

# Exercise after breast cancer treatment: current perspectives

Christina M Dieli-Conwright  
Breanna Z Orozco

Division of Biokinesiology and Physical Therapy, Women's Health and Exercise Laboratory, University of Southern California, Los Angeles, CA, USA

**Abstract:** Over the past 2 decades, great strides have been made in the field of exercise-oncology research, particularly with breast cancer. This area of research is particularly important since there are >2.8 million breast cancer survivors who are in need of an intervention that can offset treatment-related side effects. Noticeable reductions in physical fitness (ie, cardiopulmonary fitness and muscular strength), negative changes in body composition (ie, increase in body mass, decrease in lean body mass, and increase in fat mass), increased fatigue, depression, or anxiety are some of the common side effects of cancer treatments that negatively impact overall quality of life and increase the risk for the development of comorbidities. Exercise plays a vital role in improving cardiopulmonary function, psychological events, muscular strength, and endurance in breast cancer survivors, and thus should be considered as a key factor of lifestyle intervention to reverse negative treatment-related side effects. The purpose of this review is to address current perspectives on the benefits of aerobic and resistance exercise after breast cancer treatments. This review is focused on the well-established benefits of exercise on physical and emotional well-being, bone health, lymphedema management, and the postulated benefits of exercise on risk reduction for recurrence of breast cancer.

**Keywords:** breast cancer, exercise, physical well-being

## Introduction

With >2.8 million breast cancer survivors (BCSs) in the United States, physical and emotional health-related factors pertaining to improved survivorship following cancer treatments are a growing concern.<sup>1</sup> One such factor to consider during survivorship is the participation in exercise, which has been described as a modifiable risk factor for the prevention of primary and recurrent cancers.<sup>2,3</sup> The field of exercise-oncology has grown exponentially over the past 35 years, with one of the earliest studies conducted in women with breast cancer undergoing chemotherapy in the late 1980s.<sup>4,5</sup> Breast cancer has been a major focus of this area because epidemiological evidence reported that lifetime participation in physical activity may reduce the risk of breast cancer.<sup>6-8</sup>

Exercise plays a vital role in improving cardiopulmonary function, psychological events, muscular strength, and endurance in BCS.<sup>9,10</sup> These benefits are of particular importance since women diagnosed with breast cancer are estimated to decrease their physical activity levels by 11% following breast cancer diagnosis.<sup>11</sup> Greater decreases in physical activity levels are observed in BCS who are treated with chemotherapy (50%) and radiation (24%) when compared to those who do not experience these treatment regimens.<sup>11</sup> The highly noted benefits of exercise combined with the significant decreases in physical activity following diagnosis have established that the

Correspondence: Christina M Dieli-Conwright  
Division of Biokinesiology and Physical Therapy, Women's Health and Exercise Laboratory, University of Southern California, 1540 E. Alcazar St., CHP 155, Los Angeles, CA 90033, USA  
Email [Cdieli@usc.edu](mailto:Cdieli@usc.edu)

exercise after breast cancer treatment is an important area of research.

Discernible reductions in physical fitness (ie, cardiopulmonary fitness and muscular strength), negative changes in body composition (ie, increase in body mass, decrease in lean body mass, and increase in fat mass), increased fatigue, depression, or anxiety are some of the common side effects of cancer treatments that negatively impact the overall quality of life (QOL) and increase the risk for the development of comorbidities.<sup>12</sup> These side effects may increase the likelihood for the development of secondary cancers as well as reduce survival rates.<sup>13</sup> Thus, the benefits of exercise are imperative to achieve chemotherapy, radiation, and surgical treatments for breast cancer as these treatments can impair one's physical and mental capabilities.

The purpose of this review is to address current perspectives on the benefits of aerobic exercise (AE) and resistance exercise (RE) after breast cancer treatments. This review is focused on the established benefits of exercise on physical and emotional well-being, bone health, lymphedema management, and the postulated benefits of exercise on risk reduction for recurrence of breast cancer.

