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유방암 환자의 심혈관 건강을 위한 운동 처방

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이 규 완

Clinical Exercise Prescription for Cardiovascular Health in Breast Cancer Survivors

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Conventional treatments accessible to breast cancer survivors after diagnosis include cancer therapies with cardiotoxic effects such as trastuzumab and/or anthracycline-based chemotherapy, which can result in undesirable cardiac injuries known as cancer therapy-induced cardiotoxicity. Cancer therapy-induced cardiotoxicity is among a variety of cardiovascular comorbidities responsible for increased mortality in cancer survivors, and when accompanied by preexisting cardiovascular comorbidities, this detrimental side effect becomes a major health concern. Breast cancer survivors may be predisposed to this additional concern due to preexisting comorbidities related to cardiovascular diseases such as obesity, hypertension, and type 2 diabetes. Research in the rapidly emerging field of study which focuses on improving cardiovascular health in cancer survivors, known as cardio-oncology, reveals that exercise can improve the aforementioned comorbidities in clinical settings. However, the evidence has not been comprehensively evaluated to prescribe exercise as a clinical therapeutic option to improve cardiovascular health in breast cancer survivors. Therefore, the purpose of this review is to summarize the current evidence on the effects of exercise on cardiovascular outcomes in women with breast cancer at three different time points; before, during, and after cancer therapy. In addition, current knowledge gaps and future directions in the field of exercise science and cardio-oncology will be addressed.

Keywords: Cardiotoxicity, Exercise, Breast cancer

Introduction

The 5-year survival rate for breast cancer has significantly increased over the last two to three decades in multiple countries including Korea[1], Europe[2], and the United States[3]. However, although chemotherapy is essential in improving survival rates for patients with breast cancer[4,5], studies reveal that breast cancer survivors who received anthracycline-based chemotherapy have been identified with heart disease, referred to as cardiomyopathy, up to 4 to 20 years after the completion of chemotherapy[6,7], contributing to a higher risk for cardiovascular disease (CVD)

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compared to non-cancer controls[8-10]. These disadvantageous elements can be furthered supplemented by the fact that adverse effects caused by cancer therapies, accompanied by preexisting comorbidities such as obesity[11], hypertension[12], and type 2 diabetes[13], increase the risk of developing CVD in breast cancer survivors as well[14,15].

Exercise is a non-pharmacological approach implemented to strengthen the heart, and, thus, improve cardiovascular function, which can mitigate the deleterious effects of CVD. One well-known strategy to reduce the risk of developing CVD is participating in a regular exercise program that includes aerobic[16], resistance[17], or combined aerobic+resistance exercise[18]. These training regimens can be delivered as a hospital-based intervention[19], a home-based intervention[20], or a community-based intervention[21]. Exercise can subsequently be a desirable method to alleviate the burden of pharmaceutical therapies experienced by breast cancer survivors by improving cardiovascular health. Research has shown that exercise is a safe and cost-effective strategy to target cardiovascular outcomes (i.e., cardiorespiratory fitness and vascular function) in breast cancer survivors[22]. Specifically, higher levels of exercise participation after breast cancer diagnosis have been reported to be associated with lower risks of breast cancer-specific death and all-cause mortality[23]. This evidence supports the need to incorporate this intervention strategy into cancer treatment and care, but limited research may pose a barrier. Guidelines of the American College of Sports Medicine presently lack a specific exercise prescription for cardiotoxicity and/or CVD experienced in cancer survivors[24], and this may be due to a paucity of evidence on cardiovascular benefits in this population. Furthermore, the role of clinical exercise interventions in the context of cardio-vascular health, particularly based on breast cancer care time points (i.e. before, during, and after cancer therapy), have not been thoroughly discussed within the literature.

This review will summarize the current evidence for the effects of exercise interventions on cardiovascular outcomes in women with breast cancer at three different time points; before, during, and after cancer therapy. Current knowledge gaps and future directions in the field of exercise science and cardio-oncology will also be addressed. For the purpose of this review, pilot feasibility studies will be minimally covered, and multimodal lifestyle intervention studies, such as exercise+diet interventions or preclinical studies, will not be discussed.

Exercise *before* breast cancer therapy

Cancer prehabilitation is a relatively new area of research. One component of this form of preoperative rehabilitation involves structuring an exercise program before initiating cancer therapy. Physically preconditioning cancer patients before surgery can optimize health status, which can, in turn, minimize any potential negative health outcomes experienced post-surgery such as cardiovascular, psychosocial, and cognitive dysfunction[25]. Evidently, performing exercise training before initiating breast cancer therapy has already been documented to be feasible in both a home-based setting[26] and a hospital-based setting[27]. Within the literature of breast cancer prehabilitation, previous studies—which were conducted as pilot studies—explored potential improvements in patient-reported outcomes (e.g., physical function, fatigue, range of motion, and quality of life) and mainly addressed the feasibility of implementing exercise before breast cancer surgery[28].

