ORIGINAL RESEARCH

Cardiorespiratory Fitness in Breast Cancer Patients: A Call for Normative Values

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***Background*—**There is emerging evidence that adjuvant treatments for breast cancer negatively impact cardiorespiratory fitness (CRF) or Vo_{2max}, a key predictor of cardiovascular risk. Although a number of studies have measured CRF in breast cancer patients, there is currently limited data regarding expected CRF values in this patient population. Given that CRF is a poor prognostic sign and recently highlighted as a key measure to standardize by the American Heart Association, we sought to review the available literature on CRF among breast cancer patients.

***Methods and Results*—**We identified 27 clinical trials and observational studies measuring Vo_{2max} in the pre– and post–adjuvant treatment setting for breast cancer. We compared Vo_{2max} before to Vo_{2max} after adjuvant therapy and compared Vo_{2max} in female breast cancer patients with Vo_{2max} in healthy controls.

***Conclusions*—**We found that CRF was substantially lower in women with a history of breast cancer compared with healthy women and this was most pronounced among breast cancer patients in the post-adjuvant setting. We conclude that knowledge of normative CRF values is critical to tailor appropriately timed exercise interventions in breast cancer patients susceptible to low CRF and subsequent cardiovascular risk. **(*J Am Heart Assoc*. 2014;3:e000432 doi: 10.1161/JAHA.113.000432)**

Key Words: breast cancer • cardiorespiratory fitness • women

Breast cancer is the most commonly diagnosed malignancy of women in the United States, with 207 090 new cases in 2010, accounting for 28% of all cancer diagnoses.[1] Due to significant improvements in screening protocols, diagnosis, and treatment over the past few decades, breast cancer mortality continues to decrease.[2,3] As a result, more than 2.9 million American women are living with a prior history of breast cancer.[4] Importantly, women diagnosed with early-stage breast cancer are susceptible to the late occurring toxic effects of conventional treatment regimens,[5,6] and are at greater risk for death from cardiovascular disease than from breast cancer after 65 years of age.[7]

Cardiac-related effects of adjuvant therapy—namely, cardiomyocyte injury and decreases in left ventricular ejection fraction (LVEF)—are well documented.[8,9] Both left-sided radiotherapy and chemotherapy are associated with short- and long-term cardiotoxicity.[10,11] Anthracycline-containing regimens are known to cause dose-dependent, cumulative, progressive cardiac dysfunction manifested as decreased LVEF and congestive heart failure.[9] The addition of adjuvant trastuzumab to the management of human epidermal growth factor receptor (HER)-2–positive early breast cancer has further increased clinical and subclinical cardiotoxicity rates.[12,13]

There is emerging evidence that adjuvant therapy for breast cancer can also significantly affect cardiorespiratory fitness (CRF). CRF as measured by Vo_{2max} assesses global cardiovascular function, cardiopulmonary reserve, and efficiency of oxygen transport and utilization and can unmask compensatory mechanisms of abnormal cardiac function as well as defects in other vital organs.[14,15] A number of studies have shown that Vo_{2max} is impaired in breast cancer patients compared with healthy controls.[5,6,16,17] This finding is of major concern given that low Vo_{2max} is associated with higher mortality among more–advanced stage breast cancer patients.[17]

Despite evidence that low Vo_{2max} is a poor prognostic sign, there is currently little known regarding Vo_{2max} levels among

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breast cancer patients. Knowledge of Vo_{2max} values in breast cancer is of timely importance as the American Heart Association is calling for the development of a national adult database of CRF, given the critical impact of CRF on cardiovascular morbidity, all-cause mortality,[18] and cancer survival.[17,19] Moreover, Vo_{2max} values would enable health-care providers to define levels of CRF associated with poor health outcomes in the breast cancer population, elucidate therapy-related decrements in CRF, and help target appropriately timed interventions.

To address this gap in the literature, we identified 27 clinical trials and observational studies measuring Vo_{2max} in the pre– or post–adjuvant treatment setting for breast cancer. We compared mean Vo_{2max} values of female breast cancer patients in 6 studies that measured Vo_{2max} before adjuvant therapy and 21 studies that measured Vo_{2max} after adjuvant therapy was completed. We then compared mean Vo_{2max} values in female breast cancer patients with the Vo_{2max} values of healthy, sedentary, and active, endurance-trained controls. Secondary variables of interest included patients' age, body mass index (BMI), and study type and period.