## Exercise and improved physical well-being

The adverse effects of breast cancer treatments commonly impact the physical well-being of survivors. Some of these side effects include impaired cardiopulmonary fitness, reduced upper-extremity function and mobility, and elevated body weight.<sup>14,15</sup> To address these side effects, the scientific community examined the effects of AE and RE regimens in BCS following cancer-related treatments (Table 1). Promising results of exercise intervention studies report that BCS who participate in AE or RE experience significant reductions in waist circumference and body fat, improved cardiorespiratory fitness, and increased lean body mass when compared to BCS who do not participate in exercise.<sup>16–18</sup>

In BCS, AE is an effective mean for improving cardiopulmonary fitness, often assessed by maximal oxygen consumption ( $VO_{2max}$ ) and body composition (decreased percent body fat, increased lean body mass).<sup>9,16,19</sup> For example, a 3-week, twice weekly, moderate intensity (45%–65%  $VO_{2max}$ ) supervised AE program significantly improved  $VO_{2max}$  in BCS.<sup>20</sup> Furthermore, BCS participating in an 8-week (two times per week) progressive (increased intensity by 5% heart rate reserve every 2 weeks) AE program showed a decrease in waist circumference compared to a sedentary control group.<sup>21</sup> Of longer duration, Irwin et al found 6 months (three times

per week) of moderate (50%–80% maximal heart rate) gym and home-AE program increased lean body mass and decreased percent body fat in BCS.<sup>16</sup> Overall, BCS who participate in regular (3-weekly sessions) AE ranging from as few as 3 weeks to 6 months may benefit from improvements in body composition and cardiopulmonary function. However, for sustained benefits of AE, BCS should consider long-term participation in AE.

RE effectively results in positive physical well-being adaptations including improvements in appendicular and whole-body lean mass, muscle strength, and aerobic capacity.<sup>22</sup> Importantly, patients with cancer who participate in RE are at a 33% decreased risk of all-cause mortality,<sup>23</sup> thus the inclusion of RE in an exercise program should not be overlooked. Gains in muscle strength may result in as few as 8 weeks in BCS. An 8-week whole-body progressive RE (50%–80% 1-repetition maximum [RM]) program demonstrated significant strength improvements in chest press, leg press, arm curls, and chair stand exercises in BCS.<sup>24</sup> Of longer duration, Winter-Stone et al observed significant improvements in upper and lower body strength in BCS after 1 year of whole-body progressive RE (30%–80% 1-RM) compared to those who participated in a low impact, stretching program.<sup>25</sup> Increasing lean body mass is important for overall muscular strength and balance and can improve in BCS following a 3-month whole-body supervised progressive RE (60% 1-RM) program.<sup>22</sup> In addition to strength and lean body mass gains, RE is effective at improving balance in BCS, as indicated following 24-month supervised progressive RE intervention.<sup>26</sup> Overall, RE results in significant improvements in muscular strength, lean body mass, and balance in BCS. Therefore, the inclusion of an RE component, under the guidance of an exercise specialist, in an exercise intervention would be extremely beneficial for BCS to improve many aspects of physical well-being.

Researchers have manipulated the implementation of AE and RE by using a combined exercise program in BCS, composed of both AE and RE modes.<sup>27–29</sup> Combined exercise programs, ranging in duration from 3 to 8 months, can improve cardiopulmonary fitness, muscular strength, and balance.<sup>27,29–30</sup> Specifically, BCS participating in 5–6 months of combined exercise training have experienced greater decreases in central adiposity and waist-to-hip ratio, percent body fat, resting diastolic blood pressure, mean arterial pressure, and increases in fat-free mass and estimated  $VO_{2max}$ , when compared to a sedentary control group.<sup>17,29</sup> Thus, studies including combined exercise programs pose numerous benefits for BCS, which may outweigh participation in only one mode of exercise.