Only one study has reported cardiovascular-related outcomes before cancer therapy for this patient population. Brahmbhatt et al.[26] conducted a longitudinal, single-arm, mixed-methods study (n=22) to investigate the feasibility of a home-based individualized exercise intervention in women prior to breast cancer surgery and demonstrated recruitment, adherence, attrition, and intervention-related adverse event rates which suggested that prehabilitation is feasible in woman undergoing breast cancer surgery (Table 1). In addition, the study explored the efficacy of the prehabilitation program by evaluating outcome measures in the 6-minute walk test, upper body strength and mobility measurements, volumetric chances associated with lymphedema, and participant-reported quality of life, fatigue, pain, and disability. Exercise prescription was designed and delivered by a registered kinesiologist for each patients' duration of surgical wait time (7–69 days) and included both aerobic (brisk walking) and resistance exercise (standing rows, shoulder external rotation, front raise, lateral raise, biceps curls, triceps extension, wall push-ups, and chest press) at 3–5 days per week for 30–40 minutes per session and 2–3 days per week, respectively[26]. Study participants reported high satisfaction with the exercise intervention on the qualitative assessment (interviews and questionnaires). Regarding the cardiovascular

Table 1. Clinical exercise prescription and cardiovascular health in breast cancer

Study	Year	Sample (n) and design	Intervention	Adherence (%)	Cardiovascular outcomes	Treatment window
Brahmbhatt et al.[26]	2020	22 Pilot Hospital-based	31 days, brisk walking 3−5 days/wk for 30−40 min/session, and 2−3 sets of 10−12 repetitions/exercise, (standing rows, shoulder external rotation, front raise, lateral raise, bicep curls, triceps extensions, wall push-ups, and chest press) training 2-3 days/wk	76	Increased in the 6-min walk distance (+57 m)	Before therapy
MacVicar et al.[32]	1989	45 RCT Hospital-based	10 wk, aerobic interval training, cycle ergometer, 3 days/wk	NA	Increased in VO_2peak	During therapy
Segal et al.[33]	2001	123 RCT Hospital-based	26 wk, aerobic exercise: 3 days/wk, 7−10 min warm-up, walking and cool-down, 2 additional days self-directed exercise at home	71.5	Increased in VO_2peak (+3.5 mL/kg/min)	During therapy
Courneya et al.[17]	2007	242 RCT Hospital-based	17 wk, aerobic exercise: 3 days/wk, cycle ergometer, treadmill, or elliptical, beginning at 60% of their VO_2max (wk 1 to 6) and progressing to 70% (wk 7 to 12) and 80% beyond wk 12.	70.2	Increased in VO_2peak (+0.5 mL/kg/min)	During therapy
Jones et al.[34]	2013	20 RCT Hospital-based	12 wk, aerobic exercise: cycle ergometry, 3 days/wk at 60%−100% of VO_2peak, 30−45 min/session	66	Increased in VO_2peak (+2.6 mL/kg/min) and FMD (+0.7%)	During therapy
Travier et al.[35]	2015	204 RCT Hospital-based	18 wk, aerobic exercise: interval training of alternating intensity performed with a heart rate at (3×2 min increasing to 2×7 min) or below (3×4 min decreasing to 1×7 min) ventilatory threshold, based on heart rate and the Borg scale. Strength training: arms, legs, shoulder, and trunk. 2×10 repetitions (65% one-repetition maximum) and gradually increased to reach 1×10 repetitions	83	No changes in VO_2peak and peak power output	During therapy
Hojan et al.[36]	2020	47 RCT Hospital-based	9 wk, aerobic exercise: brisk walking, running on a treadmill, and cycling, 5 days/wk, 80% age-predicted maximum heart rate. Resistance exercise sessions based on isometric, concentric, and eccentric training consisted of one to 3 sets of 8-10 repetitions of selected exercises in different positions for the trunk, upper body, and leg muscles	98.7	No changes in left ventricular ejection fraction and 6-min walk distance	During therapy

