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Effects of Exercise Training on Physical Fitness and Biomarker Levels in Breast Cancer Survivors

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Background: Exercise has been identified as a beneficial intervention to enhance quality of life in breast cancer survivors. In addition, there has been a noteworthy increase in studies emphasizing the benefits of exercise in cancer. We sought to summarize the empirical literature concerning the effects of exercise on physical fitness and biomarker levels in breast cancer survivors according to the type of exercise.

Methods: We searched PubMed and PubMed Central for studies on the association of exercise with the levels of various biomarkers and physical fitness in breast cancer survivors. We investigated the effects of different types of exercise (aerobic, resistance, or combined) on breast cancer survivors, with changes in physical fitness and biomarker levels as the primary outcomes.

Results: In total, 118 research papers published from 2012 to July 2016 were retrieved from PubMed and PubMed Central. Of these, 24 papers met our inclusion criteria. All types of exercise were found to improve physical fitness in breast cancer survivors. However, the results with regard to biomarkers were controversial.

Conclusion: The findings of this review suggest that combined exercise is associated with better outcomes than aerobic or resistance exercise alone in breast cancer survivors.

Key Words: Breast cancer survivors, Types of exercise, Physical fitness, Biomarkers

INTRODUCTION

Worldwide, breast cancer is the most common type of cancer in women and the second leading cause of cancer death among women. In 2015, about 246,000 cases of breast cancer were diagnosed in the United States of America [1]. In Korea, approximately 141,300 women were diagnosed with invasive or non-invasive breast cancer in 2013. However, due to the improvement and development of new treatments and drugs, 90% of cancer patients now survive at least five years after diagnosis [2]. Breast cancer treatments include chemotherapy, surgery, radiation therapy, hormone therapy, and anticancer drugs [3]. It is highly probable that various therapies have positively influenced breast cancer patients and survivors. However, the most remarkable aspect is that the rates of breast cancer incidence and mortality have decreased. For this reason, the physical fitness of breast cancer survivors is an important concern [4].

Exercise and physical activity are vital to reduce risk factors and improve physical fitness, psychological controls, and quality of life in breast cancer survivors [5,6]. Several

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studies have reported the benefits of exercise for breast cancer survivors. Also, exercise promotes social interaction during and after treatment and can significantly enhance the ability of cancer patients and survivors to cope with fatigue, lymphedema, and bone metastasis [7]. However, the most important point is that, after diagnosis, most breast cancer patients and survivors reduce their rate of participation in physical activity by 11% [8].

Many studies have described the effects of exercise training on the levels of biomarkers, including various adipokines. Some studies have suggested that tai chi exercise induces changes in inflammatory cytokine levels [9]. However, there have been controversial results regarding the effects of exercise on leptin and adiponectin levels. Some studies have demonstrated that serum and plasma leptin levels decreased while adiponectin levels increased after weight loss accompanied by exercise. On the other hand, other studies have indicated that plasma adiponectin level did not change in a 6-month combined exercise intervention program [10,11]. However, research on the effects of different types of exercise on physical fitness and various biomarkers in breast cancer is still in an early stage.

The purpose of the present review was to outline current research trends on the benefits of combined exercise (CE), aerobic exercise (AE), and resistance exercise (RE) on physical fitness and biomarker levels in breast cancer survivors. In this review, we focused on the demonstrated health benefits of physical fitness and various biomarkers and the informed benefits of risk management for breast cancer survivors according to the type of exercise.

MATERIALS AND METHODS

We searched the electronic databases of PubMed and PubMed Central from 2012 to July 2016. Our search was limited to human studies in the English language. We only retained experimental research studies in which participants had been diagnosed with stage I-IIIc breast cancer and were free of metastatic disease and other cancers after surgery and anticancer treatments. We reviewed 118 papers, of which 114 were considered potentially relevant. Ultimately, we found 24 research papers that met our inclusion criteria.