**Table 1** Effects of exercise on physical well-being

Study	Mode of exercise, supervised vs home based, group or individual	Duration	Intensity	Outcomes
Irwin et al <sup>16</sup>	AE, supervised and home based, group and individual	6 months; 3×/wk supervised; 2×/wk at home; 15–30 min/session	Moderate; 50%–80% maximal heart rate	↓ % body fat, ↑ lean body mass
Saarto et al <sup>19</sup>	AE, supervised and home based, individual	12 months; 1×/wk supervised; 2×/wk home based	Step aerobics: 150–180 jumps (10 cm benches); pace at 118 bpm	↑ lean body mass
Brdareski et al <sup>20</sup>	AE, supervised, individual	3 weeks; 2×/wk; 20 min/session	45%–65% VO <sub>2max</sub>	↑ VO <sub>2max</sub>
Guinan et al <sup>21</sup>	AE, supervised and home based, individual	8 weeks; 2×/wk, 21–42 min/session	40%–65% heart rate reserve	↓ waist circumference
Benton et al <sup>24</sup>	RE, supervised, individual	8 weeks, 2×/wk	Whole-body progressive; 10–12 reps, three sets	↑ muscular strength
Winters-Stone et al <sup>25</sup>	RE, supervised and home based, group and individual	1 year; 2×/wk supervised, 1×/wk at home	Whole-body progressive; three sets at 30%–80% 1-RM	↑ muscular strength
Cormie et al <sup>22</sup>	RE, supervised, group	3 months; 2×/wk	Whole-body progressive; 2–4 sets; 12–8 RM load	↑ lean body mass,
Waltman et al <sup>26</sup>	RE, supervised, individual	24 months, 2×/wk	Whole-body progressive; two sets; 8–12 reps	↑ muscular strength, ↑ balance
Scott et al <sup>17</sup>	C with diet restriction, supervised, individual	6 months; 3×/wk	AE: 30 min; 65%–85% max HR RE: 10–15 min of resistance band exercises	↓ waist circumference, ↓ waist/hip ratio, ↓ resting diastolic BP, ↑ VO <sub>2max</sub>
Milne et al <sup>27</sup>	C, supervised, individual	12 weeks; 3×/wk	AE: 20 min/session  RE: whole-body progressive, two sets of 10–15 reps (intensity not defined)	↑ aerobic fitness (aerobic power index cycle test) ↑ muscular strength
Heim et al <sup>30</sup>	C, supervised, group	8 months; 2×/wk AE; 3×/wk RE	AE: walking program; 30 min (intensity not defined) RE: intensity not defined	↑ muscular strength, ↑ aerobic capacity
Mills et al <sup>29</sup>	C, supervised, individual	5 months; 3×/wk	AE: 10–20 min; 40%–75% VO <sub>2max</sub> , 8–12 reps RE: whole-body progressive; 1–3 sets at an RPE of 3–7 on the modified Borg Scale	↓ % body fat, ↑ fat-free mass, ↑ VO <sub>2max</sub> , ↑ mean arterial pressure

**Notes:** ↑, increase; ↓, decrease.

**Abbreviations:** AE, aerobic exercise; wk, week; min, minutes; VO<sub>2max</sub>, maximal oxygen consumption; RE, resistance exercise; RPE, rate of perceived exertion; bpm, beats per minute; reps, repetitions; RM, repetition maximum; max, maximal; HR, heart rate; C, combined aerobic and resistance exercise; BP, blood pressure.

The improvements in cardiopulmonary fitness and muscular strength derived from a combined exercise program may be vital toward maximizing improvements in physical well-being and overall survivorship among BCS.

## Exercise and improved emotional well-being

Emotional well-being including QOL, fatigue, and psychological or psychosocial changes experienced by BCS following treatment is a major concern impacting survivorship.<sup>31</sup> Compared to women without breast cancer, women with breast cancer experience significant declines in physical role function (the extent to which their physical ability interferes with work or other activities), bodily pain, social functioning,

and emotional health.<sup>32,33</sup> It is estimated that ~50% of women with breast cancer encounter depression, anxiety, or both upon a year following diagnosis.<sup>34</sup> A large study including 1,993 BCS found that 66.1% of study participants reported moderate-to-severe fatigue and 24.9% reported moderate-to-severe depression following treatment.<sup>35</sup> In an effort to alleviate these adverse events, exercise intervention trials have been designed and tested in BCS.

