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ORIGINAL RESEARCH

Pre-Diagnosis Exercise and Cardiovascular Events in Primary Breast Cancer

Women's Health Initiative

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ABSTRACT

OBJECTIVES The purpose of this study was to investigate whether pre-diagnosis exercise reduces the risk of subsequent cardiovascular events (CVEs) in women with primary breast cancer.

BACKGROUND Cardiovascular disease (CVD) is the leading nonmalignant cause of death in patients with cancer, and it is the leading cause of death in women with primary breast cancer who are older than 65 years of age.

METHODS Using a prospective design, 4,015 patients with confirmed diagnosis of primary breast cancer enrolled in the Women's Health Initiative (WHI) completed a self-report questionnaire assessing leisure-time physical activity (i.e., exercise) in metabolic equivalent task (MET) hours per week. Age- and multivariable-adjusted Cox proportional hazards models were used to estimate associations between pre-diagnosis exercise and new-onset CVEs (i.e., heart failure [HF], myocardial infarction [MI], angina, coronary revascularization, peripheral arterial disease [PAD], carotid artery disease, transient ischemic attack [TIA], stroke, and cardiovascular death).

RESULTS Median follow-up was 12.7 years and 8.2 years for cardiovascular disease (CVD) mortality and CVEs, respectively, with 324 CVEs, including 89 MIs, 49 new diagnoses of HF, and 215 CVD deaths. In multivariable analysis, the incidence of composite CVEs decreased across increasing total MET h/week categories ($p = 0.016$). Compared with <2.5 MET-hours per week, the adjusted hazard ratio (HR) was 0.80 (95% confidence interval [CI]: 0.59 to 1.09) for 2.5 to <8.6 MET h/week; 0.9 (95% CI: 0.64 to 1.17) for 8.6 to <18 MET h/week; and 0.63 (95% CI: 0.45 to 0.88) for ≥18 MET h/week.

CONCLUSION Pre-diagnosis exercise exposure is associated with a significant graded reduction in subsequent CVEs in long-term survivors of primary breast cancer. (J Am Coll Cardiol CardioOnc 2019;1:41–50) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVE = cardiovascular event

CRF = cardiorespiratory fitness

CT = clinical trial

HF = heart failure

HT = hormone therapy

IQR = interquartile range

MET = metabolic equivalent task

MI = myocardial infarction

OS = observational study

PAD = peripheral arterial disease

TIA = transient ischemic attack

WHI = Women's Health Initiative

Advances in screening and adjuvant therapy have led to continual improvements in cancer-specific mortality among women with primary breast cancer. The current 5-year survival rate is 89.4% compared with 74.6% from 1975 to 1979 (1). As a result, patients with breast cancer have now sufficient longevity to be at increased risk of normal age-related pathologies: primarily, cardiovascular disease (CVD). In fact, CVD has now surpassed breast cancer as the leading cause of death in patients with primary breast cancer above the age of 65 years (2,3).

Interestingly, efforts in cardio-oncology have focused primarily on the cardiac-centric consequences of breast-cancer therapy, with resting assessment of left ventricular ejection fraction being used to assess the incidence of asymptomatic and symptomatic myocardial injury that predisposes to heart failure (HF). However, it is now established that the adverse consequences of breast cancer therapy extend beyond the heart, with myocardial injury occurring in conjunction with (mal)adaptation of other organ systems. Many anticancer therapies cause unique and varying degrees of injury to other components of the cardiovascular system, including the pulmonary-vascular and blood-skeletal muscle axes.

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To this end, incremental exercise tolerance testing, which evaluates cardiorespiratory fitness (CRF), provides a robust, integrated assessment of cardiovascular reserve capacity. In previous work, we—as well as others—observed that CRF can decline between 5% and 20% in women receiving chemotherapy-containing adjuvant therapy, and this decline persists even years following the cessation of treatment. As such, intervention strategies with the capacity to not only prevent cancer-therapy-associated myocardial injury but also attenuate injury across the entire cardiovascular system may have significant clinical importance.

General physical activity, as well as planned physical activity (i.e., exercise), is a strong independent predictor of cardiovascular events (CVEs), as well as CVD and all-cause mortality in women from the general population. This reduction in risk translates into a 3-year increase in life expectancy (4). Exercise improves the reserve capacity of all organs compromising the cardiovascular system.

Much less is known regarding the impact of exercise on CVD in women with breast cancer. In one study, higher self-reported post-diagnosis exercise exposure was associated with a graded reduction in CVEs (i.e., new diagnosis of coronary artery disease [CAD], HF, valve abnormality, arrhythmia, stroke, or CVD death) in 2,973 patients with primary breast cancer (5). In another study of 55 survivors of breast cancer without cardiovascular risk factors who had received anthracyclines as part of their cancer therapy, physical activity delayed the development of diastolic dysfunction and symptoms of HF (6). Of importance, both studies evaluated the impact of exercise in the period following a diagnosis of breast cancer. A critical corollary to such work is whether exposure to exercise in the period before diagnosis affects the risk of treatment-related CVEs. In other words, are women who are regularly exercising before diagnosis better able to tolerate cancer therapy owing to lower toxicity, including cardiovascular-related toxicity? To our knowledge, whether exercise in the period before diagnosis alters subsequent risk of CVEs in the post-diagnosis period has not been investigated.