Table 1. Continued

Study	Year	Sample (n) and design	Intervention	Adherence (%)	Cardiovascular outcomes	Treatment window
Lee et al.[31]	2019	30 RCT Hospital-based	8 wk, aerobic exercise: HIIT (1:2 ratio) on a cycle, 90% peak power output 3 days/wk, 30 min/session	82.3	Maintained VO_2peak while control group reduced by 10%; significant change in FMD	During therapy
Mijwel et al.[37]	2018	240 RCT Hospital-based	16 wk, aerobic exercise: HIIT, 13−15 Borg scale, 2 days/wk. Resistance exercise: 2−3 sets of 8−12 repetitions at an intensity of 80% of the patients' estimated 1-repetition maximum	63−68	Maintained VO_2peak	During therapy
Schulz et al.[38]	2018	26 RCT	6 wk, combined HIIT and strength training	NA	VO_2peak+2%	During therapy
Schneider et al.[39]	2007	113 Hospital-based	6 mo, 2−3 days/wk 60 min/session 10-min warm-up, 40-min aerobic (outdoor or treadmill walking, stationary cycling, stepping or walking), resistance exercise and stretching, 40%−75% of heart rate reserve	89.6	Improved systolic blood pressure and time on treadmill during therapy. Increased in pulmonary function and VO_2max after therapy	During or after therapy
Courneya et al.[16]	2003	53 RCT Hospital-based	15-wk, cycle ergometers 3 days/wk for at a power output that elicited the ventilatory equivalent for carbon dioxide	98.4	Increased in VO_2peak (+0.24 L/min)	After therapy
Lee et al.[18]	2019	100 RCT Hospital-based	16 wk, 3 days/wk aerobic (treadmill, cycle) and resistance exercise (leg press, leg flexions/extensions/ chest press, seated rows, biceps curls, triceps pulldown) at 60%−80% 1-repetition maximum	96	Reduced Framingham Risk Score (12% to 2%)	After therapy
Zvinovski et al.[44]	2021	25 Pilot Hospital-based	14 wk, 60 min/session, 3 days/wk and for a minimum total of 36 sessions. 60%−85% of their VO_2max	60	Increased in VO_2peak (+0.5 mL/kg/min) and decreased in systolic blood pressure, heart rate, total cholesterol, LDL cholesterol, and fasting glucose	After therapy
Toohey et al.[45]	2020	17 RCT Hospital-based	12 wk, HIIT at max effort, gradual increase from 4×30 sec/session to 7×30 sec/session, 3 sessions/wk. 12 wk, continuous aerobic training, 20 min/session, 55%−65% of max power, 3 sessions/wk at moderate intensity	78.7	Increased in VO_2peak (19.3%) in the HIIT group	After therapy

RCT: randomized controlled trial, VO_2peak: peak oxygen uptake, VO_2max, maximal oxygen uptake; FMD: flow-mediated dilation; HIIT: high-intensity interval training, LDL: low-density lipoprotein.

outcomes, there was a statistically significant increase in the distance participants walked within the 6-minute walk test for baseline compared to the preoperative assessment (57 m; 95% CI, −7.52 to 121.7).

Currently, exercise training is encouraged for other clinical reasons, such as psychosocial outcomes, given the support found within the literature, but convincing evidence is still needed to clinically recommend exercise training as a therapeutic option that can prevent future CVD and/or cancer therapy-induced cardiotoxicity among cancer populations accordingly. Since the primary endpoint of this study was not focused on cardiac, vascular, or pulmonary function, the information is prodigiously limited on this topic and insufficient to formulate exercise recommendations aimed at preventing future CVD in breast cancer survivors altogether. Furthermore, no strong comprehensive evidence can be provided from the study to ascertain the short and long-term effects of exercise on cardiovascular-related outcomes in individuals with breast cancer. It can be argued that further research may presumably find prehabilitation to be ineffective at improving cardiovascular function when performed before cancer therapy given the short number of days available for the exercise training (7−69 days[26]), but this idea still needs to be scientifically confirmed versus simply assumed.

Exercise *during* breast cancer therapy

The feasibility of implementing an exercise intervention during breast cancer therapy has been demonstrated in a home-based setting[29,30], a hospital-based setting[31], and a community-based setting[21], and subsequently, there is evidence suggesting that exercise interventions can improve cardiovascular outcomes in breast cancer survivors undergoing chemotherapy. MacVicar et al.[32] and Segal et al.[33] utilized aerobic exercise interventions in breast cancer patients undergoing various chemotherapy regimens, and both reported improvements in aerobic capacity for patients who completed the exercise interventions; unfortunately, specific study information from these two studies are not publicly available. A later randomized controlled trial (n=242) conducted by Courneya et al.[17] compared aerobic exercise (up to 45 minutes/session, three sessions/week of cycle ergometer, treadmill, or elliptical at up to 60%−80% peak oxygen uptake [VO_2peak], for duration of chemotherapy, 9−24 weeks), resistance exercise (three sessions/week for two sets of 8−12 repetitions at 60%−70% of estimated one-repetition maximum for leg extension, leg curl, leg press, calf raises, chest press, seated row, triceps extension, biceps curls, and modified curl-ups, for duration of chemotherapy, 9−24 weeks), and usual care interventions among women receiving breast cancer chemotherapy. The researchers showed significant differences in peak oxygen consumption (VO_2peak) and chemotherapy completion rates, and, notably, found that exercise did not cause any serious adverse events. Specifically, VO_2peak was superior in the aerobic exercise group in comparison to the resistance exercise group (p=0.014), and resistance exercise was associated with a significant increase in chemotherapy completion rates overall (89.8% in the resistance exercise group vs. 84.1% in usual care group)[17]. To add further evidence, Jones et al.[34] implemented a pilot study (n=20) aimed at exploring the effects of aerobic exercise training in combination with neoadjuvant doxorubicin-cyclophosphamide relative to using only neoadjuvant doxorubicin-cyclophosphamide in women with early breast cancer and revealed findings which suggest that aerobic exercise training (45 minutes/session, three sessions/week of cycle ergometer at up to 60%−100% VO_2peak, for 12 weeks) can elicit an increase in VO_2peak as well as vascular endothelial function, as assessed by flow-mediated dilation, after a 12-week aerobic exercise intervention.