Methods

We performed a MEDLINE search for citations of peer reviewed clinical studies measuring CRF in breast cancer patients. We used the following search terms: cardiorespiratory fitness or fitness or exercise capacity and breast cancer. We excluded studies not printed in the English language. We included observational studies and clinical trials involving exercise interventions in which CRF was measured in female breast cancer patients. Clinical trials consisted of both randomized controlled trials (RCTs) and exercise intervention studies, each of which examined the effects of exercise interventions on CRF as well as other variables in breast cancer patients. RCTs also measured outcomes in control groups consisting of women without a history of breast cancer, whereas exercise intervention studies did not contain control groups. Studies were only included if CRF was measured using Vo_{2max} [mL/(kg min) or L/min] and if CRF was measured within 5 years of completion of adjuvant therapy. For RCTs and exercise intervention studies, we reported mean baseline Vo_{2max} values and associated SDs before the initiation of exercise training.

Twenty-six clinical trials and observational studies that measured Vo_{2max} in female breast cancer patients pre– or post–adjuvant therapy were identified. Because Schneider et al[20] measured Vo_{2max} in pre– and post–adjuvant therapy settings, the 2 subsets were treated as independent populations, making the effective sample size 27 studies. A control population of healthy women was identified from a previously performed meta-analysis by Fitzgerald et al,[21] which accounted for physical activity level and age-related decline in Vo_{2max}. The equations to calculate Vo_{2max} were as follows: sedentary [43.82−0.35 (age)], active [54.02−0.44 (age)], and endurance-trained [72.41−0.62 (age)].[21] Estimated rates of decline for sedentary, active, and endurance-trained women were −3.5 mL/(kg min), −4.4 mL/(kg min), and −6.2 mL/(kg min) per decade, respectively.[21] The algorithms in the Fitzgerald report have been previously used and compared in other breast cancer populations.[17]

The majority of studies (16 of 27) measured CRF using a treadmill walking test and either a Bruce, Balke, or Naughton protocol. Of the remaining studies, 8 measured CRF with an electronic cycle ergometer, 1 measured CRF with a stepping ergometer, and 2 did not report the exercise equipment used to measure CRF. Vo_{2max} was measured directly from expired gas analysis during maximal effort in 14 studies and estimated using previously derived equations in 13 studies. A majority of studies reported mean Vo_{2max} in mL/(kg min), but for studies that reported mean Vo_{2max} in L/min and also reported mean weight in kg, a conversion was done using the standard method of division of random variables for both the mean and SD.[22] Of the 1856 patients studied in this review, 709 participated in studies in the United States and 1147 participated in studies performed outside the United States. The studies performed outside the United States and Canada included Brdareski et al[23] (Serbia), Daley et al[24] (United Kingdom), Herrero et al[25,26] (Spain), Rahnama et al[27] (Iran), Scott et al[28] (United Kingdom), Turner et al[29] (Australia), and Vincent et al[30] (France).

To accurately compare Vo_{2max} pre– and post–adjuvant therapy with that of controls, the inverse-variance method of weighting assuming a random-effects model was used.[31] Fitzgerald et al[21] reported that the weighted and unweighted means for the control group were not different; thus, the mean Vo_{2max} used for the control group was un-weighted. The standard error and 95% confidence interval were also calculated according to the guidelines of Borenstein and Higgins.[31]

Raw mean and SD values for Vo_{2max} (mL/(kg min)], age, and BMI were summarized for each study. Fisher's exact tests were used to compare the distribution of study type and therapy class, and Student *t* tests were used to compare the mean age and BMI between pre– and post–adjuvant therapy breast cancer studies. Meta-regression was used to explore the linear relationship between the weighted mean Vo_{2max} of each study, age, BMI, study type, and subgroup (pre– or post–adjuvant therapy). BMI was not reported for 5 studies. A sensitivity analysis was done to determine if imputation with the mean BMI would change the results of the linear regression. Imputation did not change the results, and as

such, missing BMI values were replaced with the mean BMI for all other studies so that all 27 studies could be included in the meta-regression.