Accordingly, we determined the association between pre-diagnosis exercise and risk of CVEs in women with patients with primary breast cancer participating in the Women's Health Initiative (WHI). We hypothesized that exercise would reduce the risk of CVEs (including HF, myocardial infarction [MI], angina, coronary revascularization, peripheral arterial disease [PAD], carotid artery disease, transient ischemic attack [TIA], stroke, or cardiovascular death) in a dose-dependent manner beyond CV risk factors and treatment exposure.

METHODS

The design of the WHI clinical trial (CT) and observational study (OS) are described elsewhere (7). In brief, the WHI was initiated in 1992, recruiting postmenopausal women aged between 50 and 79 years of

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age at 1 of 40 clinical centers within the United States. The total study population included 161,808 women (OS, n = 93,646; CT, n = 61,132) between October 1993 and December 1998. Participants completed in-person visits and questionnaires at baseline and during follow-up. At the end of the main WHI study in 2005, participants were invited to enroll in an Extension Study, and those who consented were followed annually by mail from 2005 to 2010. The institutional review boards from all WHI-affiliated institutions approved the study protocol, and all participants provided informed consent.

Self-reports of cancer were verified by physician adjudicators after review of medical records and pathology reports. Final adjudication and coding of findings was done at the WHI Clinical Coordinating Center, according to the National Cancer Institute Surveillance, Epidemiology, and End Results (NCI-SEER) guidelines. Self-reports of cardiovascular outcomes similarly initiated a review of medical records by physician adjudicators. Reports of participant death and cause of death were also adjudicated by study physicians. The National Death Index was systematically searched for all participants including those lost to follow-up. At the time of this study, WHI data on mortality were complete through December 2014.

The participants in this cohort included patients with confirmed diagnoses of nonmetastatic (localized or regional stage) primary breast cancer during the main WHI study. Women with CVD (MI, angina, coronary artery bypass graft, percutaneous coronary intervention/percutaneous transluminal coronary angioplasty, TIA, stroke, heart failure), history of any other malignancy prior to enrollment in WHI, and/or body mass index (BMI) ≤18.5 kg/m^2 were excluded from this analysis (Supplemental Figure 1). Our final analytic cohort included 4,015 patients within the WHI OS and CT studies.

EXERCISE EXPOSURE ASSESSMENT. Exercise exposure was assessed as leisure-time physical activity and ascertained in the baseline and follow-up questionnaires (8). Specifically, patients were asked to report the frequency (i.e., never to 1 to 7 days per week); duration (<20 min, 20 to 39 min, 40 to 59 min, ≥1 h); and speed (<2 mph [strolling], 2 to 3 mph [average/normal walking], 3 to 4 mph [fairly fast walking], or >4 mph) of walking sessions per week. The frequency and duration of moderate (i.e., biking outdoors, exercise machine, calisthenics, easy swimming, popular or folk dancing) and vigorous (aerobics, jogging, tennis, and swimming laps) activity were also assessed. The midpoint value for ranges of frequency and exercise duration were imputed, and multiplied to calculate hours per week. Metabolic equivalent task (MET) values were assigned for walking (average = 3 METs, fairly fast = 4 METs, or very fast = 4.5 METs), and to classify moderate intensity recreational (4 METs) and vigorous-intensity recreational (7 METs) activities. The MET level was then multiplied by hours per week to calculate total MET hours per week (9). During WHI follow-up, leisure-time physical activity (exercise) was assessed for CT participants at years 1, 3, 6, and 9 and for OS participants in years 3 to 8. For the current study, we used the exercise data that were collected at the visit closest to breast cancer diagnosis and that were between 5 years and 1 month before diagnosis. We categorized exercise as quartiles: <2.50 MET h/week (n = 994); 2.50 to <8.625 (n = 1,008); 8.625 to < 18.00 (n = 1,011); and ≥ 18.00 (n = 1,002). Patients were also categorized and assessed as 2 groups (≥9 MET h/week [N = 1,976] and <9 MET h/week [N = 2,039]), based on physical activity levels according to the national exercise guidelines. The reliability and validity of the exercise instrument has been established (7). To ascertain the validity of the physical activity questionnaire, the questionnaire data were compared with accelerometer data in a previous study (r = 0.73, with 100% sensitivity for meeting the physical activity guidelines) (10).