In contrast, Travier et al.[35] conducted a randomized controlled trial (n=204) which compared a combined aerobic and resistance exercise program to usual care among breast cancer patients receiving chemotherapy and reported no significant differences in VO_2peak between the two groups. The results evidently did not show a significant change in VO_2peak following a combined aerobic (3×2 minutes increasing to 2×7 minutes at ventilatory threshold or 3×4 minutes decreasing to 1×7 minutes below ventilatory threshold) and resistance exercise (25 minutes/session, two sessions/week for one to two sets of 10−20 repetitions at 45% to 75% of estimated one-repetition maximum which was dependent on the week of intervention) training regimen comprised of two supervised 60-minute exercise sessions per week for a total of 18 weeks. These findings can support the notion that exercise prescription for patients during cancer therapy consists of many more major components than simply just exercise type (i.e. aerobic exercise, resistance exercise, or combined aerobic+

resistance exercise) alone, and each of these fundamental principles needs to be properly addressed within studies in order to effectively facilitate improvements in cardiovascular outcomes such as VO_2peak. In most of the literature regarding exercise training during breast cancer therapy, previous studies focus on aerobic capacity, as assessed by VO_2peak, without a direct observation on the cardiac, pulmonary, or vascular systems via clinical imaging modalities such as ultrasound or magnetic resonance imaging. One study (n=46) by Hojan et al.[36] utilized echocardiogram in addition to the 6-minute walk test to determine the effects of exercise on cardiac function in breast cancer survivors undergoing trastuzumab chemotherapy and found no significant changes in cardiac function, as evaluated by left ventricular ejection fraction (LVEF) and 6-minute walk distance, after a 9-week aerobic exercise intervention (45–50 minutes/session, five sessions/week at up to 80% maximum heart rate each session). Subsequently, additional studies which thoroughly further examine all integral components and procedures of cardiac function are necessary to collectively determine the optimal frequency, intensity, and duration for improving cardiovascular outcomes as well as cancer-related outcomes in breast cancer survivors.

Recently, studies have investigated the on/off interval exercise strategy, known as high-intensity interval training (HIIT), under various testing methodologies during breast cancer therapy and revealed improvements in cardiovascular outcomes (i.e., VO_2peak and vascular endothelial function). For example, Lee et al.[31] prescribed HIIT (19 minutes/session, three sessions/week, for 8 weeks) using cycle ergometer based on each participant's individual peak power output and reported a maintenance of maximal oxygen uptake (VO_2max) in the exercise group ($p=0.94$) versus a decline in VO_2max seen within the control group ($p=0.001$), whereas Mijwel et al.[37] prescribed HIIT (11 minutes/session, two sessions/week, for 16 weeks) using cycle ergometer based on the Borg Rating of Perceived Exertion scale (6–20 scale, targeted range of 16–18) and, similarly, found that VO_2peak remained unchanged after the intervention in the two exercise groups (effect size=0.41 and 0.42) compared to the decline shown in the controls. Moreover, a study conducted by Schulz et al.[38] also utilized a cycle ergometer and prescribed HIIT (19 minutes/session, two sessions/week, for 6 weeks) and documented improvements in VO_2peak (mean change of VO_2peak=12.0%±13.0%), but exercise intensity was based on peak oxygen consumption (VO_2peak of 85%–100%). All of these studies involved HIIT in women with breast cancer during cancer therapy and showed the benefits of exercise on cardiopulmonary fitness, but it is important to note that each study utilized a different exercise prescription (i.e., 7×1-minute bouts vs. 3×3-minute bouts vs. 10×1-minute bouts) and frequency (two sessions/week vs. three sessions/week) for the exercise interventions.

The variability in the HIIT exercise prescriptions used to elicit improvements in cardiovascular outcomes among breast cancer patients undergoing chemotherapy can ultimately be advantageous or disadvantageous by offering flexibility or ambiguity, respectively. Potential advantages may include more exercise options that accommodate schedules and lifestyles for both healthcare professionals and patients to choose from when selecting an appropriate exercise program. Conversely, the disadvantage pertains to how the optimal type, timing, and intensity of the exercise intervention used to prescribe HIIT remains unknown in breast cancer patients undergoing cancer therapies because of the difficulty experienced in precisely distinguishing which exercise strategy optimally improves cardiovascular outcomes in these patients. For instance, if performing HIIT for two sessions per week produces a similar cardiovascular benefit as performing HIIT for three sessions per week, it would clearly be unnecessary to prescribe three sessions and, instead, be best to choose two sessions per week; as a result, more time can be allocated to the patients with fewer obligations of performing exercise, and the reduction in the number of exercise sessions can substantially reduce the cost of health care (e.g. exercise trainer, hospital service, and etc.).

