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ORIGINAL REPORT

Cardiopulmonary Function and Age-Related Decline Across the Breast Cancer Survivorship Continuum

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ABSTRACT

Purpose
To evaluate cardiopulmonary function (as measured by peak oxygen consumption [VO_{2peak}]) across the breast cancer continuum and its prognostic significance in women with metastatic disease.

Patients and Methods
Patients with breast cancer representing four cross-sectional cohorts—that is, (1) before, (2) during, and (3) after adjuvant therapy for nonmetastatic disease, and (4) during therapy in metastatic disease—were studied. A cardiopulmonary exercise test (CPET) with expired gas analysis was used to assess VO_{2peak}. A Cox proportional hazards model was used to estimate the risk of death according to VO_{2peak} category (< 15.4 *v* ≥ 15.4 mL · kg^{-1} · min^{-1}) with adjustment for clinical factors.

Results
A total of 248 women (age, 55 ± 8 years) completed a CPET. Mean VO_{2peak} was 17.8 ± a standard deviation of 4.3 mL · kg^{-1} · min^{-1}, the equivalent of 27% ± 17% below age-matched healthy sedentary women. For the entire cohort, 32% had a VO_{2peak} less than 15.4 mL · kg^{-1} · min^{-1}—the VO_{2peak} required for functional independence. VO_{2peak} was significantly different across breast cancer cohorts for relative (mL · kg^{-1} · min^{-1}) and absolute (L · min^{-1}) VO_{2peak} ($P = .017$ and $P < .001$, respectively); VO_{2peak} was lowest in women with metastatic disease. In patients with metastatic disease (n = 52), compared with patients achieving a $VO_{2peak} \leq 1.09$ L · min^{-1}, the adjusted hazard ratio for death was 0.32 (95% CI, 0.16 to 0.67, $P = .002$) for a VO_{2peak} more than 1.09 L · min^{-1}.

Conclusion
Patients with breast cancer have marked impairment in VO_{2peak} across the entire survivorship continuum. VO_{2peak} may be an independent predictor of survival in metastatic disease.

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INTRODUCTION

Patients with breast cancer are subject to the effects of normal aging, age- and/or disease-related comorbid conditions, and deconditioning that adversely affect cardiopulmonary function. However, in contrast to women from the general population, women with breast cancer are also subjected to the use of prolonged and aggressive multimodal anticancer therapy,[1] which together are suspected to cause further impairments in cardiopulmonary function predisposing to serious health conditions (eg, cardiovascular disease).[2]

In current practice, patient cardiopulmonary function is almost exclusively evaluated through the determination of cardiac function via a resting measurement of left ventricular ejection fraction (LVEF). Although resting LVEF may have utility in prediction and/or assessment of therapy-induced cardiac toxicity,[3] it does not provide a measure of global cardiovascular function and reserve.[4] Indeed, cardiac function is only one organ component that contributes to the integrative capacity of the cardiovascular and musculoskeletal system to transport and use oxygen (O_2) for adenosine triphosphate resynthesis.[5] The efficiency of O_2 transport and use determines an individual's cardiopulmonary function (or aerobic capacity). An incremental cardiopulmonary exercise test (CPET) with gas exchange measurement, to assess peak oxygen consumption (VO_{2peak}), provides the gold standard assessment of aerobic capacity.[6] VO_{2peak} is inversely correlated

with cardiovascular and all-cause mortality in a broad range of adult populations.[7-11] Accordingly, formalized exercise testing is widely used in numerous clinical settings and provides a wealth of diagnostic, prognostic, and decision-making information.[6]

In contrast, exercise testing is not routinely performed at any stage of during breast cancer treatment or recovery. However, in clinical research, a growing number of studies are using exercise testing to determine the efficacy of exercise training interventions in patients with breast cancer both during and after adjuvant therapy.[12] However, little is known about the level of exercise tolerance in patients with breast cancer or how this may differ during treatment and recovery. We used data from our prior work[13-18] to evaluate VO_{2peak} across the entire breast cancer survivorship continuum (ie, diagnosis to metastatic disease). Secondary objectives were to compare age-related declines in VO_{2peak} between patients with breast cancer relative to age- and sex-matched healthy women, evaluate the proportion of patients falling below the VO_{2peak} required for functional independence (ie, 15.4 mL · kg $^{-1}$ · min^{-1}), and explore the prognostic significance of VO_{2peak} in metastatic disease.

