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The dose-response of resistance training in breast cancer patients undergoing primary treatment

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RESUMO

Depois do diagnóstico de câncer de mama, apesar de certo ceticismo, parte das capacidades de responder ao exercício físico, e alcançar importantes benefícios durante o tratamento quimioterápico são preservadas. Beneficiando-se das atuais evidências, estudos futuros são necessários para preencher as lacunas da dose-resposta ideal de exercício físico e seguir em frente nesta área. Entretanto, enquanto o exercício aeróbico tem sido investigado, pouco se sabe a respeito do exercício de força. Portanto, os objetivos da presente dissertação foram: I) revisar sistematicamente e explorar se existe tendência linear entre as variáveis do treinamento de força, e desfechos fisiológicos e clínicos; e II) testar experimentalmente essa hipótese, comparando diferentes doses de treinamento de força combinado com exercício aeróbico na aptidão física, composição corporal, e desfechos relatados pelo paciente durante o tratamento primário. O capítulo 4 não apresentou tendência à superioridade entre baixa- e alta-dose de exercícios de força na massa corporal, força de preensão manual, e capacidade cardiorrespiratória, mas um inesperado benefício para o baixo-volume de treinamento de força na força máxima (r^2=0.82-0.97; P<0.05). Além disso, o capitulo 5 apresentou benefícios similares-a-superiores na aptidão física, gordura corporal, fadiga, e qualidade de vida para baixa-dose comparado com a alta- em 3 meses. Portanto, a presente dissertação sugere um possível benefício usando uma abordagem de mínima dose nos desfechos físicos e clínicos em pacientes com câncer de mama durante o tratamento primário. Potencialmente são os resultados desta dissertação que proporcionam a primeira linha de evidência sobre a dose-resposta de exercício de força nesta população.

ABSTRACT

After breast cancer diagnosis, despite some previous skepticism, the human body preserves some of their capacities to respond to the different stimulus of resistance and aerobic exercise and reach important benefits during the chemotherapy. Taking advantage of this current evidence, future studies designing exercise dose-response are necessary to fill this gap and move the field forward. However, while aerobic exercise has been investigated, little is known about resistance training dose-response. Therefore, the aims of the present thesis were to: I) review systematically and explore if a linear trend for resistance training exists on physiological and clinical outcomes; and II) test this approach experimentally, comparing different doses of resistance in combination with aerobic exercise on physical fitness, body composition, and patient-rated outcomes during primary treatment. In the course, chapter four demonstrated no trend for superiority between low- and high-dose of resistance training over body mass, handgrip, and cardiorespiratory fitness, but an unexpected higher benefit in maximal strength for lower-volume of resistance training (r^2=0.82-0.97; P<0.05) based on previous literature. Moreover, testing experimentally in chapter five, similar-to-superior benefits on physical fitness, body fat, fatigue, and quality of life to single-sets compared to a higher-dose of resistance training were found at 3 months. Thus, the present thesis suggests a possible benefit using a minimal-dose approach on physical and clinical outcomes in breast cancer patients undergoing primary treatment. Is noteworthy and potentially the results of these two studies that provide the first line of evidence regarding resistance exercise dose-response in this clinical population.

SUMMARY

1. INTRODUCTION

The exercise-induced plasticity of the respiratory, cardiovascular, and musculoskeletal system is well known in the human body. After a few repeated bouts of exercise, the different human systems interacted and adapted resulting from physiological changes, such as glucose metabolism, mitochondrial biogenesis, angiogenesis, signaling pathways, and cytokine release (Fiuza-Luces *et al.*, 2013). Even in pathological conditions as following a cancer diagnosis, the human body preserves some of their ability to respond to the different stimulus of exercise and may reach important benefits during the treatment (Schmitz *et al.*, 2010). Also, several findings have supported the use of exercise as part of the standard care in different cancer types (Cormie *et al.*, 2018; Koelwyn *et al.*, 2017; Ashcraft *et al.*, 2018) due to their potential role in reducing cancer-specific mortality and cancer recurrence as see in breast cancer (Holmes *et al.*, 2005; Friedenreich *et al.*, 2016).

In the growing body of evidence, comprehensive trials have been developed for breast cancer in the field known as “exercise oncology”. The *Supervised Trial of Aerobic Versus Resistance Training* (START) and the *Physical Activity and Lymphedema* (PAL) trials are examples of impacting work that supplies evidence category A (i.e., overwhelming data from randomized controlled trials) for safety, strength, and cardiorespiratory fitness during the adjuvant treatment for breast cancer (Courneya *et al.*, 2007; 2008), and for strength and safety regarding lymphedema onset or worsening, in women at risk (Schmitz *et al.*, 2010) and with breast cancer-related lymphedema (Schmitz *et al.*, 2009), respectively. In addition, these and other important trials supplemented the guidelines of the *American College of Sports Medicine* (Schmitz *et al.*, 2010) and *American Cancer Society* (Rock *et al.*, 2012) creating consensus regarding the safety and efficacy of exercise prescription in breast cancer patients. Taking advantage of this consistent expert panel, future studies could move forward and explore different pathways to improve the exercise feasibility and attendance, mainly during the chemotherapy treatment, since the patients are affected by many side effects such as cardiovascular (Jones *et al.*, 2007) and neural toxicity (Lacourt & Heijnen, 2017), body composition worsening (Demark-Wahnefried *et al.*, 2001), and sharp decreases in quality of life (Kayl & Meyers, 2006).

Designing exercise dose-response studies is an example of how to reduce the adverse events and/or acute impact of exercise and reach clinical relevance in breast

cancer patients through the exploration of exercise prescription (i.e., resistance and/or aerobic exercises). For aerobic exercise, while a significant positive linear trend was observed for adiponectin levels (Sturgeon *et al.*, 2016) and follicular phase estrogen (Schmitz *et al.*, 2015) as the dose was increased, both low- (150min/week) and high-dose (300min/week) were efficient to improve aerobic fitness and fat tissue in women at risk for breast cancer. Regarding resistance training dose-response, previous studies (Galvão & Taaffe, 2005; Radaelli *et al.*, 2014; Cunha *et al.*, 2018) have reported similar changes on muscle strength, body composition (i.e., lean and fat mass), and functional capacity after 12 and 20-weeks of single- vs. multiple-sets (low vs. high dose) in healthy older women, but no study has investigated this issue in breast cancer patients. Although it seems reasonable that a low- and high-dose resistance training could promote similar benefits due to the lower neuromuscular adaptation threshold for untrained subjects, the immune system, which drives system regeneration and adaptation, is impacted at the same by the chemotherapy in breast cancer patients. Thus, the resistance training dose-response relationship remains to be elucidated in breast cancer patients during the treatment because it is unknown how different physiological organ systems affected by chemotherapy will adapt after repeated bouts of resistance exercise, or even more, how they will respond to a different doses of resistance exercise.

In order to investigate if resistance training will follow a linear relationship on physiological and clinical outcomes in breast cancer patients, the present thesis sought for a rational approach in previous literature to support they own experimental assumption. Thus, a systematic review aiming to elucidate the resistance training dose-response relationship in previous literature was performed in a first chapter, followed by a second chapter which comparisons over the effect of combined different resistance training doses (i.e., low- vs. high-volume) and aerobic exercise on the physiological outcomes in breast cancer patients undergoing chemotherapy treatment will be experimentally tested. It was expected that low and high-doses of resistance training results in a non-significant linear trend on physiological outcomes, corroborating with previous literature findings.

2. LITERATURE REVIEW

At the first moment, it will be important to I) understand how physical activity acts as prevention for the breast cancer, II) highlight why exercise-mediated changes

recently emerge as an important part of the standard care of cancer, to thereby, III) present the main hypothesis. Please, follow the next three subheadings:

2.1. Physical activity as a breast cancer risk factor

The high incidence of cancer in women is a well-known and concern phenomenon worldwide. Although women represent half of the world's population, cancer has reached a larger expansion and the first place in the leading cause of death compared to men in both high-, middle-, and low-income countries (Torre *et al.*, 2017). One of the most frequent and also leading cause of death is breast cancer, accounting 25% of cancer cases and 15% of cancer-related deaths in the whole world. In South America, reports of Brazil indicate that breast cancer leads the most commonly diagnosed and cause of death in women (Torre *et al.*, 2017). In this sense, the appeal of health agencies in the control and prevention of breast cancer are of utmost importance, reflecting in the availability of early detection and strategies to reduce risk factors exposition.

The non-modifiable risk factors for breast cancer such as family history of disease, mutations in BRCA1 and BRCA2, and endogenous estrogen exposure (i.e., nulliparity, early age at menarche, later menopause, and later age at first pregnancy) in despite of the great importance, are beyond the scope of the present review and could be explored in excellent previous studies as Bradbury & Olapade (2007) and Colditz & Bohlke (2014). Given the interest and awareness that modifiable risk factor accounts for ~20% of breast cancer cases worldwide (Danaei *et al.*, 2005), the present thesis focus in the promotion of health behaviors since they would potentially act in known modifiable risk factors like alcohol use, excess of body weight, and sedentary lifestyle (Colditz & Bohlke, 2014; Silva *et al.*, 2018). Moreover, it is important to note that 12% of breast cancer-related deaths in Brazil were attributable to physical inactivity, and 4-6% due to other risk factors as alcohol intake and high body mass index (Silva *et al.*, 2018). Therefore, the physical activity and exercise will be a matter of interest due to their impact on body weight and physiological markers of breast cancer in this review.

