

WJCO 5th Anniversary Special Issues (2): Breast cancer**Exercise in patients coping with breast cancer: An overview**

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Author contributions: Eyigor S designed the concept of the review; Kanyilmaz S performed literature search; Eyigor S and Kanyilmaz S drafted and revised the article accordingly.

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Received: December 24, 2013 Revised: March 12, 2014

Accepted: May 28, 2014

Published online: August 10, 2014

Abstract

Breast cancer is the most common type of cancer in women, but fortunately has high survival rates. Many studies have been performed to investigate the effects of exercise in patients diagnosed with breast cancer. There is evidence that exercise after the diagnosis of breast cancer improves mortality, morbidity, health related quality of life, fatigue, physical functioning, muscle strength, and emotional wellbeing. Based on scientific data, breast cancer patients should be recommended to participate in rehabilitation programs including aerobic and strength training. The aim of this article is to review the recently published data on the effect of exercise in patients with breast cancer in order to present the current perspective on the topic.

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Key words: Breast cancer; Exercise; Rehabilitation; Physical activity; Cancer

Core tip: Exercise is not merely safe and feasible for breast cancer patients, but is moreover a complemen-

tary treatment for achieving physiological and psychological improvements. Drawing clinicians' attention to this issue is important for improving patients' quality of life. We advise a multidisciplinary approach to encourage breast cancer patients into engaging in rehabilitation programs combining both strengthening and aerobic exercises for the most beneficial results.

Eyigor S, Kanyilmaz S. Exercise in patients coping with breast cancer: An overview. *World J Clin Oncol* 2014; 5(3): 406-411
Available from: URL: <http://www.wjgnet.com/2218-4333/full/v5/i3/406.htm> DOI: <http://dx.doi.org/10.5306/wjco.v5.i3.406>

INTRODUCTION

Breast cancer is the most frequent cancer in females, with an estimated more than 2.8 million breast cancer survivors in the United States alone^[1,2]. For many years, breast cancer has been incredibly difficult for both patients and health care providers due to its high mortality and morbidity rates^[3]. However, due to recent advances in the diagnosis and treatment of breast cancer, survival rates have increased^[3]. Overall, the 5-year survival rate for breast cancer in all stages has been reported as 89% by the American Cancer Society^[2]. Despite this successful increase in the rate of survival, there are still many problems arising from either the disease itself or relating to its treatment in patients living with the disease.

Due to the high prevalence of breast cancer, especially in developed countries, the increased rates of survival and high expectations in the quality of life for women with breast cancer ultimately led patients and health care providers to seek alternative or additional approaches in the management of the disease^[4]. All of these factors created a greater interest in the physical activity of cancer patients over time. Thus, there has been much research on the effect of exercise on breast cancer patients and survivors within the medical community in the last few

decades^[5].

The effect of exercise might be evaluated in some items according to the disease stage, which may all be considered different major topics of interest. Among them, the preventive effects of exercise for breast cancer and effectiveness of exercise in breast cancer patients are the most covered areas in the current literature. The preventive effect of exercise for breast cancer has been shown in epidemiological studies^[6,7]. Risk reduction with physical activity for breast cancer in females is estimated to be up to 25%-30%^[1,6]. To achieve such an effect, women are recommended to follow a 150-min per week exercise regime of moderate to vigorous intensity consisting of sports or other physical activity^[4].

Fortunately, in many cases, cancer patients are no longer considered isolated people in many aspects of life. The traditional approach of clinicians advising rest and the avoiding of physical activity to breast cancer patients and survivors has changed over time, and both patients and the medical community are seeking the ideal level, type, and intensity of physical activity^[8]. This brings us to the other aspect researched: the effect of exercise in breast cancer patients.

Although the additional effect of exercise in breast cancer has been investigated in numerous studies throughout the last few decades, due to the wide variety in the status of patients in such areas as disease stage, associating co-morbid conditions, and physical function, to date there has been no clear consensus or standard approach that has been agreed upon in terms of exercise in breast cancer patients^[5,8], despite recent systematic reviews and meta-analyses published on the effect of exercise interventions^[5,9,10]. Considering the quickly accumulating amount of literature on the subject, we felt the need to overview the effects of exercise specifically for breast cancer and discuss the need for research for future trials. Therefore, the aim of this article is to review the recently published data on the effect of exercise in patients with breast cancer in order to present the current perspective on the topic.