PATIENTS AND METHODS

Patient Cohorts and Setting

Women with histologically confirmed operable (stage I through IIIC) or metastatic (stage IV) breast adenocarcinoma at Duke University Medical Center, Durham, NC, or the Cross Cancer Institute, Edmonton, Alberta, Canada were studied. Specifically, data were pooled from our prior exercise intervention studies (baseline data only) or cross-sectional studies that were categorized into four cross-sectional cohorts—that is, (1) before (n = 20), (2) during (n = 46),[13,14] and (3) after adjuvant therapy (n = 130),[15-17] for nonmetastatic disease, and (4) during therapy for metastatic disease (n = 52).[14,18] The before therapy cohort constituted newly diagnosed untreated patients (ie, before receipt of surgery and any adjuvant therapy); the during therapy cohort included postsurgical patients after completion of at least two cycles of primary adjuvant chemotherapy; the after therapy cohort included patients 6 months to ~3 years after the completion of primary adjuvant therapy including radiotherapy. Finally, the metastatic cohort included patients with stage IV disease receiving some form of cytotoxic chemotherapy. Institutional review board approval and written informed consent were obtained in all studies.

Cardiopulmonary Function (VO_{2peak})

To determine VO_{2peak}, a CPET with 12-lead ECG monitoring (Mac 5000, GE Healthcare, Waukesha, WI) was performed by certified exercise physiologists. The specific protocol for this test has previously been reported in detail.[18] In brief, all tests were performed on an electronically braked cycle ergometer (Lode, Groningen, Netherlands) with breath-by-breath expired gas analysis. Three minutes of resting metabolic data were collected before participants began cycling at 20 W. Workloads were then increased 5 to 20 W/min until volitional exhaustion or until a symptom limitation was achieved. All cardiopulmonary exercise testing data were recorded as the highest 30-second value elicited during the exercise test. Age-matched normative VO_{2max} data for healthy women without a history of breast cancer were obtained from Fitzgerald et al.[19] It is important to note that our assessment of cardiopulmonary function was determined at peak exercise (ie, peak V_{O_2}) as recommended for clinical populations,[6] as opposed to maximum V_{O_2} (ie, oxygen consumption reaches a plateau despite increasing workload[20]) in the comparison data by Fitzgerald et al.[19]

Clinical Parameters and Performance Status

Medical characteristics were abstracted from medical records. Performance status was assessed using the Karnofsky performance scale and was assessed at the time of study enrollment by the attending oncologist. Hemoglobin was assessed by an automated CBC. Left ventricular function was determined using multiple gated acquisition scan or echocardiography to assess LVEF using standardized procedures. Exercise behavior was assessed by the Godin Leisure Time Exercise Questionnaire.[21]

Statistical Analysis

For continuous data, we performed a series of one-way analysis of variance to examine overall differences between the four cross-sectional cohorts with adjustment for age and study site (Edmonton *v* Durham). We conducted an overall F-test to account for multiple comparisons with post hoc (Tukey-Kramer) analysis as appropriate to control for varying sample sizes between groups. For categorical data, a χ^2 test was used to examine overall differences between the four cross-sectional cohorts. Linear regression was used to examine the relationship between VO_{2peak} and age in the total population of patients with breast cancer and after adjuvant therapy group only (this analysis was not performed on the other individual groups as a result of small sample size). Expected mean VO_{2peak} values at a given age for patients with breast cancer were compared with those of healthy, sedentary women.[19] The Cox proportional hazards model was used to explore the association between VO_{2peak} and survival in the subset of patients with metastatic disease (n = 52). VO_{2peak} was categorized using the dichotomous classification for functional dependence (< 15.4 *v* ≥ 15.4 mL · kg^{-1} · min^{-1}) and a median split for L · min^{-1} (< 1.09 *v* ≥ 1.09 L · min^{-1}). Survival was defined as the time between assessment of VO_{2peak} and death; for patients remaining alive, survival was censored at the time of last follow-up. The prognostic value of VO_{2peak} was examined individually with and without adjustment for the following covariates: age, months since diagnosis, and performance status. Statistical significance was set at $P < .05$ (two-tailed) for all analyses.

RESULTS

Details regarding the profiles of the participants are described in Table 1.