The first hypothesis that sedentarism could be a risk factor for cancer in women emerged in the '80s. Frisch *et al.* (1985) compared college athletes and non-athletes assuming that the exercise-related delays of menarche could influence the onset of cancer on the reproductive system. In fact, the results of Frisch *et al.* confirmed the

main hypothesis that women who had participated in organized athletic activity presented a lower rate of cancers than non-athletic classmates. Twenty years later, Friedenreich & Cust (2008) have designed a thorough review comprising 87 physical activity studies (cohort and case-control studies) and stated a protective factor of 25% in the most physically active women compared to the least active. In addition, the authors also examined the dose and type of activity. Risk reduction was observed in recreational (average 22% decrease) and moderate-intensity activities (average 20% decrease) with no employed statistical analysis. Finally, the study of Wu *et al.* (2012) filled this gap if physical activity has a threshold effect on breast cancer risk. The author's meta-analyzed 31 prospective studies involving 63,786 patients found an adjusted reduction of 12% of breast cancer risk. Different from the Friedenreich & Cust (2008) study, both occupational and non-occupational activities presented similar reduction (relative risk – RR = 0.90 and 0.87, respectively), with higher protection for vigorous than moderate activity (RR = 0.86 vs. 0.97). In addition, Wu *et al.* (2012) also found a decreased of 2-5% for every ~17 metabolic equivalents (MET) per hour/week increment in non-occupational, or recreational activity. Thus, it seems that the overall physical activity plays an important role in human body protection indicated by the reductions in breast cancer risk in most studies.

Although the precise pathways by which physical activity exerts a protective effect remains to be elucidated, some proposed mechanisms like the reductions of sex steroid hormones (circulating levels and cumulative exposure), and insulin-related factors are accepted in the literature. It is well known that breast tumor development is influenced by the bioavailability of estrogen levels, stimulating epithelial cells mitosis, and regulation of cell cycle (Pike *et al.*, 1993; Key *et al.*, 2001). In this sense, physical activity acts I) reducing body fat which partially mediates the exercise-induced changes in estrogen levels (McTiernan *et al.*, 2004), and II) through alterations on menstrual function and patterns as delayed the onset of menarche among others which is also associated with excess of body fat (Loucks, 2003). Regarding the insulin-related factors, glucose has been associated to breast cancer development by stimulating breast cancer cells (Okumura *et al.*, 2002) and within the indirect increasing in bioavailable estrogen by the downregulation of sex hormone binding globulin and upregulation of ovarian sex steroid production (Kaaks & Lukanova, 2001). In both

cases, physical activity acts in improving the insulin sensitivity and regulating the exposition to estrogen, which is partially mediated by the control of body weight.

Unfortunately, despite this partial protection of physical activity, the incidence of breast cancer is still high in middle-income countries as Brazil due to the increase of sedentary behavior in the overall population (Silva *et al.*, 2018). Therefore, it is important to move forward and rethink how to use non-pharmacological strategies as physical activity or exercise to help in breast cancer treatment management and explore the possible benefits to reducing symptoms and side-effects commonly reported during the treatment.

2.2. Physical exercise as part of standard care for breast cancer

Previously, the term *physical activity* defined by Caspersen *et al.* (1985) as “any bodily movement produced by skeletal muscles that result in energy expenditure” was used to picture the reduces of breast cancer risk performing any recreational or occupational movements commonly found in human daily activities. However, people became more sedentary and fatter over the years (Pontzer *et al.*, 2018), and non-structured physical activity seems not to follow the short-term demands imposed by breast cancer incidence (Nelson *et al.*, 2019). Thus, the term *physical exercise*, a subset of physical activity, defined as “planned, structured, and repetitive” which has a “final or an intermediate objective the improvement or maintenance of physical fitness” (Caspersen *et al.*, 1985) meet a major role during the treatment of breast cancer patients reinforced by physical education and health professionals. In fact, despite the number of epidemiological studies demonstrating association between overall physical activity and survival (Holmes *et al.*, 2005; Friedenreich *et al.*, 2016), it is also important to note that cancer patients undergoing at least 1-day exercise per week (in this case, resistance exercise) were associated with reduced risk of all-cause mortality (~33%) while overall physical activity was not (Hardee *et al.*, 2014).

The mainstream treatment for breast cancer involves systemic (i.e., hormone and chemotherapy) and loco-regional procedures (i.e., surgery and radiation) defined by the stage of disease (I-III). In addition, features such as the tumor size, type and histological degree, lymph node status, estrogen and progesterone receptors level, menopausal status, and clinical conditions are also relevant for medical decisions (Miller *et al.*, 2016). Although those treatment modalities aim to eliminate tumor cells and improve 5-year survival rate among patients, it is important to note that survival

cannot predict what will happen in any particular patient's case. Thus, there is a large number of women who even living long after a cancer diagnosis, will facing many side effects at risk for recurrence, mortality, and morbidity. The side effects are well known by patients who often experience neural and cardiovascular toxicity and short-term side effects which are associated with severe symptoms leading to a diminished quality of life during and after treatment (DiSipio *et al.*, 2013; Rivera & Cianfrocca, 2015). In addition, breast cancer patients also present a sharp decrease in the overall physical activity levels throughout the treatment (Nelson *et al.*, 2019), hence affecting muscle mass and strength, fatigue and a decline in the functional capacity of almost half of the patients (Demark-Wahnefried *et al.*, 2018). In this sense, the potential of *exercise as medicine* has been explored by numerous clinical trials in a field known as "exercise oncology".

Two of the first studies in this field were from Winningham *et al.* (1988; 1989) which investigated the effect of aerobic program on nausea symptoms (Winningham *et al.*, 1988) and body composition (Winningham *et al.*, 1989) in breast cancer patients undergoing chemotherapy. In the first study (Winningham *et al.*, 1988), a three-arm design comprising supervised aerobic exercise performed three-times a week (n=16), placebo groups performing low-intensity supervised flexibility training once weekly (n=14), or a control group (n=12) on nausea symptoms. The results were promising given that patients during chemotherapy often report this side-effect and the aerobic exercise group improved significantly the symptoms of nausea compared to placebo and control group. Secondly, the authors (Winningham *et al.*, 1989) focused on body composition responses and subjects were randomly assigned to supervised aerobic exercise (n=12) and control group (n=12). After 10-12 weeks of intervention, it was reported a significant improvement in lean body mass and a moderating effect on gain in body fat favors to the exercise group compared to controls. Altogether, the results of Winningham *et al.* (1988, 1989) were important to strengthen the field and provide scientific support to a thousand studies that came after. Over the past two decades, cumulative findings support the promotion of physical activity and exercise to improve and maintain quality of life, physiological and functional benefits during treatment. This evidence provides so impact that on *May 2018*, the Clinical Oncology Society of Australia (COSA) launched a position statement endorsed by leading health and care organizations, recommending that exercise should be prescribed as part of the

treatment for all cancer patients (Cormie *et al.*, 2018). After this, *The Lancet Oncology*, one of the most relevant journals in oncology, reserved the *Jun 2018* editorial for a supportive but conservative report:

> Although the decision is a welcome move that increasingly recognizes patient quality of life as a vital component of cancer care, two crucial questions remain: does the evidence base adequately support the decision, and can such an approach be suited to the diverse range of cancer types and patients who are inflicted with the disease? (The Lancet Oncology, Jun 2018, 19(6), p.715)

In September 2018, the responses of Cormie *et al.* (2018) and Mina *et al.* (2018) were published. The *Lancet Oncology* editorial was well received by the authors and both agreed that there is still more to be learned about the exercise (i.e., including dose-response) to maximize safety and feasibility. However, it is reinforced that the current evidence provides justification for including exercise as part of cancer care routine even that protective effects against survival outcomes are still to be determined (Cormie *et al.*, 2018). In order to illustrate what is the current evidence and hypothesis regarding exercise over cancer, the next topic will briefly approach the preclinical studies supporting exercise modulation on therapeutic response.

2.2.1. Exercise-mediated changes in the tumor microenvironment and antitumor immune response

In this topic, it will be of interest describe some of the main exercise-induced changes in the tumor microenvironment. Nevertheless, readers can consult excellent works as Koelwyn *et al.* (2017) and Ashcraft *et al.* (2018) for a depth read.

Most of the tumors present own microenvironment: an abnormal vasculature defined as tortuous, leaky and full of shunts. Vaupel *et al.* (2007) stated that the tumor tissue is also poorly oxygenated compared to normal tissues (<10mmHg O_2) after review 125 clinical studies. In fact, the tumor microenvironment is supported by hypoxia-induced levels of proangiogenic cytokines such as the vascular endothelial growth factor (VEGF) within the tumor (Zhang *et al.*, 2002). Thus, the antitumor therapeutics play a role in normalizing the vascularity by improving the vascular maturity (i.e., reduce permeability, increase pericyte coverage, and reduce the microvessel diameter) through antiangiogenic factors, but also require a functional vasculature comprised by mature, long and with visible lumen vessels to effectively

deliver blood and oxygen (Vasudev *et al.*, 2014). Although some trials have tested antiangiogenic agents focusing on VEGF and its receptors to improve drug delivery pathways, this type of drugs became unfavorable due to several side-effects after prolonged use (Jain, 2014).

Not surprising, it is well documented the potential effect of exercise on vascular function. It is possible to identify two related mechanisms by which exercise affects the vascular system such as I) exercise-induced vascular shear stress resulting in vascular remodeling (Schadler *et al.*, 2016), and II) changes in VEGF in conjunction with platelet-derived growth factor receptor expression affecting perfusion in tumor microenvironment (Betof *et al.*, 2015). First, the shear stress during exercise promotes the vascular maturity by the activation of transcription and nuclear factor of activated T-cells, increasing the transcription of thrombospondin 1. This has important implication to anticancer agents since previous studies demonstrated the efficacy of chemotherapy (e.g. cyclophosphamide and gemcitabine) in combination with exercise (voluntary running or at 60-70% of exercise capacity) slowing the tumor growth when compared to sedentary control mice (Betof *et al.*, 2015; Schadler *et al.*, 2016). Thus, increasing the contribution of tumor microvessels through exercise will induce tumor cells on higher chemotherapy exposure, and also normalize the tumor vasculature eliminating shunts that could unexposed to the drug. Lastly, it is expected that exercise causes associated increases in VEGF levels and reductions in platelet-derived growth factor receptor expression (Betof *et al.*, 2015). These changes could promote an angiogenic-related reduction on tumor hypoxia induced by increased microvessel density and perfusion hence optimizing drug delivery. In summary, the new pathways promoted by exercise reduce hypoxia as well as increases perfusion and drug delivery to the tumor either by shear stress or VEGF changes.

