A Review on the Role of Exercise Training to Prevent a Decline in Cardiorespiratory Fitness and Cardiac Function in Breast Cancer Survivors

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Purpose: Improvements in diagnosis and treatment mean that the long-term health of breast cancer survivors (BCS) is increasingly dictated by cardiovascular comorbidities. This is partly a consequence of exposure to cardiotoxic therapies, which result in cardiac dysfunction and decreased cardiorespiratory fitness (CRF). Exercise training (ExT) is a key therapeutic strategy for secondary prevention and increasing CRF in adults with established cardiovascular disease. Exercise-based cardio-oncology rehabilitation (CORE) has been proposed as an emerging strategy to address CRF and cardiac impairment in BCS. This review aims to (1) provide an overview of the impact of breast cancer therapy on CRF; (2) provide an up-to-date summary of the effects of ExT on CRF and cardiac function in BCS undergoing cardiotoxic therapy; and (3) discuss how traditional ExT approaches can be adapted for BCS undergoing therapy.

Review methods: A literature review was performed based on an intensive literature search for systematic reviews and meta-analyses, randomized and non-randomized controlled trials and single-arm trials investigating the impact of exercise training or cardiac rehabilitation on CRF and/or cardiac function in BCS who are undergoing or have completed cardiotoxic cancer therapy.

Summary: Overall, current evidence suggests that ExT induces clinically meaningful benefits for CRF in BCS during and after therapy. There is also emerging evidence that ExT can improve peak exercise measures of cardiac function; however, there is a need for further research to understand how to adapt these effective ExT approaches into clinical CORE-based settings.

Key Words: cardio-oncology • cardiotoxicity • exercise oncology • rehabilitation

KEY PERSPECTIVES

What is novel?

- Exercise training during and after cardiotoxic breast cancer therapy results in clinically meaningful improvements in cardiorespiratory fitness.
- Emerging evidence shows that this is partly mediated by improvements in peak exercise measures of cardiac function that is not adequately captured by traditional resting measures.

What are the clinical and/or research implications?

- Cardiorespiratory fitness should be an important therapeutic target for breast cancer survivors exposed to cardiotoxic therapy.
- Exercise-based cardio-oncology rehabilitation should be considered for breast cancer survivors at increased risk of cardiovascular disease and impaired cardiorespiratory fitness.
- Further research is needed to understand how traditional exercise-based cardiac rehabilitation models can be adapted for breast cancer survivors undergoing therapy.

Cardiovascular disease (CVD) and CVD-related mortality are major determinants of quality of life and longevity for early-stage breast cancer survivors (BCS).[1-3] This is partly not only a consequence of the shared risk factors between CVD and breast cancer (BC) but also the direct (myocardial and vascular toxicity) and indirect (deconditioning, premature menopause) cardiovascular toxicity caused by BC therapy.[4] Commonly prescribed BC therapies, including anthracycline-based chemotherapy (AC), human epidermal growth factor receptor 2 (HER2)-targeted therapies, and radiation therapy involving incidental cardiac radiation result in cardiovascular injury and an increased risk of cardiac dysfunction and heart failure (HF). Heart failure risk is further increased in BCS who receive combinations of these therapies and/or have preexisting CVD risk factors such as hypertension, hypercholesterolemia, and obesity.[2] Cardiorespiratory fitness (CRF) is an important modifiable risk factor for CVD (including HF), and impaired CRF is a hallmark feature of HF.[5] Therefore, it is notable that CRF of BCS before commencing therapy is on average 17% lower than healthy controls[6] and can decrease by a further 8-16% over the course of BC therapy,[7-9] and in advanced disease it is associated with decreased survival.[7] Current guidelines for cardiotoxicity and HF prevention are focused on commencing prophylactic pharmacologic

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therapies (beta-adrenergic blockade, angiotensin blockade/inhibition) in BCS at high baseline risk, or BCS who develop subclinical cardiac dysfunction during BC therapy.[10] However, there is also growing interest in the use of exercise training (ExT) as a holistic therapy to address CRF and cardiac impairment in BCS exposed to cardiotoxic therapy.[10,11]

Exercise training is a key component for managing CVD, including HF.[12-14] In individuals with CVD, ExT is typically incorporated as part of a multimodal cardiac rehabilitation (CR) program alongside nutritional modification, education, behavioral counseling, and psychological support.[12-14] An adapted CR model referred to as cardio-oncology rehabilitation (CORE) has been endorsed by the American Heart Association as a critical intervention for the prevention and management of CVD in at-risk cancer survivor groups (including BCS).[11] Given the importance of primary prevention in this population, current CORE referral recommendations include not only BCS with established CVD but also those at risk of future CVD due to high-dose cardiotoxic therapy, receiving a combination of low-to-moderate doses of multiple cardiotoxic agents (eg, AC + HER2-targeted therapy), or having several risk factors for CVD.[11,14] Just as for CR, ExT is recommended as a central component of CORE.[11] However, this recommendation was largely based on expert opinion and extrapolation from other CVD populations due to limited evidence in cancer survivors. There have been several notable studies published since these guidelines were made available. Therefore, the purpose of this review is to provide an up-to-date overview of the impact of ExT to address CRF and cardiac function impairment in BCS. This review will include an overview of (1) the importance of and mechanisms underlying CRF impairment in BCS, (2) a summary of the impact of ExT on CRF and cardiac function in BCS exposed to cardiotoxic therapy, and (3) recommendations on how standard ExT prescription can be adapted to BCS undergoing cardiotoxic therapy.

