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Clinically Relevant Physical Benefits of Exercise Interventions in Breast Cancer Survivors

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Abstract Evidence is currently limited for the effect of exercise on breast cancer clinical outcomes. However, several of the reported physical benefits of exercise, including peak oxygen consumption, functional capacity, muscle strength and lean mass, cardiovascular risk factors, and bone health, have established associations with disability, cardiovascular disease risk, morbidity, and mortality. This review will summarize the clinically relevant physical benefits of exercise interventions in breast cancer survivors and discuss recommendations for achieving these benefits. It will also describe potential differences in intervention delivery that may impact outcomes and, lastly, describe current physical activity guidelines for cancer survivors.

Keywords Breast cancer · Exercise · Aerobic · Resistance · Flexibility · Rehabilitation · Exercise prescription · Peak oxygen consumption · Cardiorespiratory fitness · Strength · Lean mass · Bone mineral density · Cardiovascular disease

Introduction

Exercise is a safe, accessible, and inexpensive non-pharmacological therapy associated with numerous health benefits in breast cancer survivors [1••]. General physical benefits of exercise interventions both during and after breast cancer treatment include improved cardiorespiratory and muscular fitness, body composition, and physical function [1••, 2, 3], along with a reduction in common negative side effects during active treatment including nausea and vomiting [4, 5•]. Psychological benefits include improved health-related quality of life, reduced anxiety and depression, and improved body image and self-esteem [6]. Furthermore, exercise results in benefits for biobehavorial outcomes that span these two domains including fatigue, pain, and sleep disturbance [1••, 3, 6].

Preliminary evidence suggests that exercise may also have positive effects on oncological care including chemotherapy completion rates [5•, 7] and cancer outcomes [8•]. Several of the aforementioned physical benefits of exercise also have established associations with clinically relevant outcomes. In this review, we will summarize the clinically relevant physical benefits of exercise interventions in breast cancer survivors and discuss recommendations for achieving these benefits. We will also describe potential differences in intervention delivery that may impact outcomes and, lastly, describe current physical activity guidelines for cancer survivors.

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Cardiorespiratory Fitness and Functional Capacity

Maximal (VO_2max), or peak oxygen consumption (VO_2peak), when measured by a cardiopulmonary exercise test, is the gold standard measurement of cardiorespiratory fitness [9]. Oxidative phosphorylation is the fundamental energy-producing biochemical process that utilizes oxygen within the mitochondria to produce the ATP necessary for aerobic muscular work. VO_2max represents the upper limit to the rate of oxygen utilization and therefore maximal oxidative ATP production and exercise capacity [10]; this is demonstrated by a plateau in oxygen uptake with increasing workload during cardiopulmonary exercise testing. In practice, maximal oxygen consumption may not be reached in clinical populations as a result of a variety of reasons, including unfamiliarity to maximal physical efforts or musculoskeletal limitations, and the VO_2peak, or the highest achieved level of oxygen uptake during the cardiopulmonary exercise test, is used as a surrogate marker of cardiorespiratory fitness.

A reduction in VO_2peak of 5–10 % has been reported over the course of chemotherapy in women with breast cancer [7, 11], and VO_2peak remains, on average, 22 % lower in breast cancer survivors after treatment completion than in healthy sedentary controls [12•]. This chemotherapy-induced reduction in VO_2peak, occurring over a time course of 12 to 24 weeks, is equivalent to the reduction reported with 30 years of normal aging [12•, 13]. Large cohort studies demonstrate that peak exercise capacity is the strongest predictor of all-cause mortality in healthy populations and those with heart disease [14–16]. There is also evidence of a relationship between VO_2peak and risk of cancer-related death in females and with breast cancer-specific death [14, 17]. In non-cancer populations, improvements in VO_2peak over time are associated with decreased risk of mortality [18].

Other surrogate measures of cardiorespiratory fitness include the 6-min walk test and gait speed. The 6-min walk test is a reliable, standardized, submaximal assessment of functional capacity that is increasingly being used to assess the effect of exercise in cancer populations [19]. An improvement of 50 m is considered clinically significant in most populations [20], but a specific threshold has not been established for cancer populations. Gait speed, or walking velocity, is a valid, reliable, and sensitive measure that correlates with functional ability and balance and predicts future health status, hospitalizations, falls, and mortality in non-cancer populations [21]. Usual gait speed was demonstrated to be one of the best predictors of mortality in gynecological cancer survivors aged 65 years or older [22] and predicted survival and disability in mixed-diagnoses cancer survivors aged 70 to 79 years [23]. While gait speed may be lower in cancer survivors who have received chemotherapy than in age-matched controls [24], it was not shown to be a predictor of falls in older breast cancer patients [25].