As far as known, the chaotic tumor changes are not exclusive to the vascular system. Tumors also act as “villains” on immunity, using a variety of mechanisms to affect T-cell functions as infiltration and recognition hence decreasing antitumor immunity. Two possible mechanisms are related to the contributions of exercise as the increase on interleukin-6 (IL6) and the modulation of natural killer (NK) cells on the immune system. The IL6 has an importance in the trafficking of T-cells into the tumor, and after exercise, the increases on IL6 levels also causes the redistribution of NK cells which may initiate a cytotoxic activity against cancer cells (Pedersen *et al.*, 2016).

However, it is also important to note that immune cells exhibit a bi-phasic behavior on a systemic level (Shinkai *et al.*, 1992; Shek *et al.*, 1995). During or immediately after exercise, an acute exercise-induced leukocytosis by increased concentrations of NK cells and CD8+ T-cells are observed, followed by leukopenia after the cessation. It is speculated that this phenomenon can cause immunosuppression (Peake *et al.*, 2017), but recent evidence demonstrated that this leukopenia reflects on the T-lymphocytes redistribution to peripheral tissues instead of a susceptible state for infections (Kruger *et al.*, 2016).

After the abovementioned, the background of physical exercise as a cancer risk factor and part of the standard care were constructed based on the possible effects in the human body and tumor microenvironment. However, at the same time that cancer-related treatment affects the physiological systems, they also impair the processes that repair and adapt in response to exercise (Tidball, 2017). The immune system, for example, performs an important role in tissue repair, metabolism, sleep, fatigue, and mental health and are severally affected by chemotherapy. Observing these impacts could raise some interesting hypothesis about the chemotherapy-related changes on the immune system and their effects on changes promoted by exercise. Therefore, the following topics will focus on the immune system as a possible actor on the exercise-induced changes during the adjuvant treatment for breast cancer.

2.3. Chemotherapy effects on exercise-induced changes: The role of immune system recovery after exercise

The immune system is able to monitor, recognize, and eliminate nascent tumor cells in the process named as *cancer immune surveillance* (Kim *et al.*, 2007). Three essential phases compound this process: elimination, equilibrium, and escape. First, the immune response is able to control tumor growth by the tumor cell recognition, a process that involves the secretion of proinflammatory cytokines (e.g. interleukin-12 – IL12) and innate immune cells (e.g. NK cells, dendritic cells, and macrophages). The dendritic cells will migrate to nearby lymph nodes and activate tumor-specific CD4+ and CD8+ T-cells to thereby, T-cells migrate to the tumor site and facilitate killing. Hereupon, two things can occur: tumor cells can be completely eliminated or can develop resistant clonal variants. In the second option, the clonal variants act secreting and recruiting immunosuppressive factors and here the phase of equilibrium is in force. If another cycle of immune response fails to eliminate the nascent cancer cells, so, the

third phase is reached. In the latter, tumors developed mechanisms to escape immune control by a process called immune editing, providing a selective pressure in the tumor microenvironment, which will eventually cause the tumor clinical manifestations. Thus, the first shock in the immune system occurs in disease development.

When the systemic treatment is the clinical decision, the second immune system shock happens since they are impaired to act against the tumor cells. In this case, chemotherapy, the mainstream treatment for breast cancer, is known to alter immune responses. Although drugs as *Doxorubicin*, *Paclitaxel*, and *Cyclophosphamide* are known to destroy cancer cells, they also affect proinflammatory cytokines and cause several side-effects related to the immune system after the first cycle (Panis *et al.*, 2012; Paz *et al.*, 2018). However, how long the patient will recover the immune system is an important topic given that breast cancer patients presented a lower baseline immune response than their healthy counterparts (Caras *et al.*, 2004). In order to fill this gap, the study of Kang *et al.* (2009) examined the recovery following cancer adjuvant therapy over the first year after the cancer diagnosis. The immune markers as CD4+ and CD8+ cells, IL6, interferon-γ, and NK cells were measured 4 times in 80 early stage breast cancer patients: prior, and at 2, 6, and 12 months from the beginning of adjuvant therapy. The results indicate that within 1-year follow-up, is not possible to observe the immune recovery to pretreatment levels. Therefore, the treatment leads the breast cancer patients to the worst immune status “opening” the window for infections and comorbidities.

Whether disease and treatment impair the immune system function, it seems reasonable that the exercise-induced changes on the neuromuscular system such as increases on muscle strength, endurance and muscle hypertrophy may also be impaired by this condition. After repeated bouts of exercise, involving concentric-eccentric contractions and/or stretching-shortening cycles, a process called “exercise-induced muscle damage” seems to participate in muscle remodeling (Damas *et al.*, 2018). This regenerative capacity of the skeletal muscle depends on I) the presence of satellite cells, which proliferate and differentiate to either fuse with existing fibers or other myogenic cells to generate new fibers; and II) immune cell regulation through the time course of changes in myeloid cell populations (e.g. monocytes, macrophages, neutrophils, leukocytes, among others) and lymphoid cells (e.g. T and NK cells). Although the satellite cells play an important role in muscle repair, their presence alone

is insufficient for muscle regeneration, and this cell must have the capacity to proceed through activation, proliferation, and differentiation within the muscle. Since the nature and features of satellite cells are beyond the scope of this thesis, readers can consult the works of Allen *et al.* (1995) and Petrella *et al.* (2006) for a depth review. Therefore, muscle remodeling through immune cell regulation will be the matter of this topic.

First of all, it will be important to understand the role of myeloid cell regulation I) during the early stage; II) during the transition to the terminal differentiation, and III) during the terminal differentiation and growth stage of muscle regeneration. To describe this phenomenon, the following subheadings are based on the excellent work of Tidball (2017) and readers could consult for extensive exploration.

2.3.1. Myeloid cells: Regulating muscle regeneration during the early stage

For the early stage, the exercise-induced muscle damage causes a fast response of leukocytes, neutrophils, and macrophages invading the damaged muscle. This early neutrophil invasion is an essential response enabled by the inflammatory environment which will influence the activation of subsequent immune cell populations. Following, the circulating monocytes and macrophages extravasate entering into this muscle environment, enriched with some pro-inflammatory cytokines as interferon-γ (IFNγ) and tumor necrosis factor (TNF), hence activating the pro-inflammatory phenotype of macrophages (Warren *et al.*, 2002; Wang *et al.*, 2014). Regarding this, macrophages can be distinguished by their functions (i.e., M1 and M2) at those different stages of muscle remodeling. The M1 macrophages are indicative of pro-inflammatory phenotype, while M2 macrophages are associated with the resolution of inflammation and tissue repair (Mills *et al.*, 2000). Nevertheless, the M1 and M2 nomenclature is just a didactic way to describe the predominance, and it is important to note that both phenotypes can be expressed simultaneously and at any time point following muscle damage (Lemos *et al.*, 2015).

Among the inflammatory response, the IFNγ emerges out as a potential coordinator of this process during this early stage in accordance with previous study which found an associated increase of neutrophils, macrophages, and satellite cells within the first 24h of induced muscle damage by cardiotoxin (one of the experimental models of acute muscle injury and repair). In addition, it was also observed that a blockade IFNγ signaling results in reduced expression of macrophages in injured muscle hence inactivating the M1-type macrophages (Cheng *et al.*, 2008). Moreover,

some relationship between TNF and the control of muscle regeneration is observed. Most of all macrophages and neutrophils express TNF in muscle following acute muscle damage and affecting muscle regeneration (Warren *et al.*, 2002). Given the exposed, this dominated environment by M1 phenotype begins the earliest stage of regeneration driven by IFNγ and TNF. The IFNγ will exert a dual role at this time point both activating macrophages and directly regulate myogenic cells in the differentiation process during an extended period of time (Cheng *et al.*, 2008). Although clearly observed at day 1, the expression of IFNγ remains increasing until day 5 since the M1 phenotype macrophage remove the muscle damage remains and also express IFNγ, reinforcing the macrophage phenotype itself and retaining satellite cells in a proliferative state to support tissue repair (Tidball, 2017).

In summary, these two cytokines can activate macrophages to the M1 phenotype and also regulate the proliferation and differentiation of satellite cells. However, women undergoing the primary treatment for breast cancer presented an I) reduced expression of IFNγ even after 12 months of treatment (Kang *et al.*, 2009); and II) reduced levels of neutrophils 1-hour after chemotherapy drugs (Panis *et al.*, 2012). Thus, it seems reasonable that chemotherapy effects could impair the early stage of muscle regeneration after exercise-induced muscle damage through an uncommon pro-inflammatory cytokines' levels and myeloid cells availability.

2.3.2. Myeloid cells: Regulating muscle regeneration during the transition to the terminal differentiation

As seen in the last topic, the increases on TNF and IFNγ signaling the early stage of regeneration driven the M1 stage macrophages, and myogenic differentiation and proliferation. This system allows the expansion of myogenic cells, some of which return to the reserve, whereas others differentiate and grow into fully differentiated muscle fibers. Interestingly, previous observations also linked the macrophage phenotyping to the levels of expression of CD68 and CD163 showing that these changes are associated with M1 macrophages at day 2 post-injury and the replacement by M2 macrophages at days 4 to 7 post injury, coinciding with the gene's expression of terminal differentiation of myogenic cells (St Pierre & Tidball, 1994). In this sense, it is suggested that the transition from M1 to M2 macrophages are coupled to the transition in stages of myogenesis.