REVIEW OF THE LITERATURE

CRF AS A VITAL SIGN IN BCS

Cardiorespiratory fitness is a marker of cardiovascular and skeletal muscle function and functional capacity that is endorsed by the American Heart Association as a vital sign for adults with or at risk of CVD.[15,16] In the general population, decreased CRF is a strong, independent predictor of overall and CVD-related mortality with every 1.0 mL/kg/min decrease in peak oxygen uptake ($\dot{V}O_{2peak}$) associated with an 11%, 16%, and 15% increase in all-cause, cancer-specific, and CVD mortality, respectively.[17] Similarly, emerging evidence in cancer survivors has shown every 1 metabolic equivalent (MET) decrement in post-diagnosis CRF is associated with a 26%, 25%, and 14% increased risk of all-cause, cancer-specific, and CVD mortality, respectively.[18] As such, CRF is considered a critical therapeutic target for individuals undergoing CR,[15,16] and the same should be true for BCS undergoing CORE.[11] Addressing CRF during BC therapy is important because BC therapy is associated with marked declines in CRF with a meta-analysis showing that $\dot{V}O_{2peak}$ in BCS >1-yr post-adjuvant therapy is 25% lower (7.4 mL/kg/min lower) than that in healthy sedentary females.[6] Moreover, approximately one in three BCS has been shown to have a $\dot{V}O_{2peak}$ below the threshold for functional independence (functional disability: $\dot{V}O_{2peak} \leq 18.0$ mL/kg/min or 5-6 METs),[7-9,19,20] which is associated with a substantially increased risk of future HF[21] and mortality.[22] Reductions in CRF among BCS may be partly a consequence of cardiovascular injury from BC therapies such as AC and/or anti-HER2 therapy.[4,23] For example, $\dot{V}O_{2peak}$ declines by as much as 15% over approximately 3 mo of AC[8,20] (equivalent to 12-16 yr of normal age-related decline[24]). Moreover, the AC-induced reductions in $\dot{V}O_{2peak}$ may remain below pre-chemotherapy values 12 mo later and coincide with a twofold increase in the prevalence of functional disability.[9] These reductions are not isolated to AC, with Bonsignore et al[25] demonstrating that BCS who have recently completed HER2-targeted therapy have a $\dot{V}O_{2peak}$ 16% below predicted values[26] (~3.0 mL/kg/min), with 44% classified as functionally disabled. Overall, this highlights the importance of measuring and addressing CRF impairment in BCS.

MECHANISMS UNDERLYING CRF IMPAIRMENT IN BCS

Cardiac Factors

Reductions in CRF with BC therapy rarely coincide with declines and/or impairment in standard markers of cardiac dysfunction such as resting left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS).[7-9] In a cohort of 203 cancer survivors (53% BCS), ~3 mo of AC resulted in a 2.0 mL/kg/min reduction (–8%) in $\dot{V}O_{2peak}$ that showed no association with changes in resting LVEF ($R^2 = 0.00$) or GLS ($R^2 = 0.02$).[8] Although this suggests that CRF impairment in BCS may be driven by noncardiac factors, it may also reflect the poor agreement between resting measures of cardiac function and CRF—particularly when cardiac function is within the normal range (ie, LVEF > 45-50%).[27] Indeed, studies that utilize measures of cardiac function during exertion have shown that AC ± HER2-targeted therapy is associated with impairment in submaximal and/or peak exercise measures of LVEF, stroke volume, and cardiac output.[9,28,29] Moreover, functional disability 12 mo post-AC has been linked with impairment in peak exercise cardiac output and stroke volume.[9] This highlights that CRF impairment is partly a consequence of subclinical decrements in cardiac function, and, as such, should be considered an important cardiovascular outcome, separately or in addition to standard resting metrics of cardiac dysfunction and HF risk (ie, LVEF, GLS) in BCS.

Noncardiac Factors

Although cardiotoxicity has been a key focus, noncardiac mechanisms may also contribute to CRF in BCS. An in-depth overview of these noncardiac defects is reviewed elsewhere.[23,30] In general, this includes increases in aortic stiffness, endothelial dysfunction, anemia, capillary rarefaction, muscle fat infiltration, and negative alterations in skeletal muscle fiber composition and mitochondrial function.[30] For example, Mijwel et al[31] showed that declines in CRF over the course of AC coincided with a significant reduction in muscle capillarity, mitochondrial oxidative enzymes, and a decreased proportion of highly oxidative type I muscle fibers. Similarly, Kirkham et al[32] have shown an accumulation of intermuscular fat (termed "myosteatosis") within the thigh and lower leg over 12 mo of therapy (including AC ± HER2-targeted therapy). Furthermore, cross-sectional studies of AC-treated BCS have shown that myosteatosis is a strong predictor of $\dot{V}O_{2peak}$ and peripheral oxygen extraction within the lower leg.[29,33] Therefore, the exercise and rehabilitation professional should be aware of these noncardiac defects as they provide a compelling rationale for the use and prescription of ExT.

EXT AND CRF

Meta-analysis of 48 randomized controlled trials (RCTs) in 3632 cancer survivors (44% of participants were BCS) showed that ExT is feasible, safe, and results in a 2.13 mL/kg/min net improvement in $\dot{V}O_{2peak}$.[34] Furthermore, meta-analysis of RCTs specifically focused on the effect of ExT (typically 2-3 sessions/wk of aerobic ± resistance training [RT]) in BCS undergoing cardiotoxic therapy has shown a 1.8 mL/kg/min net benefit for $\dot{V}O_{2peak}$ with ExT.[35] The effect differs on the basis of studies focused specifically on BCS undergoing AC, HER2 therapy, or spanning the entire trajectory of (neo)adjuvant therapy.[35] However, the degree to which this is reflective of the type of therapy, exercise prescription, program length, and individual participant characteristics is yet to be determined because of the paucity and heterogeneity of studies (Table 1). In studies focused on BCS undergoing AC, the majority have shown 2-4 sessions/wk of ExT, including moderate continuous training (MCT); MCT + RT or MCT + RT combined with high-intensity interval training (HIIT) typically attenuates declines in $\dot{V}O_{2peak}$ (or other measures of CRF) associated with AC.[19,20,36-39] Two studies have assessed the impact of 3-4 mo of aerobic ExT during HER2-targeted therapy.[40,41] In a single-arm study of BCS undergoing HER2-targeted therapy, Haykowsky et al[41] reported no impact of 4 mo of 3 sessions/wk of MCT on $\dot{V}O_{2peak}$ (+1.9 mL/kg/min, P = .2). In contrast, Jacquinot et al[40] reported that 12 wk of 3 sessions/wk of HIIT was associated with a 2.6 mL/kg/min improvement in $\dot{V}O_{2peak}$. The lack of $\dot{V}O_{2peak}$ improvement seen with the study of Haykowsky et al[41] may relate to the smaller sample size (n = 17[41] vs n = 75[40]) and relatively modest adherence (60% of sessions attended[41]). Indeed, Haykowsky et al[41] showed that ExT adherence predicted the change in $\dot{V}O_{2peak}$.