Impact of Exercise

During adjuvant treatment for breast cancer, aerobic exercise training can maintain or improve VO_2peak relative to usual care controls [1••, 26•]. Following treatment completion, aerobic exercise training is effective at improving VO_2peak and surrogate measures of aerobic capacity including submaximal walking tests [1••, 26•]. Interventions that have improved VO_2peak have typically lasted 8–14 weeks and involve a prescription of 20–45 min of aerobic exercise two to three times per week at moderate intensity that may progress to vigorous intensity [26•]. Many studies have also included resistance training. These varied prescriptions have resulted in improvements in VO_2peak ranging from 2 to 15 % [26•]. Most randomized controlled trials (RCTs) that measured the effect of exercise on 6MWT distance have reported a mean change less than the clinically significant improvement of 50 m [26•]. Depending on the baseline activity level, a prescription of moderate intensity aerobic exercise performed 3–5 days per week for 20–60 min is likely to result in improvements in aerobic fitness [27, 28].

While exercise interventions in community-dwelling elderly adults have consistently demonstrated improved gait speed, the impact of exercise interventions on gait speed among cancer survivors has not been well studied. In one RCT in postmenopausal women who had completed breast cancer treatment, gait speed improved in both the resistance training and impact loading group and the whole body stretching and relaxation group [29]. Similarly, improved gait speed was observed in both arms of a RCT of aerobic versus resistance training in mixed-diagnoses cancer survivors [30]. A single-arm interdisciplinary intervention consisting of aerobic, resistance, and flexibility training, concurrent with nutritional, medical, and occupational therapy intervention components, also significantly improved gait speed among mixed-diagnoses advanced cancer survivors [31]. Although it appears that all types (i.e., aerobic, resistance, flexibility) of exercise can improve gait speed, the limited number of studies measuring this outcome in exercise interventions of cancer survivors prevents determination of the required frequency, intensity, and duration at this time.

Strength and Lean Mass

Muscular strength, especially handgrip and lower extremity strength, is an established prognostic variable for disability and mortality in elderly populations [32, 33]. Handgrip strength also offers prognostic value for middle-aged adults [34, 35]. Handgrip strength is reliable and easily measured with handgrip dynamometry, and most cancer survivors can perform this test [36]. Following mastectomy, 40 % of breast cancer survivors had a handgrip strength deficit of 10 % or more on their surgical side relative to the contralateral side [37]. Handgrip strength in breast cancer survivors has also been shown to be associated with quality of life [38]. In other cancer populations, a relationship between grip strength and mortality has been examined but failed to demonstrate a relationship [22, 23].

Age-related reductions in lower extremity strength, speed, and power are associated with reduced capacity to perform basic activities of daily living such as rising from a chair, walking unassisted, and climbing stairs, as well as with increasing morbidity [39]. Lower extremity strength can be evaluated with a measured or estimated one-repetition maximum (1-RM) of leg press [40••] or with the chair-stand test, a valid surrogate measure of leg press strength [39]. The ability to perform the sit-to-stand movement is an important determinant of physical independence [39]. Loss of lean mass is a primary mechanism for decreases in muscle strength [41], and loss of skeletal muscle, a primary component of lean mass, is associated with disability and decreased quality of life [42]. Chemotherapy for breast cancer is associated with loss of lean mass, particularly in the legs [43], that worsens with time since completion of treatment [44]. Lower extremity strength, as measured by the 30-s chair-stand test, is a significant predictor of cancer-related fatigue in breast cancer survivors aged 60 or older [45]. Reduced leg strength increases future risk of fracture in breast cancer survivors [46].

Impact of Exercise

A recent systematic review reported that exercise interventions in breast cancer survivors significantly improved lean body mass and composite scores for upper and lower body strength [26•]. However, the single study that measured handgrip strength in breast cancer survivors reported no change with resistance training among both the resistance training and flexibility groups [29]. The American College of Sports Medicine recommends that cancer survivors participate in two to three resistance-based exercise sessions per week, with a particular focus on strengthening major muscle groups, such as the chest, legs, and core [47]. Further, to gain the most strength-related benefits, individuals should perform one to three sets of 8 to 12 repetitions, at an intensity of 25 to 85 % of 1-RM, which will vary depending on individual factors such as mobility and previous experience with resistance training [47]. Specific to breast cancer survivors, recommendations include teaching proper biomechanics via supervised training and starting with a low weight and progressing slowly [48].

Cardiovascular Disease and Risk Factors

Older women with breast cancer are more likely to die of cardiovascular disease than they are to die of their cancer [49]. Women who have had a breast cancer diagnosis are at elevated risk for cardiovascular diseases including heart failure and myocardial infarction relative to women who have not had a breast cancer diagnosis [50, 51]. Chemotherapy, most notably the anthracycline agents and trastuzumab, can have direct effects on left ventricular function, while radiotherapy can also lead to valvular disease and accelerated coronary artery disease [52]. Furthermore, there is an increased prevalence of cardiovascular risk factors in this population at baseline, which may further increase due to the effects of cancer treatment [52]. Established modifiable risk factors for cardiovascular disease that may be more prevalent in breast cancer patients include hypertension, dyslipidemia, overweight and obesity, and raised blood glucose or diabetes [53].

The most prevalent comorbid condition in breast cancer survivors is hypertension, which occurs in 25–50 % of survivors [54]. Hypertension is more than twice as common among breast cancer survivors than age-matched female controls [55]. Chemotherapy agents used to treat breast cancer that may cause hypertension include cyclophosphamide, cisplatin, and carboplatin [56]. On a population level, small reductions in blood pressure are associated with reduced mortality [57]. In long-term breast cancer survivors, the presence of hypertension increased the risk of coronary artery disease, emphasizing the need for long-term blood pressure control in this population [58].

