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# Effects of resistance plus aerobic training on body composition and metabolic markers in older breast cancer survivors undergoing aromatase inhibitor therapy☆

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ABSTRACT

*Objective:* To evaluate the effects of combined aerobic + resistance training on body composition and metabolic markers in older breast cancer survivors undergoing aromatase inhibitor therapy.
*Methods:* Older breast cancer survivors were randomized to an exercise [resistance + aerobic training]: n = 18, or placebo control group: n = 18. Body composition (measured by DXA) and blood markers of lipid and glucose were measured at baseline, and at 12, 24, and 36 weeks. The exercise group performed 40 min of resistance exercises on machines followed by 30 min of aerobic training on a treadmill, three times per week. Separate 2 (group) × 4 (time) repeated-measure ANOVAs were used to compare groups over time.
*Results:* Significant group × time interactions were found for total and trunk fat mass ($p < 0.001$ and $p = 0.001$) and % body fat ($p < 0.001$), where women in the exercise group lost fat compared to slight gains among women in the stretching control group. There were no significant differences between groups for lean mass, hip or spine BMD, metabolic markers, or CRP.
*Conclusion:* Our aerobic + resistance exercise program prevented fat gain, but may not have been sufficient to improve metabolic or bone health markers in older breast cancer survivors undergoing aromatase inhibitor therapy.

## 1. Introduction

Cancer is one of the major public health problems and leading causes of death in the world (National Center for Health Statistics, 2016). With the growth in the world population, the number of new cases is expected to increase considerably, reaching 20.3 million by 2030 (Ferlay et al., 2010). Among all types of cancers, breast cancer is the most common among women (International Agency for Research on Cancer, 2012). According to the National Cancer Institute, in 2017, it is estimated that over 57,960 new cases of breast cancer will occur in Brazilian women (Instituto Nacional do Câncer (INCA), 2016).

In postmenopausal women, 80% of breast cancer cases are hormone receptor positive (Bardia et al., 2012) and aromatase inhibitor therapy (AI) is typically prescribed as standard treatment, which increases survival rates upwards of 40% compared to tamoxifen (Riemsma et al., 2010). However, treatment of breast cancer with aromatase inhibitor therapy can produce alterations in body composition, such as increases in body fat mass as well as decreases in lean body mass and bone mineral density (Napoli et al., 2015; Battisti et al., 2014; Van Londen et al., 2011) and, these alterations can increase the risk of fractures, osteoporosis, and chronic diseases (Akyol et al., 2016; Saarto et al., 2008). In addition, the side effects of AI also include loss of bone mineral density of 2.6% per year and symptoms of arthralgia and myalgia (Limburg, 2007; Peppone et al., 2010). AI decreases circulating estrogens and thus may also may weaken estrogen-mediated protective effects on the cardiovascular system among women on AI (Amir et al.,

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2011; Foglietta et al., 2017).

A non-pharmacological alternative to reverse or attenuate the side effects of breast cancer treatment on body composition is exercise training. Several studies have shown that exercise is effective for improving body composition (increased lean body mass, decreased fat body mass, and body mineral density at the spine, hip, and whole body), inflammatory and metabolic blood markers, physical fitness, and quality of life of breast cancer survivors (Battaglini et al., 2014; Dieli-Conwright and Orozco, 2015; Almstedt et al., 2016). Thomas et al. (2016) demonstrated an association between 12 months of combined exercise (twice-weekly supervised resistance training program and 150 min of moderate-intensity aerobic exercise at home) with a decrease in percentage body fat and an increase in lean body mass in postmenopausal breast cancer survivors taking AI.

However, there are few studies including exercise programs which combine aerobic and resistance training for women undergoing treatment for breast cancer with aromatase inhibitor therapy. Furthermore, the long term benefits of combining resistance and aerobic training in breast cancer survivors on AI are not clear, and more studies are needed with this population, focusing on responses of combined exercise on body composition and metabolic markers. Thus, the aim of this study was to evaluate the effects of combined aerobic + resistance training on body composition and metabolic markers in older breast cancer survivors undergoing aromatase inhibitor therapy.

## 2. Methods

### 2.1. Study design

We conducted a 36 week single-blind, parallel group randomized controlled trial from March 2015 to July 2016 in a city in the southeastern region of Brazil (ClinicalTrials.gov NCT02804308). Women were randomized to a resistance + aerobic training group or a low-intensity stretching control group. All testing and exercise training took place at the Sao Paulo State University-Campus of Presidente Prudente, physical education department. This study was approved by the Research Ethics Committee of the Sao Paulo State University (Protocol number 6727715.1.0000.5402/2015).