Tests for heterogeneity were conducted to verify the appropriateness of meta-analysis for mean values of Vo_{2max} for all breast cancer studies and for pre–adjuvant therapy studies and post–adjuvant therapy studies separately. Methods described in Higgins and Thompson[32] were used to carry out this analysis. The H statistic, a modified Cochran's $\chi 2$ test (Q test) statistic that does not intrinsically depend on the number of studies, was calculated, with H=1 indicating homogeneity.[32]

Results

Fitness in the Preadjuvant and Postadjuvant Setting

Twenty-seven studies measuring Vo_{2max} in breast cancer patients were identified between 2001 and 2013, involving a total of 1856 female participants with mean ages ranging from 47 to 59 years. The 6 studies that reported Vo_{2max} prior to adjuvant therapy as well as the 21 studies that reported Vo_{2max} after completion of adjuvant therapy are summarized in Table 1. Weight percent by subgroup (pretherapy and

Table 1. Clinical Studies of Cardiorespiratory Fitness in Breast Cancer Patients

Time Period	Study	Sample Size	Vo_{2max}	Age	BMI	Study Type	Weight % by Subgroup*	Weight % Overall†
Pretherapy	Courneya et al[33]	242	25.17±6.49	49.2±—	26.6±5.5	RCT	8.73	1.59
	Kolden et al[34]	40	30.60±4.30	55.0±8.4	—±—	Exercise intervention	19.88	3.61
	Ligibel et al[35]	41	22.30±3.40	47.0±7.3	27.0±—	Exercise intervention	31.80	5.77
	Schneider et al[20]	13	22.50±6.20	54.9±10.6	25.6±—	Exercise intervention	9.56	1.74
	Segal et al[36]	123	25.50±5.57	50.9±8.7	—±—	RCT	11.86	2.15
	Vincent et al[30]	34	22.10±4.50	49.0±8.4	24.0±7.4	Exercise intervention	18.16	3.30
Posttherapy	Brdareski et al[23]	18	21.00±3.22	52.1±7.5	26.5±3.4	Exercise intervention	7.88	6.45
	Burnett et al[37]	30	25.40±5.30	50.5±5.6	29.2±5.3	Observational	2.90	2.38
	Campbell et al[38]	14	24.11 ±5.02	54.6±8.3	30.1±3.6	Exercise intervention	3.23	2.65
	Courneya et al[39]	50	18.70±3.85	59.0±6.0	29.2±6.6	RCT	5.51	4.51
	Daley et al[24]	108	29.82±5.08	51.0±8.5	28.6±5.0	RCT	3.16	2.59
	Dolan et al[16]	242	24.50±6.40	49.2±—	26.6±5.5	RCT	1.99	1.63
	Fillion et al[40]	87	25.55±5.36	52.4±10.0	—±—	RCT	2.84	2.32
	Herrero et al[25]	16	24.60±5.80	50.0±9.0	26.2±4.5	Observational	2.42	1.98
	Herrero et al[26]	11	26.70±5.60	47.0±7.0	25.2±3.2	Exercise intervention	2.60	2.13
	Hsieh et al[41]	96	20.60±6.23	57.9±10.5	28.6±—	Exercise intervention	2.10	1.72
	Hutnick et al[42]	47	19.49±5.21	50.1±10.0	26.7±4.8	Exercise intervention	3.01	2.46
	Jones et al[5]	47	17.90±4.30	59.0±7.0	28.0±5.0	Observational	4.41	3.61
	Jones et al[6]	26	19.20±4.60	48.0±8.5	29.0±6.0	Observational	3.85	3.15
	Musanti et al[43]	55	23.19±4.96	50.5±7.5	—±—	Exercise Intervention	3.31	2.71
	Rahnama et al[27]	29	15.75±5.52	57.5±—	27.7±4.0	Exercise intervention	2.68	2.19
	Rogers et al[44]	41	25.04±6.10	53.0±9.0	30.9±8.6	RCT	2.19	1.80
	Schneider et al[20]	82	20.80±6.10	56.9±9.4	28.3±—	Exercise intervention	2.19	1.79
	Scott et al[28]	90	23.70±4.53	55.7±9.6	30.3±4.5	RCT	3.98	3.26
	Taylor et al[3]	257	25.50±6.50	55.0±9.4	31.3±4.9	Observational	1.93	1.58
	Tosti et al[45]	7	22.00±1.50	50.6±3.3	29.4±1.1	Observational	36.24	29.66
	Turner et al[29]	10	23.00±7.20	47.0±8.0	—±—	Exercise intervention	1.57	1.29

Data presented as mean±SD. —, Missing or unreported data. Each study was weighted based on the inverse of the variance of that study's mean Vo_{2max} so that studies with smaller variances had a greater influence on the mean across studies. BMI indicates body mass index; RCT, randomized controlled trial.