Overall, AE improves emotional well-being in BCS (Table 2). BCS who participate in AE interventions ranging from 4 weeks to 6 months and intensities ranging from low (walking) to vigorous experience improvements in QOL, fatigue, social functioning, energy levels, and emotional distress when compared to sedentary controls.<sup>36–39</sup> Importantly,

**Table 2** Effects of exercise on emotional well-being

Study	Mode of exercise, supervised vs home based, group or individual	Duration	Intensity	Outcomes
Cadmus et al <sup>37</sup>	AE, supervised and home based, individual	6 months, 5×/wk, 30 min/session	60%–80% of predicted max HR	↔ QOL, ↑ improved social functioning
Fillion et al <sup>38</sup>	AE, supervised, group	4 wks, 1×/wk, 1 h/session	Walking (intensity not specified)	↓ fatigue, ↑ energy level, ↓ emotional distress
Courneya et al <sup>39</sup>	AE, supervised, individual	15 wks, 3×/wks, 15–45 min/session	70%–75% of VO <sub>2max</sub>	↑ QOL (FACT-B)
Murtezani et al <sup>41</sup>	AE, supervised, group	10 wks, 3×/wk, 25–45 min/session	50%–75% max HR	↑ QOL (FACT-G)
Mehnert et al <sup>42</sup>	AE, supervised, individual	10 wks, 2×/wk, 20 min/session	60% of VO <sub>2max</sub>	↑ psychosocial well-being, ↑ individual body image
Rogers et al <sup>43</sup>	AE, supervised, individual	3 months, 3×/wk, 15–25 min/session	40%–59% HR reserve	↑ emotional well-being, ↑ functional well-being
Benton et al <sup>24</sup>	RE, supervised, individual	8 wks, 2×/wk	Whole-body progressive, three sets of 8–12 reps	↑ QOL
Ohira et al <sup>44</sup>	RE, supervised and home based, group	6 months, 2×/wk	Whole-body (intensity not specified)	↑ QOL, ↔ depressive symptom score
Milne et al <sup>27</sup>	C, supervised, individual	12 wks, 3×/wk	AE: 20 min/session RE: whole-body progressive, two sets of 10–15 reps (intensity not defined)	↑ QOL
Heim et al <sup>30</sup>	C, supervised, group and individual	8 months; 2×/wk AE; 3×/wk RE	AE: walking program; 30 min (intensity not defined) RE: intensity not defined	↑ QOL (FACT-G) ↓ cancer-related fatigue
Hayes et al <sup>36</sup>	C, supervised and home based, individual	6 wks, 4×/wk, 45 min/session (2×/wk of AE and 2×/wk of RE)	AE: low to moderate to high intensity (specific AE and RE intensity not defined)	↑ QOL ↓ fatigue
Midtgaard et al <sup>40</sup>	C, supervised, group	6 wks, 9 h/wk total	Intensity not defined (ball games, aerobics, heavy resistance training, and cycling)	↑ mental health, ↑ social functioning, ↑ emotional functioning
Spector et al <sup>45</sup>	C, home based, individual	16 wks	AE: 150 min/wk; 40%–65% HR reserve RE: whole body; 12–15 reps	↑ QOL (FACT-B)
Sprod et al <sup>46</sup>	C, supervised, individual	3 months or 6 months, 2–3×/wk, 60 min/session	AE: 40 min; 30%–55% HR reserve RE: whole-body, intensity not defined	↓ fatigue

**Notes:** ↑, increase; ↓, decrease; ↔, no change.

**Abbreviations:** AE, aerobic exercise; min, minutes; max, maximum; QOL, quality of life; h, hour; FACT-B, Functional Assessment of Cancer Therapy – Breast; FACT-G, Functional Assessment of Cancer Therapy – General; RE, resistance exercise; VO<sub>2max</sub>, maximal oxygen consumption; HR, heart rate; C, combined aerobic and resistance exercise; wk, week.