POSSIBLE MECHANISMS OF EXERCISE

A variety of robust studies have clearly showed the beneficial effects of exercise in a healthy population, with a varying spectrum of positive changes in physiological and psychological effects^[11]. Hence, it is important to determine how these positive effects of exercise impact breast cancer patients.

The effect of treatment of cancer on immune functions and the positive effects of good immune function on survival and morbidity in cancer patients have been linked^[12]. Scientific data has suggested cancer and its treatment are related with a disruption of immune functions^[12,13]. Pro-inflammatory cytokines are found in higher levels in advanced stage, metastatic, and recurrent disease compared with non-metastatic, non-recurrent, and early stage disease^[14]. Although researchers have investigated

the relation between inflammatory markers and exercise in cancer patients, there is no significant data showing the effects of exercise on immune system markers in cancer patients^[13,15]. Recently, a few studies have showed some positive results in cytokine and insulin levels with Tai Chi exercises in breast cancer patients^[16,17].

Angiogenesis and apoptosis are related to the progression and metastasis of tumors, with vascular endothelial growth factor being the most studied angiogenic molecule^[18]. Ergun *et al*^[19] have showed the positive effects on levels of angiogenic molecules with supervised and home exercises in breast cancer patients compared to an education-only-group. Unfortunately, many studies investigating the relationship between immune functions and exercise in breast cancer patients are limited (*e.g.*, due to a small sample size), and so should be investigated further in future randomized clinical trials (RCT) with large populations.

Being overweight/obese is clearly associated with an increased risk of developing many cancer types, including breast cancer in postmenopausal women^[4,20]. The mechanism underlying obesity and breast cancer is considered to be immune function, inflammation, and levels of estrogen and IGF-1^[21,22]. However, there are studies exploring the effects of reducing breast cancer risk with intentional weight loss^[23,24]. The American Cancer Association recommends a healthy diet and advises against gaining weight due to its negative effects on treatment success and recurrence^[25]. The established ways for losing weight are to reduce dietary intake and/or increase physical activity. Besides obtaining a healthy diet, regular exercise in breast cancer patients would be helpful in maintaining their ideal weight.

Hahm *et al*^[26] showed that disruption of the circadian rhythm, such as by performing night shift work, might have an association with the progression of breast cancer. Exercise also acts as a regulator on the circadian rhythm and sleep; therefore regular exercise might hypothetically have an indirect effect on preventing the progression of breast cancer. However, this theory needs to be proven with clinical studies in breast cancer patients.

One descriptive study showed that the prevalence of fibromyalgia might be high in hospitalized breast cancer patients^[27]. Fibromyalgia symptoms additional to typical cancer symptoms, such as fatigue, might inversely influence the patients' quality of life. Thus, taking fibromyalgia into account when prescribing exercise to patients diagnosed with breast cancer should be considered.

EFFECTS OF EXERCISE IN BREAST CANCER

There is a growing interest among cancer patients in searching for alternative options in order to achieve a better life quality. If the effect of practicing exercise in breast cancer patients on mortality as well as morbidity were well understood, that would create an important clinical impact in the future.

Prospective observational studies have demonstrated that physical activity after cancer diagnosis is associated with a reduced risk of cancer recurrence and improved overall mortality among multiple cancer survivor groups, including breast, colorectal, prostate, and ovarian cancer^[25,28-30]. Several studies in breast cancer survivors have demonstrated that being physically active after the diagnosis of breast cancer led to a 24%-67% reduction in the risk of total deaths and a 50%-53% reduction in the risk of breast cancer deaths when compared to a sedentary lifestyle^[31-33]. Some studies have also shown that physical activity is inversely related with co-morbidities in patients diagnosed with breast cancer^[34].

Fatigue is an important symptom that occurs frequently in breast cancer patients and has a negative impact on the quality of life^[35]. Studies have reported a prevalence of fatigue in cancer patients of up to 96%^[36]. A Cochrane review published in 2006 concluded that aerobic and resistive exercise in breast cancer patients on adjuvant therapy had significant positive effects on cardiorespiratory fitness and non-significant effects on fatigue and weight gain^[37]. A meta-analysis published by McNeely *et al*^[5] also showed the significant positive effect of exercise on symptoms of fatigue in breast cancer patients. An updated Cochrane review in 2012 showed the benefits of aerobic exercise in combating fatigue in breast cancer patients during or adjuvant to chemotherapy treatment^[35].