Cardiopulmonary Function Across the Breast Cancer Trajectory

Resting Data. For the overall sample, mean resting heart rate was 89 ± 16 beats · min^{-1}; 27% of patients presented with resting tachycardia (heart rate ≥ 100 beats · min^{-1}; Table 2). Mean (± standard deviation) LVEF and hemoglobin were 62% ± 7% and 12.7 ± 1.6 g/dL, respectively. Resting heart rate was significantly higher in the during adjuvant therapy group relative to the after therapy group and significantly lower relative to the metastatic group. Incidences of tachycardia were significantly higher in the during adjuvant therapy group relative to all other groups ($P < .05$). Systolic blood pressure was significantly higher in the after adjuvant therapy group relative to all other groups, whereas diastolic blood pressure was significantly lower in the before adjuvant therapy group, relative to all other groups. Resting LVEF was not different across groups ($P > .05$). Finally, hemoglobin concentration was significantly lower in the during adjuvant group relative to all other groups ($P < .05$).

Peak Data. Peak cardiopulmonary data are presented in Table 2. For the overall sample, VO_{2peak} averaged 17.8 ± 4.3 mL · kg^{-1} · min^{-1} (range, 7.3 to 31.2 mL · kg^{-1} · min^{-1}), the equivalent to 27% ± 17% below age- and sex-predicted sedentary values (range, −73% to 25%) or 5.1 ± 1.2 metabolic equivalents. Peak heart rate was 158 ± 18 beats · min^{-1} or 96% of age-predicted maximum, whereas peak workload averaged 92 ± 26 W. Of these tests, 78% were considered to be of adequate effort given that a respiratory exchange ratio of ≥ 1.10 was achieved. Of the 22% of patients who did not achieve a respiratory exchange ratio ≥ 1.10, the tests were terminated prematurely due to other symptoms (eg, breathing or leg fatigue). For mL · kg^{-1} · min^{-1},

Table 1. Characteristics of the Participants

Variable	Overall		Nonmetastatic Disease: Before Adjuvant Therapy		Nonmetastatic Disease: During Adjuvant Therapy		Nonmetastatic Disease: After Adjuvant Therapy		Advanced Metastatic Disease	
	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	248	100	20	8	46	19	130	52	52	21
Site										
Canada	201	81	20	100	19	41	130	100	52	100
United States	47	19	—		27	59	—		—	
Age, years										
Mean	55		49		53		57		55	
SD	8		9		7		8		10	
Range	30-74		30-61		40-70		31-73		36-74	
Weight, kg										
Mean	76		78		75		77		70	
SD	17		19		16		17		16	
BMI, kg/m^2										
Mean	28		29		28		29		27	
SD	6		7		6		6		5	
Range	16-50		18-46		18-40		16-50		18-45	
KPS										
70	3	1	—		—		—		3	6
75	1	< 1	—		—		—		1	2
80	6	2	—		—		—		6	12
90	43	17	—		13	28	—		30	60
100	193	78	20	100	33	72	130	100	10	20
Exercise behavior, min · wk^{-1}										
Mean	222		135		199		270		172	
SD	269		171		275		307		192	
Meeting ACSM guidelines*	49	25	5	25	3	11	32	31	9	18
Time from primary diagnosis, months										
Mean	21		1		7		27		25	
SD	19		0.4		6		16		26	
Anatomic stage										
IA	37	15	1	5	6	13	30	23	—	
IB	37	15	4	20	3	7	30	23	—	
IIA	52	21	12	60	18	39	22	17	—	
IIB	43	17	2	10	11	24	30	23	—	
IIIA	25	10	1	5	7	15	17	13	—	
IIIB	1	< 1	—		1	2	—		—	
IIIC	1	< 1	—		—		1	1	—	
IV	51	21	—		—		—		52	100
Current cytotoxic therapy			NA				NA			
Chemotherapy	63	64			29	63			34	65
Anthracycline-containing regimen	43	68			29	100			14	41
Trastuzumab	29	30			17	37			12	23
Radiation	20	20			0	0			20	38
Prior primary cytotoxic therapy			NA		NA					
Chemotherapy	128	70					96	74	32	62
Anthracycline-containing regimen	79	62					62	65	17	53
Trastuzumab	18	10					18	14	0	0
Radiation	127	70					102	78	25	48

Abbreviations: ACSM, American College of Sports Medicine; BMI, body mass index; KPS, Karnofsky performance status; NA, not applicable; SD, standard deviation.
*ASCM guidelines defined as percentage of patients reporting ≥ 150 minutes · wk^{-1} of at least moderate and/or strenuous exercise.