RESULTS

In total, we evaluated 24 studies involving 1,351 subjects and divided them according to their focus on aerobic, resistance, or combined exercise. In the case of aerobic exercise, the intensity ranged from 50% to 85% maximal heart rate and from 2 to 3 days per week. Resistance exercise included body-weight and Thera-Band resistance and ranged from 1 to 3 sets of 8 to 20 reps. Combined exercise included both resistance and aerobic exercise.

1. Aerobic exercise and improved physical fitness

Four trials examined the effects of aerobic exercise on physical fitness in breast cancer survivors. The trials ranged from 6 to 24 weeks in duration, and the number of subjects in the trials ranged from 33 to 69. Adherence to the interventions ranged from 50% to 80% maximum intensity. The percentage of body fat, maximal oxygen consumption (VO_{2max}), hand grip strength and 6-min walking test performance were determined in four studies, and 1-mile running test performance was determined in four studies. In the four studies for aerobic exercise reported that significant physical fitness outcomes in breast cancer survivors. Aerobic exercise improved the percentage of body fat, VO_{2max}, hand grip strength, 6-min walking test performance and 1-mile running test performance.

2. Resistance exercise and improved physical fitness

Four trials examined the effects of resistance exercise on physical fitness in breast cancer survivors. The trials ranged from 8 weeks to 12 months in duration, and the number of subjects in the trials ranged from 20 to 249. The chest, hip, arm, and leg strengths were determined in four studies. In the four studies for resistance exercise reported that significant physical fitness outcomes in breast cancer survivors. Resistance exercise improved chest, hip, arm, and leg strength.

3. Combined exercise and improved physical fitness

Four trials examined the effects of combined exercise on physical fitness in breast cancer survivors. The trials ranged from 12 weeks to 3 months in duration, and the number of subjects in the trials ranged from 28 to 58. Adherence

to the interventions ranged from 60% to 85% maximal heart rate and from 8 to 15 reps using body-weight, Thera-Band and machine resistance. The chest, hip, arm, and leg strength; functional walking performance; and predicted VO_{2max} were determined. In the four studies for combined exercise that significant physical fitness outcomes in breast cancer survivors. Combined exercise improved the chest, hip, arm, and leg strength; functional walking performance; and predicted VO_{2max} (Table 1).

