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The effects of exercise on cardiovascular outcomes before, during, and after treatment for breast cancer

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Abstract

Asymptomatic cardiotoxicity following breast cancer treatment is a significant issue for many patients, as these patients typically face an increased risk of cardiovascular disease (CVD). Exercise has well established benefits to improve and maintain cardiovascular function across patients with and without CVD. However, there is a dearth of information on the effects of exercise on cardiovascular outcomes in breast cancer patients. While pre-clinical studies support the use of exercise in mitigating cardiotoxicity, only one human study has specifically investigated cardiac function following an exercise intervention during chemotherapy treatment. No significant differences were observed between groups, which highlights the unidentified role of exercise in altering the risk of cardiotoxicity in breast cancer patients. Issues such as establishing the optimal timing, type, and intensity of an exercise program before, during, or after oncologic treatment for breast cancer are unclear. CVD risk and incidence increase in breast cancer survivors post therapy, and CVD is the number one killer of women in the United States. Thus, there is an increasing need to define the efficacy of exercise as a non-pharmacologic intervention in this growing population.

Keywords

Breast cancer; Anthracyclines; Exercise; Cardiac function; Cardiotoxicity

Introduction

There are over 2.8 million current breast cancer survivors in the United States, and over 230,000 new cases of invasive breast cancer are diagnosed each year [1]. While significant advances in early detection and therapy for breast cancer have improved the 5 year survival rate from 75 % in 1977 to 90 % in the present era, secondary sequelae such as cardiovascular disease (CVD) are increasingly important in cancer survivorship. [2–4] It is well established that cardiotoxicity is a serious side effect of chemotherapy agents such as anthracyclines, taxanes, 5-fluorouracil, cyclophosphamide, and trastuzumab [5–7]. The

pathophysiology of cardiovascular dysfunction in cancer patients may be very different from CVD in individuals that were not provided cancer therapies due to the independent adverse effects cancer therapies have on the cardiovascular system.

Most notably, trastuzumab, anthracyclines, and their combination are well known to induce both asymptomatic subclinical dysfunction and potentially significant cardiomyopathy [8–10]. In a retrospective study of 12,500 patients diagnosed with invasive breast cancer, 20–25 % of patients with breast cancer have tumors that overexpress HER2 and are recommended for trastuzumab therapy. 29.6 % of breast cancer patients received anthracycline-based chemotherapy alone, and 3.5 % received anthracyclines and trastuzumab [11]. After adjusting for age, Charlson comorbidity index, cancer stage, year of diagnosis, and presence or absence of radiation treatment, the cumulative incidence of heart failure and or cardiomyopathy 5 years following treatment was 12.1 % for trastuzumab, 4.3 % for anthracyclines, and 20.1 % for anthracyclines+trastuzumab. Further, a meta-analysis of patients treated with trastuzumab indicates a greater than twofold risk for left ventricular ejection fraction (LVEF) decline [12]. Most women experience no clinical cardiac dysfunction secondary to chemotherapy. Among those who do, most will exhibit Type II chemotherapy-related cardiac dysfunction. That said, not all women who experience chemotherapy-related cardiac dysfunction will experience a reversal of this issue over time. LV dysfunction is worsened with prior anthracycline exposure, and women receiving anthracycline-containing regimens have a fivefold increased risk of developing cardiotoxicity compared to women receiving non-anthracycline-containing regimens (5.4 vs. 0.1 % absolute risk) [8]. Additionally, radiotherapy, a common treatment in breast cancer, is also associated with cardiotoxicity [13].

Breast cancer patients typically suffer from multiple comorbidities such as diabetes, chronic obstructive pulmonary disease, heart disease, arthritis, and/or hypertension. The presence of chronic conditions in breast cancer patients prior to treatment predisposes women to cardiotoxicity and increases the lifetime risk of developing CVD. Long term consequences of subclinical LV dysfunction seen after chemotherapy for breast cancer are not entirely known. However, increased susceptibility to progressive cardiac dysfunction associated with aging and CVD is supported by evidence that breast cancer survivors have an increased risk of heart failure and coronary artery disease (hazard ratio: 1.95 and 1.27, respectively) [14]. In fact, 9 years following breast cancer treatment, survivors are more likely to die of CVD than of breast cancer recurrence [3].