DEFINITION OF CARDIOVASCULAR OUTCOMES. The primary CVD outcome was the first occurrence of newly diagnosed heart failure, MI, angina, coronary revascularization, PAD, carotid artery disease, TIA, stroke, or cardiovascular death, occurring after diagnosis of breast cancer. For this study, the combined CVD event was ascertained through the end of the Extension Study. Individual incident CVEs were also studied; these were MI, HF, coronary heart disease (CHD) death, and CVD death. CHD was defined as acute MI necessitating overnight hospitalization, death due to CHD, or silent MI identified on serial electrocardiography.

STATISTICAL ANALYSIS. Demographic information, physical measurements, and medication inventories were collected at WHI enrollment. When available, information that had been updated closer to the breast cancer diagnosis was used. Characteristics were described by quartiles of exposure to exercise (in MET hours per week) and compared using chi-square tests for categorical variables. Age-adjusted and multivariable-adjusted Cox proportional hazards models were used to assess the associations of quartiles of METs and incident CVD events presented as hazard ratios (HRs) and 95% confidence intervals

TABLE 1 Participant Characteristics for Breast Cancer Cases, by Level of Exercise in the 5 Years Before Diagnosis (N = 4,015)

	MET h/week								
	<2.50 (n = 994)		2.50 to <8.625 (n = 1,008)		8.625 to <18.00 (n = 1,011)		≥18.00 (n = 1,002)		
	n	%	n	%	n	%	n	%	p Value
Age at cancer diagnosis, yrs									0.647
50 to 59	140	14.1	133	13.2	122	12.1	153	15.3	
60 to 64	202	20.3	217	21.5	228	22.6	223	22.3	
65 to 69	241	24.2	239	23.7	257	25.4	224	22.4	
70 to 74	217	21.8	210	20.8	206	20.4	218	21.8	
75+	194	19.5	209	20.7	198	19.6	184	18.4	
Disease stage									0.717
Localized	744	74.8	760	75.4	744	73.6	758	75.6	
Regional	250	25.2	248	24.6	267	26.4	244	24.4	
Disease grade									<0.001
Well differentiated	219	22.0	266	26.4	272	26.9	259	25.8	
Moderately differentiated	350	35.2	389	38.6	379	37.5	396	39.5	
Poorly differentiated/anaplastic	294	29.6	241	23.9	276	27.3	243	24.3	
Unknown/not done	131	13.2	112	11.1	84	8.3	104	10.4	
Race									<0.001
White	840	84.5	889	88.2	897	88.7	904	90.2	
Black	90	9.1	49	4.9	58	5.7	45	4.5	
Hispanic/Latino	43	4.3	27	2.7	19	1.9	17	1.7	
Other/unspecified	21	2.1	43	4.3	37	3.7	36	3.6	
BMI (kg/m^2)									<0.001
<25	186	18.7	292	29.0	397	39.3	453	45.2	
25 to <30	342	34.4	345	34.2	354	35.0	332	33.1	
≥30	457	46.0	358	35.5	255	25.2	211	21.1	
Unknown	9	0.9	13	1.3	5	0.5	6	0.6	
Smoking status									<0.001
Never	489	49.2	532	52.8	495	49.0	465	46.4	
Past	427	43.0	421	41.8	470	46.5	497	49.6	
Current	75	7.5	55	5.5	43	4.3	40	4.0	
Unknown	3	0.3	0	0.0	3	0.3	0	0.0	
Education									<0.001
Less than high school	42	4.2	32	3.2	24	2.4	21	2.1	
High school diploma or GED	205	20.6	171	17.0	138	13.6	92	9.2	
School after high school	353	35.5	346	34.3	348	34.4	341	34.0	
College degree or higher	387	38.9	448	44.4	493	48.8	537	53.6	
Unknown	7	0.7	11	11.1	8	0.8	11	1.1	
Family history of MI	520	55.3	502	52.3	509	52.7	489	51.2	0.455

Continued on the next page

(CIs). For analysis of the combined CVD event, follow-up was the number of days from cancer diagnosis to the first incident CVE. In analyses of MI and HF as individual incident events, women who had experienced an earlier CVE (e.g., angina before MI) continued to be followed for the specific outcome being studied. Otherwise, follow-up was censored at the last documented follow-up contact, death, or September 30, 2010 (whichever came first) for analyses of the combined CVD event, MI, and HF. For death from CHD or CVD, women were followed until September 30, 2015. CHD-specific mortality and CVD-specific mortality were defined as the time from cancer diagnosis to a CHD death or CVD death, respectively. Women who experienced earlier nonfatal CVD events continued to be followed for CVD-specific mortality events. Event times were censored at the time of a death from another cause. Otherwise, women were followed until September 30, 2015.