*Weight percent by subgroup indicates the influence of the study on the mean across all pretherapy or posttherapy studies.

†Weight percent overall indicates the influence of that study on the mean across all pretherapy and posttherapy studies.

Table 2. Comparison of Descriptive Variables for Pre– and Post–Adjuvant Therapy Groups

Variable	All Breast Cancer Studies (N=27)	Pre–Adjuvant Therapy (N=6)	Post–Adjuvant Therapy (N=21)	*P* Value*
Age, y	52.3±3.7	51.0±3.3	52.7±3.8	0.332
BMI, kg/m^2	28.0±1.9	25.8±1.3	28.4±1.7	0.009
Study type				0.407
RCT	8 (30%)	2 (33%)	6 (29%)	
Observational	6 (22%)	0 (0%)	6 (29%)	
Exercise intervention	13 (48%)	4 (67%)	9 (43%)	
Therapy class				
Surgery+ adjuvant therapy	27 (100%)	6 (100%)	21 (100%)	

BMI indicates body mass index; RCT, randomized controlled trial.
*Fisher's exact *P*-value for categorical variables; *t* test *P*-value for continuous *P*-values.

posttherapy) and weight percent overall of each of the 27 studies are also shown in Table 1.

Table 2 shows descriptive variables from all 27 studies as well as a comparison among the overall and pre– and post–adjuvant therapy breast cancer groups. Overall, 20% were RCTs, 22% were observational studies, and 48% were exercise intervention studies. In the preadjuvant setting, 33% were RCTs, and 67% were exercise interventions. Of the studies performed in the postadjuvant setting, 29% were RCTs, 29% were observational studies, and 43% were exercise interventions. Adjuvant therapy included chemotherapy in 78% (predominantly anthracycline-based), radiotherapy in 56%, and hormonal therapy in 33% of patients.

The mean age and BMI for all breast cancer studies were 52±4 years and 28±2 kg/m^2. The mean age was similar in the pre– and post–adjuvant therapy settings (*P*=0.33, Table 2). The weighted mean Vo_{2max} before adjuvant therapy was 24.6 mL/(kg min). For the 21 studies reporting Vo_{2max} after adjuvant therapy, the weighted mean Vo_{2max} was 22.2 mL/(kg min). The Vo_{2max} in the postadjuvant setting was 10% lower [−2.4 mL/(kg min)] than the mean Vo_{2max} value assessed at the beginning of adjuvant therapy. The mean BMI measured after adjuvant therapy was completed was 2.6 kg/m^2 higher than the BMI prior to adjuvant therapy (28.4±2 kg/m^2 versus 25.8±1 kg/m^2, *P*=0.009).

Table 3 contains the results of the linear meta-regression examining the relationship between age, BMI, study type and period, and weighted mean Vo_{2max} levels. There was no evidence for an association between weighted mean Vo_{2max} and the study variables of interest such as age and BMI (*P*>0.05 for all). We also performed a test for heterogeneity for both preadjuvant and postadjuvant studies. The H value was 1 (95% CI 1 to 1.99, *P*=0.72) for the preadjuvant breast cancer studies and 1 (95% CI 1 to 1.37, *P*=0.98) for the postadjuvant breast cancer studies, respectively.

Fitness Compared With Healthy, Sedentary, and Endurance Trained Women

The weighted mean Vo_{2max} measured in breast cancer patients prior to adjuvant therapy [24.6 mL/(kg min)] was 17% lower than the Vo_{2max} of healthy, sedentary women [29.7 mL/(kg min)], or 83% of predicted (*P*=0.007) (Figure 1). After completion of adjuvant therapy, weighted mean Vo_{2max} in breast cancer patients [22.2 mL/(kg min)] was 25% lower than the Vo_{2max} of healthy, sedentary women (75% of predicted, *P*<0.001). Figure 2 illustrates Vo_{2max} by age and physical activity level for healthy women based on Fitzgerald et al[21] and weighted Vo_{2max} among breast cancer patients in the current study. Vo_{2max} varied with age and physical activity level. The weighted mean Vo_{2max} of a 50-year-old breast cancer patient [22.6 mL/(kg min)] was most similar to that of sedentary, 60-year-old women [≈22.7 mL/(kg min)].