Clinical strategies to alter these adverse cardiac outcomes in response to chemotherapy have been developed, including monitoring of symptoms, serial echocardiograms, and subsequent treatment regimen modifications for chemotherapy dose and/or drug type. Traditional interventions for LV dysfunction such as beta blockers, ACE-inhibitors, angiotensin receptor blockers, diuretics, and nitrates have shown promise [15, 16]. Recently, retrospective analysis of breast cancer patients on uninterrupted statin therapy initiated before and concurrent with anthracycline-based chemotherapy revealed reduced risk for incident heart failure [17]. While these pharmacologic approaches are clinically useful, they have the potential to produce side effects such as excessive hypotension, fatigue, weight gain, nausea, diarrhea, and muscle soreness. Thus, adjunctive therapies are needed to more optimally treat chemotherapy-induced cardiotoxicity.

One potential strategy is exercise training. The American Heart Association has developed general guidelines on cardiovascular health in women [18]. Additionally, the American Cancer Society, with support from the American College of Sports Medicine, has established recommendations for exercise during and after cancer treatment, and these recommendations have recently also been adopted by the National Comprehensive Cancer

Network as well [19, 20]. Exercise has demonstrated effects on cardiovascular reserve, hypertension, high cholesterol, obesity, and overall reductions in mortality in individuals without cancer [21, 22]. However, there is a paucity of studies specifically investigating the effect of exercise on cardiovascular function across the breast cancer continuum, and thus, exercise receives no specific mention in clinical cardio-oncology guidelines [15, 23, 24]. Therefore, this paper summarizes findings from preclinical data providing scientific rationale toward the cardioprotective effects of exercise against cardiotoxicity, exercise intervention studies conducted prior to, during, and after breast cancer therapy and makes suggestions for future studies in women with breast cancer.

Methods

The following databases were searched: Pubmed (1966–2013), Ovid Medline (1948–2013), and the Cochrane Library (1993–2013). A literature search was conducted using the search terms: cardiotoxicity, cardiomyopathy, cardiac function, cardiac dysfunction, cardiovascular, heart rate, blood pressure, exercise, physical activity, exercise training, breast cancer, breast cancer survivors, neoadjuvant, and adjuvant. 265 manuscripts were returned in Pubmed, 350 were returned in Ovid Medline, and 14 were returned in the Cochrane Database of Systemic Reviews. Of these search results, 15 articles in Pubmed, 4 more articles in Ovid Medline, and 1 systemic review in the Cochrane Library were relevant to the population (breast cancer), outcome (cardiovascular), and modality (exercise).

Articles were excluded if the research was not conducted in breast cancer patients prior to treatment, during treatment, or in survivorship. Articles were also excluded if they did not include an exercise intervention or a measurement of cardiovascular function. Additional searching of articles on exercise interventions in breast cancer patients revealed four studies that reported cardiovascular measures as secondary outcomes. Nine studies in total met the inclusion criteria.

Results

Preclinical studies

Exercise interventions in animal models have reported a significant attenuation of anthracycline-induced cardiac injury and have been well reviewed elsewhere [25]. Animal models investigating the mechanisms by which exercise is cardioprotective have been largely conducted using anthracycline-induced cardiotoxicity due to the permanent damage this chemotherapy induces. These pre-clinical studies provide distinct mechanisms by which exercise provides cardiac protection.

Doxorubicin induces apoptosis in part through intrinsic mitochondrial pathways and redox uncoupling [26]. Ascensao et al. [27] observed acute exercise protected against doxorubicin-induced decreases in mitochondrial function through maintenance of cardiac mitochondrial chain complexes I and V. This group also used a moderate endurance training intervention in rats and observed significant mitigation of the doxorubicin-induced changes in mitochondrial state 3 respiration, uncoupled respiration, aconitase activity, and calcium sensitivity [28]. They further observed that training inhibited the doxorubicin-induced increases in mitochondrial protein carbonyl groups and apoptotic protein activity. Work by Kavazis et al. [29] also points to blunting of doxorubicin-induced reactive oxygen species emission from cardiac mitochondria by exercise training.

In another stress response, cardiac protein 53 (p53) expression is enhanced by doxorubicin-induced DNA damage. However, exercise training before treatment can reduce this stress response in part through upregulation of telomere stabilizing protein [30]. Moreover,

exercise training prior to anthracycline treatment has shown significant myocardial tolerance to doxorubicin through decreased rise of plasma cardiac troponin and lowered cardiac carbonyl groups content [31]. The investigators suggest this response may be related to significantly higher levels of glutathione and heat shock protein 60 expression found in the hearts of exercise-trained mice treated with doxorubicin compared to sedentary mice treated with doxorubicin.