Our group has recently completed the BReast cancer EXercise InTervention (BREXIT) trial[19] to investigate the impact of 12 mo of 3-4 sessions/wk combined MCT + HIIT + RT in BCS scheduled for AC ± HER2-targeted therapy on functional disability, $\dot{V}O_{2peak}$, and cardiac function. Consistent with previous studies, 3 mo of ExT during AC attenuated declines in $\dot{V}O_{2peak}$ (ExT: –1.5 mL/kg/min vs usual care [UC]: –2.9 mL/kg/min) and resulted in a 68% lower likelihood of functional disability.[19] However, the participants in this study continued ExT after finishing AC using a pragmatic step-down model (3 mo of semisupervised ExT, followed by 6 mo of independent ExT with remote support via telehealth). Overall, 12 mo of ExT resulted in a significant improvement in $\dot{V}O_{2peak}$ relative to pre-AC levels (+2.0 mL/kg/min) and a marked 3.5 mL/kg/min (1 MET) net difference versus the control group.[19] Notably, 58% of the BREXIT ExT cohort achieved a minimally clinically important increase in $\dot{V}O_{2peak}$ from baseline, with 23% achieving a >1 MET improvement in $\dot{V}O_{2peak}$ (Figure 1). Evidence from BCS and other CVD populations described earlier suggests that these changes in CRF portend profound clinical benefit.[17,18,42] However, ExT did not significantly reduce the prevalence of functional disability at 12 mo (OR = 0.27: 95% CI, 0.06-1.12, P = .07), which may be partly related to increased attrition in the UC control group (a majority of whom were functionally disabled after completing AC).[19] Exercise adherence was a key effect modifier, with participants who were adherent to ExT (defined as >66% attendance over 12 mo) experiencing greater CRF improvement (+2.45 mL/kg/min vs +0.11 mL/kg/min, P = .037) and complete protection from functional disability.[19] This finding highlights the importance of ExT models that foster sustained adherence for addressing CRF and functional disability during BC therapy. Another component of BREXIT efficacy may be the focus on multiple forms of ExT throughout the entire (neo)adjuvant BC therapy continuum. Indeed, BC therapy induces multiple repeated insults to the cardiovascular and skeletal muscle systems underlying CRF. Consequently, these multiple hits may require both several modalities of ExT (such as RT that can address skeletal defects[31]) and a longer period of ExT than a standard 12-wk intervention. In support of this, Scott et al[39] recently demonstrated that compared with 16 wk of 3 sessions/wk ExT prescribed during or after AC, delivering 32 wk of ExT both during and after AC resulted in the greatest benefit to $\dot{V}O_{2peak}$. However, this length of program may not be feasible in all settings or centers, and so further work is needed to determine how these principles can be adopted or adapted in CR and/or CORE-based intervention models.

An alternative and pragmatic approach may be to focus on ExT following the completion of BC therapy. Meta-analysis shows that ExT commenced after completion of adjuvant cancer therapy coincides with a 1.0 mL/kg/min greater improvement in $\dot{V}O_{2peak}$ than ExT during therapy.[34] However, few studies have specifically focused on the effects of ExT in BC survivors who have completed cardiotoxic therapy. Scott et al[43] investigated the effects of 24 wk of either MCT or combined MCT + HIIT versus attention control (static stretching) on $\dot{V}O_{2peak}$ in survivors of BC who had completed adjuvant therapy and reported relatively modest improvements in $\dot{V}O_{2peak}$ (+0.6-0.8 mL/kg/min) with ~40% exceeding the threshold for minimal detectable (and clinically important) change in both groups. However, whether this reflects a decreased adaptability to ExT due to irreversible cardiotoxic effects of AC (and other BC therapy), older age, and/or other ExT or patient-related factors is unknown. This highlights the need for further studies assessing the impact of ExT-based rehabilitation in older BCS. This is particularly important because older BCS (>60-65 yr) are at the greatest risk of functional impairment,[44] CVD events, and cardiovascular mortality.[2,45]

EXT AND CARDIAC (DYS)FUNCTION

Separate from addressing CRF, there is substantial interest on the direct effect of ExT on cardiac (dys)function. There are now several studies that investigated the impact of ExT on cardiotoxicity and resting cardiac function during cardiotoxic BC therapy (Table 1).[19,20,37,39-41,46] A recent meta-analysis of trials investigating ExT during AC and/or anti-HER2 therapy shows no favorable effect of ExT on resting LVEF.[35] Fewer studies have assessed the impact on resting GLS, but available evidence shows no effect of ExT on GLS—which typically shows a small reduction of negligible clinical significance.[19,20,40,46,47] In addition, no studies have demonstrated that ExT prevents clinical cardiac dysfunction during AC and/or HER2-targeted therapy (based on guideline-based LVEF ± GLS criteria).[19,20,40,46] This may reflect the small sample sizes, small changes in resting cardiac function, and/or low rates of cardiac dysfunction reported in the majority of studies. The discordance between ExT-induced changes in $\dot{V}O_{2peak}$ and resting left-ventricular (LV) function (which is the core component of cardiotoxicity definitions) also highlights the insensitivity of resting measures to detect clinically meaningful changes in CRF and cardiac function (Figure 2).