improvements in emotional well-being can result from as few as 6 weeks of AE. Midtgaard et al observed improved emotional functioning, social functioning, and mental health in BCS participating in a 6-week (9 hours/week) group AE program.<sup>40</sup> A 10-week moderate intensity (50%–75% maximal heart rate) AE intervention resulted in significant improvements in QOL assessed by the Functional Assessment of Cancer Therapy – General score in BCS when compared to a sedentary control group.<sup>41</sup> Participation in 10–15 weeks of moderate intensity (60% VO<sub>2max</sub>) AE resulted in improvements in psychosocial, functional, emotional well-being, self-esteem, happiness, and individual body image.<sup>39,42,43</sup> Accordingly, evidence strongly suggests that AE can target outcomes associated with overall

emotional well-being in BCS, achievable within 6–24 weeks of regular exercise participation.

Although most commonly acknowledged for the established physical well-being adaptations, the effects of RE on emotional well-being have been investigated, minimally, posttreatment (Table 2). Participation in an 8-week progressive whole-body RE program resulted in significant improvements in QOL examined in younger (40–59 years) BCS.<sup>24</sup> Additionally, BCS who participated in a 6-month progressive RE program reported improvements in the QOL.<sup>44</sup> These investigations suggest that participation in RE can improve emotional well-being and may be beneficial when prescribing and implementing exercise programs for BCS.

Similar to physical well-being adaptations, studies addressing the emotional well-being of BCS have used combined AE and RE programs. Combined programs ranging from 3 to 8 months lead to improvements in emotional well-being, including outcomes such as cancer-related fatigue, social well-being, and overall QOL.<sup>27,30</sup> Specifically, a recent study found improvements in the breast cancer QOL questionnaire (Functional Assessment of Cancer Therapy – Breast) following the completion of a 16-week home-based combined exercise program.<sup>45</sup> Further, significant fatigue reductions can occur in BCS following participation in the home-based combined exercise program. A 3-month or 6-month combined exercise program resulted in improvements in behavioral fatigue, sensory fatigue, affective fatigue, cognitive fatigue, and overall total fatigue in BCS.<sup>46</sup> Thus, a combined RE and AE program should be considered to improve measures of emotional well-being, in particular, due to the strong effects on physical well-being that are elicited.

## Exercise and management of lymphedema

Lymphedema secondary to breast cancer is a chronic debilitating condition and treatment-related sequelae, which is a substantial concern during survivorship. Lymphedema is caused by the disruption of the lymphatic system, leading to the accumulation of fluid in the interstitial space and clinically presented as swelling of the arm, shoulder, neck, or torso.<sup>47,48</sup> Chronic swelling leads to soft tissue fibrosis and deposition of adipose tissue. Further, this increases the patients' risk of cellulitis causing additional damage to the lymphatic capillaries.<sup>49</sup> Lymphedema is reported to develop in ~20% of women following breast cancer treatments.<sup>50</sup> However, the incidence rates vary based on the clinical definition. Importantly, lymphedema can develop years (>2) after the initial cancer treatment,<sup>51–53</sup> and irrespective of onset, lymphedema often causes emotional distress and compromised QOL.<sup>54,55</sup> The recommended management of lymphedema by the National Lymphedema Network and the International Society of Lymphology is complete decongestive therapy, involving manual lymphatic drainage compression bandages, remedial active exercises, skin care, and patient education.<sup>56,57</sup>

Exercise may aid in the management of lymphedema with research limited to breast cancer-related lymphedema.<sup>58</sup> Upper body exercise has traditionally been discouraged for BCS following axillary lymph node dissection and/or radiation.<sup>59</sup> This advisement, largely unsubstantiated, arose from the belief that upper body exercise may initiate or worsen upper extremity lymphedema.<sup>60,61</sup> However, recent

randomized controlled trials have challenged this belief and found no association between upper body exercise and the onset or worsening of breast cancer-related lymphedema.<sup>13,62</sup> Furthermore, some forms of exercise, mainly progressive RE, is associated with less exacerbation of lymphedema-related symptoms in BCS.<sup>63,64</sup> The largest exercise and lymphedema trial, the Physical Activity and Lymphedema Trial, demonstrated that supervised, slowly progressive RE performed twice weekly while wearing a compression garment is protective against lymphedema flare-ups.<sup>64</sup> Importantly, a recent meta-analysis by Cheema et al examined the safety and efficacy of progressive RE on breast cancer-related lymphedema.<sup>65</sup> Results from the meta-analysis, including nine studies, indicated that progressive RE actually reduced the risk of breast cancer-related lymphedema and did not worsen arm volume or symptom severity.

