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Exercise Training in the Spectrum of Breast Cancer

Ana Cristina Corrêa Figueira, Ana Pereira, Luis Leitão, Rita Ferreira and José Alberto Duarte

Abstract

Exercise training and regular physical activity have been mentioned as one of the non-pharmacological approaches to enhance breast cancer outcomes. Such evidence encourages health professionals to recommend it as an adjuvant in treatment conditions to improve cardiorespiratory fitness that, can increase the rate of completion of pharmacologic therapies, reduce cancer-related fatigue, and improve muscle strength and quality of life. Research results have highlighted a positive relationship between exercise and breast tumor outcomes, that seem to be dose dependent (the more activity the more protection) and can be mediated through several biological mechanisms. In this chapter, we intend to summarize the current knowledge about the effects of exercise in the regulation of metabolic and steroid hormones, tumor-related inflammation, and the attenuation of cancer-induced muscle wasting, highlighting the exercise designs that can prompt the best results.

Keywords: exercise training, breast cancer, physical activity

1. Introduction

Cancer remains not only one of the most daunting diseases worldwide, but also a major public health concern. Although extensive research has been conducted on cancer prevention, diagnosis, and treatment, statistics of cancer's effects are disheartening [1].

Among cancer's various types, breast cancer is the second-most common and the most common among women, and it is assumed that one of every eight women will develop this type of cancer at some point in their lives [2].

The risk of developing breast cancer encompasses reproductive factors, hormonal factors, genetic alterations, age, race, sex, and factors related to lifestyle [3, 4].

Among the lifestyle factors that increase the risk of breast cancer, alcohol consumption [5], tobacco use [6], unhealthy diet [7], and reduced levels of daily physical activity or exercise are ranked among the most major [8].

Unlike determined genetic factors, regular physical activity and/or regular exercise training (RPA/REX) are modifiable ones [9].

In general, RPA/REX can contribute to overall health, with undeniable benefits for cardiorespiratory fitness (CRF), muscle strength insulin resistance, immune function, and body mass index (BMI) maintenance which can particularly be extended to the prevention of several diseases, including breast cancer [10, 11].

Nevertheless, the biological mechanisms underlying the protective effect of RPA/REX on breast cancer remain poorly understood. Biomarkers proposed to support that association include the modulation of circulating levels of both metabolic hormones (e.g., insulin, and insulin-like growth factors, IGFs) and steroid hormones (e.g., estradiol and progesterone), the reduction of pro-inflammatory and anti-inflammatory factors (e.g., interleukins, IL-6 and IL-10; tumor necrosis factor- α TNF- α ; C-reactive protein, CRP; adiponectin and IL-1), immune function (e.g., natural killers cells and leukocytes), and oxidative stress (i.e., reactive oxygen species) [8, 12, 13].

A considerable number of reviews have reported epidemiological evidence that establishes a connection between RPA/REX and cancer prevention by associating the amount of exercise performed with a decreased risk of developing cancer. Although the role of RPA/REX following the diagnosis of cancer has received less attention from researchers, its importance in controlling and reducing the side effects of cancer therapy is evident [14]. This evidence inspires health professionals to recommend RPA/REX as an adjuvant to improve cardiorespiratory fitness that, consecutively, can improve the rate of completion of pharmacologic therapies, reduce cancer-related fatigue, and improve the quality of life (QoL) [15].

To enhance the survival of patients with breast cancer early detection and improved treatments are fundamental [16]. Researchers in the exercise-oncology field have several concerns regarding therapies that best suit specific cases, minimize the number of deaths, and reduce recurrence. Thus, targeting the association between active behaviors and the cellular and molecular mechanisms underlying that association has been the main target in recent years [17].