All models were adjusted for age at WHI enrollment as a continuous variable. We also adjusted for race or ethnicity (white, black, Hispanic, other), smoking status (never, past, current), BMI (<25, 25 to <30, ≥30 kg/m^2 [corresponding to categories of normal weight, overweight, and obese]), stage (localized, regional), education (less than high school, high school diploma/GED, school after high school, college degree, or higher), WHI study (HT randomized, DM randomized, not in HT, OS enrolled), hormone therapy/trial arm (nonuser, estrogen-alone,

TABLE 1 Continued

	MET h/week								
	<2.50 (n = 994)		2.50 to <8.625 (n = 1,008)		8.625 to <18.00 (n = 1,011)		≥18.00 (n = 1,002)		
	n	%	n	%	n	%	n	%	p Value
Comorbidities Index									<0.001
0	282	28.4	349	34.6	375	37.1	388	38.7	
1	405	40.7	403	40.0	422	41.7	386	38.5	
2	211	21.2	164	16.3	132	13.1	145	14.5	
3+	45	4.5	51	5.1	35	3.5	33	3.3	
Unknown	51	5.1	41	4.1	47	4.6	50	5.0	
Cardiovascular conditions									
Treated hypercholesterolemia	121	12.8	112	11.6	114	11.8	91	9.6	0.151
Treated diabetes	82	8.2	54	5.4	45	4.5	29	2.9	<0.001
Hypertension (measured or treated)	556	55.9	520	51.6	474	46.9	446	44.5	<0.001
Medication use									
Statins	120	12.1	111	11.0	119	11.8	83	8.3	0.026
ACE inhibitors	100	10.1	88	8.7	66	6.5	75	7.5	0.025
Beta-blockers	114	11.5	98	9.7	64	6.3	82	8.2	<0.001
Angiotensin II receptor antagonists	19	1.9	27	2.7	18	1.8	21	2.1	0.514
Regular aspirin use	246	24.7	216	21.4	229	22.7	244	24.4	0.261
Hormone therapy use at WHI baseline									<0.001
Nonuser	475	47.8	459	45.5	412	40.8	408	40.7	
Estrogen alone	238	23.9	224	22.2	231	22.8	220	22.0	
Estrogen + progesterone	281	28.3	325	32.2	368	36.4	373	37.2	
Unknown type							1	0.1	

Values are n (%). The p values were based on chi-square tests that excluded the unknown category.

ACE = angiotensin converting enzyme; BMI = body mass index; GED = general education degree; MET = metabolic equivalent task; MI = myocardial infarction; WHI = Women's Health Initiative.

estrogen + progestin), family history of MI, and comorbidities index (count of diabetes, hypertension, history of high cholesterol treated with pharmacotherapy, history of chronic obstructive pulmonary disease (COPD), lupus/rheumatoid arthritis, history of liver disease, history of stomach ulcer). We included strata for age at diagnosis (50 to 59, 60 to 64, 65 to 69, 70 to 74, ≥75 years) and time-varying extension study participation (yes/no) in the models, allowing the baseline hazards to vary in these strata. Tests for linear trend across increasing categories of exercise were conducted by modeling the median values of each category as a single continuous variable in the models. We also estimated associations between CVD outcomes and exercise levels defined by national exercise guidelines (≥9 MET h/week [N = 1,976] referent to <9 MET h/week [N = 2,039]). As a sensitivity analysis, we analyzed a subset of women (n = 1,603) with cancer-treatment information available from Medicare data. For this group, cancer-treatment variables were included in the models as surgery (none, lumpectomy, mastectomy); chemotherapy (yes/no); radiation (yes/no). All analyses were conducted using SAS (version 9.4, SAS Institute Inc., Cary, North Carolina) or Stata (version 12, StataCorp, College Station, Texas). All statistical tests were 2-sided, and statistical significance was defined as $p < 0.05$.

RESULTS

The median time from exercise assessment to breast cancer diagnosis was 12 months (interquartile range [IQR]: 6 to 23 months). The median duration of follow-up for cardiovascular events analysis was 8.2 years, IQR: 6.0 to 10.6 years. For death outcomes, median follow-up was 12.7 years (IQR: 10.4 to 14.9 years). During this period, a total of 324 CVEs, including 89 MIs, 49 new diagnoses of HF, and 215 CVD deaths (96 attributed to CHD) were observed. As expected, disease grade, race, BMI, smoking status, education, family income, and comorbidities index were associated with total METs (Table 1).