Lipid abnormalities are also associated with increased risk of cardiovascular disease [59]. Prior to treatment, women with breast cancer have higher total cholesterol, triglyceride, and low-density lipoprotein (LDL) levels and lower high-density lipoprotein (HDL) levels than healthy controls [60–64]. Chemotherapy treatment may also increase triglyceride levels [65], while tamoxifen decreases total cholesterol and LDL levels [66].

Up to 84 % of women gain weight following a breast cancer diagnosis [67, 68], and the average reported gains range from 2.5 to 5.2 kg [69•]. Overweight and obesity are established risk factors for the development of cardiovascular disease [70] and are also associated with reduced survival and an increased risk of cancer recurrence [69•]. The prevalence of type II diabetes mellitus (T2DM) appears to be approximately double that of age-matched women [55]. Breast cancer survivors with T2DM also have an elevated risk of mortality [54]. In newly diagnosed early breast cancer survivors, high blood insulin levels are indicative of insulin resistance and are associated with obesity, poor lipid profiles [71], and greater risk of cancer recurrence or death [72].

Impact of Exercise

The benefits of exercise in preventing direct cardiotoxic effects of cancer therapy are not clear. Although animal studies have suggested that exercise may be protective against the harmful effects of anthracycline chemotherapy, benefits have yet to be demonstrated in human studies [73•]. However, several studies have demonstrated exercise benefits on cardiovascular risk factors in breast cancer survivors.

Trials of exercise interventions during and after breast cancer treatment have consistently demonstrated reductions in systolic blood pressure [73•]. During treatment, exercise interventions reduced systolic blood pressure by 4.4 ± 2.0 mmHg and diastolic blood pressure by 1.3 ± 0.1 mmHg on average, while posttreatment, interventions reduced systolic blood pressure by 4.6 ± 4.6 mmHg and diastolic blood pressure by 4.4 ± 3.0 mmHg [74]. Large epidemiologic studies in the general population have estimated that a 5-mmHg decrease in systolic blood pressure is associated with reductions in the risk of coronary artery disease and stroke mortality of 9 and 14 %, respectively [57].

In non-cancer patients with hypertension, as little as 4 weeks of either aerobic or resistance exercise training can significantly improve both systolic and diastolic blood pressure and other measures of vascular function [75]. The exercise interventions reporting a positive impact on blood pressure in breast cancer survivors included at least 20-min sessions of aerobic exercise two to three times per week, and some also included resistance training [74]. Aerobic exercise intensity prescriptions were 60 to 90 % of VO_2peak or 40–75 % of heart rate reserve (the difference between maximum and resting heart rates) or a rating of perceived exertion of 11–13. The exercise intervention periods ranged from 8 to 16 weeks long [74].

Studies of the impact of exercise interventions, with or without dietary interventions, on serum triglycerides and HDL in breast cancer survivors have had conflicting results [73•]. Future research in this area is needed to better understand the potential favorable influence of exercise on these important cardiovascular risk factors. Comparing the effects of different exercise prescriptions, including resistance versus aerobic training, would be useful in future trials to explore the potential link between exercise and positive changes in blood lipid levels.

Exercise is effective in controlling cardiometabolic factors including obesity, insulin resistance, glucose intolerance, and T2DM in non-cancer populations [28]. Trends in weight gain among breast cancer survivors, especially during adjuvant chemotherapy, appear to be offset by exercise interventions [69•]. Women who participate in an aerobic exercise program during adjuvant chemotherapy are more likely to maintain their pre-chemotherapy weights [76]. A systematic review and meta-analysis of recent exercise RCTs in breast cancer survivors reported an overall significant decrease in body fat percentage and increase in lean body mass [26•]. Trials that included resistance training produced significant increases in lean body mass (+0.65 kg) among exercise groups [26•]. Another systematic review noted that weight loss interventions in breast cancer survivors that included a combination of diet, physical activity, and behavior modification were typically able to achieve mean weight losses of 5 % or greater from initial body weight [77]. This is an important benchmark, as a decrease in body weight of 5 % of baseline has been associated with significant improvements in waist circumference, plasma glucose, serum insulin, serum lipid levels, blood pressure, and risk of diabetes in overweight adults [78].

Interventions lasting longer than 6 months often achieve greater weight loss, while interventions with more segregated physical activity and dietary components and a weaker focus on behavior modification tend to result in less weight loss [77]. Among exercise trials in breast cancer populations, beneficial body composition and body weight changes do not occur until approximately week 20 of an intervention [26•]. There is no clear evidence on the best time to intervene with a weight loss intervention in breast cancer survivors, and positive effects of exercise and other weight management interventions have been demonstrated both during and after cancer treatment [77].

