± 4.8	1.3 ± 1.0	3.0 ± 3.4
Metabolic risk factors			
Total cholesterol (mmol/L)	5.3 ± 1.3	4.9 ± 0.6	5.2 ± 0.7
Triglyceride (mmol/L)	1.5 ± 0.5	2.5 ± 2.2	1.9 ± 1.6
High-density lipoprotein (mmol/L)	1.3 ± 0.2	1.3 ± 0.3	1.5 ± 0.2
Low-density lipoprotein (mmol/L)	3.3 ± 1.3	2.8 ± 0.7	3.1 ± 0.7
Fasting insulin (mU/L)	11.4 ± 9.4	12.7 ± 6.7	8.7 ± 3.9
Fasting glucose (mmol/L)	4.9 ± 0.6	5.1 ± 0.5	4.6 ± 0.4

NOTE: Group comparisons were not significant for any CVD outcome ($P > 0.05$).
Abbreviations: TCH, docetaxel/carboplatin/herceptin; AC → TH, doxorubicin/cyclophosphamide/docetaxel/herceptin; AC → T, doxorubicin/cyclophosphamide/docetaxel.

LVEF of 10 percentage points or more from baseline, whereas 18.9% of patients in the combined NSABP B-31/NCCTG N9831 report (3) had therapy discontinued due to subclinical reductions in cardiac function. Finally, in our parent trial (BCIRG 006), Slamon et al. (4) recently reported that 9% to 18% of patients receiving trastuzumab had an asymptomatic decrease in LVEF of 10% or more.

Although our presently reported cardiac data seems divergent with those reported in these four large-scale trials, intertrial differences in study design and the definition of grade 1 LVEF dysfunction preclude direct comparisons. First, in the HERA trial, patients were randomized to receive trastuzumab following the completion of adjuvant chemotherapy (2). In contrast, the other three trials randomized patients to receive trastuzumab with concurrent adjuvant chemotherapy, thus explaining the higher incidence of asymptomatic cardiac dysfunction (~18%; refs. 3, 4). Accordingly, patient baseline LVEF eligibility was also higher in the HERA trial than in other investigations (55% versus 50%), which might also partially explain the discrepant findings. Second, we defined grade 1 cardiac toxicity as a decrease in LVEF of 10 percentage points or more (≤20 percentage points). In the HERA and NSABP B-31/NCCTG N9831 trials, grade 1 left ventricular dysfunction was defined as a decrease in the LVEF of 10 percentage points or more from baseline to an LVEF below the lower limit of normal (50%; refs. 2, 3). In light of the different definitions, generalizations across trials are not prudent.

This study does have several limitations. Two obvious limitations are the relatively small sample size and cross-sectional study design. To adequately investigative the effect of adjuvant breast cancer therapy on cardiovascular health, large prospective studies are required. A third important limitation is that selection biases are likely to exist because of the transparent purpose of the study. As such, women more interested in exercise and health, and experiencing less treatment-related complications, were probably more likely to participate in this study. Finally, it is also important to note that although the cardiotoxic effects of anthracycline-containing chemotherapeutic regimens with or without trastuzumab have received the most attention in this domain, other systemic agents commonly used in breast cancer management (e.g., aromatase inhibitors, taxane, and platinum-based chemotherapy) may also impair cardiovascular health in these patients (19) and need to be considered in future investigations in this area. In summary, this pilot study provides preliminary data for future studies to further investigate the clinical value of cardiopulmonary fitness, body composition, and brain natriuretic peptide in the assessment of breast cancer treatment–related CVD and identifying patients at high-risk for late-occurring CVD.

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