Discussion

The current review demonstrates impairment in Vo_{2max} among female breast cancer patients compared with healthy controls, as well as lower Vo_{2max} depending on the timing of measurement in relation to breast cancer treatment status. These data suggest existing normative CRF values in healthy women may not be representative of breast cancer populations. Based on our previous work, the decline in CRF appears sustained in breast cancer patients even 7 years after treatment compared with age-matched controls.[46] These findings are of key importance given even small differences in CRF [eg, 1 MET or 3.5 mL/(kg min)] are associated with a significantly higher risk for cardiovascular mortality (≈18%).[47,48]

The reason for impairment in CRF is likely multifactorial, involving multiple organ components of oxygen transport. Of the major components of oxygen transport—namely, pulmonary, cardiac, vascular, and skeletal muscle function, a limitation in cardiac function is the most well studied in breast cancer patients. Chemotherapeutic agents used in breast cancer management are associated with both short- and long-term cardiac complications, which can ultimately lead to congestive heart failure.[49] Anthracycline-based adjuvant chemotherapy in particular carries a substantial long-term risk of heart failure. The mechanism of action of anthracyclines involves intercalation between DNA base pairs, inhibition of DNA topoisomerase II with subsequent blocking of replication and transcription, and the generation of iron-

Table 3. Association Between Weighted Mean Vo_{2max} and Clinical Study Variables

Model #	Dependent Variable	Independent Variables	Parameter Estimate (SE)	*P* Value	Model *P*-Value	*R*-Squared
1	Weighted mean Vo_{2max}	Intercept	1.031 (7.289)	0.889	0.641	0.140
		Age	−0.073 (0.106)	0.497		
		BMI*	0.191 (0.275)	0.495		
		Study type (RCT)	−1.424 (1.004)	0.171		
		Study type (exercise)	−1.125 (0.998)	0.272		
		Period (posttherapy)	−0.380 (0.959)	0.696		
2	Weighted mean Vo_{2max}	Intercept	−0.460 (6.811)	0.947	0.732	0.053
		Age	−0.093 (0.104)	0.382		
		BMI*	0.238 (0.249)	0.349		
		Period (posttherapy)	−0.099 (0.941)	0.917		
3	Weighted mean Vo_{2max}	Intercept	4.709 (4.944)	0.351	0.567	0.120
		Age	−0.043 (0.096)	0.656		
		Study type (RCT)	−1.440 (0.992)	0.161		
		Study type (exercise)	−1.370 (0.923)	0.152		
		Period (posttherapy)	−0.140 (0.883)	0.876		
4	Weighted mean Vo_{2max}	Intercept	−0.534 (6.846)	0.939	0.567	0.120
		BMI*	0.113 (0.247)	0.654		
		Study type (RCT)	−1.482 (0.988)	0.148		
		Study type (exercise)	−1.266 (0.965)	0.203		
		Period (posttherapy)	−0.399 (0.947)	0.678		
5	Weighted mean Vo_{2max}	Intercept	3.973 (4.982)	0.433	0.827	0.016
		Age	−0.056 (0.097)	0.567		
		Period (posttherapy)	0.277 (0.853)	0.749		
6	Weighted mean Vo_{2max}	Intercept	−3.026 (6.146)	0.627	0.778	0.021
		BMI*	0.156 (0.230)	0.504		
		Period (posttherapy)	−0.107 (0.937)	0.910		
7	Weighted mean Vo_{2max}	Intercept	2.538 (1.111)	0.032	0.425	0.112
		Study type (RCT)	−1.476 (0.971)	0.142		
		Study type (exercise)	−1.399 (0.904)	0.136		
		Period (posttherapy)	−0.223 (0.849)	0.795		
8	Weighted mean Vo_{2max}	Intercept	3.870 (4.882)	0.436	0.596	0.011
		Age	−0.050 (0.093)	0.596		
9	Weighted mean Vo_{2max}	Intercept	−2.776 (5.630)	0.626	0.480	0.020
		BMI*	0.144 (0.201)	0.480		
10	Weighted mean Vo_{2max}	Intercept	2.315 (0.702)	0.003	0.249	0.110
		Study type (RCT)	−1.421 (0.929)	0.139		
		Study type (exercise)	−1.330 (0.849)	0.130		
11	Weighted mean Vo_{2max}	Intercept	1.113 (0.728)	0.139	0.829	0.002
		Period (posttherapy)	0.181 (0.826)	0.829		

BMI indicates body mass index; RCT, randomized controlled trial.
*Missing BMI values were imputed with the mean BMI.