Exercise training, via repeated muscular contractions that occur with both aerobic and resistance exercise, has significant effects on glucose transport and insulin sensitivity [69•]. However, results from studies testing the effect of exercise training on fasting insulin and glucose levels or markers of insulin resistance have not consistently demonstrated clinically relevant benefits of this strategy in breast cancer survivors [79–86]. The only study to report significant improvements in fasting insulin and glucose implemented 25 to 45 min of light intensity aerobic exercise twice weekly in addition to twice weekly full body resistance exercise on different days [84]. In contrast, a similar exercise program with a larger sample size did not result in significant between-group differences in metabolic parameters [83], indicating further research is needed to clarify the optimal exercise prescription for metabolic improvements.

Bone Health

Breast cancer survivors are at an elevated risk for osteoporosis, falls, and fractures [25, 87]. Chemotherapy can inhibit bone proliferation directly and, along with ovarian ablation or suppression, indirectly reduces bone turnover via reduced estrogen [88]. The hormonal treatment, tamoxifen, improves bone mineral density (BMD), while aromatase inhibitors can increase the risk of fractures [88]. As in the general population, osteoporosis has been associated with increased risk of fracture among breast cancer patients who fall [64], and 58 % of early-stage breast cancer survivors currently receiving hormonal therapy reported a fall within the past year [25]. In addition, both hip and vertebral fractures have been associated with increased mortality among breast cancer survivors [88].

Impact of Exercise

Exercise effects on bone health outcomes, including BMD and bone remodeling markers, in breast cancer survivors are mixed. Relative to usual care controls, aerobic exercise, but not home-based Thera-band resistance exercise training, maintained spinal BMD during treatment [89]. After treatment, aerobic exercise maintained total body BMD, and resistance training plus impact training preserved spinal BMD [90, 91]. A program of walking with a weight belt resulted in a decrease in total body BMD and bone remodeling, while resistance training combined with bisphosphonate treatment increased BMD at the hip and spine [91]. In contrast, while the addition of resistance training to bisphosphonate treatment did not improve BMD or bone remodeling markers in another study, it did reduce the number of women with reduced BMD at 24-month follow-up [92]. It is encouraging, however, that in the general population, a 1–2 % improvement in BMD reported in some of the aforementioned studies has been associated with a 7–14 % decrease in fracture risk [90].

Based on this limited evidence, moderate-intensity aerobic or resistance exercise may preserve bone health during or after breast cancer treatment but may have limited benefits relative to bisphosphonate treatment alone [91]. There are several exercise prescription recommendations for influencing bone health outcomes specific to cancer survivors. First, exercise programs should specifically load target bones at risk of fracture, such as the hip and spine, using exercises such as lunges, squats, and rows [91]. Second, exercise programs must be of greater intensity than loading experienced in daily life, in order to stimulate bone remodeling and improve BMD, especially among postmenopausal women, where greater loading may be required to offset estrogen-induced bone loss [91]. Further recommendations for the optimization of bone health in postmenopausal women include strength training more frequently than twice weekly and resistance training program durations of at least 400 days [92].

Impact of Exercise on Cancer Outcomes

Recently, the role of exercise in modifying cancer-related outcomes has been explored [5•, 7, 8•]. Two large RCTs have reported a small positive benefit on chemotherapy completion rate with resistance exercise only or a combined aerobic and resistance intervention completed during chemotherapy for breast cancer [5•, 7]. In a three-arm RCT of early-stage breast cancer survivors randomized to aerobic exercise, resistance exercise, or usual care during adjuvant chemotherapy, Courneya et al. reported a mean relative dose intensity of 89.9 % in the resistance exercise group, which was significantly higher than the usual care mean of 84.1 %, but not different from the aerobic exercise group mean of 87.4 % [7]. In a three-arm RCT of supervised aerobic and resistance intervention, home-based aerobic intervention, or usual care in early-stage breast cancer survivors during adjuvant chemotherapy, van Waart et al. used binary logistic regression to determine whether group assignment predicted the occurrence of a single dose reduction. Although a dose reduction was less likely in the exercise groups, it should be noted that a single dose reduction could result in the patient still receiving 96.4 % of their planned treatment dose [93].

The potential of exercise to improve chemotherapy completion rate is a promising potential link to understanding if exercise can improve cancer outcomes, as chemotherapy dose reductions are associated with worse cancer outcomes [94]. However, it is unclear whether the small effects reported by these studies are of clinical importance. An 8-year follow-up to the study by Courneya et al. reported a trend toward improved disease-free, distant disease-free, and overall survival in the participants in the exercise groups relative to the usual care group [8•]. However, the authors duly noted that the original study was not powered for this outcome and a larger sample size would be required to establish a statistically significant effect. Although the currently available evidence in this area is limited, as outlined in this review, a number of the established benefits of exercise for cancer survivors are predictors of disability, morbidity, and mortality.

Impact of Exercise Intervention Delivery Method

In the studies discussed above, the type and structure of the exercise interventions varied widely, which may be a reason for differences in observed training effects. For example, home-based interventions, which may or may not include counseling through phone calls, emails, and face-to-face sessions, may result in smaller effect sizes relative to supervised exercise programming administered by exercise professionals with accountability for missed sessions, and potentially higher prescribed exercise intensity. In fact, the single RCT comparing a supervised aerobic and resistance program to a home-based aerobic program in breast cancer survivors reported greater improvements with the supervised exercise arm relative to the home-based exercise arm in cardiorespiratory fitness, physical functioning, treatment symptoms, and less chemotherapy dose adjustments [5•].