Literature provides sufficient evidence to suggest that RPA/REX, when performed at moderate to vigorous intensity for at least 30 min/day, is safe and well-tolerated by patients both during and after therapy [18]. The American College of Sports Medicine (ACSM) recommends that patients with breast cancer avoid inactivity. They should be as active as tolerable by their conditions and should follow the guidelines for healthy individuals when possible: 150 min/week of exercise training at moderate intensity or 70 min/week of exercise training at a vigorous intensity, combining endurance and resistance exercises [19]. Furthermore, these are also the recommendations supported by the American Cancer Society (ACS) [18]. Nevertheless, the patient's overall status should always be examined to ensure an individually adjusted amount of activity by defining personal thresholds of activity determined on a symptom-based approach [20].

A considerable number of studies have provided sufficient evidence that supports those recommendations. Almost a decade ago, a systematic review with meta-analysis, that considered 14 randomized controlled trials (RCT) involving 715 patients with breast cancer, concluded that resistance exercise training (RET) and aerobic exercise training (AET) increase self-esteem, body composition, physical fitness, and the rate of chemotherapy completion [21]. Two years later, a prospective study that involved more than 4000 patients, disclosed that being active during and after treatment for breast cancer can reduce mortality among women regardless of age, state of the disease, and the body mass index (BMI) [22], while a short after, another study, involving more than 14,000 women, showed that high levels of cardiorespiratory fitness were strongly associated with fewer deaths [23]. Similar results were found in another six prospective cohort studies involving more than 12,000 breast cancer survivors gathered in a meta-analysis; results showed that physical activity after the diagnosis of breast cancer reduced death by 34% and recurrence by 24%, regardless of BMI, while pre-diagnosis physical activity reduced the risk of mortality only in women with a BMI $<25 \text{ kg/m}^2$ [24]. In more recent years, Lahart et al. [25] and Lipsett et al. [26] quantified the effects of

exercise training in breast cancer outcomes during therapy with two meta-analyses. Both revealed that patients with breast cancer benefited by engaging in exercise training activities. While Lahart et al. [25] determined that a combination of RET and AET affords significant benefits by reducing fatigue, Lipsett et al. [26] reported an inverse relationship between RPA levels and breast cancer-related deaths and recurrence.

The results observed, most of which have stemmed from epidemiological evidence, have highlighted a positive association between RPA/REX and breast tumor-associated deaths and recurrence which, apparently, seems to be dose-dependent, meaning more activity, more protection. Nevertheless, confusion remains about the specific amount of exercise that can induce the greatest outcomes.

In contrast, to the studies in clinical contexts that have provided extensive evidence showing that RPA/REX promotes patients' survival and reduced recurrence, such linearity in animal studies has not been found. Furthermore, although evidence showing a positive relationship between RPA/REX and the development of mammary tumors [27] exists, the opposite has also been reported by several researchers [28].

The up mentioned uncertainty has determined interest in understanding whether RPA/REX has a considerable role in tumorigenesis-related outcomes by modulating tumor behavior [24]. Researchers in this area have sought to confirm a relationship between RPA/REX and concurrent biological changes that can determine better outcomes. That association encompasses the intensity, type, and duration of exercise bouts, possible pathophysiological pathways, and breast cancer-associated mechanisms within the context of the advantageous effects of exercise [29]. The present chapter presents an attempt to summarize the insights that linked exercise training and cancer-associated mechanisms along the breast cancer continuum.

2. Exercise training and glucose-related factors

The modulation of metabolic hormones, including markers of glucose-insulin homeostasis are reported to relate to exercise. An altered cellular metabolism that favors aerobic glycolysis to support rapid cell proliferation and high-energy turnover, are features from which the tumors are recognized. The increased consumption of glucose by some tumors, such as those in the breast, that result in increased lactate production (i.e., the Warburg effect), is a well-described mechanism [30]. It seems that limiting glucose availability should restrict the capacity of growth factors to preserve cellular viability, thereby leading to cell death, is a process in which RPA/REX might be crucial. Further, RPA/REX has been hypothesized as an inducer of perturbations in the insulin-glucose axis, enhanced insulin sensitivity, and therefore, promoting a reduction in the circulating levels of insulin and glucose [31].