AGE-ADJUSTED ANALYSES. There was a decreasing trend in age-adjusted HR for the primary endpoint of CVEs (HR: 0.77 [95% CI: 0.58 to 1.03], 0.75 [95% CI: 0.56 to 0.99], 0.59 [95% CI: 0.43 to 0.80]; p for trend = 0.001) across increasing quartiles of exercise, compared with the referent first quartile (Table 2). Findings were similar for secondary endpoints of

TABLE 2 Age-Adjusted and Multivariable-Adjusted Hazard Ratios of Cardiovascular Events According to Categories of Pre-Diagnosis Exercise (MET h/week)

		MET h/week				
	Total (N = 4,015)	**<2.50 (n = 994)**	**2.50 to <8.625 (n = 1,008)**	**8.625 to <18.00 (n = 1,011)**	**≥18.00 (n = 1,002)**	**p Value for Trend**
Median MET h/week	8.67	0.0	5.25	13.00	26.33	
Cardiovascular events*						
No. of events (annualized %)	342 (1.14)	103	88	86	65	
Age-adjusted HR (95% CI)		Ref.	0.77 (0.58–1.03)	0.75 (0.56–0.99)	0.59 (0.43–0.80)	0.001
Multivariable-adjusted HR (95% CI)†		Ref.	0.80 (0.59–1.09)	0.86 (0.64–1.17)	0.63 (0.45–0.88)	0.016
MI						
No. of events (annualized %)	89 (0.29)	25	22	24	18	
Age-adjusted HR (95% CI)		Ref.	0.79 (0.45–1.40)	0.84 (0.48–1.48)	0.67 (0.37–1.24)	0.262
Multivariable-adjusted HR (95% CI)†		Ref.	0.83 (0.44–1.53)	1.05 (0.57–1.92)	0.68 (0.34–1.36)	0.373
Heart failure						
No. of events (annualized %)	49 (0.16)	18	11	12	8	
Age-adjusted HR (95% CI)		Ref.	0.58 (0.27–1.22)	0.63 (0.30–1.31)	0.43 (0.19–1.00)	0.075
Multivariable-adjusted HR (95% CI)†		Ref.	0.64 (0.29–1.43)	0.94 (0.43–2.04)	0.57 (0.23–1.44)	0.366
Cardiovascular death						
No. of events (annualized %)	215 (0.44)	69	54	45	47	
Age-adjusted HR (95% CI)		Ref.	0.68 (0.47–0.98)	0.56 (0.38–0.82)	0.62 (0.43–0.90)	0.022
Multivariable-adjusted HR (95% CI)‡		Ref.	0.73 (0.50–1.06)	0.60 (0.40–0.90)	0.69 (0.46–1.04)	0.109
CHD death (annualized %)						
No. of events	96 (0.22)	36	25	19	16	
Age-adjusted HR (95% CI)		Ref.	0.59 (0.36–0.99)	0.45 (0.26–0.79)	0.40 (0.22–0.72)	0.003
Multivariable-adjusted HR (95% CI)‡		Ref.	0.65 (0.38–1.10)	0.46 (0.25–0.83)	0.41 (0.21–0.78)	0.006

Annualized percentage is the total number with the event divided by the total person-years for all women at risk for the event. *Cardiovascular events include heart failure, myocardial infarction, angina, coronary revascularization, peripheral artery disease, carotid artery disease, transient ischemic attack, stroke, and cardiovascular death. †Follow-up through September 30, 2010. Adjusted for age at WHI enrollment (continuous), race (white, black, Hispanic, other), smoking status (never, past, current), body mass index (<25, 25 to <30, ≥30 kg/m^2), stage (localized, regional), education (less than high school, high school diploma/GED, school after high school, college degree or higher), study (HT randomized; DM randomized, not in HT; OS enrolled), hormone therapy/trial arm (non-user, estrogen-alone, estrogen + progestin), family history of MI, and comorbidities index (count of diabetes, hypertension, treated hypercholesterolemia, history of chronic obstructive pulmonary disease (COPD), lupus/rheumatoid arthritis, history of liver disease, history of stomach ulcer). Models are stratified by age at diagnosis (50 to 59, 60 to 64, 65 to 69, 70 to 74, ≥75 years) and extension study participation (yes/no), allowing the baseline hazards to vary in these strata. ‡Deaths as of September 30, 2015, including from NDI searches. Adjusted for age at WHI enrollment (continuous), race (white, black, Hispanic, other), smoking status (never, past, current), body mass index (<25, 25 to <30, ≥30 kg/m^2), stage (localized, regional), education (less than high school, high school diploma/GED, school after high school, college degree or higher), study (HT randomized; DM randomized, not in HT; OS enrolled), hormone therapy/trial arm (nonuser, estrogen-alone, estrogen + progestin), family history of MI, and comorbidities index (count of diabetes, hypertension, treated hypercholesterolemia, history of COPD, lupus/rheumatoid arthritis, history of liver disease, history of stomach ulcer). Models are stratified by age at diagnosis (50 to 59, 60 to 64, 65 to 69, 70 to 74, ≥75 years).

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent task; MI = myocardial infarction; WHI = Women's Health Initiative.