Functionally, researchers have observed a significant exercise-induced attenuation of cardiac dysfunction in rats given doxorubicin. Isolated rat hearts obtained from animals perfused over 60 min with doxorubicin steadily declined in left ventricle developed pressure (LVDP), LV-dP/dt, and LV+dP/dt. However, doxorubicin-induced decrements in LV function were attenuated in hearts of rats that voluntarily ran on wheels for 8 weeks prior to treatment [32]. Echocardiographic evaluation also indicated that at 10 days following doxorubicin injections, in exercise-trained animals (10 weeks, wheel running or treadmill running) cardiac function was preserved compared to their sedentary counterparts [33]. Sedentary animals exhibited a 15 % decrease in fractional shortening, while treadmill and wheel running exercise-trained animals had a 3 and 2 % decrease in fractional shortening. Additionally, acute exercise (60 min) 24 h prior to a bolus dose of doxorubicin demonstrated a cardioprotective effect. Rats that performed acute exercise had significantly higher LVDP and LV+dP/dt than sedentary rats 5 days following doxorubicin treatment [34]. These results suggest that exercise training as cardiac pre-habilitation works at both the cellular and functional level to mitigate anthracycline-induced cardiomyopathies. However, more work is needed to examine both metabolic and non-metabolic exercise-induced cardioprotection.

Clinical studies

Primary prevention—exercise before cancer treatment

There are no published reports of clinical exercise interventions prior to chemotherapy treatment in breast cancer patients, and only one currently ongoing clinical trial is investigating exercise as pre-habilitation. Merely one published case study has initiated an exercise intervention prior to treatment. The researchers did observe improvements in functional measures via a program that started 1 week prior to chemotherapy and continued for 8 weeks during treatment [35].

Primary prevention—exercise during cancer treatment

Fitness capacity, or VO_{2max} , is a predictor of anthracycline and trastuzumab-induced left ventricular dysfunction and CVD risk in breast cancer patients. This association has been reviewed previously [36]. VO_{2max} is in part determined by cardiac function, i.e., cardiac output. However, limited data exist on factors relating to cardiac function in conjunction with exercise training and VO_{2max} in breast cancer patients. Haykowsky et al. [37] provide the only published evidence of an exercise training program during chemotherapy treatment that specifically targeted cardiovascular outcomes. Using MRI, they examined cardiac function before and following 4 months of trastuzumab therapy in combination with 4 months of exercise training (3 day/week for 30–60 min at 60–90 % VO_{2max}). They observed a significant decrease in LVEF and significant increases in end diastolic volume (EDV) and end systolic volume (ESV) following the intervention. The authors suggest that the lack of exercise-induced cardio-protection may be due to low adherence (59 %) to the program.

Endothelial dysfunction is an initiating event in CVD, and it is now being recognized that damage to endothelial cells via cytotoxic agents creates a dysfunction that increases risk for CVD [38]. This is relevant to changes in vascular function as well, which has also been shown to be important to determining risk for incident CVD [39]. Vascular function is compromised during treatment with anthracyclines, tyrosine kinase inhibitors, alkylating

agents, anti-metabolites, anti-microtubules, and other biologic agents [40–42]. Table 1 outlines information relating to any reported effects of exercise training on cardiac function (LVEF, LVEDV, LVESV) or cardiovascular variables such as resting heart rate (RHR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) during treatment for breast cancer. In the three studies that report resting HR, SBP, and DBP, before and following an exercise intervention during breast cancer treatment, the change in RHR is -1.6 ± 2.8 bpm, the change in SBP is -4.4 ± 2.0 mmHg, and the change in DBP is -1.3 ± 0.1 mmHg [37, 43–46]. These changes are consistent with a 20 % alteration of risk for cardiovascular events based on the decrease in SBP [47].

Secondary prevention—exercise following treatment

Exercise can be viewed as part of a comprehensive program of cancer rehabilitation. Exercise has known advantages for heart failure, coronary artery disease, dilated cardiomyopathy, and left ventricle hypertrophy [48–50]. However, given the therapy-induced insults to the cardiovascular system of breast cancer patients and the potential for differences in etiology of pathologic cardiac issues, it is unknown if these patients respond to exercise training in the same manner.