In the past few years, several studies, mostly RCT, have sought to elucidate whether RPA/REX acts in the modulation of glucose-related factors improving the outcomes in women with breast cancer. In an RCT conducted by Fairey et al. [32] that aimed to determine the effects of REX in glucose-related markers of 53 postmenopausal breast cancer survivors, the women that trained on cycle ergometers for 15 weeks (3 days/week for 35 min) at a moderate intensity have not shown significant changes in fasting insulin, glucose, insulin resistance, or Insulin-like growth factor binding protein-1 (IGFBP). However, the exercise training markedly improved the levels of Insulin-like growth factor (IGF) and Insulin-like growth factor binding protein-3 (IGFBP-3). Theoretically, increases in IGF-1 imply

improvements in cell division and the inhibition of cell death [33]; however, also theoretically, because IGFBP-3 is responsible for binding the majority of IGF-1, increased levels of IGFBP-3 should be a good sign. In a different exercise paradigm, Schmitz et al. [34] also led an RCT with 85 postmenopausal breast cancer survivors who experienced a twice-weekly (60 min/session) weight training for one year. The training sessions were supervised for 6 months, and all the participants learned how to work alone and how to improve their workload. Thereafter, and for another 6 months, they continued the training unsupervised. Positive results were found regarding IGF-2 levels, but no evidence was detected concerning improvements in insulin sensitivity and glucose levels [34]. The above-mentioned results, which are both discouraging and challenging, do not indicate that REX can effectively improve glucose levels, insulin levels, or insulin resistance. Although a positive relationship regarding IGF-2 levels was found, this can be related to the different exercise designs presented in both studies, namely the different lengths of exercise exposure, the differences in the types of exercise, or the reductions in women's BMI, that was reported in the latter but not in the former study.

A few years later, 101 sedentary and overweight breast cancer survivors, were randomly assigned by Ligibel et al. [35] to either a 16-week program of unsupervised AET (90 min/week) combined with RET (2 days/week for 50 min with supervision) or to a control group. Aiming to analyze the influence of REX on insulin concentrations, positive changes were reported for fasting insulin with some evidence for improvement in insulin resistance but not for fasting glucose [35]. Likewise, Irwin et al. [31] studied 75 postmenopausal breast cancer survivors who were subjected to an exercise program involving three weekly supervised sessions and twice-weekly unsupervised sessions (30 min of moderate AET for 6 months). Women with higher exercise levels were reported to show a decrease in insulin, IGF-1, and IGFBP-3. Interestingly and despite other evidence [36], the authors assumed that the decrease in IGFBP-3 was probably related to a similar reduction of IGF-1 levels.

In the same line of research, an RCT conducted by Guinan et al. [37] with 26 breast cancer survivors, that combined supervised exercise with a home-based program, performed twice a week for 60 min during 8 weeks, did not find any evidences of positive changes in the circulating levels of glucose and insulin. Likewise, Thomas et al. [38] included 65 postmenopausal breast cancer survivors in an exercise program that combined supervised (3 days/week) and unsupervised (2 days/week) 30-min training sessions of moderate exercise, aimed to achieve 150 min/week during a period of 6-month. Significant results were found, translated into a reduction in fasting glucose among the more active women (>120 min/week). Again, the different results are probably related to the different exercise designs used, which prevent us to reach a satisfactory conclusion about the type and amount of exercise to prescribe for breast cancer patients and that best contribute to positive outcomes. Two recently published meta-analyses did not highlight any clues to clarify this matter. Albeit demonstrating that exercise can reduce fasting insulin levels and IGFs [39] in breast cancer survivors, differences in the exercise training protocols prevent the attempt of a strength subgroup analysis in one of them [39]. On the other, the heterogeneity in exercise designs was mentioned as a limitation, and no subgroup analysis was performed [40]. Comparably, to trends in human studies, contrasting results also characterize preclinical data. Several reports have associated RPA/REX with increases in the levels of glucose-related factors [41], whereas others have related the opposite [42]. Additionally, and similarly to the research in human populations, the use of different exercise training programs prevents any clear understanding of the amount of exercise needed to enhance the glucose-related indicators.