4. Aerobic exercise and improved biomarkers

Four trials examined the effects of aerobic exercise on

Table 1. Effects of exercise on physical fitness

Reference	Cancer stage	Participants	Mode	Intervention	Outcome
Pinto et al. [12] (2005)	Stage I-II	3 yrs after treatment. 12 control 12 exercise	AE	2 x / wk for 12 wks at 55-65% maximum intensity.	↑ △1-mile walking test ↓ △%body fat
Ohira et al. [13] (2006)	Stage I-III	Completing treatment. 43 control 43 exercise	RE	2 x / wk for 24 wks.	↑ △Bench press
Helen et al. [14] (2008)	Stage I-IIIa	58 mo. after treatment. Pre- and post-intervention	Comb	3 x / wk for 12 wks. AE: 20 min, cycling and rowing. RE: Whole-body progressive, 10-15 reps, two sets.	↑ △Leg press ↑ △Chest extension
Irwin et al. [15] (2009)	Stage I-IIIa	6 mo. after treatment. 33 control 36 exercise	AE	3 x / wk for 24 wks at 50-80% maximum intensity.	↓ △%body fat
Antonia et al. [16] (2010)	N/A	2 yrs after treatment. 13 control 14 exercise	AE	Dance exercise. 3 x / wk for 24 wks at 65-80% maximum intensity.	↓ △Hand grip strength ↓ △6-min walk
Waltman et al. [17] (2010)	Stage I-V	6 mo. after treatment. 125 control 123 exercise	RE	2 x / wk for 24 mo. 8-12 reps, two sets.	↑ △Hip extension ↑ △Hip flexion ↑ △Knee extension ↑ △Knee flexion
Winters et al. [18] (2011)	Stage I-IIIa	1 yr after treatment. 54 control 52 exercise	RE	1 x / wk for 12 mo. 8-12 reps, three sets.	↑ △Bench press ↑ △Leg press
Laura et al. [19] (2012)	Stage I-IIIa	2 mo. after treatment. 13 control 15 exercise	Comb	2 x / wk for 3 mo. AE: Moderate, 150 min/week. RE: Whole-body band exercise, 20 reps.	↑ △Predicted VO_{2max} ↑ △Back / leg strength
Benton et al. [20] (2014)	Stage I-III	Completing treatment. 20 pre- and post-intervention	RE	2 x / wk for 8 wks. 10-12 reps, three sets.	↑ △Chest press
Hannah et al. [21] (2015)	Stage I-III	6 mo. after treatment. 38 control 45 exercise	Comb	2 x / wk for 12 mo. AE: 60-80% maximum intensity. RE: Whole-body progressive, 9-12 reps, three sets.	↑ △VO_{2max}
Lianne et al. [22] (2015)	Stage I-IIIa	Completing treatment. 10 control 23 exercise	AE	6 wks at 55-80% maximum intensity.	↑ △VO_{2max}
Michael et al. [23] (2016)	N/A	17 mo. after treatment. 52 pre- and post-intervention	Comb	3 x / wk for 12 wks. AE: 70-85% maximum intensity. RE: Whole-body progressive, 8-12 reps, two sets.	↑ △Timed up and go ↑ △Leg press ↑ △Chest press ↑ △Back scratch ↑ △Single-leg stand

Notes: ↑ Increase, ↓ Decrease.
AE: aerobic exercise, Comb: combined exercise, RE: resistance exercise, reps: repetitions, VO_{2max}: maximal oxygen consumption.

biomarker levels in breast cancer survivors. The trials ranged from 6 to 15 weeks in duration, and the number of subjects in the trials ranged from 23 to 94. Adherence to the interventions ranged from 55% to 80% maximal heart rate. The levels of inflammatory cytokines, metabolic biomarkers, and cancer biomarkers were determined in four studies. Only one study reported that aerobic exercise improved the levels of cancer markers. Giallauria and colleagues conducted a randomized controlled trial involving a supervised aerobic exercise intervention among 94 breast cancer survivors. The serum level of High-mobility group box 1 (HMGB-1) was obtained at baseline and at the 12-week follow-up. The authors reported that aerobic exercise reduced the serum level of HMGB-1, which consequently enhanced the health status of cancer patients.

5. Resistance exercise and improved biomarkers

Four trials examined the effects of resistance exercise on biomarker levels in breast cancer survivors. The trials ranged from 24 hours to 3 months in duration, and the number of subjects in the trials ranged from 12 to 103. The levels of inflammatory cytokines, metabolic biomarkers, and cancer biomarkers were determined in four studies. Two trials reported that resistance exercise improved serum interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels.

6. Combined exercise and improved biomarkers

Four trials examined the effects of combined exercise on biomarker levels in breast cancer survivors. The trials ranged from 8 weeks to 6 months in duration, and the number of subjects in the trials ranged from 16 to 79. The levels of inflammatory cytokines, metabolic biomarkers, and can-