It is evident that additional questions may need to precede and be taken into consideration when developing an exercise program during breast cancer therapy. These questions include the following: "does participating in exercise interfere with cancer therapies aimed at reducing tumors? If not, do breast cancer patients really need to push themselves to perform exercise during cancer therapy or is focusing only on their cancer therapy the best approach? Even if the benefits are favorable, if patients can improve cardiovascular health later during survivorship[39], should they still push themselves to exercise during breast cancer therapy or simply focus on the cancer therapy and wait until only after the therapy is finished before participating in exercise?" Consequently, more studies which examine the effects of exercise on tumor-reducing

cancer therapies are necessary in the field of cardio-oncology to adequately determine if exercise compromises the integrity of cancer therapy or not. Additionally, exploring the timing of the exercise intervention is just as paramount as examining the effects of exercise in women with breast cancer since exercise programs may impede cancer therapy or lifestyle during a difficult time in one's life. Lastly, although current evidence may suggest that a combined aerobic+resistance exercise or HIIT program can be beneficial for other clinical diagnoses that are detrimental to one's health, strong evidence is still needed within the literature to clearly demonstrate the efficacy of exercise on cardiotoxicity and preventable CVD risk factors among women with breast cancer.

Exercise *after* breast cancer therapy

Exercise after breast cancer therapy may be the most widely studied area among the three time points (i.e. before, during, and after therapy). Breast cancer survivors during this specific survivorship period have presumably been subjected to an extensive amount of aggressive cancer therapies involving surgery, chemotherapy, and/or radiation therapy and are more likely to initiate an endocrine therapy, such as aromatase inhibitor or tamoxifen, based on their current hormone receptor status. Courneya et al.[16] conducted a randomized controlled trial of aerobic exercise training in postmenopausal breast cancer survivors (n=53), which showed an increase in VO_2peak (17.4%) following 15 weeks of cycle exercise training. Similarly, Schneider et al.[39] reported that exercise elicited benefits in blood pressure and VO_2peak in 113 women with breast cancer post-cancer therapy, although study participants were not hypertensive before exercise participation. It is evident that these studies address the benefits of exercise on cardiopulmonary fitness during the survivorship phase of breast cancer, but their findings cannot be generalized to all breast cancer survivors in the survivorship period. Numerous studies in breast cancer survivors have shown the effects of exercise on health-related outcomes such as quality of life[40], fatigue[41], physical function[42], lymphedema[20], or anxiety[43] and strongly recommend exercise as an effective intervention to improve these health-related outcomes. However, the research focusing on examining the cardiovascular outcomes of exercise training during breast cancer survivorship is still limited, and thus, specific exercise prescriptions that can optimally improve future CVD mortality currently remain unclear.

Recently, Lee et al.[18] demonstrated that combined aerobic+resistance exercise significantly reduced future CVD risk, assessed by the Framingham Risk Score (12%–2%, $p<0.001$), as early as within 6 months of completing breast cancer therapy (n=100). The improved Framingham Risk Score was mainly due to the increases in the levels of high-density lipoprotein cholesterol, reductions in the levels of low-density lipoprotein cholesterol, lower systolic blood pressures, and decreases in the number of patients with type 2 diabetes which were documented following the 16-week exercise intervention. Nevertheless, no direct observations on the cardiovascular system were reported because no clinical imaging modalities, such as ultrasound and cardiac magnetic resonance imaging (CMR), were used. Further, it is unclear whether the reduced Framingham Risk Score can actually decrease future CVD in 10 years. Another study utilized a cardiac rehabilitation model in breast cancer survivors who were between the ages of 30 and 75 years with stages 0–III breast cancer and within 18 months of their respective cancer therapies[44]. Since this study was conducted as a pilot feasibility study (n=25), a conclusive scientific statement on the exercise benefits on cardiovascular function was not achieved. However, results from this study suggests that an existing cardiac rehabilitation program can be utilized in breast cancer survivors and may be consistent at improving cardiovascular function—so as long as an optimal cardiovascular exercise prescription is established.