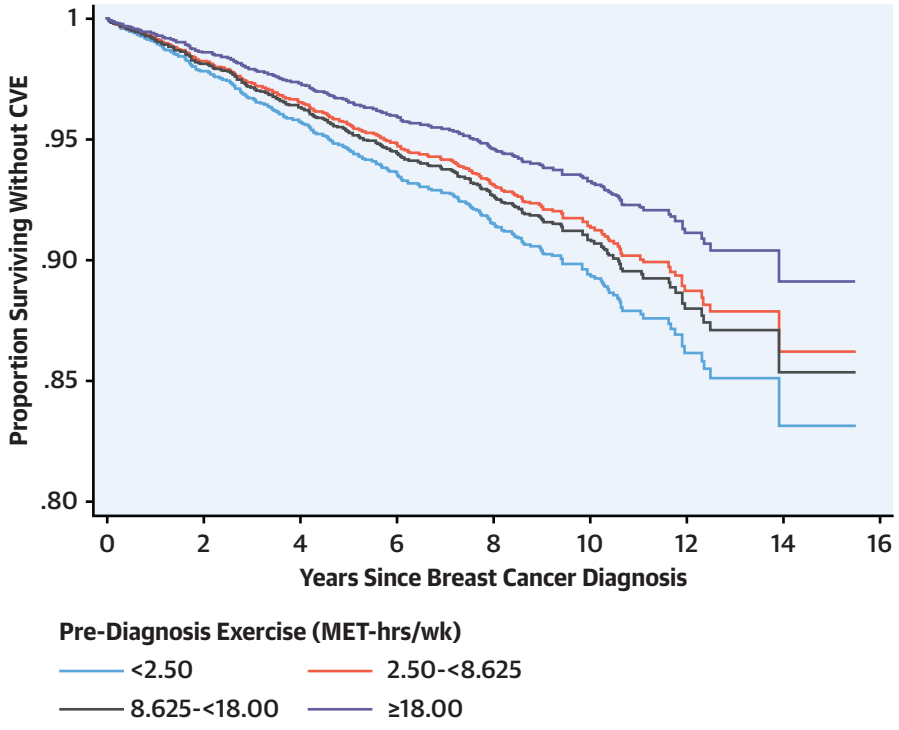
cardiovascular death (HR: 0.68 [95% CI: 0.47 to 0.98], 0.56 [95% CI: 0.38 to 0.82], 0.62 [95% CI: 0.43 to 0.90] p = 0.022) across increasing quartiles of physical activity; and CHD death (HR: 0.59 [95% CI: 0.36 to 0.99], 0.45 [95% CI: 0.26 to 0.79], 0.40 [95% CI: 0.22 to 0.72]; p = 0.003). There was a similar but nonsignificant age-adjusted trend for HF (p = 0.08) and nonsignificant age-adjusted associations for MI (p = 0.26).

MULTIVARIABLE-ADJUSTED ANALYSES. Compared with the referent first quartile, there was a decrease in HR across increasing quartiles of exercise for the primary endpoint (HR: 0.80 [95% CI: 0.59 to 1.09 for the second quartile]; 0.86 [95% CI: 0.64 to 1.17 for the third quartile); and 0.63 [95% CI: 0.45 to 0.88 for the fourth quartile]; p for trend = 0.016) (**Central Illustration**). A similar relationship was observed for CHD death (HR: 0.65 [95% CI: 0.38 to 1.10 for the second quartile]; 0.46 [95% CI: 0.25 to 0.83 for the third quartile]; and 0.41 [95% CI: 0.21 to 0.78 for the fourth quartile]; p = 0.006) as shown in **Table 2**. The p values for trend across increasing quartiles of exercise for MI, HF, or CVD death were not statistically significant.

CVEs BASED ON EXERCISE GUIDELINES. In multivariable analyses, only CHD death remained statistically significant (HR: 0.56 [95% CI: 0.35 to 0.89]; p = 0.014) when high exercise level was compared with low exercise level (**Table 3**). The multivariable HRs for the primary endpoint and cardiovascular death were lower (0.84 [95% CI: 0.67 to 1.06] and 0.79 [95% CI: 0.35 to 0.89], respectively), but this did not reach significance.

In a sensitivity analysis of Medicare subset of 1,603 participants, in which we adjusted for breast cancer-treatment variables, including chemotherapy and/or radiation therapy, and surgery, our findings were similar (Supplemental Tables 1 to 3).

CENTRAL ILLUSTRATION **Pre-Breast Cancer Diagnosis Exercise and Cardiovascular Disease Outcomes in 4,015 Participants From the WHI (Women's Health Initiative)**



Okwuosa, T.M. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):41-50.

Estimated survival probabilities from multivariable Cox models in relation to quartiles of pre-breast cancer diagnosis exercise exposure (MET h/week). Figure details the proportion surviving without a CVE (first occurrence of newly diagnosed heart failure, myocardial infarction, angina, coronary revascularization, peripheral artery disease, carotid artery disease, transient ischemic attack, stroke, or cardiovascular death occurring after diagnosis of breast cancer [n = 342 with CVD]). CVD = cardiovascular disease; CVE = cardiovascular event; IQR = interquartile range; MET = metabolic equivalent task; WHI = Women's Health Initiative.