The TNF and IFNγ signaling were presented as important cytokines in the early stage process, but they are not the only involved in the whole process. Marked increases in the expression of interleukin-10 (IL10) are associated with the transition from M1 to M2 macrophages phenotype, inhibiting the M1 phenotype and inducing the transition to M2 phenotype (Deng *et al.*, 2012). This is a strong indicator for the transition from a regeneration state to the differentiation and growth stage of myogenesis. In addition, although the early stages of muscle regeneration were driven by cytokines and chemokines, growth factors induced by myeloid cells themselves have also the influence on macrophage phenotype and in the course and success of muscle regeneration. An example is the insulin-like growth factor 1 (IGF1) released by M1 macrophages. This growth factor is a strong mitogen for satellite cells in muscle and their deletion can slow muscle growth following injury, besides their loss in myeloid cells affects the transition from M1 to M2 phenotype stage (Musarò *et al.*, 1999; Tonkin *et al.*, 2015). Not far, perturbations in the phagocytic removal of apoptotic cells were also associated with delayed regeneration. In cases of physical barriers to the regeneration as prolonged accumulation of debris and lack of space for repair could be considered an impairment to the transition to M2 stage due to the role of phagocytic removal on suppression and expression of TNF and tumor growth factor, respectively (Tonkin *et al.*, 2015; Fadok *et al.*, 1998).

As seen during this phase of transition, the IGF1 is an important inductor for satellite cells mitogen and its deletion or loss within the myeloid cells affects the transition between phenotype stages. However, this protein when dysregulated has been shown to be associated to the development and progression of many cancers such as in the breast cancer (Elstrom *et al.*, 2004) as well as the resistance against some drugs during treatment. An example is regarding the HER2-positive breast cancer. The use of a monoclonal antibody as *Trastuzumab* has prolonging overall survival of patients in this metastatic setting, but at the same time, a considerable number of patients also does not benefit, developing resistance within the 1-year of treatment (Vogel *et al.*, 2002; Marty *et al.*, 2005). One of the mechanisms behind this resistance is the IGF-mediated pathways which have autocrine, paracrine and endocrine roles in breast cancer supporting the interaction between host and metastatic sites. In fact, it is observed that IGF1 high expression was associated with an inferior prognosis (HR = 2.37 [95% CI: 1.21 to 4.64], p=0.012) in HER2 receptor-

positive breast cancer (Yerushalmi *et al.*, 2012). Thus, it is unknown how the transition to terminal differentiation will be affected by the development of breast cancer because of the abnormal levels of IGF1 during treatment, but impairments over the macrophage's phenotypes transition caused by the current status of disease and treatment it is expected.

2.3.3. Myeloid cells: Regulating muscle regeneration during the terminal differentiation and growth stage of muscle regeneration

Following the course of muscle regeneration, the terminal differentiation and growth stage are also linked with the specific marker of CD163 coinciding with the replacement by M2 macrophages at days 4 to 7 post-injury (St Pierre & Tidball, 1994). Its expression is influenced by cytokines such as TNF and IL10, previously reported in the early and within the transition stage of muscle regeneration, which downregulates and induces powerfully the expression of this glycoprotein, respectively. The role of CD163 is on facilitating tissue regeneration by the degradation of hemoglobin-haptoglobin complexes (known as one of the muscle damage amplifiers) and also increase IL10 expression in the same process (Philippidis *et al.*, 2004). The CD163 importance in the terminal differentiation is also reinforced by other facts as its systemic ablation exacerbated muscle damage, slowed muscle growth and delayed the myogenic program for regeneration (Philippidis *et al.*, 2004). Finally, the CD163 released into the serum will inactivate one kind of TNF, known as TNFSF12 (or TNF-related weak inducer of apoptosis), promoting the myogenic cells proliferation and preventing perturbations during the terminal differentiation and growth stage of muscle regeneration.

2.4. Exercise dose-response in breast cancer: How much does she needs to do?

The above considerations about immune-related factors involving muscle regeneration and adaptation were important to set some assumptions. Whether breast cancer disease and treatment affect the immune system, responsible in part for the muscle regeneration and adaptation, how the body of a breast cancer patient will adapt after repeated bouts of exercise? Taking these issues into account, it is already known that muscle strength should be increased after an exercise program probably due to the neural plasticity (i.e., in a short-term intervention), as indicated by the level A of evidence in breast cancer patients (Schmitz *et al.*, 2010), but the chemotherapy-toxicity

also affects neuromuscular system, in addition to body composition parameters such as the muscle mass which were not so evidenced in previous literature (i.e., considered as a level B of evidence). In fact, although the mechanisms related to adaptations in hypertrophy are not so understood even in healthy people, it is well documented the effects of resistance training in increase muscle size through different types of prescription (i.e., high-load or high-volume resistance exercises). Thus, this section will briefly explore some ideas about the dose of resistance training that a person needs to respond in muscle strength and size, and why this could be different for breast cancer patients.

The acute variables of resistance training such as frequency, number of sets and repetitions, and intensity are manipulated to reach desirable outcomes such as muscle hypertrophy and strength in the most different populations. In respect to these adaptations in older people, while the prescription of intensity seems to be well defined (i.e., 60-80% of 1-RM), the resistance training volume is not so conclusive as indicated by a wide range of “one to three sets per exercise” in respectful guidelines (ACSM, 2009). In fact, several studies claimed to a lower threshold for adaptations on muscle strength and size in older people after comparing single- and multiple sets of resistance exercise (Galvão & Taaffe, 2005; Radaelli *et al.*, 2014; Cunha *et al.*, 2018). For example, the study of Galvão & Taaffe (2005) reported similar improvements on chest and leg press maximal strength (5.7±6.3 vs. 9.1±6.1kg; and 10.5±9.9 vs. 14.6±7.6kg, respectively), but with no such magnitude on fat and lean mass (-0.5 vs. -0.9kg; and 0.5 vs. 0.7kg, respectively) comparing 20-week resistance exercise performed with single- vs. multiple-sets in older people. Searching for a short-term effect, the study of Radaelli *et al.* (2014) also reported similar augments on knee extension maximal strength (11.0 vs. 9.5kg, respectively) after 12-week single- vs. multiple-sets resistance training in older women. Nevertheless, the novelty of Radaelli *et al.* (2014) was the exploration of muscle hypertrophy of quadriceps femoris (evaluated by muscle ultrasound) in which the authors reported similar increments (4.6% vs. 6.9%, respectively) at the final of the study. From the conclusions of both studies which single-sets, i.e., a condition that imposes less impact on the body systems; is equally efficient to promote similar benefits over the muscle strength, body composition, and even muscle hypertrophy compared to multiple-sets that was possible to draw questions about resistance training dose-response for breast cancer. Thus, do the

adaptations regarding single- and multiple-sets for breast cancer patients would be similar as found in older women?

Before trying to speculate the answers, it is important to explain what happens to our body after a single session of resistance exercise regardless of the dose itself. As mentioned before, the “exercise-induced muscle damage” is an injury caused by mechanical stress over the muscle, possibly involving rupture and inflammation of muscle, connective or nervous system after an unaccustomed exercise. In the case of resistance exercise, induced stress imposed by concentric and eccentric contractions affects muscle homeostasis and causes changes in the muscle morphology such as disturbances in the cytoskeleton, sarcomere proteins, connective tissue among others hence promoting muscle soreness, decreases in muscle function as strength and power, and reduced range of motion (Clarkson & Hubal, 2002). This process, as commented in *section 2.3.*, awake the immune system to regulate muscle regeneration after exercise, promoting the satellite cells proliferation throughout the differentiation and growth stage of regeneration. Notwithstanding, does the exercise-induced muscle damage really mandatory for muscle adaptations? Although there is no evidence regarding the role of muscle damage building a muscle, an excellent review of Damas *et al.* (2018) gave strong suggestions that this phenomenon trend towards muscle remodeling in the first sessions of resistance exercise (i.e., evidenced by the proliferation and differentiation of satellite cells) to thereby be replaced by a truly muscle hypertrophy around 10-weeks of resistance exercise (Damas *et al.*, 2018). However, the exercise-induced muscle damage seems not to be obligatory neither potentiates muscle hypertrophy or strength since is reported no differences between its responses between eccentric-only contractions (i.e., a higher magnitude of muscle damage) and concentric-only or traditional resistance training (Douglas *et al.*, 2017) challenging the “no pain-no gain” paradigm. Therefore, if the exercise-induced muscle damage is not a mandatory condition to improve muscle mass or strength, seems reasonable that a condition which imposes less damage in the muscle could rebound in significant chronic improvements on neuromuscular system and muscle mass chronically, as well as protect against muscle soreness in the subsequent exercise sessions (Chen *et al.*, 2013).

As abovementioned, the effects of a single bout of exercise comprises some events as muscle soreness, decreases in muscle function and range of motion in a

healthy body (i.e., without signals of disease), besides structural and inflammatory shifts throughout the muscle. Although could seems that the same happen in a breast cancer patient after a single session of resistance exercise, the time course and success of these events may not be exactly as well. As speculated before, in *section 2.3.* and followed subsections, many alterations in the immune system and inflammatory markers in breast cancer patients make to believe that, when the muscle damage appears significantly, the recovery could take a longer period [i.e., more than 4-5 days as often reported by previous studies (Clarkson & Dedrick, 1988; Radaelli *et al.*, 2012)], and/or not recover in a sufficient time before the next bout of exercise. Therefore, it is expected that this phenomenon may cause an "overlap" of unrecovered muscle damage and metabolic impacts in women with breast cancer. However, these issues remain just speculative and the closest evidence that has is from a study involving breast cancer survivors with the diagnosis of lymphedema (i.e., after the primary treatment). The study of Cormie *et al.* (2016) randomized 25 breast cancer survivors on three acute conditions of resistance training: low- (3 sets of 15-20 repetitions maximum – RM, or 55-65% of 1-RM), moderate- (3 sets of 10-12RM, or 65-75% of 1-RM), and high-load (3 sets of 6-8RM, or 80-85% of 1-RM) in a crossover like design, separated by a wash-out period of at least 1 week. Given the hesitancy to recommend resistance exercise for women with breast cancer-related lymphedema, specifically with moderate to high loads to upper limbs, the authors aimed to explore whether these conditions promote significant inflammatory markers response after 24h of the experiment. In fact, the results presented no significant alterations on the inflammatory markers as creatine kinase, C-reactive protein, IL6, and TNF-α, besides no extent of swelling (evaluated by bioimpedance spectroscopy) after 24h of each of three conditions. In addition, no exacerbation of lymphedema symptoms (i.e., pain, heaviness, and tightness) was also observed. Although promising, the results of Cormie *et al.* (2016) should not be extrapolate to breast cancer patients during primary treatment due to the difference in the period of treatment and therapies since chemotherapy alter immune and inflammatory parameters even after 1-year treatment.