As stated in section 2, findings on HIIT are significant because they demonstrate potential for uncovering diverse exercise methodologies that can be an alternative or be just as safe and effective as traditional aerobic or resistance exercise alone. In particular, Toohey et al.[45] compared aerobic fitness between groups that performed HIIT (gradual increase from 4–7×30 seconds/session, three sessions/week, max effort, for 12 weeks), continuous aerobic training at moderate intensity (20 minutes/session, three sessions/week, 55%–65% of max power, for 12 weeks), and no exercise training (delayed controls) and found that continuous moderate-intensity exercise did not significantly increase VO_2peak whereas HIIT safely produced a significant improvement in VO_2peak in breast cancer survivors within 2 years post-cancer therapy (n=17)

after 12 weeks of training. The HIIT prescription was notably different from the previously mentioned studies as exercise prescription involved 7×30-second bouts interspersed with a 2-minute active recovery period between each bout of exercise; this offers more insight on additional exercise prescriptions to choose from regarding HIIT and on the fact that not all exercise prescriptions are effective at improving cardiovascular health in this patient population. Currently, the evidence suggests that an exercise program utilizing either combined aerobic+resistance exercise or HIIT can improve cardiovascular health, but the interventions are limited between as early as 6 months and up to 2 years after chemotherapy only. There is no sufficient evidence that can be provided for the effects of exercise on cardiovascular outcomes 2 years post-chemotherapy in breast cancer survivors, where needs more attention because the time window to participate in an exercise intervention "after" breast cancer therapy extends far beyond 2 years since women with breast cancer survive longer and are expected to continue surviving longer than 2 years accordingly. This phase ultimately presents the longest opportunity to improve cardiovascular health in breast cancer survivors, so future studies are warranted to reveal the effects of exercise on cardiovascular health and should specifically target long-term (e.g., >10 years) survivor's cardiovascular function as well as CVD mortality. A hypothetical figure (Fig. 1) of exercise benefits is included below to depict the optimal trends of cardiovascular health in this population.

Current knowledge gaps in the field of exercise and breast cancer

As discussed, multiple studies have examined the effects of exercise on cardiovascular health before, during, and after breast cancer therapy. However, only a few randomized controlled trials have determined the impact of an exercise program on cardiovascular health in these survivors. Previous studies mainly focused on improving physical function, fatigue, and quality of life and employed insufficient exercise durations, short periods of total exercise intervention (<8 weeks), no long-term follow-ups, and/or lack objective outcome measures (i.e. patient-reported outcomes). It is important to emphasize that these studies did not identify patients at risk for developing CVD to appropriately demonstrate the potential benefits of an exercise program on cardiovascular health. As a result, these studies included participants who received any cancer therapies without taking into consideration individual's CVD risk factors. This unspecified inclusion of participants may have inadvertently led to an underestimation of exercise effects, which has consequently hindered the development of optimal exercise programs for breast cancer survivors.

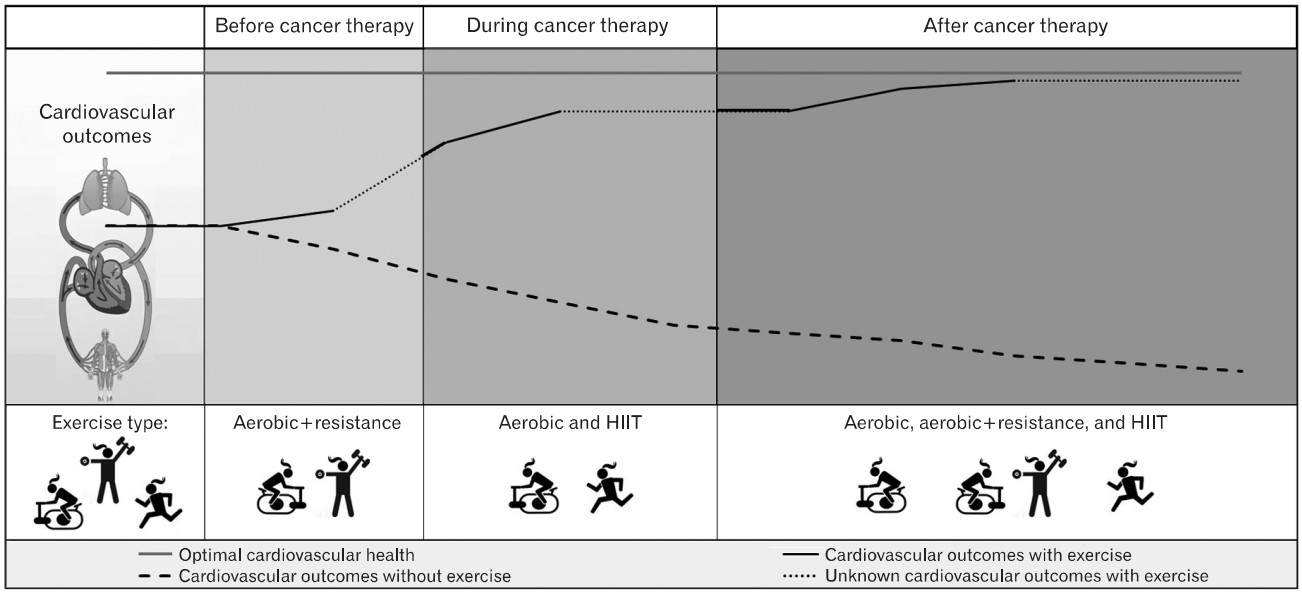

Fig. 1. Hypothetical trends of cardiovascular health with or without exercise before, during, and after breast cancer therapy. HIIT: high-intensity interval training.