Despite the fact that strong evidence exists on the safety of progressive RE without an increase in risk of lymphedema for breast cancer patients,<sup>13</sup> one should strongly consider safety precautions when initiating an AE or RE program. Although exercise, AE and/or RE, is safe, appropriate exercise programming should be executed. It is advised that exercise be initiated in a progressive manner such that the intensity, volume, and frequency are slowly progressed over time, under the supervision of a health care professional or certified cancer exercise specialist.

## Exercise and maintaining bone mineral density

Various forms of breast cancer treatment can be detrimental to bone health, which would increase one's risk of osteoporosis and subsequent bone fractures. Adjuvant forms of therapy such as aromatase inhibitors are known to accelerate bone loss as a result of the estrogen deprivation effects of the treatment.<sup>66</sup> Benefits of exercise are documented for bone mineral density (BMD) maintenance (assessed by dual-energy X-ray absorptiometry) in BCS<sup>67,68</sup> and further warrants investigations, since treatment side effects such as chemotherapy-induced amenorrhea and chemotherapy itself may pose even greater losses of BMD in premenopausal BCS.<sup>69–71</sup> These adverse effects have evoked the use of AE and RE as a prevention mechanism for deterring bone loss.

Although RE is traditionally utilized to prevent the loss of or maintenance of BMD, AE may also contribute to the maintenance of bone health (Table 3). For example, a 12-month supervised and home-based aerobic and circuit training program emphasizing in vigorous step aerobics (defined by the authors as 150–180 jumps) and circuit training (defined

**Table 3** Effects of exercise on bone mineral density

Study	Mode of exercise, supervised vs home based, group or individual	Duration	Intensity	Outcomes
Saarto et al <sup>19</sup>	AE, supervised and home based, individual	12 months; 1×/wk supervised; 2×/wk home based	Step aerobics: 150–180 jumps (10 cm benches); pace at 118 bpm + circuit training (150–180 steps with a 40:60 s training/rest ratio)	↔ femoral neck BMD
Irwin et al <sup>16</sup>	AE, supervised and home based, group and individual	6 months; 3×/wk supervised; 2×/wk at home; 15–30 min/session	Moderate; 50%–80% maximal heart rate	↔ total BMD
Winter-Stone et al <sup>67</sup>	RE, supervised and home based, individual	1 year, 2×/week supervised + 1×/wk home based	Whole body; 60%–70% 1-RM for 1–3 sets of 8–12 reps	↔ lumbar spine BMD
Dobek et al <sup>68</sup>	RE, supervised and home based, individual	1 year, 2×/wk + 1×/wk home exercise	Whole body; two sets of 8–12 reps	↔ lumbar spine BMD
Winter-Stone et al <sup>73</sup>	RE, supervised and home based, individual	12 months, 2×/wk + 1×/wk at home	Body weight loaded vest at 8–15 reps of two footed jumps	↔ lumbar spine BMD

**Notes:** ↑, increase; ↓, decrease; ↔, no change.

**Abbreviations:** AE, aerobic exercise; s, second; min, minutes; wk, week; BMD, bone mineral density; RE, resistance exercise; bpm, beats per minute; reps, replications.

as 150–180 steps with a 40:60 seconds of training:rest ratio), maintained BMD at the femoral neck when compared to a sedentary control group in BCS.<sup>19</sup> Additional studies noted prevention of bone loss at the femoral neck and total body following participation in 6–12 months of moderate-to-vigorous AE.<sup>16,19</sup> Overall, it may be plausible to prevent bone loss in BCS with a minimum of 6 months of participation in AE.