post hoc tests revealed that VO_{2peak} was significantly lower in the metastatic group (mean difference, −2.1 mL · kg^{-1} · min^{-1}; $P <$ .05; Fig 1) and the during adjuvant therapy group (mean difference, −1.0 mL · kg^{-1} · min^{-1}; $P <$ .05; Fig 1) relative to the after adjuvant therapy group. For L · min^{-1}, VO_{2peak} was significantly lower in the metastatic group (mean difference, −0.28 L · min^{-1}; $P <$ .05), the before adjuvant therapy group (mean difference, −0.03 L · min^{-1}; $P <$ .05), and the during adjuvant therapy group (mean difference, −0.13 L · min^{-1}; $P <$ .05) relative to the after adjuvant therapy group.

Table 2. Cardiopulmonary Data Across the Breast Cancer Continuum[a]

Variable	Overall	Nonmetastatic Disease			Advanced Metastatic Disease	Overall Adjusted *P*[a]
		Prior to Adjuvant Therapy	During Adjuvant Therapy	After Adjuvant Therapy		
Patients						
No.	248	20	46	130	52	
%	100	8	19	52	21	
Resting data						
HR, beats · min^{-1}						< .001
Mean	89	74	91[b]	89	92	
SD	16	10	17	16	17	
Tachycardia (HR ≥ 100 beats · min^{-1}), %						.001
No.	67	1[c]	17[d]	31	18	
%	27	5	37	24	35	
Systolic blood pressure, mmHg						< .001
Mean	126	121	116	133	123	
SD	18	13	14[e]	19[d]	14	
Diastolic blood pressure, mmHg						< .001
Mean	86	78	96	85	80	
SD	18	8[d]	34[c]	12	8	
RPP						.555
Mean	11,258	9,002	10,476	11,872	11,307	
SD	2,705	1,418	1,939	2,993	2,299	
LVEF, %[f]						.172
Mean	62	62	62	62	59	
SD	7	6	6	7	7	
Hemoglobin, g/dL[g]						< .001
Mean	12.7	13.3	11.5	13.5	12.6	
SD	1.6	1.2	1.3[d]	1.0[h]	1.7	
Peak exercise data						
HR, beats · min^{-1}						.007
Mean	158	158	164	157	153	
SD	18	23	14	17	18	
HR, beats · min^{-1}, predicted %						
Mean	−4	−8	−2	−3	−8	
SD	10	11	8	10	10	
Cardiac reserve, beats · min^{-1}						.001
Mean	68	83	72	68	60	
SD	21	22	22	20[i]	18	
Systolic blood pressure, mmHg						.008
Mean	165	154	162	170	160	
SD	31	23	25	35[i]	23	
Diastolic blood pressure, mmHg						.026
Mean	86	86	83	87	87	
SD	11	8	10[b]	11	11	
VO_{2peak}, mL · kg^{-1} · min^{-1}						< .001
Mean	17.8	18.5	17.4	18.4	16.3	
SD	4.3	6.3	4.3	4.1[i]	3.5	
Range	7.3-31.2	7.3-30.2	10.2-28.2	9.9-31.2	8.8-27.0	
VO_{2peak}, mL · kg^{-1} · min^{-1}, predicted %						
Mean	−27	−31	−31	−22	−33	
SD	17	20	18	16	16	
Range	−73-25	−73-0	−59-25	−58-25	−62-12	
VO_{2peak}, L · min^{-1}						< .001
Mean	1.32	1.38	1.28	1.41	1.13	
SD	0.33	0.38	0.33	0.30[d]	0.28	
Workload, Watts						< .001
Mean	92	96	90	98	80	
SD	26	37	24	23[d]	26	

(continued on following page)

Table 2. Cardiopulmonary Data Across the Breast Cancer Continuum[a] (continued)

Variable	Overall	Nonmetastatic Disease			Advanced Metastatic Disease	Overall Adjusted *P*[a]
		Prior to Adjuvant Therapy	During Adjuvant Therapy	After Adjuvant Therapy		
O_2 pulse, LO_2/beat						.181
Mean	0.10	0.09	0.10	0.11	0.11	
SD	0.03	0.02	0.03	0.03	0.02	
RER[k]						< .001
Mean	1.18	1.09	1.22	1.15	1.22	
SD	0.10	0.07	0.12	0.09[i]	0.10	
RER ≥ 1.10						
No.	143	12	24	63	48	
%	78	60	83	76	92	