Adherence to prescribed exercise is critical for the efficacy of interventions, whether supervised or home-based. The goal of behavioral change interventions is to improve adherence to physical activity levels long term. A systematic review and meta-analysis of interventions aimed at physical activity behavior change in breast cancer survivors reported that more intense supervision and/or monitoring produced larger improvements in physical activity levels [95]. A positive trend toward improved physical activity levels was observed in the treatment groups who received behavioral counseling, and many of the larger effect sizes were associated with interventions supported by phone or email counseling [95].

Home-based exercise interventions can also improve physical health outcomes in breast cancer survivors and may be easier for patients to adhere to during chemotherapy [5•]. In a three-arm RCT by Yuen et al., the efficacy of 12-week home-based aerobic versus home-based resistance exercise interventions was compared to usual care [96]. The aerobic intervention reduced patient-reported fatigue, while the resistance intervention improved functional capacity, as measured by the 6-min walk test. Due to the accessibility of home-based exercise interventions, evaluating and improving the impact of these interventions is of high interest. Increasing communication and support through phone calls, emails, and face-to-face sessions with research staff may be ways to increase the overall impact of the home-based interventions [95].

Exercise Guidelines for Breast Cancer Survivors

Participation in physical activity during cancer treatment has been established as both safe and effective for numerous health benefits [1••]. The American College of Sports Medicine encourages individuals undergoing treatment for various types of cancer to aim to achieve the same physical activity guidelines for health as the general population [1••]. These guidelines include 75 to 150 min of moderate- to vigorous-intensity aerobic exercise per week, two to three days per week of resistance-based training, and flexibility exercises performed daily to maintain range of motion and reduce risk of injury [1••]. It is important to note that when developing an exercise program for cancer survivors, individual differences must be considered and adjusted for when necessary, including individual fitness level, health status, treatment protocols, and side effects, surgeries, and disease stage [1••]. In addition, potential risks related to side effects associated with cancer treatment, such as increased risk of fracture due to hormonal therapies, should be considered when developing an exercise program, as inappropriately performed or planned exercise programs may increase risk of injury [1••]. In summary, physical activity during cancer treatment should be tailored to appropriately suit the individual's diagnosis, exercise tolerance, and physical ability in order to gain the most benefits and avoid injury.

User-friendly, evidence-based resources around physical activity both during treatment and following treatment are available from the American Cancer Society (http://www.cancer.org/treatment/survivorshipduringandaftertreatment/stayingactive/physical-activity-and-the-cancer-patient). An article providing recommendations by an expert panel around lifestyle factors for cancer survivors has recently been updated and published for clinicians [97].

Conclusion

Although direct evidence of the benefit of exercise for clinically relevant cancer and mortality outcomes in breast cancer survivors is currently limited, a number of the reported physical benefits of exercise training have established associations with disability, mortality, and fracture risk in cancer and non-cancer populations. Improvements in cardiorespiratory fitness, muscle strength and lean mass, body composition, cardiovascular risk factors, and bone health are reported benefits of exercise training in breast cancer survivors with established associations with clinical outcomes. However, RCTs with long-term follow-up are required to confirm that the beneficial effect of exercise on these surrogate markers translates to improved clinical outcomes in breast cancer survivors.

Compliance with Ethical Standards

Conflict of Interest Amy A. Kirkham, Kelcey A. Bland, Sarah Sayyari, Kristin L. Campbell, and Margot K. Davis declare that they have no conflict of interest

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.•• Schmitz KH, Courneya K, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42:1409–26. **This is a consensus document published by experts in the field on the established benefits of exercise in cancer survivors.**

2. Fong DYT, Ho JWC, Hui BPH, Lee AM, Macfarlane DJ, Leung SSK, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. BMJ. 2012;344:e70.

3. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ. 2006;175:34–41.

4. Lee J, Dodd MJ, Dibble SL, Abrams DI. Nausea at the end of adjuvant cancer treatment in relation to exercise during treatment in patients with breast cancer. Oncol Nurs Forum. 2008;35:830–5.

5.• van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. J Clin Oncol. 2015;33:1918–27. **This is the only randomized control trial to compare supervised exercise to home-based exercise with a usual care control group. This study demonstrated several important benefits for both exercise groups.**

6. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, et al. Exercise interventions on health-related quality of life for cancer survivors (review). Cochrane database of systematic reviews (Online). 2012;8.
7. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007;25:4396–404.
8.• Courneya KS, Segal RJ, McKenzie DC, Dong H, Gelmon K, Friedenreich CM, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. Med Sci Sports Exerc. 2014;46:1744–51. **This is the single study to report on the effect of a supervised exercise intervention on breast cancer outcomes.**
9. Jones LW, Eves ND, Haykowsky M, Freedland SJ, Mackey JR. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. Lancet Oncol. 2009;10:598–605.
10. Levine BD. V_{O2}max: what do we know, and what do we still need to know? J Physiol. 2008;586:25–34.
11. Hornsby WE, Douglas PS, West MJ, Kenjale AA, Lane AR, Schwitzer ER, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. Acta Oncol. 2014;53:65–74.
12.• Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol. 2012;30:2530–7. **This is an excellent summary paper of the effects of breast cancer treatment on cardiorespiratory fitness and selected cardiovascular measures at different time points during treatment.**
13. McGuire DK, Levine BD, Williamson JW, Snell PG. A 30-year follow-up of the Dallas Bed Rest and Training Study I. Effect of age on the cardiovascular response to exercise. Circulation. 2001;104:1358–66.
14. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA. 1989;262:2395–401.
15. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, et al. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J. 2008;156:292–300.
16. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood J. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346:793–801.
17. Peel JB, Sui X, Adams SA, Hébert JR, Hardin JW, Blair SN. A prospective study of cardiorespiratory fitness and breast cancer mortality. Med Sci Sports Exerc. 2009;41:742–8.
18. Blair SN, Kohl HW, Barlow CE, Paffenbarger RS, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. JAMA. 1995;273:1093–8.
19. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the six-minute walk test in cancer patients. Int J Sports Med. 2013;34:631–6.
20. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. Int Med J. 2009;39:495–501.
21. Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign.". J Geriatr Phys Ther. 2009;32:2–5.
22. Cesari M, Cerullo F, Zamboni V, Di Palma R, Scambia G, Balducci L, et al. Functional status and mortality in older women with gynecological cancer. J Gerontol A Biol Sci Med Sci. 2013;68:1129–33.
23. Klepin HD, Geiger AM, Tooze JA, Newman AB, Colbert LH, Bauer DC, et al. Physical performance and subsequent disability and survival in older adults with malignancy: results from the Health, Aging and Body Composition Study. J Am Geriatr Soc. 2010;58:76–82.
24. Niederer D, Schmidt K, Vogt L, Egen J, Klingler J, Hübscher M, et al. Functional capacity and fear of falling in cancer patients undergoing chemotherapy. Gait Posture. 2014;39:865–9.
25. Winters-Stone KM, Torgrimson B, Horak F, Eisner A, Nail L, Leo MC, et al. Identifying factors associated with falls in postmenopausal breast cancer survivors: a multi-disciplinary approach. Arch Phys Med Rehabil. 2011;92:646–52.
26.• Battaglini CL, Mills RC, Phillips BL, Lee JT, Story CE, Nascimento MG, et al. Twenty-five years of research on the effects of exercise training in breast cancer survivors: a systematic review of the literature. World J Clin Oncol. 2014;5:177–90. **This is the most recent review summarizing the benefits of exercise training on numerous health outcomes.**
27. Jones LW, Eves ND, Peppercorn J. Pre-exercise screening and prescription guidelines for cancer patients. Lancet Oncol. 2010;11:914–6.
28. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults. Med Sci Sports Exerc. 2011;43:1334–59.
29. Winters-Stone KM, Dobek J, Bennett JA, Nail LM, Leo MC, Schwartz A. The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: a randomized controlled trial. J Cancer Surviv. 2011;6:189–99.
30. Litterini AJ, Fieler VK, Cavanaugh JT, Lee JQ. Differential effects of cardiovascular and resistance exercise on functional mobility in individuals with advanced cancer: a randomized trial. Arch Phys Med Rehabil. 2013;94:2329–35.
31. Gagnon B, Murphy J, Eades M, Lemoignan J, Jelowicki M, Carney S, et al. A prospective evaluation of an interdisciplinary nutrition-rehabilitation program for patients with advanced cancer. Curr Oncol. 2013;20:310.
32. Rantanen T. Muscle strength, disability and mortality. Scand J Med Sci Sports. 2003;13:3–8.
33. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci. 2006;61:72–7.
34. Rantanen T, Guralnik JM, Foley D, Masaki K, Leveille S, Curb JD, et al. Midlife hand grip strength as a predictor of old age disability. JAMA. 1999;281:558–60.
35. Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. Am J Med. 2007;120:337–42.
36. Kirkham AA, Neil-Sztramko SE, Morgan J, Hodson S, Weller S, Mcrae T, et al. Health-related physical fitness assessment in a community-based cancer rehabilitation setting. Support Care Cancer. 2015;23:2525–33.
37. Rietman JS, Dijkstra PU, Debreczeni R, Geertzen JH, Robinson DP, de Vries J. Impairments, disabilities and health related quality of life after treatment for breast cancer: a follow-up study 2.7 years after surgery. Disabil Rehabil. 2015;26:78–84.
38. Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodríguez L, Fernández-de-las-Peñas C, Ruiz JR, Arroyo-Morales M. The handgrip strength test as a measure of function in breast cancer survivors. Am J Phys Med Rehabil. 2012;91:774–82.
39. McCarthy EK, Horvat MA, Holtsberg PA, Wisenbaker JM. Repeated chair stands as a measure of lower limb strength in sexagenarian women. J Gerontol A Biol Sci Med Sci. 2004;59:1207–12.
40.•• Pescatello LS, Arena R, Riebe D, Thompson PD, editors. ACSM's guidelines for exercise testing and prescription. 9th ed.

Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2014. **This book is the gold standard resource on exercise testing and prescription.**
41. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006;61:1059–64.
42. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc. 2002;50: 889–96.
43. Kutynec CL, McCargar L, Barr SI, Hislop TG. Energy balance in women with breast cancer during adjuvant treatment. J Am Diet Assoc. 1999;99:1222–7.
44. Harvie MN, Campbell IT, Baildam A, Howell A. Energy balance in early breast cancer patients receiving adjuvant chemotherapy. Breast Cancer Res Treat. 2004;83:201–10.
45. Winters-Stone KM, Bennett JA, Nail L, Schwartz A. Strength, physical activity, and age predict fatigue in older breast cancer survivors. Oncol Nurs Forum. 2008;35:815–21.
46. Winters-Stone KM, Nail L, Bennett JA, Schwartz A. Bone health and falls: fracture risk in breast cancer survivors with chemotherapy-induced amenorrhea. Oncol Nurs Forum. 2009;36:315–25.
47. Irwin ML, editor. ACSM's guide to exercise and cancer survivorship. Windsor: Human Kinetics; 2012.
48. Schmitz KH, Speck RM. Risks and benefits of physical activity among breast cancer survivors who have completed treatment. Women's Health. 2010;6:221–38.
49. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011;13:R64.
50. Hooning MJ, Botma A, Aleman BMP, Baaijens MHA, Bartelink H, Klijn JGM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. J Natl Cancer Inst. 2007;99:365–75.
51. Riihimaki M, Thomsen H, Brandt A, Sundquist J, Hemminki K. Death causes in breast cancer patients. Ann Oncol. 2012;23:604–10.
52. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. J Am Coll Cardiol. 2007;50:1435–41.
53. World Heart Federation. Cardiovascular disease risk factors. World Heart Federation; 2013 pp. 1–4.
54. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. 2001;285:885–92.
55. Yancik R, Havlik RJ, Wesley MN, Ries L, Long S, Rossi WK, et al. Cancer and comorbidity in older patients: a descriptive profile. Ann Epidemiol. 1996;6:399–412.
56. Mouhayar E, Salahudeen A. Hypertension in cancer patients. Tex Heart Inst J. 2011;38:263–5.
57. Stamler J, Rose G, Stamler R, Elliott P, Dyer A, Marmot M. INTERSALT study findings. Public health and medical care implications. Hypertension. 1989;14:570–7.
58. Harris EER, Correa C, Hwang WT, Liao J, Litt HI, Ferrari VA, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. J Clin Oncol. 2006;24: 4100–6.
59. Mendis S, Puska P, Norrving B, editors. Global atlas on cardiovascular disease prevention and control. Geneva: World Health Organization; 2011.
60. Thompat W, Sukarayodhin S, Sornprom A, Sudjaroen Y, Laisupasin P. Comparison of serum lipid profiles between normal controls and breast cancer patients. J Lab Physicians. 2013;5:38.
61. Hasija K, Bagga HK. Alterations of serum cholesterol and serum lipoprotein in breast cancer of women. Indian J Clin Biochem. 2005;20:61–6.
62. Kökoğlu E, Karaarslan I, Karaarslan HM, Baloğlu H. Alterations of serum lipids and lipoproteins in breast cancer. Cancer Lett. 1994;82:175–8.
63. Lopez-Saez J-B, Martinez-Rubio JA, Alvarez MM, Carrera CG, Dominguez Villar M, de Lomas Mier AG, et al. Metabolic profile of breast cancer in a population of women in southern Spain. Open Clin Cancer J. 2008;2:1–6.
64. Yadav NK, Poudel B, Thanpari C, Chandra KB. Assessment of biochemical profiles in premenopausal and postmenopausal women with breast cancer. Asian Pac J Cancer Prev. 2012;13:3385–8.
65. Alexopoulos CG, Pournaras S, Vaslamatzis M, Avgerinos A, Raptis S. Changes in serum lipids and lipoproteins in cancer patients during chemotherapy. Cancer Chemother Pharmacol. 1992;30:412–6.
66. Love RR, Wiebe DA, Newcomb PA, Cameron L, Leventhal H, Jordan VC, et al. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. Ann Intern Med. 1991;115:860–4.
67. Irwin ML, McTiernan A, Baumgartner RN, Baumgartner KB, Bernstein L, Gilliland FD, et al. Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol. 2005;23:774–82.
68. Goodwin PJ, Ennis M, Pritchard KI, McCready D, Koo J, Sidlofsky S, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. J Clin Oncol. 1999;17:120.
69.• Ghose A, Kundu R, Toumeh A, Hornbeck C, Mohamed I. A review of obesity, insulin resistance, and the role of exercise in breast cancer patients. Nutr Cancer. 2015;67:197–202. **This is a comprehensive review focusing on the interactions between breast cancer treatment, weight gain, and insurance resistance, with a discussion of the role of exercise.**
70. Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med. 2002;162:1867–72.
71. Goodwin PJ, Ennis M, Bahl M, Fantus IG, Pritchard KI, Trudeau ME, et al. High insulin levels in newly diagnosed breast cancer patients reflect underlying insulin resistance and are associated with components of the insulin resistance syndrome. Breast Cancer Res Treat. 2008;114:517–25.
72. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Madarnas Y, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol. 2001;20:42–51.
73.• Kirkham AA, Davis MK. Exercise prevention of cardiovascular disease in breast cancer survivors. J Oncol. 2015;Article ID 917606. **This is the most recent review on the evidence for the role of exercise in preventing cardiovascular disease in breast cancer survivors. It summarizes the available animal research demonstrating the ability of aerobic exercise to attenuate direct effects of doxorubicin on the heart, as well as the effects of exercise on cardiovascular risk factors in breast cancer survivors.**
74. Sturgeon KM, Ky B, Libonati JR, Schmitz KH. The effects of exercise on cardiovascular outcomes before, during, and after treatment for breast cancer. Breast Cancer Res Treat. 2014;143:219–26.
75. Collier SR, Kanaley JA, Carhart R, Frechette V, Tobin MM, Hall AK, et al. Effect of 4 weeks of aerobic or resistance exercise training on arterial stiffness, blood flow and blood pressure in pre- and stage-1 hypertensives. J Hum Hypertens. 2008;22:678–86.
76. Schwartz AL. Exercise and weight gain in breast cancer patients receiving chemotherapy. Cancer Pract. 2000;8:231–7.
77. Reeves MM, Terranova CO, Eakin EG, Demark-Wahnefried W. Weight loss intervention trials in women with breast cancer: a systematic review. Obes Rev. 2014;15:749–68.
78. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New Engl J Med. 2001;344:1343–50.
79. Demark-Wahnefried W, Case LD, Blackwell K, Marcom PK, Kraus W, Aziz N, et al. Results of a diet/exercise feasibility trial to prevent