Assessing cardiac function *during* exertion may provide greater insight into the impact of ExT on cardiac function and CRF in this setting.[48] Consequently, a critical component of the BREXIT study was the inclusion of cardiac function assessment during exertion using exercise

Table 1

Summary of Key Studies Assessing the Effect of Structured Exercise Training During Cardiotoxic Breast Cancer Therapy on $\dot{V}O_{2peak}$ and Cardiac Function[a]

Author	Study Design	Sample Size	Age, yr	CTx BC Therapy	ExT Intervention	ExT Length	ExT Adherence	$\dot{V}O_{2peak}$		Cardiac Function	
								Δ vs Baseline	vs Control Δ	Δ vs Baseline	vs Control Δ
Hornsby et al (2014)[37]	RCT	N = 20	51 ± 6	AC (100%)	3 sessions/wk MCT (2-3/wk): 15-45 min at 60-65% PPO HIIT (0-1/wk): 10 × 30 sec at 100% PPO, 60 sec recovery	12 wk ExT during AC	82%[b]	Post-chemo ↑ +2.6 mL/kg/min[c]	Post-chemo ↑ +4.1 mL/kg/min[c]	Post-chemo $LVEF_{rest}$ +1.0% NS	Post-chemo ↔ $LVEF_{rest}$ −1.0% NS
Jacquinot et al (2022)[40]	RCT	N = 89	51 (43-56)	HER2 therapy (100%) Prior-AC (81%)	3 sessions/wk HIIT (3/wk): 9 × 1 min PO at RCP, 4 min PO at VT	12 wk ExT during HER2 therapy	NR	12 wk F/U ↑+2.6 mL/kg/min[c]	12 wk F/U ↑+2.4 mL/kg/min[c]	12 wk F/U ↔ $LVEF_{rest}$+0.1% NS ↔ GLS_{rest}+0.5%[c]	12 wk F/U ↔ $LVEF_{rest}$+0.8% NS ↔ GLS_{rest} −1.1% NS
Scott et al (2023)[39]	RCT	N = 128	50 ± 11	AC (75%) HER2 therapy (24%)	Concurrent (during chemo) 3 sessions/wk MCT: 15-45 min at 55-80% $\dot{V}O_{2peak}$ HIIT: 6-12 × 1-2 min at 95-100% PPO, 2-3 min recovery	14-20 wk ExT during chemo + No ExT post-chemo	70%[d]	Post-chemo ↓ −2.0 mL/kg/min[c] 28-40 wk F/U ↔ 0.8 mL/kg/min NS	Post-chemo ↔ 0.7 mL/kg/min NS 28-40 wk F/U ↔ 1.0 mL/kg/min NS	Post-chemo NR 28-40 wk F/U ↓ $LVEF_{rest}$ −1.5%[c]	Post-chemo ↔ $LVEF_{rest}$+0.5% NS 28-40 wk F/U ↔ $LVEF_{rest}$ −1.1% NS
			46 ± 10		Sequential (after chemo) 3 sessions/wk MCT: 15-45 min at 55-80% $\dot{V}O_{2peak}$ HIIT: 6-12 × 1-2 min at 95-100% PPO, 2-3 min recovery	No ExT during chemo 14-20 wk ExT post-chemo	84%[d]	Post-chemo NR 28-40 wk F/U ↔ 0.7 mL/kg/min NS	Post-chemo NR 28-40 wk F/U ↔ 0.9 mL/kg/min NS	Post-chemo NR 28-40 wk follow-up ↔ $LVEF_{rest}$ −0.6% NS	Post-chemo NR 28-40 wk F/U ↔ $LVEF_{rest}$ −0.4% NS
			48 ± 12		Continuous (during ± after chemo) 3 sessions/wk MCT: 15-45 min at 55-80% $\dot{V}O_{2peak}$ HIIT: 6-12 × 1-2 min at 95-100% PPO, 2-3 min recovery	28-40 wk ExT during + after chemo	82%[d]	Post-chemo NR 28-40 wk F/U ↑ +1.7 mL/kg/min[c]	Post-chemo NR 28-40 wk F/U ↑ +1.9 mL/kg/min[c]	Post-chemo NR 28-40 wk F/U ↔ $LVEF_{rest}$ −0.3% NS	Post-chemo NR 28-40 wk F/U ↔ $LVEF_{rest}$+0.2% NS

(*continues*)

Table 1

Summary of Key Studies Assessing the Effect of Structured Exercise Training During Cardiotoxic Breast Cancer Therapy on $\dot{V}O_{2peak}$ and Cardiac Function[a] (*Continued*)