3. Exercise training and inflammation-related factors

Another key factor in the improvement and progression of breast cancer is chronic inflammation. RPA/REX could neutralize the permanent state of inflammation by promoting a systemic anti-inflammatory environment. One of the mechanisms by which exercise can reduce cancer-related inflammation is through the increasing levels of anti-inflammatory myokines produced by the working skeletal muscles. Such decreases in cancer-related inflammation could be related to the frequency, intensity, type, and duration, of the exercise training sessions. In fact, it seems that the intensity may be the key. Higher levels of RPA/REX intensity (i.e., moderate or vigorous) can promote the reduction of the circulating levels of proinflammatory cytokines and improve immune function [43].

The collected data relating to cancer-induced inflammation and exercise training in human patients can illustrate the urgency for more studies.

In an RCT with 52 breast cancer survivors, Fairey et al. [44] exposed the participants to 15 weeks of moderate exercise in cycle ergometer and observed significant enhancements in immune function expressed by exercise-induced natural killer cell activity, but any association between REX and anti-inflammatory interleukins (i.e., IL-4 and IL-10), pro-inflammatory interleukins (i.e., IL-1 and IL-6), tumor necrosis factor- α (TNF- α) and cytokines, were not detected. With the same intervention group, the authors reported positive associations between REX and the C reactive protein (CRP) levels. Equally, Hutnick et al. [45] in a study involving 28 breast cancer survivors exposed to moderate treadmill exercise program combined with resistance training for 6 months, did not observe any association between REX and plasma IL-6 levels and interferon-gamma (IFN- γ). Nevertheless, the improved activation of lymphocytes in women who exercised showcased a positive relationship between immune function and exercise. In another RCT, conducted by Gómez et al. [46] with 16 breast cancer survivors exposed to an 8-week, a three-times-weekly program that combined resistance exercise training with aerobic training, did not detect significant changes in their inflammation-related systemic markers (e.g., IL-6, IL-10, and TNF- α). Rogers et al. [47] after a 3-month training program combining AET and RET in breast cancer survivors, found a positive relationship between leptin levels and REX, showing relevant evidence of the benefits induced by REX in proinflammatory cytokines (i.e., IL-6 and TNF- α).

Likewise, Campbell et al. [48] did not find significant associations between a 24-week home-based program of moderate exercise and inflammatory markers in 37 postmenopausal breast cancer survivors.

Although the amount of research performed in the last decade, the importance of RPA/REX to induced changes in the systemic repercussions of breast cancer, remains doubtful. Once again, differences among studies can confound the true benefits of exercise training in inflammation-related markers and enhancing immune response.

Trying to overtake this uncertainty, a recent meta-analysis highlighted the positive effects of chronic exercise training in low-grade inflammation in women with breast cancer. The benefits associated with the intervention program duration (>45 minutes/session) and length (>11 weeks) showed that a significant decrease in TNF- α levels were associated with decreased levels of adiposity [49]. Yet encouraging, such results should be interpreted with caution given the number of correlations performed, which in some cases were quite a few.

Similarly, the preclinical data about the advantages of RPA/REX to modulate inflammation are also diverse, including the improved expression of several inflammation biomarkers (e.g., CRP, TNF- α , IL-6, INF- γ , monocyte chemoattractant protein 1 [MCP1], serum amyloid P [SAP], leptin and spleen weight) [50], although other data has reported the opposite, primarily regarding in IL-6 regulation [51].

In that case, the considerable variety of exercise designs and breast tumor models might have significantly influenced the outcomes.

4. Exercise training and estrogen levels along the breast cancer continuum

RPA/REX has been associated with lower levels of circulating estrogen, which could describe its positive association with breast cancer. Cell proliferation and the inhibition of apoptosis via ER (estrogen receptor)-mediated mechanisms have been associated with the circulating levels of estrogen [52]. Apparently, physically active women with breast cancer, shows lower estrogen levels that can improve survival, particularly with tumors overexpressing positive estrogen receptors (ER+) and positive progesterone receptors (PR+), though the lack of data from human studies to support that hypothesis [24].