As far as known, there is a lack of studies investigating the acute inflammatory and functional responses after a session of resistance training in breast cancer patients during primary treatment. Altogether, it remains unknown I) what happens after a single bout of resistance exercise; II) whether a low- or a high-dose will provide a different

time course of exercise-induced muscle damage markers, and immune system; and III) may these different doses (i.e., low- vs. high-impact in the system) rebound in similar chronic adaptations after a short-term intervention in breast cancer patients. These questions are complex and involve non-defined paradigms and mechanisms even in healthy people. Furthermore, the first two questions are outside of the aims of the present thesis, and future studies should approach them for further clarification of resistance training concerns in breast cancer or other cancer patients. Notwithstanding, the last question will be addressed in two studies (*chapter 4* and *5*) aiming to move forward and take the first steps regarding the dose-response of resistance training in this population.

2.5. Conclusion

The exercise oncology is a growing field of investigation that has gained more attention in the last 20 years. The larger body of evidence and increased interest to move forward boosted out international societies to call for evidence-based exercise implementation by all health professionals in the care of cancer (Cormie *et al.*, 2018), besides evoking important repercussion among exercise oncology scientists (Newton *et al.*, 2019; Mina *et al.*, 2018), and clinical journals as *The Lancet Oncology* (The Lancet Oncology, 2018) that cannot be laid aside. Moreover, move forward to investigate the gaps regarding exercise dose-response in breast cancer patients seems to be an alternative way to collaborate with current literature, bringing evidence-based practices and increase adherence on physical exercise programs. Given the barriers related to supervised exercise (i.e., displacements, nauseas, fatigue, and chemotherapy) that limit time availability, exercise prescriptions that improve time-efficiency and reduce side-effects of treatment is of utmost importance for this population.

3. AIMS AND HYPOTHESES

The general aims of this master thesis were to explore if resistance training dose-response will follow a linear trend on physiological and clinical outcomes in breast cancer patients. To do so, the present thesis sought for a rational approach in previous literature to support they own experimental assumption. Thus, the systematic review aiming to elucidate the resistance training dose-response relationship in previous literature, and the experimental study comparing the effect of combined aerobic and different resistance training doses over the physiological outcomes in breast cancer patients undergoing chemotherapy treatment were performed as follow:

3.1. First study: The dose-response of resistance training in breast cancer patients undergoing treatment: training principles and scientific rationale.

Study aims: Considering the need to look for a scientific rationale of resistance training dose-response in previous literature, the specific aim of the first study was to I) review and report adherence of the components (i.e., frequency, intensity, time, and type - FITT factors) and principles of resistance training, to add future specific information about this type of exercise; and II) elucidate the resistance training dose-response relationship in breast cancer patients undergoing primary treatment considering FITT factors among other components of resistance training (number of sets and repetitions).

Research hypothesis: It would be expected, based on previous studies comparing single- vs. multiple-sets (Galvão & Taaffe, 2005; Radaelli *et al.*, 2014; Cunha *et al.*, 2018) in older, that there is no linear relationship between low- and high-dose of resistance training in breast cancer patients undergoing primary treatment. Given the outcomes of interest as body composition and measures (i.e., body weight, body mass index, body fat and lean body mass), and physiological outcomes (i.e., maximal strength measured by one-repetition maximal (1-RM), isometric and isokinetic tests, cardiorespiratory fitness, and immune markers), it would be expected no differences between low- and high-dose of resistance training (defined by number of contractions and intensity of exercise).

3.2. Second study: Dose-response effects of resistance exercise in breast cancer patients undergoing primary treatment: a pilot study from a randomized controlled trial.

Study aims: Considering the chemotherapy-related side effects during primary treatment for breast cancer and the need to attempt a minimal dose approach of exercise, the aim of the second study was to test experimentally and compare different doses of resistance exercise in combination with aerobic exercise on maximal strength, body composition, muscle thickness, cardiorespiratory fitness, fatigue, and quality of life in breast cancer patients receiving primary treatment.

Research hypothesis: In this three-arm clinical trial designed to compare the effects of a 12-week combined low- (i.e., single-sets) or a traditional-dose (i.e., multiple-sets) resistance training with aerobic exercise, we hypothesized that both doses of resistance training combined with aerobic exercise would be equally superior to usual care in these respective outcomes.

4. THE DOSE-RESPONSE OF RESISTANCE TRAINING IN BREAST CANCER PATIENTS UNDERGOING TREATMENT: SYSTEMATIC REVIEW OF TRAINING PRINCIPLES AND SCIENTIFIC RATIONALE.

Abstract

Background: Several findings strengthen the promotion of physical exercise as part of the standard care of cancer, but little is known about its dose-response effect in breast cancer patients, mainly in resistance exercise.

Objective: The aim of this systematic review was to report adherence of the components (i.e., frequency, intensity, type and time - FITT factors) and principles of exercise; and elucidate the resistance training dose-response considering its components in breast cancer patients.

Methods: Searches in three electronic databases were conducted to retrieve studies published from 1995 to 2018. Experimental studies that evaluated resistance training alone or combined with aerobic exercise in women with breast cancer undergoing treatment were included. We extracted information about resistance exercise components, and calculate outcomes relative changes to allow comparisons between different lengths. Furthermore, regression analyses were employed in order to predict the weekly rate of change related to resistance training components (volume and intensity).

Results: A total of 25 studies describing 18 trials (1,982 patients) were included. No trend linear relationship was found between resistance training components, and body mass, handgrip, and cardiorespiratory fitness ($p>.05$). However, weekly volume was negatively associated with increases on maximal strength ($r^2=0.82-0.97$; $p<0.05$). Lastly, because of the lack of data, no relationship could be explored on body measures and composition, physiological markers, and specific strength measures, in addition to no trial reported or attended to all key principles of exercise training.

Conclusions: Resistance training could produce greater changes in muscle strength with lower-doses without hampering other physiological adaptations in breast cancer patients.

4.1. Introduction

Several findings strengthen the promotion of physical exercise as part of the standard care of cancer due to the physiological, functional and quality of life (QoL) benefits found during and after primary treatment of cancer (Schmitz *et al.*, 2010; Rock *et al.*, 2012; Fuller *et al.*, 2018). In breast cancer, for example, impactful reductions in cancer-specific mortality (21-41%) and recurrence (21-43%) are part of the benefits of exercise following the diagnostic (Holmes *et al.*, 2005; Friedenreich *et al.*, 2016). However, even with support of international organizations as American College of Sports Medicine (ACSM) (Schmitz *et al.*, 2010), and American Cancer Society (Rock *et al.*, 2012), concerns regarding survivorship and exercise dose-response evidence is needed to move forward and definitely change clinical practice (The Lancet Oncology, 2018; Hayes *et al.*, 2019).

In respect of the dose-response in breast cancer patients, little is known about how much exercise is needed to reach clinically relevant improvements on physiological and functional endpoints during mainstream treatment (i.e., chemotherapy and/or radiotherapy). Among this wide range of outcomes, exercise benefits are evidenced on cardiovascular capacity, physical function, body composition, and QoL, besides considered as safe and efficacy intervention during treatment to improve reserve capacity (Schmitz *et al.*, 2010; Scott *et al.*, 2018). Given the abovementioned potential of exercise as medicine, the exploration of exercise dose-response is of particular interest to designing efficient and safety physical interventions beyond the general recommendations of physical activity (i.e., one size does not fit all approach) (The Lancet, 2018; Adams *et al.*, 2018; Newton *et al.*, 2019). Indeed, despite the number of epidemiological studies demonstrating association between overall physical activity and survival (Holmes *et al.*, 2005; Friedenreich *et al.*, 2016), it was reported that cancer patients undergoing at least 1-day exercise per week (in this case, resistance training) are associated with a likely reduced risk of all-cause mortality (~33%) while overall physical activity is not (Hardee *et al.*, 2014). Thus, it seems reasonable to investigate if a lower dose of resistance training can significantly improve physiological and body composition outcomes as a time-efficient strategy that may reduce barriers related to supervised exercise and potentially enhance exercise adherence.

Methodological considerations are also of fundamental importance when design exercise oncology trials. The control and reporting of training components (e.g. frequency, intensity, type, and time – FITT factors), and principles (e.g. specificity, progression, overload, initial values, reversibility, and diminishing returns), are needed to ensure that well-structured exercise prescription is being delivered, and biological individualities considered in cancer patients (Hayes *et al.*, 2019). In fact, concerns have been raised about the adequate use of training principles in cancer survivors (Campbell *et al.*, 2012; Neil-Sztramko *et al.*, 2017). Neil-Sztramko *et al.* (2017) reported that among 80 studies, neither report or attend to all key principles of exercise training in breast cancer. Interestingly, less than 30% of studies reported the exercise progression (i.e., increased of volume or intensity to continues/improves adaptation) in prescription (Neil-Sztramko *et al.*, 2017). This issue is of particular interest and concern for exercise oncology field given that exercise benefits are dependent from the adequate prescription of volume and intensity (i.e., exercise dose), and trials should attempt these factors from FITT to reach relevant improvements on clinical outcomes of interest. Moreover, considering the lack of reports of FITT factors and resistance training components as volume and intensity, it is unknown the resistance training dose-response for this population, in addition to the lack of comparisons in exercise oncology trials (i.e., dose-response design studies).