Abbreviations: HR, heart rate; LVEF, left ventricular ejection fraction; O_2, oxygen; RER, respiratory exchange ratio; RPP, rate pressure product (calculated as [resting heart rate × resting systolic blood pressure]/1,000; cardiac reserve calculated as peak heart rate − resting heart rate); SD, standard deviation; VO_{2peak}, peak oxygen consumption.
[a]Adjusted for age and site.
[b]Significantly different from after adjuvant therapy and metastatic disease groups.
[c]Significantly different from after adjuvant therapy group.
[d]Significantly different from all other groups.
[e]Significantly different from metastatic disease group.
[f]Data available on 143 participants.
[g]Data available on 174 participants.
[h]Significantly different from prior adjuvant therapy and metastatic disease groups.
[i]Significantly different from during adjuvant therapy and metastatic disease groups.
[j]Significantly different from prior and during adjuvant therapy groups.
[k]Data available on 184 participants.

Age-Related Functional Dependence and VO_{2peak} Decline

In healthy older women, the minimal aerobic reserve capacity required for functional independence is a VO_{2peak} rate of 15.4 mL · kg^{-1} · min^{-1}.[22] For the overall sample, 32% had a VO_{2peak} less than 15.4 mL · kg^{-1} · min^{-1} (Fig 2). The corresponding values for the four cross-sectional cohorts were as follows: 35% for before adjuvant therapy, 37% for during adjuvant therapy, 25% for after adjuvant therapy, and 44% for metastatic disease.

We also descriptively compared the age-related decline in VO_{2peak} of patients with breast cancer relative to age- and sex-predicted sedentary healthy women (n = 106 groups). For the entire breast cohort, the regression equation was as follows: VO_{2peak} (mL · kg^{-1} · min^{-1}) = 24.701 − (0.1251 × age), relative to the reference relationship of VO_{2peak} (mL · kg^{-1} · min^{-1}) = 46.82 − (0.35 × age) for sedentary, healthy women (Fig 2). For the after adjuvant therapy group, the regression equation was as follows: VO_{2peak} (mL · kg^{-1} · min^{-1}) = 27.201 − (0.1538 × age). In both circumstances, the regression lines did not overlap at any point across the entire age continuum. The expected mean VO_{2peak} across decades 40 to 70 years between patients with breast cancer and sedentary, healthy women revealed differences across all decades. For instance, the mean VO_{2peak} for patients with breast cancer is 34% less than that for healthy, sedentary

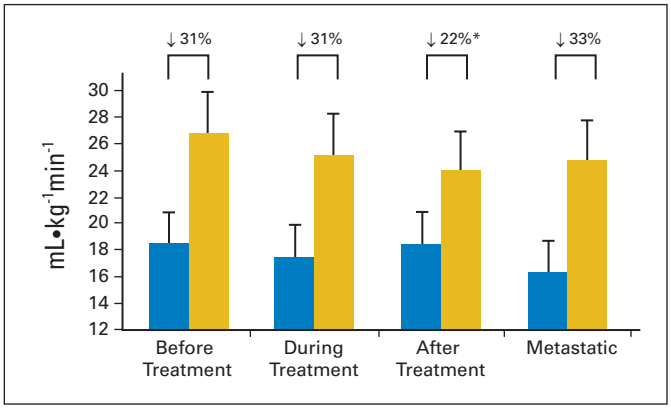

Fig 1. Differences in peak oxygen consumption (mL · $kg^{-1}min^{-1}$; gray bars represent age-sex predicted value) in operable patients with breast cancer before (n = 20), during (n = 46), and after (n = 130) adjuvant therapy, and with metastatic disease (n = 52). Statistical tests: (*) Significantly different from during adjuvant therapy and metastatic disease groups.