Using 1970 women from a previous cohort study to assess the levels of RPA/REX self-reported on a questionnaire, Sternfeld et al. [53] found no differences in levels of RPA/REX, tumors' hormonal status, or the number of breast cancer deaths. Curiously, the number of all-cause deaths was markedly lower among women who presented ER+ and PR+ tumors and had engaged in RPA/REX programs of moderate intensity. Irwin et al. [54] measured the self-reported data of 2910 women with breast cancer regarding their RPA/REX behaviors, to examine whether such behaviors influenced mortality, but did not find significant results between the RPA/REX levels and mortality in women with ER+ and negative Human Epithelial Growth Factor Receptor (HER-) tumors. The methodological approach of the study conducted by Chen et al. [55] was identical, but the results differed starkly. The authors observed significant effects between RPA/REX levels and the reduced number of total mortalities only among women with ER- or PR- tumors, but not with ER+ or PR+ ones. Human studies have divergent results and evidence even though most have used the same or similar methodological processes. Of note are the reduced number of studies concerning the relationship between RPA/REX condition and the circulating levels of estrogen in the progression and development of breast cancer, especially because those concentrations are associated with the growth of tumor cells [56].

The lack of data in preclinical research also restrains any understanding of the role of RPA/REX and the circulating levels of progesterone and estrogen. In this field, some studies have shown a positive association [41, 57], between RPA/REX and the circulating levels of sex hormone, while the contrary can be also found [58]. These findings suggest that methodological limitations, including heterogeneous cohorts, small sample sizes, and randomized characteristics, could translate the conflicting results regarding the effect of RPA/REX on breast cancer-associated markers.

A recent systematic review with meta-analysis in pre-clinical data reported considerable improvements in sex hormone concentrations, cancer-induced inflammation, and glucose-related factors among the animals exposed to exercise [59]. Performing vigorous exercise for 85 min per week improved sex hormone levels and reduced systemic inflammation.

5. Exercise training and muscle mass in the breast cancer continuum

The loss of skeletal muscle is a well-documented process in cancer that affects most patients, even though different degrees [60]. The musculoskeletal system

provides the basic functions of strength generation, locomotion, and respiration. The protection of muscle mass whether in disease or with health is crucial [61]. The preservation of muscle fiber size and muscle mass depends on protein turnover, in which the balance between protein synthesis and protein breakdown should be maintained. A complex system of signaling pathways regulates that stability, and under pathological conditions, such regulation can be compromised and result in muscle decrease and atrophy [62]. Muscle function in oncology relies on the study of cancer-associated cachexia. Systemic metabolic disorder and inflammation caused by tumors seem to affect protein turnover by promoting wasting in muscle mass involving diminished muscle fiber diameter, reduced protein content, decreased fatigue resistance, and force production [63].

In disease the loss of muscle mass reduces the patients' functional capacity, thus considerable efforts have been made in the past few years to find an effective anticachectic agent, and exercise has been suggested as a possible measure to mitigate or reverse muscle dysfunction and wasting or both [64]. Studies in humans with different types of cancer have reached different conclusions although, most of them, normally favor exercise. Unfortunately, in patients with breast cancer, results are insufficient due to the lower incidence of breast cancer patients who suffer from cachexia. As mentioned in a study conducted by Schmitz et al. [34], with 85 cancer survivors divided into two exercise training groups (immediate treatment and delayed treatment), that performed a twice-weekly (60 min/session) during 12 or 6 months, both groups exhibited increases in lean mass and the results were more expressed in the immediate treatment group, whereas the delayed treatment group did not show differences in lean mass across the study period [34]. Courneya et al. [65] obtained similar results after randomizing into three groups 242 patients with breast cancer receiving ongoing treatments. An exercise group that performed AET with different ergometers of moderate-to-vigorous intensity 45 min/day three times weekly, another exercise group that performed RET involving two sets of 8/12 repetitions in different muscle groups three times weekly, and a control group. Both exercise training groups showed significant results relating to the increased lean mass, after 17 weeks, more expressed in women who received RET treatment [66].