While many studies have used an exercise intervention for breast cancer survivors, few studies have investigated the effect of exercise training on cardiac function in breast cancer survivors. Table 2 outlines information relating to any reported effects of exercise training on cardiovascular variables following treatment for breast cancer. Again, it appears that RHR, SBP, and DBP all decreased in breast cancer survivors following an exercise intervention [51–54]. For the 5 studies, the change in RHR is -3.5 ± 1.2 bpm, the change in SBP is -4.6 ± 4.6 mmHg, and the change in DBP is -4.4 ± 3.0 mmHg.

Discussion

Among areas with a paucity of research is the effect of exercise on cardiovascular outcomes in breast cancer patients. This is concerning as CVD is the most common cause of mortality in breast cancer patients that live longer than 9 years following treatment [3]. There has been one case study that initiated an exercise program prior to breast cancer treatment. Jones and Alfano [55] report that currently there is one ongoing 3–6 week exercise training intervention prior to treatment in breast cancer patients. The lack of human research studies at this time point may be due in part to the urgency to initiate curative breast cancer treatment. Neoadjuvant chemotherapy may be initiated quickly following diagnosis. Although in regard to overall survival or disease free survival, there is no difference in neoadjuvant compared to adjuvant chemotherapy [56]. Though the differential value of exercise in relationship to treatment timing is currently unknown, there are windows of opportunity prior to chemotherapy. The diagnosis interval for breast cancer ranges from 23–36 days, and adjuvant chemotherapy may be delayed up to 12 weeks following definitive surgery without significant impact on overall survival or relapse-free survival [57–59].

Reports indicate that breast cancer patients are highly motivated to make lifestyle changes, specifically during the period following diagnosis and before treatment. 38.8 % of breast cancer survivors report they would have preferred receiving exercise counseling before treatment, compared to 18.7 % during treatment, 21.5 % immediately following treatment, and 21.2 % 3 months or more following treatment [60]. Further, in patients with cardiovascular conditions such as hypertension or coronary artery disease, researchers have observed that as little as 4 weeks of exercise training can significantly improve cardiac and vascular function [61, 62].

Many studies have investigated the effects of exercise training during cancer treatments, and there are documented improvements in quality of life, physiologic variables, and psychosocial status [63]. This information is important at the patient level for fatigue, lymphedema, depression, weight management, and other concerns. However, with the incidence of CVD increasing in breast cancer patients, it would be advantageous to investigate the effects of exercise during breast cancer treatment as a modality designed to mitigate cardiotoxicity. There has been only one study which specifically investigated LV function during concurrent exercise and trastuzumab therapy, whereby a lack of effect was seen with exercise [37].

Exercise may operate as secondary prevention of cardiotoxicity for some breast cancer patients that might experience late-onset cardiotoxicity. Further, exercise rehabilitation concomitantly functions as primary prevention against CVD for a majority of breast cancer patients. Resting heart rate is an independent predictor of CVD [64–66]. Exercise training is responsible for a 9 beats/min reduction in RHR following cardiac rehabilitation in heart failure patients, and it appears exercise has a positive effect on RHR in breast cancer survivors [67]. Fahey et al. [52] observed a 5.5 beats/min reduction in RHR for postmenopausal breast cancer survivors following a 15 week exercise intervention, and a significant increase in heart rate reserve as well. Heart rate during peak exercise also increased significantly in this same cohort of breast cancer survivors [53]. Indices of heart rate parameters have long been correlated with mortality, and they are robust indicators of cardiac function.

Elevated SBP and DBP levels are associated with adjusted hazard ratios of 1.24 and 1.26, respectively, for 60–74 year old women with regard to 25-year mortality rates for CVD [64]. Blood pressure levels are expected to change with exercise training [68]. All exercise intervention studies in breast cancer survivors that were reviewed were successful in lowering RHR, SBP, and DBP.