The literature suggests that exercise in breast cancer survivors or in patients receiving therapy improves cardiorespiratory fitness, physical function, and muscular strength^[5,37-39]. However, there is a need for long-term studies for a better interpretation of these results.

Studies show that exercise and physical activity improve depression and anxiety in breast cancer patients receiving adjuvant therapy^[38-40]. Carayol *et al*^[40] suggested that, according to their meta-analysis, relatively low doses consisting of 90-120 min of weekly moderate physical exercise is efficacious for such improvements in patients receiving adjuvant therapy.

A meta-analysis performed for trials on the effect of exercise in breast cancer patients showed a significant pooled effect of exercise on patients' quality of life^[5]. Confirming this data, recent Cochrane reviews evaluating the effects of exercise on health-related quality of life in cancer patients and survivors in randomized and controlled trials have suggested that cancer patients may benefit from exercise in some domains, including physical function, role function, social function, and fatigue^[38,39].

INDICATIONS AND CONTRAINDICATIONS

Indications for exercise treatment in this patient population include regaining or improving physical functions, aerobic capacity, strength, flexibility, body image, body composition, quality of life, the ability to physically and psychologically withstand to any current and/or future

cancer treatments, and to withstand anxiety due to living with current or recurrent disease^[41]. Indications also include the reduction of long-term and late effects of cancer treatment, and the potential delay in any recurrence or progress of the disease^[41].

Contraindications for exercise prescription in breast cancer patients include, but are not limited to: acute post-operative period (up to 8 wk); acute arm and shoulder problems for upper body exercises; patients with extreme fatigue, anemia, or ataxia; and general cardiovascular and respiratory contraindications for an exercise regimen^[41].

Traditionally, upper extremity exercises were avoided in breast cancer patients with lymph node dissection and radiotherapy. However, some recent studies have shown that upper body exercises do not have a negative impact on lymphedema^[42].

EXERCISE TYPE AND CONTENT

There is no standard approach to exercise regimens for breast cancer patients. This is mainly due to the wide spectrum of such patients in terms of age, stage of the disease, co-morbid situation, physical function, etc. Considering this variety, it seems impossible to ever have a standard approach for each individual patient. In addition, the prior functional status and exercise habits of each patient should always be taken into account when an exercise program is being prescribed.

There are various studies concerning the effects of different types of exercise on breast cancer patients. Types of exercises studied in breast cancer patients range from regular aerobic exercise to such activities as Tai Chi^[16,17,42]. The most frequently studied in these patient populations are aerobic exercises (*i.e.*, group, home, walking, and cycling), resistive exercises, and special types of exercise like Pilates, Tai Chi, and Yoga^[17,42-44]. Exercise regimens can be prescribed as either group exercises instructed by a trainer or self-practiced home exercises.

Resistance exercises in breast cancer patients are gaining more attention due to their ability to decrease muscle waste and fatigue^[45]. A combined Aerobic and Resistance Exercises (CARE) trial has investigated standard dose aerobic (25-30 min per session of 3 d per week), high dose aerobic (50-60 min per session of 3 d per week), and combined aerobic and resistive exercise (standard aerobic in addition to standard resistance training; 3 d per week, 2 set of 10-12 repetitions) schemes in breast cancer patients. The results showed that higher intensity and resistance exercises are safe in this population, and that high and combined resistive-aerobic exercise regimens are superior to standard aerobic ones in terms of certain domains such as muscle strength, endocrine symptoms, and quality of life aspects like bodily pain^[45].

Pilates exercises improve physical strength, flexibility, and postural control, and it is commonly-accepted by women as a fitness activity in developed countries^[45]. In a randomized clinical trial, it was shown that Pilates exercises have significant effects in females with breast cancer

in terms of functional capacity, fatigue, flexibility, and quality of life compared to the control group.

Tai Chi exercises are respected as exercises of mindfulness, and are known to improve physical and psychological well-being. Some studies demonstrated that Tai Chi exercises for 10-12 wk improved fatigue, body composition, and quality of life, as well as muscular, memory, and cognitive functions, in breast cancer survivors^[16,17].