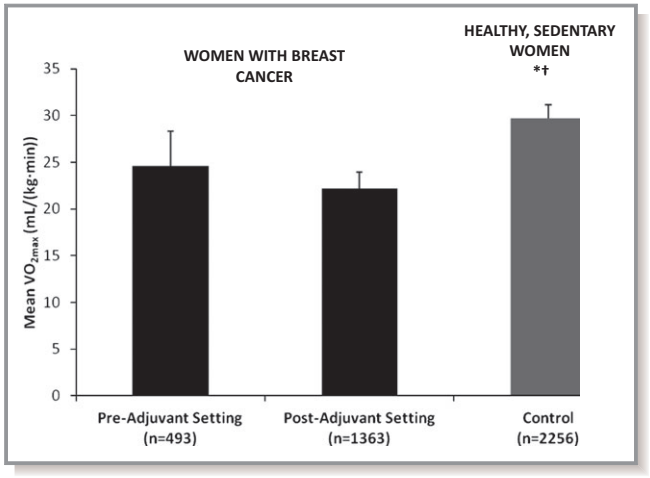

Figure 1. Mean Vo_{2max} [mL/(kg min)] in breast cancer patients before and after adjuvant therapy and in healthy, sedentary controls.[20] *P=0.007 comparing breast cancer patient before adjuvant therapy to control. †P<0.001 comparing breast cancer patients after adjuvant therapy to control.

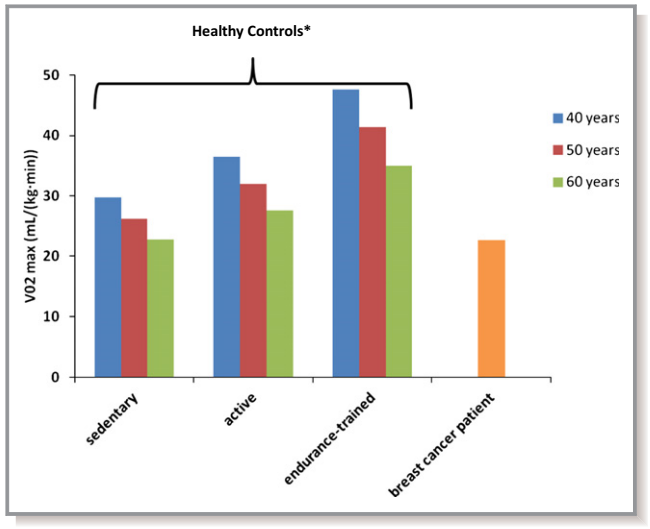

Figure 2. Mean Vo_{2max} among sedentary, active, and endurance-trained healthy women by age category* compared with mean Vo_{2max} among breast cancer patients. *The equations to calculate Vo_{2max} were as follows: sedentary [43.82−0.35 (age)], active [54.02−0.44 (age)], endurance-trained [72.41−0.62 (age)]. Estimated rates of decline per decade for sedentary, active, and endurance-trained women were −3.5 mL/(kg min), −4.4 mL/(kg min), and −6.2 mL/(kg min) per decade, respectively.[21]

mediated oxygen free radicals that damage DNA as well as proteins and cell membranes.[50] These oxygen free radicals are thought to play a central role in the evolution of the cardiotoxic effects of anthracyclines.[8] Moreover, several lines of evidence suggest that cytotoxic damage caused by anthracyclines leads to compensatory alterations in autonomic tone, which may have important implications for heart rate reserve and CRF.[51,52] Radiotherapy used to treat breast cancer can cause cardiac perfusion defects that are associated with abnormalities in regional wall motion.[53] Furthermore, radiotherapy-induced cardiotoxicity is amplified by the use of adjuvant systemic chemotherapy—particularly anthracycline-based regimens[54] and newer agents such as trastuzumab.[55]