DISCUSSION

In this large prospective observational cohort study, pre-diagnosis exercise was associated with substantial graded reductions in composite of subsequent newly diagnosed, first-incident cardiovascular events or CHD death in patients with primary breast cancer (**Central Illustration**). Conversely, meeting national exercise guidelines for healthy adults was associated with decreased risk of CHD death but not the primary endpoint of CVEs. This study is the first to show that exposure to exercise before a diagnosis of cancer may protect against or mitigate the established adverse cardiovascular consequences observed in patients with breast cancer, adding to the growing evidence base supporting the importance of exercise to prevent CVEs in high-risk populations.

As hypothesized, our primary analyses demonstrated that pre-diagnosis exercise was associated with a 20% to 37% reduction in the risk of CVEs, even after controlling for important clinical covariates including pre-existing cardiovascular risk factors and other chronic health conditions. However, risk of individual events—specifically, MI and HF—were not affected, suggesting that exercise may confer greater risk reduction in other events included in the composite endpoint, such as angina, coronary revascularization, PAD, or stroke. Isolating the impact of exercise on these individual conditions was not possible, however, because of a low number of events. Given that this is the first study to investigate the impact of pre-diagnosis exercise on CVEs in patients with cancer, direct comparisons with previous work is not possible. Nevertheless, 2 studies have examined the impact of post-diagnosis,

TABLE 3 Multivariable-Adjusted Hazard Ratios of Cardiovascular Events According to National Exercise Guidelines (Pre-Diagnosis Exercise Level) for Breast Cancer for Breast Cancer Patients (N = 4,015)

	MET h/week		
	<9 (n = 2,039)	≥9 MET (n = 1,976)	p Value
Median MET h/week	2	18	
Cardiovascular events*			
No. of events	193	149	
Age-adjusted HR (95% CI)	Ref	0.77 (0.62–0.95)	0.015
Multivariable-adjusted HR (95% CI)†	Ref	0.84 (0.67–1.06)	0.153
MI			
No. of events	47	42	
Age-adjusted HR (95% CI)	Ref	0.89 (0.58–1.34)	0.574
Multivariable-adjusted HR (95% CI)†	Ref	0.99 (0.62–1.58)	0.970
Heart failure			
No. of events	29	20	
Age-adjusted HR (95% CI)	Ref	0.71 (0.40–1.25)	0.237
Multivariable-adjusted HR (95% CI)†	Ref	0.95 (0.51–1.78)	0.885
Cardiovascular death			
No. of events	123	92	
Age-adjusted HR (95% CI)	Ref	0.74 (0.57–0.97)	0.031
Multivariable-adjusted HR (95% CI)‡	Ref	0.79 (0.59–1.06)	0.117
CHD death			
No. of events	61	35	
Age-adjusted HR (95% CI)	Ref	0.57 (0.37–0.86)	0.007
Multivariable-adjusted HR (95% CI)‡	Ref	0.56 (0.35–0.89)	0.014

*Cardiovascular events include heart failure, myocardial infarction, angina, coronary revascularization, peripheral artery disease, carotid artery disease, transient ischemic attack, stroke, and cardiovascular death. †Follow-up through September 30, 2010. Adjusted for age at WHI enrollment (continuous), race (white, black, Hispanic, other), smoking status (never, past, current), body mass index (<25, 25 to <30, ≥30 kg/m^2), stage (localized, regional), education (less than high school, high school diploma/GED, school after high school, college degree or higher), study (HT randomized; DM randomized, not in HT; OS enrolled), hormone therapy/trial arm (nonuser, estrogen-alone, estrogen + progestin), family history of MI, and comorbidities index (count of diabetes, hypertension, treated hypercholesterolemia, history of COPD, lupus/rheumatoid arthritis, history of liver disease, history of stomach ulcer). Models are stratified by age at diagnosis (50 to 59, 60 to 64, 65 to 69, 70 to 74, ≥75 years) and extension study participation (yes/no), allowing the baseline hazards to vary in these strata. ‡Deaths as of September 30, 2015, including from National Death Index (NDI) searches. Adjusted for age at WHI enrollment (continuous), race (white, black, Hispanic, other), smoking status (never, past, current), body mass index (<25, 25 to <30, ≥30 kg/m^2), stage (localized, regional), education (less than high school, high school diploma/GED, school after high school, college degree or higher), study (HT randomized; DM randomized, not in HT; OS enrolled), hormone therapy/trial arm (nonuser, estrogen-alone, estrogen + progestin), family history of MI, and comorbidities index (count of diabetes, hypertension, treated hypercholesterolemia, history of COPD, lupus/rheumatoid arthritis, history of liver disease, history of stomach ulcer). Models are stratified by age at diagnosis (50 to 59, 60 to 64, 65 to 69, 70 to 74, ≥75 years).