Yoga is another type of meditative physical activity including breathing, posture, flexibility, and core strength exercises that can be used in breast cancer patients. In 2013, Sudarshan *et al*^[46] published a study on breast cancer patients which reported that weekly Yoga therapy improved physical function.

According to the data pooled from cancer studies, the American Cancer Society recommends that cancer survivors engage in regular physical activity, avoid inactivity, and exercise for at least 150 min per week, including strength-training for at least 2 d per week, to obtain a healthy weight^[25].

Kirkham *et al*^[47] compared different intensity arrangement methods for the precise prescription of aerobic exercise regimens. The American College of Sports Medicine's metabolic equation for treadmill walking and heart rate reserve are found to be the most accurate methods for exercise intensity prescription in breast cancer patients and survivors^[47].

Enjoyable exercises like Pilates, Tai Chi, Yoga, Nordic walking, and dance may be chosen according to the expectations and motivations of patients by carefully adjusting intensity on an individual-by-individual basis.

ADVERSE EVENTS

In most clinical trials that evaluate different types of exercises, adverse events are not even reported^[38,39]. In the clinical studies that have reported safety associated with exercise, most of them either reported no adverse events at all or only those that are very rare and usually non-serious. The reported exercise-related adverse events are mainly dizziness, dyspnea, musculoskeletal injuries, or lymphedema, which were similar to the control group in terms of numbers^[38-39]. In general, no differences whatsoever were observed regarding recurrence, disease progression, or increased mortality in exercise *vs* control groups. Although limited, these studies show that appropriate exercise regimens in breast cancer patients are quite safe to implement. However, the adverse events of exercise regimens in this patient group should be further studied and reported more thoroughly in future trials.

LIMITATIONS AND RECOMMENDATIONS

Although many studies have investigated the effects of exercise in breast cancer patients, there is still a need for randomized controlled trials for the clarification of exercise type, duration, and intensity for program standardization.

Most reported trials are conducted in small groups

and for short-term periods. Therefore, the results of these trials are difficult to implement for a long-term period and large populations. While advantageous that most cancer trials on the impact of exercise are researched in breast cancer survivors, it is unfortunate that very few of these are powered randomized controlled trials with large enough sample sizes^[9,10].

Considering the heterogeneity of breast cancer patients, individualized programs according to disease stage, treatment status, and co-morbid situation should be tailored and addressed in future research questions. Along with RCTs, long-term real life data from registries and databases on the outcome of exercises in female breast cancer patients might help in directing these questions.

Additionally, compounding factors that would have an effect on exercise and its outcome, such as the patients' previous exercise habits, co-morbid situation (*i.e.*, lymphedema), and functional status need to be evaluated.

Lack of knowledge on the effects of exercise and physical activity among the medical community and fear in creating an exercise regimen with regards to the seriousness of the disease is a social burden that results in unnecessary avoidance from physical activity in patients diagnosed with breast cancer. Therefore, in order for this substantial issue to be settled, the mindset of physicians should be changed, which should happen naturally over time as the evidence-based data accumulates.

Raising awareness and improving information in this area for patients, caregivers, and healthcare providers would have a great impact in approaching these patients' exercise needs. This emphasizes the importance of a multidisciplinary approach in overcoming the barriers in this area and helps patients get the best outcome from treatment. Little to no data is available on the cost-effectiveness of exercise treatment for breast cancer patients, which in the long-term needs to be evaluated.

Despite the crucial need for physical activity and exercise in this patient population, patients' demand for physical treatment greatly varies from 2%-81%^[3,48]. Patient awareness about physical activity after diagnosis can be a vital factor in determining this variation.

CONCLUSION

Exercise is not merely safe and feasible for breast cancer patients, but is moreover a complementary treatment for one to achieve physiological and psychological improvements. There is increasing evidence that regular exercise after the diagnosis of breast cancer might have a substantial positive impact in mortality, morbidity, prognosis, and quality of life. We advise a multidisciplinary approach in order to encourage breast cancer survivors into engaging in rehabilitation programs combining both strengthening and aerobic exercises for the most beneficial results.

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P- Reviewer: Arsenijevic N, Hojan K, Harrington SN, Lacomba MT
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