It is critical to properly identify and target the survivors at risk of developing CVD and provide them with an effective exercise intervention before serious CVD occurs. Diaz-Balboa et al.[19] recently published their study protocol evaluating the impact of exercise-based cardiac rehabilitation for the prevention of chemotherapy-induced cardiotoxicity in patients with breast cancer. Three hundred and 40 women with breast cancer receiving cardiotoxic chemotherapy are projected to be randomly assigned (1:1) to participate in the study. Primary outcomes are intended to include objective clinical biomarkers such as changes in LVEF and global longitudinal strain as markers of cardiac dysfunction assessed by two-dimensional (2D) echocardiography (echo). Secondary outcomes are expected to investigate levels of cardiovascular blood biomarkers and cardiopulmonary function through VO_2peak as well as physical performance and psychosocial status. This large randomized controlled trial may provide direct evidence on cardiopulmonary fitness and cardiac function as assessed by a conventional imaging method, and their findings may potentially elucidate the preventive effects of exercise on cardiotoxicity in breast cancer survivors.

Future directions with other cardiovascular assessments (Table 2)

Cardiopulmonary exercise testing (CPET) has been widely used in clinical oncology settings to assess VO_2peak, which is an indicator of cardiopulmonary fitness based on maximal O_2 uptake capacity[46-48]. CPET is considered the gold standard for assessing VO_2peak, and the application of such testing has been emphasized in cancer survivors[49]. For example, breast cancer survivors have 27% less VO_2peak, compared to age-matched non-cancer controls[49]. Despite the safety concerns related to CPET, previous studies reported no serious adverse events and only minimal adverse events (2 of 242 breast cancer patients) which had recovered quickly (e.g., lightheaded, hypotensive, nauseous, dizziness, and weakness)[17]. Furthermore, although CPET is a useful tool to identify patient's overall cardiovascular health, therapy-induced changes in VO_2peak still remain poorly defined in women with breast cancer at the three time points of cancer therapy. CPET measures the integral components of cardiopulmonary fitness and represents the integration of multiple organ systems such as cardiac, pulmonary, hematologic, vascular, and muscular systems[50,51]. However, due to the "integration" characteristics, it is difficult to exactly pinpoint which organ systems function properly versus those that do not. Importantly, breast cancer survivors may not be able to reach their true VO_2max due to clinical limitations[52]. In this case, further knowledge gains can be achieved with other variables measured during CPET[53,54] or submaximal exercise[55] test. Pulmonary function tests such as total lung capacity, forced vital capacity, and forced expiratory volume in 1 second are typically performed prior to CPET and may provide further insights. Lastly, other imaging modalities (see below) may supplement this gap as well and could enable the detection of subclinical CVD in breast cancer survivors, which can potentially lead to

Table 2. Future directions for cardiovascular outcome measures in breast cancer

Modality	Outcome variable
CPET	Rate of VO2 at ventilatory threshold, VE/VO_2, VE/VCO_2, volume of oxygen/work rate, and maximum voluntary ventilation
PFT	TLC, FVC, FEV1, FEV1/FVC ratio, DLCO, and DLCO/VA
Echo	LVEF, E/A ratio, isovolumic relaxation time, LVEDD/LVESD, LVPWs, LVPW at end-diastole, and global longitudinal strain
CMR	LVEF, global longitudinal strain, T1 relaxation time, and myocardial extracellular volume
Ultrasound and applanation tonometry	Pulse wave velocity, augmentation pressure, and augmentation index

CPET: cardiopulmonary exercise test, PFT: pulmonary function test, Echo: two-dimensional echocardiography, CMR: cardiac magnetic resonance imaging, VO_2: oxygen consumption, VE/VCO_2: ventilatory equivalent of oxygen, VE/VCO_2: ventilatory equivalent of carbon dioxide, TLC: total lung capacity, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, DLCO: diffusing capacity of the lungs for carbon monoxide, VA: volume of air, LVEF: left ventricular ejection fraction, E/A ratio: peak early atrial velocities divided by peak late atrial velocities, LVEDD: left ventricle end-diastolic dimension, LVESD: left ventricle end-systolic dimension, LVPW: left ventricular posterior wall thickness.

earlier and more accurate exercise interventions for the patients at high risk for overt CVD.