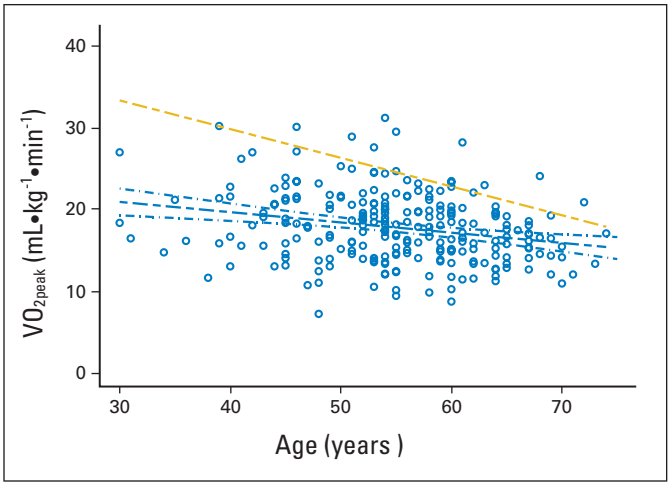

Fig 2. The linear relationship between peak oxygen consumption (VO_{2peak}) and age for patients with breast cancer (scatterplot and blue regression line with 95% CI; regression equation: VO_{2peak} [mL · kg^{-1} · min^{-1}] = 24.701 – [0.1251 × age]), and healthy, sedentary adult women (gold dotted regression line; regression equation: VO_{2peak} [mL · kg^{-1} · min^{-1}] = 46.82 – [0.35 × age]).

Table 3. Association Between VO_{2peak} (L · min^{-1} and mL · kg^{-1} · min^{-1}) and Survival in Women With Metastatic Disease

Analysis	VO_{2peak} (L · min^{-1}) ≤ 1.09	> 1.09	P
No. of events	23	18	
No. at risk	26	26	
Survival, months			
Median	16	36	
Range	7-27	24-57	
Adjusted*			.002
HR	Referent	0.32	
95% CI		0.16 to 0.67	

Analysis	VO_{2peak} (mL · kg^{-1} · min^{-1}) ≤ 15.4	> 15.4	P
No. of events	20	21	
No. at risk	24	28	
Survival, months			
Median	22	29	
Range	12-40	18-42	
Adjusted*			0.141
HR	Referent	0.59	
95% CI			0.29 to 1.19

Abbreviations: HR, hazard ratio; VO_{2peak}, peak oxygen consumption.
*Adjusted for age, months since diagnosis, and Karnofsky performance status.

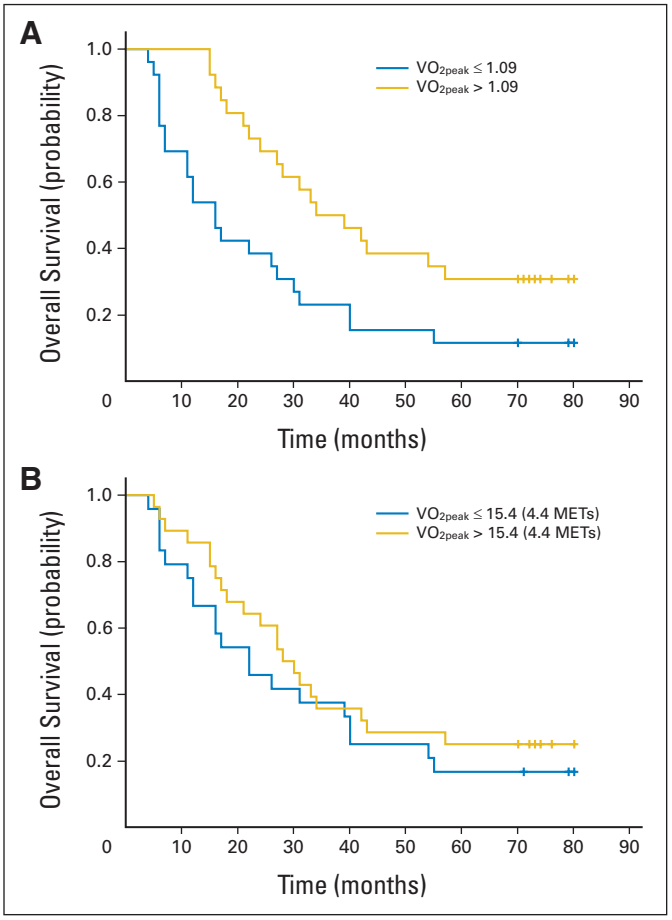

Fig 3. Association between peak oxygen consumption (VO_{2peak}) and survival for (A) VO_{2peak} (L · min^{-1}) and (B) VO_{2peak} (mL · kg^{-1} · min^{-1}) in women with metastatic disease (n = 52). METs, metabolic equivalents.

women at age 40 years, 30% less at age 50 years, 25% less at 60 years, and 17% less at age 70 years. The mean VO_{2peak} of 19.7 mL · kg^{-1} · min^{-1} for a 40-year old patient with breast cancer is of the same magnitude as that of a 70-year old healthy, sedentary woman (19.3 mL · kg^{-1} · min^{-1}).