Recommendations for future research

While the studies assembled in this review show exercise-induced improvements in RHR, SBP, and DBP, these are non-specific indicators of cardiovascular health. Thus, future investigations should utilize more sensitive measures of cardiac function such as LVEF, E/A ratio, and longitudinal strain if available. Additionally, cardiotoxicity is only one of the mechanisms by which breast cancer patients are predisposed to CVD. The off-target effects of chemotherapy drugs influence the function of endothelial cells, renal cells, and other tissues [38]. Recently, reduced glomerular filtration rate was identified as a strong predictor of trastuzumab cardiotoxicity 12 months following treatment [69]. This association was independent of doxorubicin treatment and LVEF in breast cancer patients. Further, anthracycline therapy is associated with a significant decrease in vascular reactivity in pediatric cancer patients [38]. Thus, future studies should include both cardiac and vascular function measures.

Pre-clinical animal studies support the use of exercise in decreasing cardiac apoptosis. Yet, it is unknown if this phenomenon will translate to humans. Biomarker analysis of cardiac damage would enable researchers to determine if exercise was responsible for mitigation of chemotherapy-induced cell death and inflammation in the cardiovascular system. Future studies are necessary to understand the anticipated magnitude of cardioprotective effects and optimal timing of exercise prescriptions, in conjunction with identification of patients that would benefit the most given their treatment plan.

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Table 1
Exercise interventions reporting cardiovascular outcomes in breast cancer patients during treatment

Study	Population (N)	Intervention	Adherence	Changes in CV variables
Noble et al. [43]	Cancer patients during treatment (386) BC patients (234, 60.6 %)	1 h of: variable aerobic exercise at an RPE of 11–13, variable resistance and flexibility training, 2×/week for 12 weeks	Not reported	Pre to post RHR ↓ SBP ↓* DBP ↓*
Haykowsky et al. [37]	BC patients during adjuvant treatment (17)	30–60 min cycling at 60–90 % VO_{2max} , 3×/week for 16 weeks	59 %	Pre to post EDV ↑* ESV ↓* EF ↓*
Kim et al. [45]	BC patients during adjuvant treatment (41, 19 control, 22 intervention)	30 min aerobic exercise at 60–70 % of VO_{2max} , 3×/wk for 8 weeks	78.3 %	Pre to post Intervention RHR ↓* SBP ↓*
Kolden et al. [46]	BC patients during adjuvant treatment (40)	20 min aerobic exercise at 70 % VO_{2max} + 20 min resistance training and stretching, 3×/week for 16 weeks	88 %	Pre to post RHR ↓* SBP ↓* DBP ↓*

CV cardiovascular, BC breast cancer, RPE rate of perceived exertion, RHR resting heart rate, SBP systolic blood pressure, DBP diastolic blood pressure, VO_2 max maximal oxygen consumption, EDV end diastolic volume, ESV end systolic volume, EF ejection fraction

* $P < 0.05$

Table 2

Exercise interventions reporting cardiovascular outcomes in breast cancer survivors

Study	Population (N)	Intervention	Adherence	Changes in CV	variables
Hsieh et al. [54]	BC survivors categorized by treatment (96)	40 min of aerobic exercise, resistance training, and stretching 3×/week for 16 weeks	90 %	Pre to post RHR ↓ SBP ↓ DBP ↓	
Schneider et al. [44]	BC patients during treatment (17) and BC survivors (96)	40 min of aerobic exercise, resistance training, and stretching at 40–75 % HRR, 2–3×/week for 16 weeks	89.6 %	Pre to post During RHR ↓* SBP ↓* DBP ↓*	Following RHR ↓ SBP ↓* DBP ↓
Fairey et al. [52]	Postmenopausal BC survivors (52)	35 min cycling at 70–75 % $VO_{2\text{ max}}$, 3×/week for 15 weeks	98.4 %	Pre to post Intervention RHR ↓ HRR ↑* SBP ↓ DBP ↓	Control RHR ↑ HRR ↓ SBP ↔ DBP ↔
Courneya et al. [53]	Postmenopausal BC survivors (53)	35 min cycling at 70–75 % $VO_{2\text{ max}}$, 3×/week for 15 weeks	98.4 %	Pre to post Intervention PHR ↑*	Control PHR ↓
Pinto et al. [51]	BC survivors (24, 12 control, 12 intervention)	30 min aerobic exercise at 60–70 % HRR, 3×/week for 12 wks	88 %	Pre to post Intervention RHR ↓ SBP ↓* DBP ↓*	

CV cardiovascular, BC breast cancer, RHR resting heart rate, SBP systolic blood pressure, DBP diastolic blood pressure, $VO_{2\text{ max}}$ maximal oxygen consumption, HRR heart rate reserve, PHR peak heart rate

* $P < 0.05$