Author	Study Design	Sample Size	Age, yr	CTx BC Therapy	ExT Intervention	ExT Length	ExT Adherence	$\dot{V}O_{2peak}$		Cardiac Function	
								Δ vs Baseline	vs Control Δ	Δ vs Baseline	vs Control Δ
Foulkes et al (2023)[19]	RCT	N = 102	50 ± 8	AC (100%) HER2 therapy (22%)	3-4 sessions/wk MCT (2-3/wk): 30-60 min (HR 0-30 b/min below VT) HIIT (1-2/wk): 4 × 2-4 min >85% HR_{peak}, 3 min recovery RT (2/wk): 1-2 sets, 8-15 reps at 60-85% 1RM	52 wk during + after AC	73%[b]	Post-chemo ↓ –1.5 mL/kg/min[c] 52 wk F/U ↑ +2.0 mL/kg/min[c]	Post-chemo ↑ +1.4 mL/kg/min[c] 52 wk F/U ↑ +3.5 mL/kg/min[c]	Post-chemo ↓ $LVEF_{rest}$ –2.9%[c] ↓ GLS_{rest} +1.3%[c] ↑ CO_{peak} +1.2 L/min[c] ↑ SV_{peak} +7 mL[c] ↑ $LVEF_{peak}$ +1.4%[c] ↑ $RVEF_{peak}$ +2.3%[c] 52 wk follow-up ↓ $LVEF_{rest}$ –2.2%[c] ↓ GLS_{rest} +1.0%[c] ↑ CO_{peak} +1.6 L/min[c] ↑ SV_{peak} +8 mL[c] ↑ $RVEF_{peak}$ +1.8%[c] ↔ $LVEF_{peak}$ –0.7% NS	Post-chemo ↔ $LVEF_{rest}$ –0.8% NS ↔ GLS_{rest} +0.4% NS ↑ CO_{peak} +2.2 L/min ↑ SV_{peak} +16 mL ↑ $LVEF_{peak}$ +5.6% ↑ $RVEF_{peak}$ +5.8% 52 wk follow-up ↔ $LVEF_{rest}$ –0.9% NS ↔ GLS_{rest} +0.4% NS ↑ CO_{peak} +2.9 L/min ↑ SV_{peak} +17 mL ↑ $LVEF_{peak}$ +6.1% ↑ $RVEF_{peak}$ +6.3%
Kirkham et al (2023)[46]	RCT	N = 74	53 ± 10	AC (69%) HER2 therapy (30%)	2 sessions/wk MCT (2/wk): 10-60 min at 60-90% HR_{peak} RT (2/wk): 2 sets, 10-15 repetitions, RPE 3-8/10	52 wk during and after AC and/or HER2 therapy	70%[b]	24 wk F/U ↓ –2.2 mL/kg/min[c] 52 wk F/U ↔ +0.7 mL/kg/min NS	24 wk F/U ↔ –0.5 mL/kg/min NS 52 wk F/U ↔ +0.5 mL/kg/min NS	24 wk F/U ↔ $LVEF_{rest}$ –2.0% NS ↔ GLS_{rest} –0.1% NS 52 wk F/U ↔ $LVEF_{rest}$ –1.0% NS ↔ GLS_{rest} –0.5% NS	24 wk F/U ↔ $LVEF_{rest}$ +0% NS ↔ GLS_{rest} –0.3% NS 52 wk F/U ↔ $LVEF_{rest}$ +1.0% NS ↔ GLS_{rest} –0.3% NS
Howden et al (2019)[20]	NRCT	N = 28	42 ± 9	AC (100%)	2 sessions/wk HIIT (2/wk): 4 × 4 min at 70% PPO, 2 min at 55% PPO RT (2/wk): 3 sets, 12 repetitions at 70% 1RM	8-12 wk during AC	76%[b]	Post-chemo ↓ –1.4 mL/kg/min[c]	Post-chemo ↑ +2.0 mL/kg/min[c]	Post-chemo ↓ $LVEF_{rest}$ –3.5%[c] ↔ GLS_{rest} +0.1% NS ↔ CO_{peak} +0.1 L/min NS ↔ SV_{peak} +0 mL NS ↔ $LVEF_{peak}$ NR ↔ $RVEF_{peak}$ NR	Post-chemo ↔ $LVEF_{rest}$ +0.2% NS ↔ GLS_{rest} +0.8% NS ↔ CO_{peak} +0.3 L/min NS ↔ SV_{peak} +3 mL NS ↔ $LVEF_{peak}$ NR ↔ $RVEF_{peak}$ NR
Haykowsky et al (2009)[41]	Single arm	N = 17	53 ± 7	HER2 therapy (100%) Prior-AC (53%)	3 sessions/wk MCT: 30-60 min at HR corresponding to 60-90% $\dot{V}O_{2peak}$	4 mo	59%[b]	4 mo F/U ↔ +1.9 mL/kg/min NS	NA	4 mo F/U ↓ $LVEF_{rest}$ –5.0%[c] ↔ $LVEF_{Dobutamine}$ –3.0%	NA

Abbreviations: AC, anthracycline-based chemotherapy; BC, breast cancer; CO_{peak}, peak exercise cardiac output; CTx, cardiotoxic therapy; ExT, exercise training; F/U, follow-up; GLS_{rest}, resting global longitudinal strain; HER2, human epidermal growth factor receptor 2; HIIT, high-intensity interval training; HR, heart rate; HR_{peak}, peak exercise heart rate; $LVEF_{Dobutamine}$, $LVEF_{peak}$, $LVEF_{rest}$, left ventricular ejection fraction dobutamine stress, peak exercise, or at rest, respectively; MCT, moderate-intensity continuous training; NA, not applicable; NR, not reported; NRCT, nonrandomized controlled trial; NS, not statistically significant; 1RM, 1 repetition maximum; PO, power output; PPO, peak power output; RCP, respiratory compensation point; RCT, randomized controlled trial; RPE, rating of perceived exertion; RT, resistance training; $RVEF_{peak}$, peak exercise right ventricular ejection fraction; SV_{peak}, peak exercise stroke volume; $\dot{V}O_{2peak}$, peak oxygen uptake; VT, ventilatory threshold.

[a]Data are mean Δ, mean ± SD, or median (IQR).

[b]Assessed from number of sessions attended versus prescribed.

[c]$P < .05$ vs baseline or control.

[d]Assessed from percentage of exercise volume completed versus prescribed.

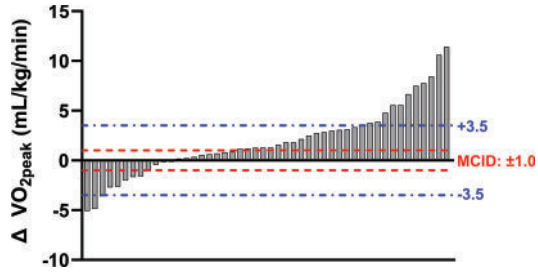

Figure 1. Individual changes in $\dot{V}O_{2peak}$ from pre-anthracycline-based chemotherapy to 12 mo in breast cancer survivors undergoing structured exercise training as part of the BReast cancer EXercise InTervention study.[19] MCID was classified as those who exceeded 1.0 mL/kg/min based on the study by Imboden et al[17] (dashed red line). Super responders were those who exceeded a 3.5 mL/kg/min (1 MET) increase from baseline (dashed blue line). Abbreviations: MCID, minimal clinically important difference; $\dot{V}O_{2peak}$, peak oxygen uptake. This figure is available in color online (www.jcrpjournal.com).

cardiac magnetic resonance imaging.[19] In doing so, we showed that while ExT failed to impact resting LVEF or GLS, it resulted in marked improvement in peak exercise cardiac output and stroke volume, preserved peak exercise LVEF (all of which declined in the control group), and attenuated AC-induced troponin increases.[19] Moreover, we showed that the changes in peak exercise cardiac output were significantly associated with changes in $\dot{V}O_{2peak}$, while changes in resting LVEF were not (Figure 3).[19] This provides the first clear evidence that ExT during cardiotoxic BC therapy has a beneficial impact on cardiac function (when assessed during exertion), and this contributes to improved CRF. However, these findings require further validation, particularly with pragmatic, translational ExT and imaging approaches that could be directly adopted in the clinical setting.