VO_{2peak} and Survival in Metastatic Disease

Median follow-up was 122 months (95% CI, 119 to 127 months) after testing, and 41 deaths were recorded (79% of the total sample). The median time from VO_{2peak} assessment to death was 27 months (95% CI, 17 to 34 months). For L · min^{-1}, the adjusted hazard ratio for death was 0.32 (95% CI, 0.16 to 0.67; $P = .002$) for a VO_{2peak} of more than 1.09 L · min^{-1} compared with a VO_{2peak} of ≤ 1.09 L · min^{-1} (Table 3; Fig 3A). Median survival was 16 months (95% CI, 7 to 27 months) for those reporting ≤ 1.09 L · min^{-1} compared with 36 months (95% CI, 24 to 57 months) for those reporting more than 1.09 L · min^{-1}. Compared with a VO_{2peak} less than 15.4 mL · kg^{-1} · min^{-1}, the adjusted hazard ratio for death was 0.59 (95% CI, 0.29 to 1.19; $P = .141$) for a VO_{2peak} of ≥ 15.4 mL · kg^{-1} · min^{-1} (Table 3; Fig 3B).

DISCUSSION

Here we show that despite normal cardiac function (ie, LVEF ≥ 50%), women with breast cancer have significant and marked impairments in cardiopulmonary function. On average, VO_{2peak} was 27% less than that of age-matched sedentary but otherwise healthy women without a history of breast cancer. The impairments in VO_{2peak} were particularly striking during primary adjuvant chemotherapy and in those patients with metastatic disease, with VO_{2peak} 31% and 33% less than that of healthy sedentary women, respectively. Remarkably, we found that patients with breast cancer reach a predicted VO_{2peak} for a particular age group (eg, 40 years) approximately 20 to 30 years earlier than healthy women without a history of breast cancer. Sweeney et al[23] found that elderly cancer survivors (of mixed diagnoses) were less likely to be able to do heavy household tasks, walk half a mile, or walk up and down stairs, compared with women without a history of cancer. Our findings indicate that approximately one third of patients with breast cancer have a VO_{2peak} less than the functional independence threshold and, by definition, are unlikely to be able to perform such tasks. However, the present results must be interpreted with caution given potential unaccounted differences between patients and controls, including the prevalence of comorbidities and V_{O_2} measurement (peak V_{O_2} *v* maximum V_{O_2}, respectively). These differences may have resulted in an overestimation of the marked differences in cardiopulmonary function between patients and controls. Follow-up prospective studies with appropriate control groups are warranted.

We contend that such VO_{2peak} impairment is a consequence of the direct as well as the indirect (ie, lifestyle perturbations) effects of anticancer therapy (ie, anticancer therapy refers to any type of cancer treatment) that simultaneously impair the reserve capacity of organ systems that govern VO_{2peak} (ie, pulmonary, cardiac, blood-vascular, and skeletal muscle function).[2] For example, it is well-established that

both locoregional radiotherapy, particularly left-sided radiation,[24] as well as anthracycline[25,26] and/or trastuzumab-containing[27] chemotherapy, can cause acute and late-occurring cardiac injury manifest as impaired global pump function leading to a reduction in O_2 delivery and diminished exercise tolerance. Anemia is also a frequent complication of various anticancer therapies,[28] an effect that impairs convective oxygen delivery. Finally, preclinical data suggest that chemotherapy (eg, doxorubicin) and antiangiogenic therapy may cause significant alterations in skeletal muscle capillarity, glycolysis, and fatty acid oxidation and reductions in muscle capillary density, respectively[29,30]; both would directly impair diffusive oxygen transport and oxygen use, resulting in decreased exercise tolerance. The relative contributions of central (ie, cardiac) and peripheral (ie, circulation and skeletal muscle O_2 extraction) factors to exercise tolerance have long been debated,[31] although the role of these factors in explaining impaired cardiopulmonary function in patients with cancer has received scant attention. In the present study, given the relatively large proportion of patients receiving and/or treated with doxorubicin, one may suspect that symptomatic or asymptomatic cardiotoxicity is largely responsible for the observed VO_{2peak} impairment. However, resting LVEF was within the normal range, suggesting that concomitant or independent injury to the other O_2 transport components (ie, pulmonary, vascular, and skeletal muscle function) must therefore play a contributing role.