1. 2D Echocardiography

Echo is typically recommended first as the initial assessment on cardiac function in cancer patients due to the inherent advantages of the technique which involve a low-cost, widespread availability, lack of ionizing radiation, and patient's acceptability.[56] While existing cancer supportive care and survivorship guidelines uniformly recommend echo for the diagnosis of cardiotoxicity[3,10-14], the effects of exercise on echocardiographic parameters (i.e. systolic/diastolic function and strain analysis) in breast cancer survivors have been incompletely determined by echo. Along with LVEF, diastolic function measurements such as E/A ratio (peak early atrial velocities divided by peak late atrial velocities) and isovolumic relaxation time can also be measured. Reduction in E/A ratio in the absence of systolic dysfunction is often observed in long-term survivors treated with anthracycline-based chemotherapy[57,58]. However, the effects of exercise on diastolic parameters in breast cancer survivors are not yet known. Other echocardiographic measurements of early left ventricular dysfunction include an increase in end-diastolic/systolic size and a decrease in systolic left ventricular posterior wall thickness[59]. Notably, 2D speckle tracking echo (STE) has emerged as an alternative to tissue Doppler imaging in oncology populations[60,61], allowing for more accurate measurements of regional myocardial systolic performance[62]. Strain is a dimensionless parameter representing global or segmental myocardial deformation, relative to original dimensions within a given systolic frame[58,62]. In non-oncology as well as in oncologic populations at risk for cardiac dysfunction, STE has been successfully used to monitor subclinical disease[63-65]. Unfortunately, there is a paucity of knowledge regarding the utility of echo for evaluating the effects of exercise on cardiac function in breast cancer survivors.

2. Cardiac magnetic resonance imaging

While echo is widely available and relatively less expensive than CMR, an overestimation of LVEF from using echo has been described in other cancer survivors[66]. Compared with CMR, echo has a significantly lower sensitivity and higher false-negative rate when screening patients with LVEF of <50%[66]. CMR is superior to echo for quantification of LVEF with high inter-study reproducibility[67,68]. CMR remains the gold standard for accurate and reproducible quantification of cardiac function. Multiple studies have utilized CMR to precisely assess myocardial structure/function and found significant changes in myocardial extracellular volume[69], right ventricular structure and function[70], and global longitudinal strain[71] among patients treated with cardiotoxic chemotherapies. These approaches can be combined and tailored to determine the effects of exercise on cardiac function in breast cancer survivors. Although clinical implications still rely predominantly on the LVEF, more subtle changes may occur in these imaging biomarkers. However, no exercise intervention studies have been conducted to show the effects of exercise on CMR-measured cardiovascular function in breast cancer survivors in any of the three time points.

3. Pulse wave analysis

Although experts from the American Society of Echocardiography and the European Association of Cardiac Imaging both agree that the guidelines should focus on the performance of the left ventricle of the heart[72], cancer therapy-induced cardiotoxicity has been documented to extend further across the entire "cardiac" and "vascular" systems because the left ventricle and arterial vasculature act as a coupled hemodynamic system[73]. Moreover, anthracycline-related vascular impairment may occur as a result of chemotherapy side effects[74,75]. For example, adult survivors of breast cancer present increased pulse wave velocities that represent aortic and/or arterial stiffness after anthracycline or trastuzumab chemotherapy[76-78]. Increased arterial stiffness is associated with the development of cardiovascular events including atrial fibrillation[79] and stroke[80] in non-cancer populations. Thus, assessment of arterial stiffness is a useful tool for the identification of asymptomatic individuals at high cardiovascular risk. While arterial stiffness is an independent predictor of cardiovascular events, there is a paucity of information on the effects of exercise on the therapy-induced vascular impairments in breast cancer survivors treated with cardiotoxic cancer therapies. With the recent noninvasive techniques such as oscillometry, tonometry, ultrasound, and CMR[81,82], exercise benefits on cancer therapy-induced vascular impairments in breast cancer survivors can be revealed.

Conclusion

The benefits of exercise in breast cancer survivors have been well-described and include eliciting improvements in physical function, body composition, fatigue, quality of life, activities of daily living, emotional well-being, overall health, and disease risk modification[83,84]. However, an optimal exercise prescription has not been established to improve cardiovascular health in breast cancer survivors despite the convincing evidence that breast cancer survivors are at a high risk for clinically significant CVD, which continues to increase over time[49]. Exercise has a great potential to impact CVD risk profiles in breast cancer survivors which may lead to a reduction in cancer therapy-induced cardiotoxicities and comorbidities as a result. Current evidence suggests that participating in an exercise intervention before, during, and after cancer therapy is feasible. However, optimal exercise strategies should be tested at each specific time point to allow for the establishment of exercise guidelines for this population. Lack of randomized controlled trials limits the understanding of optimal exercise prescriptions for women with breast cancer. Addressing this knowledge gap is critical to developing exercise guidelines for cardiac function during cancer survivorship. With scientific advances and additional use of imaging modalities, exercise can prove to be a vital component of the cancer rehabilitation process by optimizing the cardiovascular health of breast cancer survivors.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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