No studies have investigated the effect of ExT on cardiac (dys)function in BCS who have completed therapy. Cardiac dysfunction and HF may not develop until several years following therapy, in which myocardial injury can be harder to address.[10] Therefore, the impact of ExT on cardiac function in older, longer-term BCS is a critical question—particularly as these may be the individuals presenting with more overt forms of cardiac dysfunction and/or functional disability several years post-therapy. Regardless, the BREXIT trial findings reinforce the use of exercise-based measures such as exercise imaging or CRF (ie, $\dot{V}O_{2peak}$) as a central outcome for ExT (and CORE) interventions.[19] Notably, a lack of improvement in resting LVEF or GLS in spite of a clinically meaningful increase in CRF should not be taken as a failure of ExT to address the cardiovascular consequences of BC therapy.

EXT, PHYSICAL ACTIVITY, AND CARDIOVASCULAR MORBIDITY

Exercise-based CR has been associated with substantial benefits for CRF and clinical outcomes in individuals with CVD.[14] However, the impact of ExT on clinical outcomes such as HF incidence and CVD events in BCS has not been established. Several observational studies of BCS have now linked increased physical activity (PA) to reduced risk of cardiac dysfunction. For example, BCS who self-reported insufficient PA (determined by PA guidelines[49]) experienced subsequent deterioration in LVEF and left ventricular circumferential strain, which remained stable in BCS reporting sufficient PA.[50] In another study of BCS ~9 yr post-therapy, those who self-reported >3.5 hr/wk or >7 hr/wk of moderate-intensity PA had a 45% and 49% lower risk of having abnormal GLS (GLS ≤18%) than BCS classified as sedentary.[51] The benefits of PA in BCS may also extend to improved HF risk and CVD mortality. Breast cancer survivors who reported pre- or post-diagnosis PA levels consistent with the PA guidelines[49,52] (>8.6-9 MET hr/wk) have a 10-23% lower risk of future CVD events and a 36-44% lower risk of CVD mortality than those who were below this threshold.[53,54] The low incidence and/or long duration required to experience adverse CVD outcomes following BC therapy makes assessing the impact of ExT with a traditional RCT design difficult. Consequently, growing adoption and implementation of ExT rehabilitation within the clinical setting (such as CORE) may be an important driver of the evidence base to assess the impact of ExT on long-term CVD outcomes in BCS.

FROM CR TO CORE: ADAPTING EXERCISE PRESCRIPTION FOR BCS

Because of the paucity of high-quality studies, there are no evidence-based exercise prescription guidelines for addressing cardiotoxicity (and reduced CRF) in BCS or other cancer populations. Exercise prescription recommendations

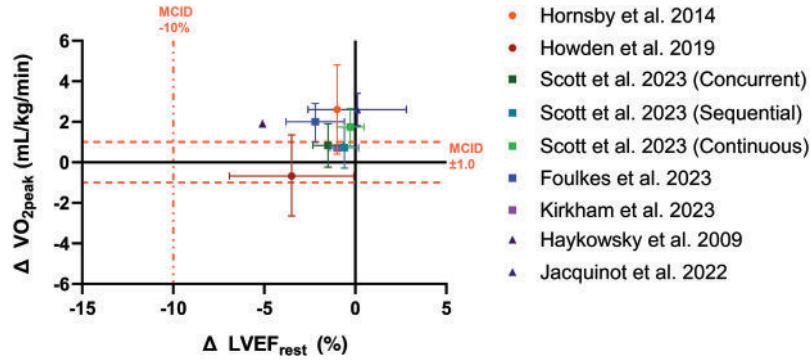

Figure 2. Comparison of within-group changes in resting $LVEF_{rest}$ and $\dot{V}O_{2peak}$ pre- and post-exercise training in breast cancer survivors (BCS) undergoing treatment with anthracycline-based chemotherapy (AC) and/or human epidermal growth factor receptor 2 (HER2)-targeted therapy. Symbols are mean and error bars represent 95% CI (when available) with dashed red lines corresponding to MCID for $\dot{V}O_{2peak}$[17,42] and $LVEF_{rest}$.[10] Circles represent studies with post-assessment completed <4 wk following AC; squares represent studies with follow-up assessment completed ≥4 wk following AC; and triangles represent studies assessing BCS undergoing HER2-targeted therapy only. Abbreviations: $LVEF_{rest}$, left ventricular ejection fraction at rest; MCID, minimal clinically important difference; $\dot{V}O_{2peak}$, peak oxygen uptake. This figure is available in color online (www.jcrpjournal.com).

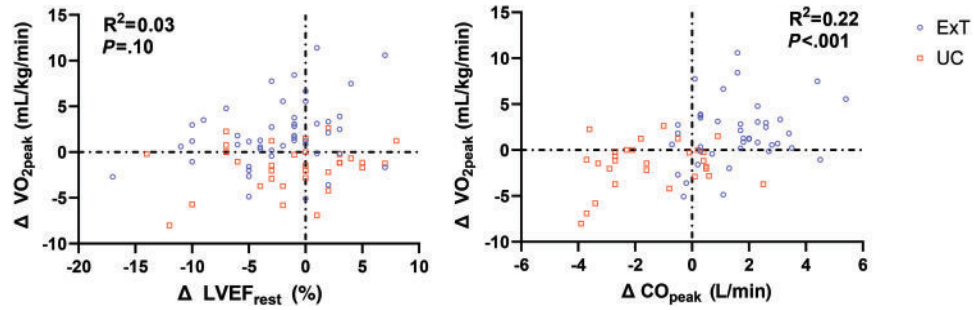

Figure 3. Association between pre–anthracycline-based chemotherapy to 12-mo changes in $\dot{V}O_{2peak}$ with resting $LVEF_{rest}$ and CO_{peak} from BREXIT study.[19] Abbreviations: CO_{peak}, peak cardiac output; ExT, exercise training; $LVEF_{rest}$, left ventricular ejection fraction at rest; UC, usual care; $\dot{V}O_{2peak}$, peak oxygen uptake. This figure is available in color online (www.jcrpjournal.com).