Animal studies have also highlighted the benefits of exercise against the depletion of muscle mass in the cancer context. Al-Majid et al. [67] described the benefits of REX program in the lower limb muscles of tumor-bearing animals subjected to eight sessions of electrical stimulation modeling RET. Puppa et al. [55] also reported the beneficial effects of moderate-intensity REX in the treadmill for 55 min/day 6 days/week for 11 weeks on muscle mass, in cancer-induced cachectic animals overexpressing systemic IL-6.

The study of Franjacomo et al. [68] aimed to examine if the studies involving cachexia could use the model of mammary neoplasms. They determined that the model, involving Ehrlich carcinoma cells inoculation could feature systemic inflammation and the muscle wasting of cachexia in a less aggressive manner suitable for studying new pharmacological approaches. Nevertheless, using an inoculation model of Walker-256 cancer cells subjected rats to a 6-week RET program, Padilha et al. [69] concluded that RET performed prior to tumor implantation prevented the development of cachexia by attenuating tumor-induced systemic proinflammatory conditions, oxidative stress, and damage in the muscles, which suggest the advantages of exercise training prior to tumor onset.

Above the heterogeneity of results and research designs in animal models and clinical conditions, it seems that the severity and incidence of cachexia depend on a reasonable range of factors and can vary according to the site and mass of the tumor, tumor type, interindividual differences in susceptibility to cachexia, and abnormal metabolism or reductions in food intake [70].

Evidence from animal studies demonstrates that RPA/REX might play an important role in attenuating cancer-induced muscle wasting by regulating or inhibiting, if not both, several factors at a molecular level. Apparently, exercise activates a network of transcription factors, kinases, and coregulator proteins that can change in gene expression and prompt increases in mitochondrial biogenesis, which in turn cause metabolic reprogramming in skeletal muscle. Consistent evidence shows that endurance training induces mitochondrial biogenesis and a fast-to-slow fiber-type switch in skeletal muscles, expressed in type 1 and type 2A fibers [71].

Clearly, additional studies are needed in the context of cancer-induced muscle wasting, to date, no medical intervention has completely reversed cachexia, and no approved drug therapies are available [72]. Nevertheless, according to recent data [73], molecular mechanisms underlying such beneficial effect of exercise seems to be by the contribution of TNF-like weak inducer of apoptosis (TWEAK) signaling to cancer-induced skeletal muscle wasting. The authors concluded that exercise training prevented tumor-induced TWEAK/NF- κ B signaling in skeletal muscle with a beneficial impact on fiber cross-sectional area and metabolism. Indeed, 35 weeks of exercise training promoted the upregulation of oxidative complexes. An active lifestyle for the prevention of muscle wasting secondary to breast cancer, highlighting TWEAK/NF- κ B signaling as a potential therapeutic target for the preservation of muscle mass.

6. Conclusion

The diversity of designs and protocols of exercise training used in the reviewed documents, create serious difficulties to achieve a clear understanding of the best exercise training designs that better suit greater outcomes for breast cancer patients.

More powerful studies involving similar protocols could enhance the knowledge of the ideal amount of exercise needed in clinical contexts. However, despite the diversity of results reported, evidence of the benefits of exercising after a breast cancer diagnosis does exist.

Exposure to programs of regular exercise training combining AET and RET seems to promote better results along with the moderate-to-vigorous intensity through which the exercise is performed.

Exercise programs to breast cancer patients should include organized and supervised activities, considering a symptom-based approach, tailored to each patient.

Performing vigorous exercise 85 min/week can reduce the levels of systemic inflammation and improve circulating sex hormone levels in animals, but in human populations, such evidence needs to be supported with more studies. The present chapter has some limitations mainly related to the studies included. The difference in study designs along with the lack of published information in some of them creates a difficult understanding and a more accurate analysis. Future studies should be performed with the knowledge already achieved in mind reporting, when published, the necessary information that allows their replication.

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