Table 2. Effects of exercise on mediators of inflammation

Reference	Cancer stage	Participants	Mode	Intervention	Outcome
Martina et al. [24] (2016)	Stage I-IIIa	Completing treatment. 49 control 54 exercise	RE	2 x / wk for 12 wks. 8-12 reps, three sets.	↓ △IL-6
Amanda et al. [25] (2016)	Stage I-IIIa	17 wks after treatment. 19 control 20 exercise	RE	3 x / wk for 16 wks. 8-10 reps, three sets.	≒ △TNF-α ≒ △IL-6 ≒ △IL-10 ≒ △hs-CRP ↓ △TNF-α
Nigel et al. [26] (2015)	Stage I-IIIc	12 mo. after treatment. 22 control 20 exercise	RE	15-20 reps, three sets. 24 hours.	≒ △IL-6 ≒ △TNF-α ≒ △hs-CRP
Swisher et al. [27] (2015)	Stage I-III	3 mo. after treatment. 10 control 13 exercise	AE	2 x / wk for 12 wks at 60-75% maximum intensity.	≒ △hs-CRP ≒ △IL-6 ≒ △TNF-α ≒ △Adiponectin ≒ △Insulin ≒ △Leptin
Lianne et al. [22] (2015)	Stage I-IIIa	Completing treatment. 10 control 23 exercise	AE	6 wks at 55-80% maximum intensity.	≒ △Insulin ≒ △Glucose ≒ △HOMA-IR ≒ △hs-CRP
Giallauria et al. [28] (2014)	Stage I	N/A 33 control 62 exercise	AE	3 x / wk for 12 wks at 70% maximum intensity.	↓ △HMGB-1
Laura et al. [19] (2014)	Stage I-II	4 wks after treatment. 22 control 20 exercise	Comb	2 x / wk for 3 mo. AE: 48-52 heart reserve. RE: Whole-body band exercise, 15 reps, two sets.	≒ △IL-6 ≒ △IL-8 ↓ △IL-10 ≒ △TNF-α

Table 2. Continued

Reference	Cancer stage	Participants	Mode	Intervention	Outcome
Scott et al. [29] (2013)	Stage I-III	18 mo. after treatment. 38 control 42 exercise	Comb	3 x / wk for 3 mo. AE: 65-85% maximum intensity. RE: Whole-body band exercise 10-15 min.	↓ △Leptin ↓ △Total cholesterol
Tish et al. [30] (2016)	N/A	3 yrs after treatment. 78 control 76 exercise	Comb	3 x / wk for 12 mo. AE: 65-70% maximal heart rate. RE: Whole-body progressive, 8 reps, one set.	≒ △Osteocalcin ≒ △Vitamin D
Gomez et al. [31] (2011)	Stage I-II	18 mo. after treatment. 8 control 8 exercise	Comb	3 x / wk for 8 wks AE: 70-80% maximal heart rate. RE: Whole-body progressive, 12-15 reps, three sets.	↓ △CTACK
Adrian et al. [32] (2005)	Stage I-IIIb	Completing treatment. 28 control 25 exercise	AE	2 x / wk for 15 wks at 70-75% maximum intensity.	≒ △IL-1 ≒ △IL-4 ≒ △IL-6 ≒ △IL-10 ≒ △TNF-α
Sara et al. [33] (2012)	Stage I-IIIa	12 mo. after treatment. 37 intervention 38 control	Comb	3 x wk for 6 mo. AE: 60-80% maximum intensity. RE: Whole-body yoga exercise, 30 min.	≒ △IL-6 ≒ △hs-CRP ≒ △TNF-α
Nora et al. [35] (2013)	Stage I-III	12 mo. after treatment. 19 pre- and post-intervention	Comb	2 x / wk AE: walking 3-3.5 mph 30 min. RE: Whole-body progressive, 8-12 reps, two sets.	↓ △C-peptide
Guinan et al. [36] (2013)	Stage I-III	2 mo. after treatment. 10 control 16 exercise	AE	2 x / wk for 8 wks at 45-65% maximum intensity.	≒ △Insulin ≒ △HbA1c
Campbell et al. [37] (2012)	Stage I-IIIa	3 mo. after treatment. 14 pre- and post-intervention	AE	2 x / wk for 24 wks at 60% maximum intensity.	↓ △HDL-c
Emily et al. [38] (2014)	Stage I-III	5 yrs after treatment. 12 pre- and post-intervention	RE	2 x / wk for 6 mo. 8-12 reps, two sets.	≒ △hs-CRP
Befort et al. [39] (2012)	Stage I-IIIc	3 mo. after treatment. 36 pre- and post-intervention	AE	225 min / wk for 12 wks. Moderate walking, 225 min per week.	↓ △Insulin ↓ △Leptin
Kerri et al. [18] (2011)	Stage I-IIIa	1 yr after treatment. 54 control 52 exercise	RE	12 mo. 8-12 reps, three sets.	↑ △Osteocalcin
Waltman et al. [17] (2010)	Stage I-II	6 mo. after treatment. 113 control 110 exercise	RE	2 x / wk for 24 mo. 8-12 reps, two sets.	↓ △Alkphase B ↓ △NTx
Irwin et al. [15] (2009)	Stage I-IIIa	6 mo. after treatment. 33 control 36 exercise	AE	3 x / wk for 24 wks at 50-80% maximum intensity.	↓ △Insulin ↓ △IGF-1 ↓ △IGFBP-3
Ligibel et al. [40] (2007)	Stage I-III	After 3 mo. treatment. 42 intervention 40 control	Comb	16 wks. RE: whole-body exercise, 50 min per week. AE: 90 min per week.	↓ △Insulin