outlined by the American Heart Association's position statement on CORE[11] are largely extrapolated from the American College of Sports Medicine exercise guidelines for improving physical function in cancer survivors[49] (summarized in Table 2). However, the impact of this CORE-based model on key outcomes such as CRF and cardiac function in BCS is a matter of ongoing investigation.[46,47,55] In a pragmatic RCT, Kirkham et al[46] investigated the impact of a 52-wk multidisciplinary CORE-based intervention in BCS scheduled for AC and/or HER2 therapy. The intervention consisted of CVD risk assessment, individualized nutrition support, and 2 sessions/wk of group-based ExT consisting of MCT + RT (with additional recommendation to complete home-based MCT).[46] There was no effect of CORE on cardiotoxicity (which did not occur in either group), nor on the deleterious changes in resting cardiac function and $\dot{V}O_{2peak}$ during BC therapy.[46] Rather than inferring CORE is ineffective in BCS, these findings suggest that a more intensive ExT/CORE approach may be required to elicit clinical benefit. In support of this notion, Kerrigan et al[47] showed that 10 wk of CORE incorporating 2-3 sessions/wk of HIIT resulted in significant benefits for $\dot{V}O_{2peak}$ (but not GLS) in 29 female cancer survivors (n = 29, 97% BCS) presenting with subclinical cardiotoxicity during AC and/or anti-HER2 therapy. Indeed, BCS experience fluctuating and repeated insults from bouts of treatment (eg, oxidative stress, inflammation, ovarian suppression) and treatment-related side effects (eg, fatigue, nausea, headaches) that alter the typical rehabilitation trajectory and necessitate adaptations from traditional ExT models used in CR, such as increased intensity or adaptive program designs. Therefore, the following sections will provide an overview of potential adaptations based on previous studies and our experience from the BREXIT trial one can consider when adopting traditional CR exercise prescription models to CORE models in BCS.

TIMING: IMPACT OF EXT DURING VERSUS AFTER THERAPY

The current view of AC-mediated cardiotoxicity is that a certain degree of myocardial injury is irreversible.[10] This provides a compelling rationale for primary prevention with ExT *during* AC. Both Scott et al[39] and van der Schoot et al[38] compared the effects of ExT commenced during versus after AC on $\dot{V}O_{2peak}$. Consistent with previous studies, van der Schoot et al[38] reported ExT during therapy attenuated declines in $\dot{V}O_{2peak}$, while Scott et al[39] reported no effect. The lack of effect seen with Scott et al[39] may be due to the high number of patients undergoing dose-dense AC (one cycle every 2 wk instead of every 3 wk), which results in more profound acute side effects, including fatigue and anemia. Indeed, findings from the BREXIT study[19] showed that AC markedly blunts the acute effects of ExT on $\dot{V}O_{2peak}$ (Figure 4). Importantly, both studies[38,39] found that ExT after AC improves $\dot{V}O_{2peak}$ such that the long-term trajectory from diagnosis to the end of therapy was comparable regardless of when it was performed. This has important implications for rehabilitation professionals as it highlights that ExT could be implemented as a rehabilitation strategy following the completion of therapy when acute side effects may be less and ExT feasibility may be higher. However, it is unclear whether the comparable trajectory for $\dot{V}O_{2peak}$ seen

Table 2

FITT Exercise Prescription Guidelines Adapted From the American College of Sports Medicine for Improving Physical Function in Cancer Survivors[49]

Type	Frequency	Intensity	Time or Sets/Reps	Program Length
Aerobic only	3 d/wk	60-85% HR_{max} 60-85% $\dot{V}O_{2max}$ RPE 12-13	30-60 min	8-12 wk
Resistance only	2-3 d/wk	60-75% 1RM RPE 13-15	2 sets 8-12 reps	8-12 wk
Aerobic + resistance	3 d/wk	60-85% HR_{max} 60-85% $\dot{V}O_{2max}$ RPE 12-13 60-75% 1RM RPE 13-15	20-40 min 2 sets 8-12 reps	8-12 wk

Abbreviations: HR_{max}, maximal heart rate; 1RM, 1 repetition maximum; FITT, frequency, intensity, time and type; RPE, rating of perceived exertion; $\dot{V}O_{2max}$, maximal oxygen uptake.

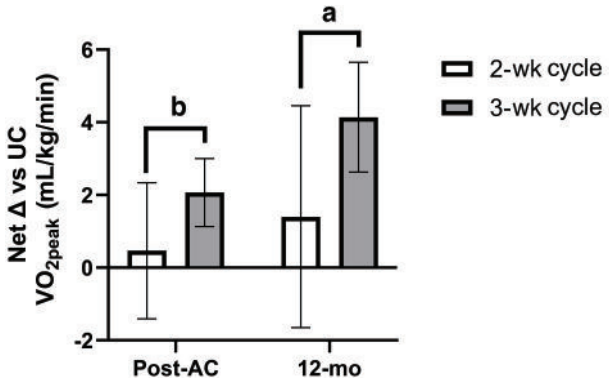

Figure 4. Impact of AC dosing schedule (2-wk vs 3-wk cycle) on exercise training–induced changes in $\dot{V}O_{2peak}$ from BREXIT study.[19] Data are mean and error bars are 95% CI for the net difference in $\dot{V}O_{2peak}$ changes from baseline to post-AC (4 mo) and 12 mo in exercise training participants undergoing 2-wk or 3-wk AC dose schedule. $^{a}P < .05$, $^{b}P < .001$ for difference versus 2-wk cycle. Abbreviations: AC, anthracycline-based chemotherapy; UC, usual care; $\dot{V}O_{2peak}$, peak oxygen uptake.

with these studies[38,39] represents a comparable trajectory for cardiac function and/or cardiac injury.