### 2.2. Subjects

According to the Medical records in the Oncology Department of the Regional Hospital in Presidente Prudente, São Paulo state, Brazil, a total of 348 registered breast cancer survivors were found, including all types of treatment for cancer. In the present study, only postmenopausal breast cancer survivors undergoing aromatase inhibitor therapy were recruited, totaling 124 women invited to participate in the study. The study inclusion criteria were the following: current use of AI, diagnosis of stage 0–3a breast cancer, aged between 50 and 80 years, no participation in supervised exercise in the previous six months, no musculoskeletal injuries, clearance from a physician to participate in physical training, and living in the city of Presidente Prudente/Sao Paulo.

To calculate the sample size, we performed a power analysis based on observations from a previous study that verified a difference in bone mineral density ($g/cm^2$) at the lumbar spine of 0.013 kg and standard deviation of 0.011 after 12 months of exercise training in postmenopausal breast cancer survivors (Saarto et al., 2012). Using a power (1-type II error) of 0.80 and a type I error of 0.05, according to PS software (see 3.1.2, Dupont and Plummer, http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize), it was estimated that we would need 12 subjects per group. Considering a dropout rate of 20%, we over-recruited the number of subjects to recruit a target sample of n = 14.

A total of 36 women were included in this study: 18 women in the exercise group (EX) and 18 in the stretching control group (CG). The participant flow is outlined in Fig. 1.

### 2.3. Study interventions

#### 2.3.1. Combined training group

*2.3.1.1. Aerobic and strength assessment and training protocol.* Maximal muscle strength was evaluated by a predicted one repetition maximum test. The submaximal load of each individual was established and the maximum of 10–12 repetitions was considered in this study. The participants performed the test in bench press and leg press exercises. Predicted 1-RM was determined using a standard equation (Adams, 1994). The protocol used to predict maximum aerobic capacity was a single-stage submaximal treadmill Walking Test according to Ebbeling et al. (1991). Each participant performed a 4 minute warm up at a speed that elevated the HR to between 50% and 70% of estimated HRmax (HRmax = 220-age). Next, the inclination of the treadmill was adjusted to 5% and maintained at the same speed for 4 min. The value of HRmax was recorded every 30 s during the final 2 min and values could not differ more than 5 bpm in each stage. Maximum oxygen uptake ($VO_{2max}$) was predicted using standard equations.

Participants in the exercise group participated in the combined aerobic + resistance program (Paulo et al., 2018) three times per week for 36 weeks for approximately 100 min per session. All sessions were supervised by physical education professionals and were performed in a gym at Sao Paulo State University, Presidente Prudente campus, physical education department. Each daily session began with a 5 minute warm up and ended with 10 minute cool-down. After the warm-up, resistance training was performed, including exercises for the main muscle groups on weight machines: seated cable row, bench press, leg extension, leg press, and leg curl, as well as bridge, abdominal, and standard plank exercises. The training volume of workload, number of sets, and number of repetitions of each resistance training series consisted of four progressive stages, as shown in Table 1. Next, the aerobic training was performed on a treadmill (Movement, LX-160, Fitness Equipment, Pompeia, Sao Paulo, Brazil) for 30 min with the intensity based on estimated maximum heart rate (HR) within the target training zone and monitored via heart rate monitors (model S810i; Polar Electro, Kempele, Finland). The aerobic protocol consisted of four progressive stages, also described in Table 1.

Participants in the exercise group were invited to attend 1.5 h health education lectures once per month. The topics discussed were related to breast cancer, health promotion, quality of life, physical activity, well-being, and mental health.

#### 2.3.2. Stretching control group

The control group was invited to participate in stretching and relaxation exercises, 2 times per week, with 45 minute sessions, for 36 weeks. Each exercise lasted 10–15 s, in the seated or lying position, and selected exercises minimized muscular force so that little stimulus was applied to the musculoskeletal system. The main goal of the stretching and relaxation exercises was to provide similar attention to the control group and minimize drop out and contamination.

### 2.4. Measures

#### 2.4.1. Self-reported demographics and health status

Characterization of the sample was performed through a sociodemographic self-reported questionnaire and clinical information; including demographic data, breast cancer stage, treatment type, use of medication, and health history.

#### 2.4.2. Anthropometry, body composition, and dietary intake

To calculate the body mass index - BMI ($kg/m^2$) – weight was assessed on a mechanical scale (Fillizola) to the nearest 0.1 kg and height was measured with the use of a fixed stadiometer (Sanny) to the nearest 0.1 cm. Body composition (total fat, trunk fat, and lean mass (kg), percentage of fat mass (%), and spine and hip bone mineral density - BMD ($g/cm^2$)) were estimated by Dual-Energy X-ray Absorptiometry