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent task; MI = myocardial infarction; WHI = Women's Health Initiative.

post-adjuvant therapy exercise exposure on CVD-specific morbidity and mortality in adult patients with cancer (5,11). Congruent with the current data, both studies found that exercise was associated with between a 9% to 35% and 13% to 53% reduction in a composite measure of CVEs among 2,973 patients with primary breast cancer (median age of 57 years, 8.6 years median follow-up) (5) and 1,187 adult survivors of Hodgkin's lymphoma (median age of 31.2 years, 11.9 years median follow-up) (11), respectively. Despite similar magnitude of risk reduction, there were notable differences between the findings related to post-diagnosis exercise compared with pre-diagnosis exercise in the current study. Specifically, in this study, for the primary endpoint, only 18 MET hours per week were associated with a significant reduction in risk of composite CVEs. This is in contrast to our previous findings, in which 9 MET h/week, approximately equivalent to the Centers for Disease Control (CDC) guidelines for healthy adults, was sufficient to significantly reduce risk. The reasons for these discrepancies are not clear but may relate to methodological differences across studies pertaining to exercise assessment, categorization, as well as ascertainment and classification of CVEs. Nevertheless, although the current findings suggest that protection from breast-cancer-related cardiovascular injury requires 18 MET h/week —double the current CDC guidelines—it is noteworthy that 9 MET h/week is the minimal recommended level of exercise, and greater benefits are observed above this level. As such, the findings of our study still support current guideline recommendations.

From a mechanistic perspective, the protective effects of pre-diagnosis exercise may work in a distinct but complementary manner of exercise performed during cytotoxic therapy. First, patients engaging in higher pre-diagnosis exercise will likely have a more favorable cardiovascular risk profile, including higher cardiorespiratory fitness (or cardiovascular reserve capacity) in comparison with less active or inactive patients. It is conceivable that patients with higher cardiovascular reserve capacity tolerate the unique and varying degrees of direct cardiovascular toxic effects of locoregional and systemic therapy (12). However, data to support the notion that women with higher cardiorespiratory fitness at diagnosis experience less treatment-related toxicities are not currently available. Another explanation is that patients engaging in regular exercise before diagnosis have higher proclivity to maintain regular exercise post-diagnosis during adjuvant therapy; exercise data collected on a small subsample of patients in this study support this notion (data not shown). Randomized trials demonstrate that structured aerobic training attenuates treatment-induced declines in cardiorespiratory fitness and other markers of cardiovascular health (e.g., endothelial function, resting heart rate, body composition) compared with nonexercising, usual care in patients undergoing conventional combination chemotherapy for primary breast cancer (13–17). Whether exercise attenuation of cancer therapy-associated cardiovascular injury lowers long-term CVEs is not known.

There is an anticipated substantial increase in the number of patients at high risk of cardiovascular toxicity over the next 20 years (18). As such, the

growing importance of late-occurring cardiovascular toxicity in breast as well as a number of long-term cancer survivors cannot be understated, as such toxicities may be starting to—or have the potential to—offset further improvements in overall survival witnessed over the past 4 decades (3). Our initial data, together with previous epidemiological findings and data from a growing number of small clinical trials creates a strong rationale to develop a research agenda to investigate comprehensively the role of pre-diagnosis cardiovascular risk profiles as well as exposure to nonpharmacological and pharmacological cardiovascular protective therapies on subsequent incidence of CVEs, together with role of such factors after diagnosis and across the treatment continuum.

STUDY LIMITATIONS. Our study has limitations. Of these, the most important is that exercise exposure was assessed by a self-administered questionnaire with well-known limitations, and therefore some misclassification of exposure is possible. In addition, residual confounding through the impact of other lifestyle factors is likely. Although assessment of pre-diagnosis exercise is less prone to reverse causality in comparison with exercise assessed in the post-diagnosis setting, it is not possible to delineate whether higher exercise exposure reflects lower CV or other chronic disease burden as opposed to a direct exercise-induced effect. Only randomized trial data can answer this question. Our study questionnaire only assessed exercise exposure that ranged from immediately to 5 years before diagnosis of breast cancer, creating interpatient heterogeneity in timing of assessment of exposure to exercise. Our study also lacked consideration of modifiable risk factors.

CONCLUSIONS

Pre-diagnosis exercise exposure may be a strategy to lower CVD risk in patients with primary breast cancer. These findings add to the growing evidence highlighting the importance of exercise to manage cancer treatment-related acute and chronic late effects in the large and growing number of cancer survivors.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this prospective cohort study of 4,015 women from the Women's Health Initiative Study, pre-diagnosis exercise in breast cancer patients is associated with a significant graded reduction in subsequent cardiovascular events.

TRANSLATIONAL OUTLOOK: Randomized clinical trials are necessary to determine the cardioprotective benefits of exercise in patients with cancer and survivors.

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KEY WORDS **breast cancer, cardiovascular disease, cardiovascular events, exercise, physical activity, survivors, Women's Health Initiative**

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