Since the evidence of the benefits of resistance training in breast cancer patients undergoing primary treatment are well known, but information about its dose is scarce, it will be of benefit to: I) review and report adherence of the components (i.e., FITT factors) and principles of resistance exercise, to improve and encourage future exercise trials, mainly prescribing resistance exercise; and II) elucidate the resistance training dose-response relationship in breast cancer patients undergoing primary treatment considering FITT factors among other components of resistance training (number of sets and repetitions). Considering previous reports that resistance exercise performed with single- and multiple-sets could promote similar short-term adaptations on neuromuscular, hypertrophy, and body composition endpoints in older adults (Galvão & Taaffe, 2005; Radaelli *et al.*, 2014; Cunha *et al.*, 2018), we would expect that higher volume of resistance training will not elicit greater changes in physiological outcomes in breast cancer patients.

4.2. Methods

4.2.1. Study selection procedure

The study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati *et al.*, 2009) and the method used was based on the minimum criteria established by the Cochrane Back Review Group (CBRG) (Furlan *et al.*, 2015). The search was conducted from October 2016 up to September 2018, using the following electronic databases: MEDLINE, CINAHL, and SPORTDiscus. The terms used were: 'Breast cancer', and 'resistance training' in association with a list of sensitive terms to search for experimental studies. In addition, we performed a manual search of references in published studies. Reference lists provided in the selected papers were also examined to detect studies potentially eligible for inclusion. The search strategy used for the MEDLINE (PubMed) database is shown in the Supplementary Material (SM) Table S1. Studies reported in languages other than English were not included.

4.2.2. Intervention, controls and outcome measures

This review included experimental studies that evaluated the effects of resistance training alone or combined resistance and aerobic exercise training in women with breast cancer undergoing treatment. Exclusion criteria included studies using home-based exercise (non-supervised) interventions. The reasons for this exclusion are the lack of control on variables of interest such as FITT factors and components of the resistance training intervention.

4.2.3. Components of resistance training prescription

The prescribed resistance training for each study was summarized according to an adaptation of FITT factors as follow: frequency (number of sessions per week), intensity (prescribed intensity of the resistance training), type (resistance training or combined resistance and aerobic training), and volume (sets and repetitions). This format was used due to the use of volume (sets and repetitions) instead of the *time of session* to prescribe resistance training. The percentage of studies meeting each criterion was calculated, but no statistical techniques were used.

4.2.4. Principles of exercise training assessment

The principles of exercise training assessment were performed by two investigators independently (P.L. and G.S.) and took into consideration the following

characteristics of the included studies: specificity (i.e., appropriate population targeted and intervention given based on primary outcome), overload (i.e., rationale provided that program was of sufficient intensity/exercise prescribed relative to baseline fitness), progression (i.e., stated exercise program was progressive and outlined training progression), initial values (i.e., selected population with low level of primary outcome measure and/or baseline physical activity levels), reversibility (i.e., performed follow-up assessment on participants who decreased or stopped exercise training after conclusion of intervention) and diminishing returns (performed follow-up assessment of primary outcomes on participants who continued to exercise after conclusion of intervention) as previously reported (Campbell *et al.*, 2012; Neil-Sztramko *et al.*, 2017). Each study was assigned a rating for each of the principles of exercise training based on the application of the principle. Application of the specific principle was assigned a '+', whereas 'NR' (not reported) was assigned if the principle was not used in the prescription. A '?' was assigned if it was unclear whether or not the principle was used, or if the principle was reportedly used but inconsistently applied or was unclear.

4.2.5. Attendance rate of prescribed interventions

The attendance rate refers to the number of attended supervised exercise sessions and was extracted for each study when reported. In most of the studies reviewed, the authors reported the attendance rate in percentage (%) of the total number of sessions. Sometimes, when absolute values were used, in such cases, the attendance rate was measured. The percentage of attendance rate of studies was calculated and expressed as mean, standard deviation (SD) and 95% confidence intervals (95% CI).

4.2.6. Quantification of resistance training prescription

In the present study, training volume refers to all sessions performed in the week and was determined as the product of sessions per week, sets and repetitions [frequency x sets x repetitions] for lower and upper limbs, or total volume. Exercise intensity was presented as a percentage of the 1-RM value. In cases where the intensity was expressed only as a function of how many repetitions the participant was able to perform (e.g. repetitions maximum), we estimated the relative intensity based on data on the relationship between the number of repetitions performed and the 1-RM for the same or similar exercises (Wernbom *et al.*, 2007). When the resistance

training volume or intensity was not reported, their values were reported as “unknown” in further analysis.

4.2.7. Calculation of changes and rate of changes

In most of the studies reviewed, the authors reported the changes in muscle strength or at least the pre- and post-training values. Sometimes, figures were used instead of numerical data; in such cases, the graphs were measured if possible. The relative changes were calculated by dividing the post- with the pre-training values. To allow for comparisons between studies of different length, percent changes per week were calculated by dividing the change in the outcome with the length of the training period. The values were expressed as mean, SD and 95% CI.

4.2.8. Data extraction and analysis

Titles and abstracts of all articles identified by the search strategy were independently evaluated in duplicate (P.L. and G.S.). Abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated these full-text articles and selected them in accordance with the eligibility criteria. Disagreements between reviewers were resolved by consensus.

The data extraction was performed by the same two reviewers independently via a standardized form. Information on interventions, outcomes, and patients was collected. Discordance between reviewers was resolved by consensus. Studies characteristics as intervention length, components of resistance training prescription (i.e. frequency, intensity, volume, and modality), adverse events, feasibility, and attendance rate were extracted, besides the main outcomes, techniques assessment, and results. In addition, principles of exercise training (i.e., specificity, overload, progression, initial values, reversibility, and diminishing returns) were analyzed as described in the previous section. The outcomes analyzed in the present study were body composition, physiological, and muscle strength outcomes.

When four or more data points were extracted, scatter plots and regression analyses were employed in order to predict the rate of change per week regarding components of resistance training as volume and intensity. In addition, studies which did not report those components were also computed and presented as “?”. The α level of significance for all tests was set at 0.05, and the coefficient of determination (r^2) and

β values were also reported. All statistical analyses were conducted using SPSS for Windows version 20.0 (SPSS Inc. USA).

4.3. Results

4.3.1. Studies included

All studies selected reported the aim to investigate the effect of resistance training (i.e. resistance exercises or combined resistance and aerobic exercises) in breast cancer patients undergoing primary treatment. We retrieved 388 studies, 178 of which were retained for full-text assessment (Figure 1). Of these, one-hundred thirteen studies were excluded and 65 full-text articles were assessed for eligibility. Forty exclusions due to unsuitable experimental design (n=18), different population (n=15), and different intervention (n=7) were performed. The eligibility assessment resulted in 25 studies describing 18 trials published since 1995 which were included in this present review.

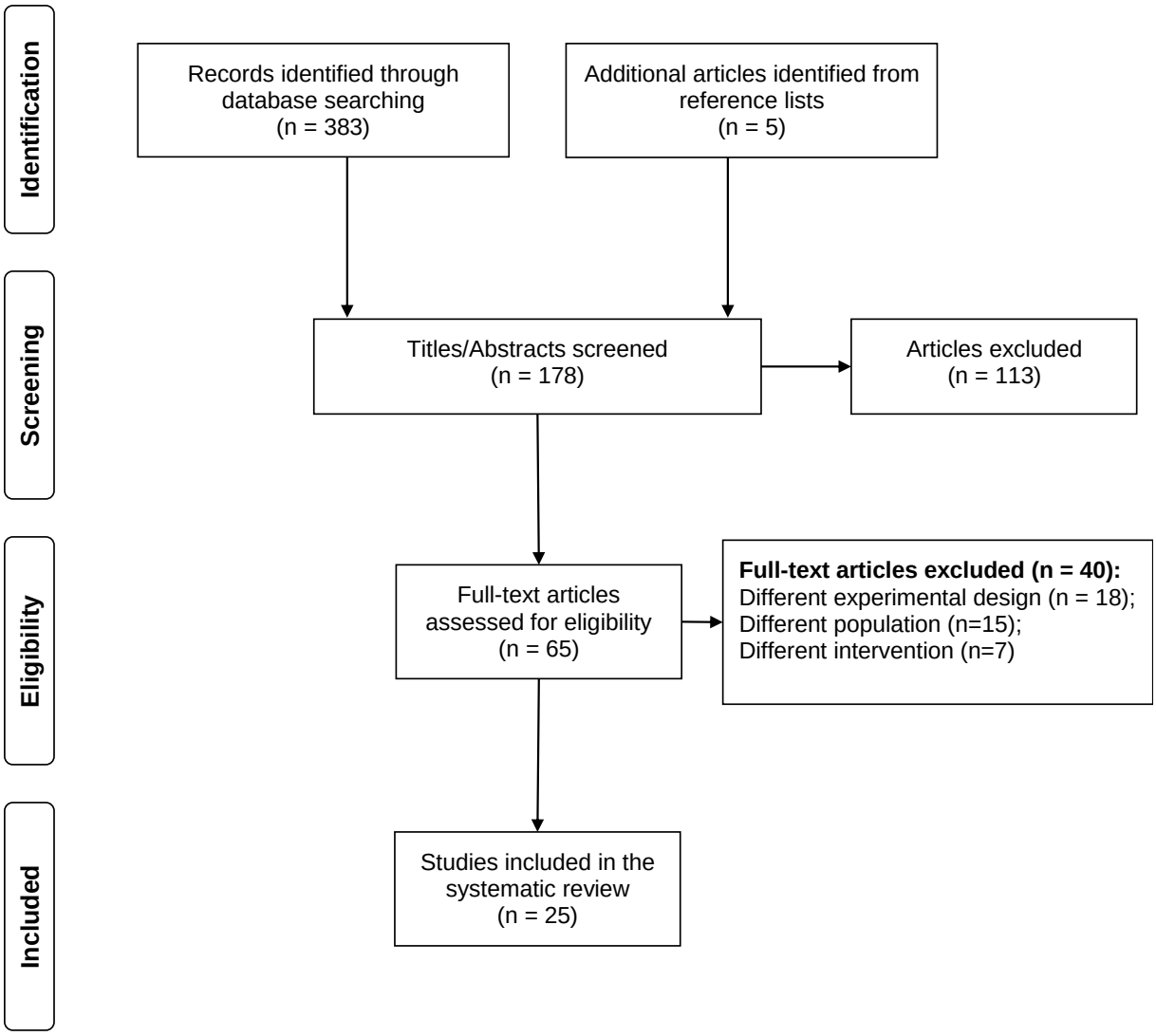

Figure 1. Flow chart of study selection process.