Jones et al[17] has previously shown that mean Vo_{2max} is markedly impaired in a population of breast cancer patients despite normal cardiac function (as indicated by LVEF ≥50%). This important finding suggests that injury to other components of oxygen transport (ie, pulmonary, hematologic, vascular, and skeletal muscle function) must contribute to CRF decline.[17] In particular, incidental radiation to the lungs during radiotherapy for breast cancer causes fibrosis and a subsequent impairment in pulmonary gas exchange.[56] Anemia, a frequent complication of treatment while undergoing therapy,[57] reduces oxygen delivery to muscle cells.[58] Dolan et al[16] found a significant correlation between hemoglobin levels and percent change in Vo_{2max} in women receiving adjuvant therapy for breast cancer. Both radiotherapy and chemotherapy for breast cancer, especially anthracyline-containing chemotherapy, cause increases in reactive oxygen species generation, which can lead to endothelial injury, endothelial dysfunction, vascular remodeling, and increased arterial stiffness,[59] further affecting oxygen delivery. Finally, preclinical studies have shown that anthracyclines impair both maximal twitch force and muscle relaxation.[60,61] Such impairments in skeletal muscle function decrease oxygen utilization and thereby contribute to reduced CRF. To compound the effects of chemotherapy, numerous studies have also shown that chemotherapy negatively affects skeletal muscle mass in cancer patients. Although chemotherapy is associated with weight gain among breast cancer patients,[62–67] chemotherapy-induced weight gain tends to occur in the absence of gains in muscle mass or in the presence of muscle loss and can lead to the development of sarcopenic obesity.[66]

Importantly, the summation of these insults decreases cardiopulmonary reserve and increases the susceptibility of female breast cancer patients to late-occurring adverse cardiovascular effects and premature mortality. This phenomenon has been labeled the “multiple hit hypothesis” by Jones et al.[49] In keeping with this hypothesis, women with breast cancer in the current review at 50 years of age had a similar CRF to sedentary, 60-year-old women without a history of breast cancer (Figure 2). This finding points to an accelerated aging process among female breast cancer patients that can negatively affect CRF and potentially prognosis.

Recent evidence suggests that exercise training is an effective intervention to improve CRF as well as quality of life,

physical functioning/strength, and symptoms of fatigue in breast cancer patients.[2] These findings are supported in several of the studies presented in this review. For example, Courneya et al[39] reported a 14.5% increase in Vo_{2max} after 15 weeks of aerobic exercise training at an intensity of 70% to 75% of maximal oxygen consumption. Daley et al[24] also demonstrated significant increases in Vo_{2max} with both light (<40% of maximum heart rate) and moderate (65% to 85% of maximum heart rate) intensity exercise training for 8 weeks. Scott et al[28] showed a 32% increase in Vo_{2max} after a 24-week lifestyle intervention combining exercise and a hypocaloric healthy eating program. Exercise interventions that resulted in significant improvements in Vo_{2max} varied widely, ranging from home-based[30] and telephone-based[35] interventions to individual[20,41] and group[23,24,26–28,34,38,39] sessions with certified trainers. Interventions also varied with respect to type of exercise, intensity of exercise, and study length. Further study is needed to understand the propensity of newer exercise strategies as well as combinations of treatments (ie, statins, angiotensin-converting enzyme inhibitors, β-blockers) to protect against cardiotoxicity leading to lower CRF.

We analyzed data presented in 27 selected clinical studies with patient populations ranging from 7 to 257 women. Although we were able to draw several conclusions about CRF in breast cancer patients based on these studies, further work is required to assess CRF in ethnically diverse populations at multiple different time points in breast cancer treatment. Importantly, the timing of these decrements and potential recovery can be determined with prospective studies evaluating sequential changes in CRF across patient populations receiving adjuvant therapy regimens.[46] For exercise training interventions to maximally decrease cardiovascular risk in the breast cancer population, interventions should be used before, during, and after treatment, as well as specifically at the time of greatest CRF decline. Other therapeutic modalities, such as statin therapy, angiotensin-converting enzyme inhibitors, and β-blockers, should also be considered in the setting of cardiac dysfunction.

In summary, breast cancer patients are subjected to sequential cardiovascular insults throughout their treatment regimens that decrease their CRF and increase their susceptibility to premature cardiovascular mortality compared with the general population.[17,49] CRF has been shown to be a strong predictor of the adverse health outcomes that can result from breast cancer treatment regimens. Normative Vo_{2max} data for this patient population will allow healthcare providers to predict which patients are at particular risk for late-occurring cardiotoxicity that may be amenable to exercise interventions. This is of key importance given that exercise training can ameliorate impairments in Vo_{2max} and may thereby have the potential to enhance prognosis in breast cancer patients and in other cancer patients as well.[2,68]

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Disclosure

None.

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