Cardiopulmonary dysfunction was also apparent at rest. Strikingly, 5% of patients presented with resting sinus tachycardia before adjuvant therapy, the incidence of which significantly increased to 37% in those undergoing anticancer therapy. The causes of sinus tachycardia are poorly understood, but may include the effects of treatment-induced anemia, autonomic neuropathy, and/or cardiac dysfunction.[32] The clinical consequences of tachycardia in breast cancer are unknown, but resting heart rate is a strong independent predictor of cardiovascular disease mortality in healthy women.[33] The resting blood pressure data also were indicative of vascular dysfunction. This was especially apparent in the after adjuvant therapy group, which presented with a mean blood pressure in the range of prehypertension[34]; the prognostic value of blood pressure is well established.[35]

A major research and clinical goal in oncology practice is accurate quantification of functional/physical performance status or physiologic age in patients with cancer.[36,37] Our findings indicate that CPET is one tool that may provide complementary information to existing assessments because it provides a comprehensive, integrative assessment of the reserve capacity of the heart, as well as other O_2 transport components (ie, VO_{2peak}), which is not captured by current measures used in clinical practice. Furthermore, exercise capacity is an established, strong predictor of mortality in numerous clinical populations.[22,38-40] For example, Gulati et al[38] found a two-fold risk of death in women achieving less than 85% of age-predicted exercise capacity relative to those achieving $\geq$ 85% in 5,721 asymptomatic women. In our study, 78% of operable patients did not achieve 85% of age-predicted sedentary VO_{2peak}. As a consequence, these patients have increased susceptibility to late-occurring cardiovascular disease[41] and premature mortality. Our exploratory analyses provide the first data to suggest that the prognostic significance of VO_{2peak} extends to women with metastatic breast cancer. Large-scale prospective studies are now warranted. The prognostic value of VO_{2peak} in women with operable breast cancer remains to be determined.

Preventive and/or treatment strategies will be required to offset the direct and indirect effects of anticancer therapy. Aerobic (exercise) training is the most effective therapy to improve VO_{2peak} in healthy individuals given that it improves the reserve capacity of all O_2 transport organs, which together lead to favorable improvements in VO_{2peak}.[5] A meta-analysis by our group found that exercise training in patients with cancer caused a significant improvement in VO_{2peak} (weighted mean difference = $+2.90\ mL \cdot kg^{-1} \cdot min^{-1}$; 95% CI, 1.16 to $4.64\ mL \cdot kg^{-1} \cdot min^{-1}$), relative to sedentary control.[42] Investigation of the most effective type and intensity of exercise training to augment VO_{2peak} and other outcomes, as well as the physiologic mechanisms underlying the exercise training–VO_{2peak} relationship in breast and other cancer populations, is the focus of ongoing trials.

This study has important limitations. Our findings are based on cross-sectional (involving different patients in the breast cancer subgroups) as opposed to prospective data. Also, there is treatment heterogeneity and likely comorbidity differences among patient cohorts. Patient selection bias may exist as a result of different patient inclusion and exclusion criteria adopted across pooled studies as well as exclusion of patients deemed physically unable to perform CPET. Relatedly, our comparison "healthy" sedentary data were obtained from population-based normative data with differences in prevalence of comorbidities and V_{O_2} assessment (peak v maximum V_{O_2}); in addition, 22% of patients did not achieve the criteria for a true peak V_{O_2} (ie, respiratory exchange ratio $\geq$ 1.10). Together, these factors may have resulted in an overestimation of the observed impairment in cardiopulmonary function in patients with breast cancer. Finally, the survival analysis only included death from any cause. The specific cause of death is not known. With the exception of performance status, months since diagnosis and age analyses were also not adjusted for other established parameters of survival in the metastatic setting. Future studies are needed to fully define the point at which functional dependence occurs, as well as evaluate the concordance between VO_{2peak} and other existing functional measurement tools.

In summary, patients with breast cancer have significant and marked impairment in cardiopulmonary function over the entire continuum of disease. As a result, approximately one third of patients with breast cancer have a VO_{2peak} less than the functional independence threshold and reach a predicted age-related VO_{2peak}, on average, 20 to 30 years earlier than healthy women without a history of breast cancer. Given the projected number of cancer survivors, future studies investigating the clinical utility of quantitative measures of functional capacity as well as the efficacy of exercise interventions to offset the devastating consequences of the "multiple hit" are a high priority.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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