adverse body composition change in breast cancer patients on adjuvant chemotherapy. Clin Breast Cancer. 2008;8:70–9.
80. Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR. Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. Cancer Epidemiol Biomarkers Prev. 2003;12:721–7.
81. Guinan E, Hussey J, Broderick JM, Lithander FE, O'Donnell D, Kennedy MJ, et al. The effect of aerobic exercise on metabolic and inflammatory markers in breast cancer survivors—a pilot study. Support Care Cancer. 2013;21:1983–92.
82. Irwin ML, Varma K, Alvarez-Reeves M, Cadmus L, Wiley A, Chung GG, et al. Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship Study. Cancer Epidemiol Biomarkers Prev. 2009;18:306–13.
83. Ligibel JA, Campbell N, Partridge A, Chen WY, Salinardi T, Chen H, et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. J Clin Oncol. 2008;26:907–12.
84. Nuri R, Kordi MR, Moghaddasi M, Rahnama N, Damirchi A, Rahmani-Nia F, et al. Effect of combination exercise training on metabolic syndrome parameters in postmenopausal women with breast cancer. J Cancer Res Ther. 2012;8:238–42.
85. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomarkers Prev. 2005;14:1672–80.
86. Campbell KL, Van Patten CL, Neil SE, Kirkham AA, Gotay CC, Gelmon KA, et al. Feasibility of a lifestyle intervention on body weight and serum biomarkers in breast cancer survivors with overweight and obesity. J Acad Nutr Diet. 2012;112:559–67.
87. Chen Z, Maricic M, Bassford TL, Pettinger M, Ritenbaugh C, Lopez AM, et al. Fracture risk among breast cancer survivors: results from the Women's Health Initiative Observational Study. Arch Intern Med. 2005;165:552–8.
88. Lester J, Dodwell D, McCloskey E, Coleman R. The causes and treatment of bone loss associated with carcinoma of the breast. Cancer Treat Rev. 2005;31:115–42.
89. Schwartz AL, Winters-Stone K, Gallucci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum. 2007;34:627–33.
90. Winters-Stone KM, Dobek J, Nail L, Bennett JA, Leo MC, Naik A, et al. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. Breast Cancer Res Treat. 2011;127:447–56.
91. Winters-Stone KM, Schwartz A, Nail LM. A review of exercise interventions to improve bone health in adult cancer survivors. J Cancer Surviv. 2010;4:187–201.
92. Waltman NL, Twiss JJ, Ott CD, Gross GJ, Lindsey AM, Moore TE, et al. The effect of weight training on bone mineral density and bone turnover in postmenopausal breast cancer survivors with bone loss: a 24-month randomized controlled trial. Osteoporos Int. 2009;21:1361–9.
93. Chia S. BCCA protocol summary for adjuvant therapy for breast cancer using doxorubicin and cyclophosphamide followed by pAclitaxel [Internet]. British Columbia Cancer Agency. 2000. http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Breast/BRAJACT_Protocol_1Dec2014.pdf. Accessed 10 Jul 2015.
94. Chang J. Chemotherapy dose reduction and delay in clinical practice: evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. Eur J Cancer. 2000;36:11–4.
95. Bluethmann SM, Vernon SW, Gabriel KP, Murphy CC, Bartholomew LK. Taking the next step: a systematic review and meta-analysis of physical activity and behavior change interventions in recent post-treatment breast cancer survivors. Breast Cancer Res Treat. 2015;149:331–42.
96. Yuen HK, Sword D. Home-based exercise to alleviate fatigue and improve functional capacity among breast cancer survivors. J Allied Health. 2007;36:e257–75.
97. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Shwartz A, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62:275–6.