Notes: ↑ Increase, ↓ Decrease, ≒ No change.

AE: aerobic exercise, Comb: combined exercise, RE: resistance exercise, reps: repetitions, VO_{2max}: maximal oxygen consumption. IL-1: interleukin-1, IL-4: interleukin 4, IL-6: interleukin-6, IL-8: interleukin-8, IL-10: interleukin-10, TNF-α: tumor necrosis factor-α, CTACK: cutaneous T-cell-attracting chemokine, hs-CRP: high sensitivity C-reactive protein, HbA1c: hemoglobin A1c, HDL-c: high-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment of β-cell function and insulin resistance, HMGB-1: high-mobility group box-1, Alkphase-B: bone-specific alkaline phosphatase, NTx: N-telopeptides of type 1 collagen, IGF-1: insulin-like growth factor gene-1, IGFBP-3: insulin-like growth factor-binding protein-3.

cer biomarkers were determined in four studies. Two trials reported that combined exercises improved leptin, total cholesterol, and cutaneous T-cell-attracting chemokine (CTACK) levels (Table 2).

DISCUSSION

In recent years, it has been suggested that it is necessary to continue to study the guidelines for exercise prescriptions for breast cancer survivors, especially the types, localization, and side effects associated with exercise [42]. Generally, the available exercise guidelines for breast cancer survivors emphasize the importance of participating in moderate aerobic exercise, recommend with flexibility, and intermittent or minimally mention of resistance exercise [43,44]. Despite the importance of exercise, up to date, there has been minimal research regarding the effects of different types of exercise on physical fitness and biomarker levels in breast cancer survivors. Therefore, the purpose of this review is to propose the most effective type of exercise by reviewing the effects of each type of exercise on breast cancer survivors.

Some previous studies have suggested that the importance of resistance exercise for breast cancer survivors [45,46]. Although resistance exercise enhances musculoskeletal strength and bone mineral density, but has smaller effects on body composition and lipid profiles [17,25]. And also, single-type aerobic exercise interventions improve body composition and some adipokine levels, but do not affect musculoskeletal strength or the levels of biomarkers associated with bone mineral density [16,39]. In general, we found that combined exercise improves not only body composition and adipokine levels, but also musculoskeletal strength and the levels of biomarkers associated with bone mineral density [14,19,21,23]. Therefore, in view of this evidence, we suggest that the type of combined exercise is more effective for breast cancer survivors than single aerobic exercise or resistance exercise.

In conclusion, our review suggests that combined exercise could be considered a beneficial and effective exercise type for breast cancer survivors. Future trials with strict randomized controlled methodology are needed to verify the effects of different types of exercise on physical fitness and the levels of various biomarkers in breast cancer survivors.

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