4.3.2. Patients and interventions

Study characteristics such as authors, sample size, intervention length, resistance training weekly volume, resistance and aerobic exercise intensity, outcomes, and techniques assessment are presented in Table 1. The trials involved 1982 breast cancer patients undergoing treatment in which 918 breast cancer patients were enrolled or randomized to resistance exercise or combined resistance and aerobic exercise (sample size ranged 10-103). The intervention period for all studies varied from 4 to 24 weeks. Twelve trials included combined resistance and aerobic exercise, and six trials included only resistance training.

Table 1. Study characteristics: trial, sample size, treatment used, intervention time, intervention modality, frequency, resistance training volume and intensity, outcomes and assessment techniques.

Author, year	Disease stage	N	Length	Weekly volume	Intensity	Outcome (Assessment)
Resistance training only						
Courneya *et al.*, 2007 (START trial)	I-IIIa	223	Median of 17w	3 days/week; RT: 2 sets of 8-12 reps	RT: 60-70%1-RM	Body weight; BP and LE strength (8-RM); VO_2peak (Treadmill protocol); LBM, FM, %BF (DXA); QoL and Fatigue (FACT-An); Depressive symptoms (CESD); Self-esteem (Rosenberg Self-esteem scale);
Dolan *et al.*, 2010 (START trial)						Anxiety (Spielberg State Anxiety Inventory). VO_2peak (Treadmill protocol); Hemoglobin (Blood samples).
Kilbreath *et al.*, 2012	I-III	160	8w	1 day/week; RT: 2 sets of 8-15 reps	RT: missing	BP, HFlx, HExt, FwdFlx, LatPD, IntRot, Abd (MVIC), Self-reported arm Symptoms (EORTC-Br23)
Schmidt ME *et al.*, 2015 (BEATE trial)	I-III	101	12w	2 days/week; RT: 3 sets of 8-12 reps	RT: 60-80%1-RM	Fatigue (FAQ); QoL (EORTC-QLQ 30 and Br23); Depressive symptoms (CESD); Cognitive function (Trail making test); Upper and lower-body strength (MVIC and MIPT); VO_2peak (?)

Steindorf *et al.*, 2014 (BEST trial) Schmidt ME *et al.*, 2016 (BEST trial)	0-III I-III	160	12w	2 days/week; RT: 3 sets of 8-12 reps	RT: 60-80%1-RM	Fatigue (FAQ); QoL (EORTC-QLQ 30 and Br23); Depressive symptoms (CESD); Cognitive function (Trail making test); Upper and lower-body strength (MVIC and MIPT); VO_2peak (Cycle ergometer protocol) IL-6, IL-1ra, IL-6/IL-1ra (Blood samples)
Wiskemann *et al.*, 2016 (BEST trial)	0-III			2 days/week; RT: 3 sets of 12 reps	RT: 12RM's	KFlx, KExt, IntRot, ExtRot (MIPT 60º/sec); KFlx, KExt, IntRot, ExtRot (MIPT 180º/sec); KExt, IntRot (MVIC)
Schmidt T *et al.*, 2015 Schmidt T *et al.*, 2018	Missing	67	12w	2 days/week; RT: 1 set of 20 reps	RT: 50%1-RM	Body weight; BP, LP, and LatPD (MVIC); QoL (EORTC-QLQ 30 and Br23) CD16/56, CD19, CD3, CD4, CD8, αβ, γδ (Blood samples)
Vollmers *et al.*, 2018	Missing	43	-	2 days/week; RT: missing	RT: missing	Postural stability (Fullerton Advanced Balance Scale); HGrip (Dynamometer); QoL (EORTC-QLQ 30 and Br23, CIPN20, MFI-20)
Resistance and aerobic exercise						
Bataglini *et al.*, 2007 Bataglini *et al.*, 2008	Missing	20	21w	2 days/week; RT: 3 sets of 6-12 reps AT: 6-12min	RT: 40-60%1-RM; AT: 40-60% maximum heart rate	Muscle strength (1-RM); VO_2 (Treadmill protocol); LBM and %BF (Skinfold technique) Caloric intake (Food diary)

Campbel *et al.*, 2005	Receiving chemotherapy and/or radiotherapy	22	12w	2 days/week; RT and AT: missing	RT and AT: 60–75% age-adjusted heart rate maximum	QoL (FACT-G, FACT-B); Satisfaction with Life scale (SWLS); Fatigue (PFS)
Courneya *et al.*, 2013 (CARE trial)	I-IIIc	301	16,4±3.6w	3 days/week; RT: 2 sets of 10-12 reps AT: 25-30min	RT: 60-75%1-RM; AT: 50-75% of VO_2peak	Body weight; Physical functioning (SF-36); VO_2peak (Treadmill protocol); BP and LE strength (7-10RM's); LBM, FM, %BF (DXA)
Heim *et al.*, 2007	Receiving chemotherapy and/or radiotherapy	63	12w	3 days/week; RT and AT: missing	RT and AT: missing	QoL (FACT); Depressive symptoms (HADS); Fatigue (MFI); Muscle strength (MVIC); Aerobic capacity (Harvard step test)
Hutnick *et al.*, 2005	I-IIIc	49	24w	3 days/week; RT: 1-3 sets of 8-12 AT: 10-20min	RT: 60-75%1-RM; AT: 60-75% functional capacity	Body weight, BMI; %BF (?); %CD-4+CD69, IFN, IFN/IL-6, IL-6, SIL-6R, ssgp130, total-CD4+CD69 BAIL-6, (Blood samples); triceps-curl, biceps-curl (?) HGrip (dynamometer); VO_2max, frequency-of-breaths, peak-heart-rate (?)
Kolden *et al.*, 2002	I-III	51	16w	3 days/week; RT: missing; AT: 20min	RT: missing AT: 40–70% of estimated maximal aerobic capacity	Body weight; %BF (Skinfold technique); VO_2max (Treadmill walking test);

						Flexibility (Sit-and-reach test); BP and LP strength (estimated 1-RM); Depressive symptoms (BDI; HRSD); Anxiety (STAI); Positive and negative affect (PANAS); QoL (FACT, CARES, GAS, LFS)
Mijwel *et al.*, 2017 (OPTITRAIN trial)	I-III	240	16w	2 days/week; RT: 2-3 sets of 8-12 reps; AT: 3 × 3-min bouts of HIIT	RT: 70-80%1-RM; AT: 16-18 – Borg Effort Scale, interspersed with one min of low-intensity active recovery.	Fatigue (CRF); QoL (EORTC-QLQ 30, MSAS) Body weight; Fatigue (PFS); QoL (EORTC-QLQ 30, MSAS); Mid-thigh pull strength (MVIC); HGrip (dynamometer); VO_2peak (Cycle ergometer protocol); Pain (PPT); Hemoglobin (Blood sample)
Mijwel *et al.*, 2018a (OPTITRAIN trial)						
Mijwel *et al.*, 2018b (OPTITRAIN trial)		50				CS activity and oxphos complexes (muscle biopsy); Type I, IIA, and all fibers CSA (muscle biopsy); MHC distribution % type I, IIA, and IIx (muscle biopsy); Satellite cells (muscle biopsy); Capillaries (muscle biopsy);
Mostarda *et al.*, 2017	I-III	18	4w	3 days/week; RT: 3 sets of 8-12 reps; AT: 30min	RT: missing; AT: 60%VO_2max	Body weight, BMI; VO_2max (Cycle ergometer protocol); Time domain RR, SDNN, RMSSD (tachogram); Frequency domain LF, HF, LF, HF, LF/HF (tachogram); Symbolic analysis 0V, 1V, 2LV, 2UV (tachogram)

Mutrie *et al.*, 2007	0-III	203	12w	2 days/week; RT and AT: missing	RT and AT: missing	BMI; QoL (FACT-G, FACT-B, FACT-F, FACT-ES); Positive and negative affect (PANAS); Depressive symptoms (BDI); Functional capacity (12-min walk test); Shoulder mobility (Shoulder mobility score)
Reis *et al.*, 2018	Receiving chemotherapy and/or radiotherapy	31	12w	3 days/week; RT: 3 sets of 12 reps; AT: missing	RT: missing; AT: 50–60%/ 80–90% of the target heart rate	BMI; Pain (BPI); Fatigue (PFS); VO_2max (Cycle ergometer protocol); Flexibility (Sit-and-reach test); HGrip (Dynamometer).
Schulz *et al.*, 2017	Receiving chemotherapy and/or radiotherapy	26	6w	2 days/week; RT: 2 sets of 8-15 reps; AT: 10 x 1-min bouts of HIIT	RT: 50-80%1-RM; AT: 85–100%VO_2peak	BP, LP, LatPD, LegB, LegS strength (estimated 1-RM); VO_2peak (Treadmill protocol); QoL, anxiety, depressive symptoms (HADS-D)
Travier *et al.*, 2015 (PACT trial)	Receiving chemotherapy	204	18w	2 days/week; RT: 1-2 sets of 10-20 reps; AT: 3 × 2 min/ 2 × 7min or 3 × 4 min/ 1 × 7min	RT: 60-75%1-RM; AT: missing	Body weight; KFlx, KExt (MIPT 60º/sec); KFlx, KExt (MIPT 180º/sec); HGrip (Dynamometer); VO_2peak (Cycle ergometer protocol); Fatigue (MFI-20, and FQL); QoL (EORTC-QLQ 30 and SF-36)