RE has been used to maintain BMD in BCS (Table 3) due to the mechanical loading nature of RE that enhances osteoblastic activity in bone.<sup>72</sup> For example, BCS who participated in 1-year supervised and home-based RE programs demonstrated lumbar spine BMD maintenance when compared to those who did not participate in RE.<sup>68,73</sup> Additionally, supervised progressive RE and home-based RE were shown to preserve BMD at the lumbar spine, improve femoral neck BMD, and total body BMD in BCS compared to those who did not participate in the intervention.<sup>67</sup> Overall, RE is an effective method of exercise to maintain bone mass in BCS following cancer treatments and is important in the prevention of bone loss related to cancer and its associated treatments. To date, a review of literature revealed that there are no studies investigating the effects of a combined exercise program on BMD in BCS.

## Exercise and risk reduction for breast cancer recurrence

One of the lifestyle factors most strongly and consistently associated with breast cancer recurrence is exercise.<sup>74</sup> Numerous studies have associated moderate exercise with lower risk of breast cancer recurrence.<sup>2,75–79</sup> However, timing of exercise participation needs to be considered in relation to the cancer diagnosis. A meta-analysis of studies examining

the timing of exercise and risk of recurrence in pre- and postmenopausal women found that exercise participation after diagnosis was associated with 34% fewer deaths from breast cancer ( $P < 0.001$ ), 41% fewer deaths from all causes ( $P < 0.001$ ), and 24% reduction in recurrence.<sup>80</sup> Epidemiologically, exercise is often assessed by interviewer-administered or self-administered questionnaires, involving patient recall of previous participation in exercise and commonly quantified using a range of metrics including hours per week, metabolic equivalent-hours per week, metabolic equivalent-hours per week per year, times per week. Overall, quantifying the exact volume of exercise to prevent disease recurrence is challenging; however, observational evidence indicates that  $\geq 3$  hours of moderate-to-vigorous intensity AE per week may be beneficial in reducing mortality and morbidity in BCS.<sup>81</sup>

Perhaps one of the most profound clinical investigations studying this topic was that of Courneya et al who sought to examine disease-free survival (DFS) following AE (three times per week; 60%–80%  $VO_{2max}$ ) or RE (three times per week; two sets of 8–12 replications; 60%–70% 1-RM) performed while undergoing chemotherapy.<sup>82</sup> Overall, when compared to the control group, the exercise group experienced a higher 8-year DFS, overall survival, and distant DFS. The effect of exercise on DFS was potentially stronger for women who were overweight/obese, had stage II/III cancer, had estrogen receptor-positive tumors, had human epidermal growth factor receptor 2-positive tumors, received taxane-based chemotherapies, and completed  $\geq 85\%$  of their planned chemotherapy. Definitive Phase III trials are warranted to confirm these findings.

Potential mechanisms to mediate postmenopausal risk of recurrence through exercise participation are proposed

to be driven by changes in body fat and inflammation ultimately affecting changes in specific biomarkers. Levels of insulin, estrogen, insulin-like growth factor-1, and markers of inflammation (eg, tumor necrosis factor [TNF]- $\alpha$  and interleukin[IL]-6) are potential biomarkers, which are influenced by exercise and may affect breast cancer recurrence.<sup>83</sup> Evidence from cohort analyses and randomized trials has found the aforementioned biomarkers to be reduced with exercise, demonstrating that exercise can affect systemic biomarker levels in postmenopausal BCS.<sup>84–87</sup> Overweight and obese BCS have elevated blood levels of estrogens and androgens<sup>88</sup> and being overweight, obese, or sedentary is associated with elevated insulin and inflammatory markers including C-reactive protein, serum amyloid A, IL-6, IL-1, and TNF- $\alpha$ .<sup>89</sup> These biomarkers combined with elevated body fat may drive tumor growth, yet the exact mechanisms are unclear. Furthermore, these findings are not well-established in premenopausal patients with breast cancer, thus underlying mechanisms have not yet been determined to explain how exercise may impact the risk of recurrence in this population. Large randomized clinical trials have yet to determine specific exercise program parameters that will reduce the recurrence of breast cancer. These studies are challenging due to cost, large sample size needed, and duration of study to address appropriately what types of exercise may reduce the risk of recurrence.