EXERCISE PRESCRIPTION

The majority of studies investigating the impact of ExT on $\dot{V}O_{2peak}$ during or after therapy have reported beneficial and largely comparable effects with at least 2-4 sessions/wk of MCT, combined MCT + HIIT, MCT + RT, or MCT + HIIT + RT.[34,56] However, meta-analyses of ExT in cancer survivors have shown that exercise dose is a key modifier of $\dot{V}O_{2peak}$ improvement,[56] whereby ~600 intensity min (equivalent to 3 × 30 min sessions at 70% $\dot{V}O_{2peak}$ performed for 10 wk) was necessary for clinically meaningful effects. Similarly, in BCS undergoing chemotherapy (predominantly AC) high-dose MCT (50-60 min/session at 55-75% $\dot{V}O_{2peak}$; equivalent to double the PA recommendations) had the greatest impact on $\dot{V}O_{2peak}$, with similar effects seen with the standard (25-30 min/session at 55-75% $\dot{V}O_{2peak}$; equivalent to PA recommendations[49]) and combined standard MCT + RT approaches (10 exercises, 2 × sets of 10 reps at 60-75% 1 repetition maximum [RM]).[57] However, increasing duration and/or frequency may not always be feasible in the CORE setting—particularly among BCS experiencing significant treatment-related side effects. As such, HIIT may be a time-efficient strategy to achieve an optimal or increased ExT dose. In the OptiTrain study,[58] 16 wk of 2 sessions/wk of HIIT (3 × 3 min cycling at rating of perceived exertion [RPE] 16-18 interspersed with 1-min recovery) supplemented with either MCT (20 min of moderate-intensity cycling) or RT (2-3 sets × 8-12 reps at 70-80% 1RM) during BC therapy resulted in significant improvements in CRF relative to UC. However, the degree to which HIIT-based approaches are superior to MCT-based approaches for addressing CRF and cardiac impairment in BCS remains unclear. Home-based approaches with remote support via telehealth or mobile apps may be a lower cost alternative to increase exercise dose outside of supervised ExT. For example, Murphy et al[59] recently demonstrated that a home-based intervention using a smartphone app focused on CVD risk factor modification and increasing PA resulted in clinically meaningful increase in 6-min walk test distance (+43 m) in BCS undergoing therapy. However, it may not have been sufficiently intense to improve other markers of cardiovascular health. Therefore, it may be that combined approaches (such as the multicomponent HIIT + MCT + RT and step-down models used in BREXIT) allow for greater balance between intervention fidelity, variety, and feasibility for delivery over extended periods.

EXERCISE PERIODIZATION

Standard ExT approaches use a linear progression model that starts with an achievable baseline dose and incorporates small, progressive increases in frequency, intensity, and/or duration over the course of the intervention. In cancer populations there is now growing application of nonlinear periodization models that incorporate multiple types and varying doses of exercise within and across weeks.[60-62] This is a principle adapted from athletic training, where multiple physiologic factors contribute to improved $\dot{V}O_{2peak}$ and should be targeted with different forms of ExT.[61] Similarly, there are multiple pathophysiologic processes mediating BC therapy-induced CRF impairment.[30] Moreover, varied BC treatments and side effect profiles may necessitate a model with greater flexibility to account for these fluctuations. A nonlinear chemotherapy-periodized model that included an anticipatory 10% reduction in ExT intensity during the first week after chemotherapy (when acute symptoms were greatest) resulted in greater session attendance during the week of chemotherapy (77 vs 57%) and overall (78 vs 63%) compared with linear periodization.[60] The BREXIT trial used and adapted this model and had good adherence and efficacy.[19] The BREXIT trial also included additional training modalities such as HIIT, tempo, and long-endurance and recovery sessions with undulations in training stimulus similar to that used by endurance athletes.[19] Meta-analysis of mixed cancer types suggests that nonlinear ExT periodization results in a 1.38 mL/kg/min greater improvement in $\dot{V}O_{2peak}$ than standard linear dosing.[34] However, in AC-treated BCS >1 yr post-therapy, Scott et al[43] showed that a nonlinear periodization model incorporating MCT + HIIT had slightly better adherence than linear periodization, but improvements in $\dot{V}O_{2peak}$ were comparable between the two approaches.[43] As such, there is no consensus on the optimal approach for addressing CRF impairment in BCS, and so ExT periodization should be guided by clinician and patient preference.

ADDITIONAL CONSIDERATIONS BEYOND THE TYPICAL PARTICIPANT IN CR

In addition to chemotherapy periodization, BC-related side effects may necessitate additional adaptations to ExT prescription, delivery, and monitoring. For example, side effects such as anemia and autonomic changes associated with chemotherapy result in resting and exercise tachycardia.[63] Kirkham et al[63] showed that anemia and heart rate (HR) elevation can be particularly pronounced in the second week following chemotherapy and becomes progressively worse with each subsequent cycle of chemotherapy. Consequently, this HR fluctuation can render exercise prescription using the standard percentage of maximal HR approach inaccurate and will result in an underestimation of exercise dose. Therefore, methods such as the RPE or the HR reserve method can overcome this by focusing on either subjective (RPE) intensity or accounting for fluctuations in resting/exercise HR (HR reserve method). Peripheral neuropathy is also common in BCS treated with taxane chemotherapy.[49] This does not preclude and may possibly be improved by ExT, particularly RT ± balance exercise.[64] However, balance and sensation alterations should be considered in exercise selection.[49] Peripherally inserted central

catheters and implanted chemotherapy ports are also common in BCS undergoing therapy. There are no clear evidence-based guidelines on exercising with a peripherally inserted central catheter line or port. However, it is well established that complete avoidance of activity is harmful for many aspects of health, so exercise should be considered on a case-by-case basis in consultation with each individual and their care team.[49] Our experience is that ExT (including upper body RT) can be safely performed 2-wk following peripherally inserted central catheter insertion with adaptations that avoid excessive end range of motion or high impact. Lymphedema is also an important consideration for BCS with lymph node removal and/or radiation.[49] However, ExT (including heavy-load RT: 80-85% 1RM) is not considered detrimental and may help manage or reduce the risk of lymphedema.[65] Moreover, the regular patient contact places the CR professional in an ideal position to identify lymphedema early to ensure prompt management. Arthralgias and myalgias are also commonly experienced by BCS undergoing aromatase inhibitor therapy or with treatment-induced menopause.[66] Similarly, ExT has not been shown to be harmful for this side effect, and there is some evidence that RT or combined MCT + RT can decrease joint-related symptoms.[66]

SUMMARY

Cardiovascular disease and HF are important competing risks for long-term BCS. A growing evidence base is demonstrating ExT is a promising therapy for addressing BC therapy-related CRF and cardiac impairment. Cardio-oncology rehabilitation represents a key pathway to deliver ExT in BCS at risk of CVD; however, further work is needed to understand how best to adapt standard CR ExT approaches to account for the additional challenges imposed by BC therapy.

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