An important consideration in examining the risk of breast cancer recurrence and posttreatment exercise is obesity. A large body of evidence exists to suggest that elevated BMI or body weight is associated with poorer breast cancer outcomes.<sup>80,90,91</sup> To examine this association, Ibrahim and Al-Homaidh conducted a meta-analysis and reported that postdiagnosis exercise reduced the risk of breast cancer mortality only in women with a BMI  $\geq 25$  kg/m<sup>2</sup>,<sup>80</sup> indicating that exercise may mediate prognosis through reducing body weight in women who were overweight or obese. This has been proposed only for postmenopausal women through mechanisms described previously. Future investigations are warranted to determine whether exercise affects tumor progression via the aforementioned mechanisms and with consideration of the influence of menopausal status and body weight.

Overall exercise prescription during survivorship is based on recommendations by the American College of Sports Medicine, American Cancer Society, and American Heart Association. These organizations along with the US Department of Health and Human Services recommend an overall volume of weekly activity of 150 minutes of moderate-intensity AE or 75 minutes of vigorous-intensity AE, or an

equivalent combination and 2–3 weekly strength training sessions including exercises for major muscle groups.<sup>13,92</sup> Although these exact recommendations are not prescribed specifically for risk reduction of recurrence, they are recommended for overall health and fitness improvements and maintaining a healthy body weight and should be considered when initiating or executing an exercise program for BCS.

## Future directions

The exercise-oncology research pertaining to breast cancer has made significant strides over the years. As summarized in this review, exercise performed after breast cancer treatments can be effective at improving physical and emotional well-being, maintaining bone health, managing symptoms of lymphedema and perhaps even reducing the risk of lymphedema, and reducing the risk of breast cancer recurrence via reductions in body weight and associated inflammatory and endocrine biomarkers, as noted in previously published reviews.<sup>93,94</sup> However, the potential to conduct future investigations is substantial due to the gaps in knowledge in posttreatment exercise and breast cancer research. This includes mechanisms to prevent or attenuate chronic and late effects of treatment (eg, peripheral neuropathy, cardiotoxicity, and bone mass declines); factors that predict response to exercise for prevention and attenuation of chronic and late effects; determining the optimal exercise prescription parameters (eg, dose, timing, type, and intensity) to prevent or attenuate chronic and late effects; examining optimal exercise prescription parameters that influence tumor progression; and expanding the epidemiological evidence of the association between exercise participation and risk of cancer recurrence.<sup>94</sup>

Overall, when assessing the literature to prescribe exercise for a survivor of breast cancer, one should refer to the recommendations by the American College of Sports Medicine, American Cancer Society, and American Heart Association. These organizations along with the US Department of Health and Human Services recommend an overall volume of weekly activity of 150 minutes of moderate-intensity AE or 75 minutes of vigorous-intensity AE, or an equivalent combination and 2–3 weekly strength training sessions including exercises for major muscle groups.<sup>13,92</sup> These are recommendations for overall health and fitness improvements, and maintaining a healthy body weight should be considered when initiating or executing an exercise program for BCS.

## Conclusion

Based on the current findings, exercise participation after cancer-related treatments elicits beneficial effects on physical

and emotional well-being, lymphedema management, and maintenance of BMD in BCS. Large randomized controlled trials are necessary to determine whether exercise can reduce the risk of cancer recurrence in BCS. Participation in regular exercise, preferably both AE and RE modes, can alleviate some cancer treatment-related side effects and improve survivorship. Although the scientific knowledge supporting participation in exercise is profound, exercise adherence remains a challenge in BCS. In future, health care-supported exercise programs for cancer survivors may be necessary, similar to cardiac rehabilitation exercise programs for cardiac patients, to promote a behavioral change to a more active lifestyle.

## Disclosure

The authors report no conflicts of interest in this work.

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