%1-RM, Percentage of 1-repetition maximum; %BF, Percentage of body fat; Abd, Adbominal; BP, Bench press; BMI, Body mass index; CS, Citrate synthase; CSA, Cross-sectional area; DXA, Dual-energy X-ray absorptiometry; ExtRot, Shoulder external rotation; FM, Fat mass; FwdFlx, Forward flexion; HF, High frequency component; HGrip, Handgrip; HExt, Horizontal extension; HFlx, Horizontal flexion; IntRot, Shoulder internal rotation; KExt, Knee extension; KFlx, Knee flexion; LatPD, Lateral pull-down; LBM, Lean body mass; LE, Leg extension; LegB, Leg bender; LegS, Leg stretcher; LF, Low frequency component; LP,

Leg press; MHC, Myosin heavy chain; MIPT, Maximal isokinetic peak torque; MVIC, Maximal voluntary isometric contraction; QoL, Quality of life; RR, Inter-beat interval; RMSSD, Root mean square from SDNN; SDNN, Standard deviation from inter-beat interval.

4.3.3. Exercise trials design

4.3.3.1. Reporting of the exercise prescription components

As presented in Table 1, components of resistance training exercise as type, frequency, volume, and intensity were assessed. Since the present study reviewed exercise trials which comprise resistance training or combined resistance and aerobic training, all studies reported these types of exercise (6 trials comprising 10 manuscripts which prescribed resistance training, and 12 trials comprising 15 manuscripts which prescribed combined resistance and aerobic exercise, resulting in 18 trials). From six trials which prescribed resistance training only, all reported the frequency (n=6 trials, 100%), five trials reported the resistance training volume (n=5 trials, 83.3%), and four trials reported the resistance training intensity (n=4 trials, 66.7%). From 12 trials which prescribed combined resistance and aerobic exercise, all reported frequency (n=12 trials, 100%), eight trials reported the resistance and aerobic training volume (n=8, 66.7%), seven trials reported the resistance training intensity (n=7, 58.3%) and ten reported the aerobic training intensity (n=9, 75%).

4.3.3.2. Application of the principles of exercise training

The application of the principles of exercise training is detailed and evaluated in Table 2. The principle of specificity was applied by all trials of resistance training, and by 8 of 12 trials of combined resistance and aerobic exercise. The principle of progression was applied by 4 of 6 trials of resistance training, and by 5 of 12 trials of combined resistance and aerobic exercise. The principle of overload was applied by 3 of 6 trials of resistance training, and by 6 of 12 trials of combined resistance and aerobic exercise. The principle of initial values was applied by 4 of 6 trials of resistance training, and by 8 of 12 trials of combined resistance and aerobic exercise.

The follow-up after an intervention allows evaluating the principles of reversibility and diminishing returns. Of the trials reviewed, no results regarding reversibility and diminishing returns were provided.

4.3.3.3. Attendance rate of participants to the prescribed intervention

From trials which prescribed resistance training (n=6), four reported the attendance rate (n=4, 66.7%) reaching 75.9±6.2% (95% CI: 70.5 to 81.4%) of sessions. Regarding trials which prescribed combined resistance and aerobic

exercise, six reported the attendance rate (n= 5, 41.7%) reaching 74±11.3% (95% CI: 68.3 to 86.9%) of sessions.

Table 2. Application of the principles of exercise training, results, feasibility and adverse events in exercise intervention studies in breast cancer patients.

Author, year	Sp	Pr	OV	IV	Rev	DR	Results	Feasibility	Adverse events
Resistance training only									
Courneya *et al.*, 2007 (START trial)	+	+	+	+	NR	NR	↔Body weight; ↑BP and ↑LE strength; ↓VO_2peak; ↔LBM, ↔FM, ↔%BF; ↔FACT-An*****; ↔CESD; ↑Rosenberg Self-esteem scale; ↔Spielberg State Anxiety Inventory.	242 admitted 223 randomized 92.1% adherence	1 reported hypotensive symptoms; 1 reported dizziness
Dolan *et al.*, 2010							↓VO_2peak (Treadmill protocol); ↓Hemoglobin (Blood samples).		
Kilbreath *et al.*, 2012	+	+	?	NR	NR	NR	↔BP, ↔HFlx, ↔HExt, ↔FwdFlx, ↔LatPD, ↔IntRot, ↑Abd strength, ↔EORTC-Br23*****	457 admitted 160 randomized 88.1% adherence	Not reported
Schmidt ME *et al.*, 2015 (BEATE trial)	+	+	+	+	NR	NR	↔FAQ*; ↔EORTC-QLQ 30 and Br23; ↔CESD; ↔Trail making test; ↑Upper and ↑lower-body strength MVIC; ↑Upper and ↑lower-body strength MIPT; ↔VO_2peak	112 admitted 101 randomized 94.1% adherence	No
Steindorf *et al.*, 2014 (BEST trial)	+	+	+	+	NR	NR	↑FAQ*****; ↔EORTC-QLQ 30 and Br23; ↔CESD; ↔Trail making test; ↑Upper and ↑lower-body strength MVIC; ↑Upper and ↑lower-body strength MIPT; ↔VO_2peak	170 admitted 155 randomized 96.9% adherence	No
Schmidt ME *et al.*, 2016 (BEST trial)							↑IL-6, ↔IL-1ra, ↑IL-6/IL-1ra	160 admitted 103 randomized	Not reported

Wiskemann *et al.*, 2016 (BEST trial)							↑KFlx, ↔KExt, ↑IntRot, ↑ExtRot MIPT 60º/sec; ↑KFlx, ↔KExt, ↑IntRot, ↑ExtRot MIPT 180º/sec; ↔KExt, ↑IntRot MVIC	91.3% adherence 321 admitted 160 randomized 96.9% adherence	No
Schmidt T *et al.*, 2015	+	NR	NR	+	NR	NR	↔Body weight; ↑BP, ↔LP, and ↑LatPD MVIC*****; ↔EORTC-QLQ 30 and Br23	100 admitted 67 randomized 82.7% adherence	Not reported
Schmidt T *et al.*, 2018							↔CD16/56, ↑CD19, ↔CD3*****, ↑CD4, ↔CD8, ↑αβ, ↔γδ	100 admitted 81 randomized 82.7% adherence	14 reported chemotherapy related side effects
Vollmers *et al.*, 2018	+	?	?	NR	NR	NR	↑FABS*; ↑HGrip	90 admitted 43 randomized 83.7% adherence	Not reported
Resistance and aerobic exercise									
Bataglini *et al.*, 2007 Bataglini *et al.*, 2008	+	?	+	NR	NR	NR	↑Muscle strength; ↑VO_2 peak; ↔LBM and ↑%BF ↑Caloric intake	20 admitted 20 randomized 100% adherence	No
Campbel *et al.*, 2005	?	NR	NR	NR	NR	NR	↑FACT-G and ↔FACT-B; ↔SWLS; ↔PFS; ↑12-min walk test	? admitted 22 randomized 86.4% adherence	No
Courneya *et al.*, 2013 (CARE trial)	+	+	+	+	NR	NR	↔Body weight; ↔SF-36*****; ↔VO_2peak; ↑BP and ↑LE strength; ↔LBM, ↔FM, ↔%BF	728 admitted 301 randomized 99.0% adherence	No
Heim *et al.*, 2007	+	NR	NR	+	NR	NR	↔FACT-F; ↑FACT-G; ↑HADS; ↔MFI; ↑Muscle strength MVIC; ↔Aerobic capacity	220 admitted 90 randomized 65.5% adherence	Not reported
Hutnick *et al.*, 2005	?	+	+	NR	NR	NR	↔Body weight, ↔BMI; ↔%BF; ↑%CD-4+CD69, ↔IFN, ↔IFN/IL-6, ↔IL-6, SIL-6R,	? admitted 49 randomized 73.5% adherence	Not reported

Kolden *et al.*, 2002	?	NR	NR	NR	NR	NR	↔ssgp130, total-↑CD4+CD69, ↔BAIL-6; ↑triceps-curl, ↑biceps-curl; ↑HGrip; ↑VO_2max, ↑frequency-of-breaths, ↑peak-heart-rate ↔Body weight; ↔%BF; ↑VO_2max; ↑Sit-and-reach test; ↑BP and ↑LP strength; ↑BDI; ↑HRSD; ↔STAI; ↑PANAS; ↑FACT, ↑CARES, ↑GAS, ↔LFS	? admitted 51 randomized 78.4% adherence	No
Mijwel *et al.*, 2017 (OPTITRAIN trial)							↑PFS*****; ↑EORTC-QLQ 30, ↑MSAS	628 admitted 182 randomized 87.9% adherence	No
Mijwel *et al.*, 2018a (OPTITRAIN trial)	+	+	+	+	NR	NR	↓Body weight; ↑Mid-thigh pull strength MVIC; ↑HGrip; ↔VO_2peak; ↑PPT; ↔Hemoglobin	240 admitted 240 randomized 85.8% adherence	No
Mijwel *et al.*, 2018b (OPTITRAIN trial)							↑CS activity and ↔oxphos complexes; ↑Type I, ↑IIA, and ↑all fibers CSA; ↔MHC distribution % type ↔I, ↔IIA, and ↔IIx; ↑Satellite cells; ↑capillaries	240 admitted 50 randomized 46.0% adherence	No
Mostarda *et al.*, 2017	+	NR	NR	+	NR	NR	↔Body weight, ↔BMI; ↑VO_2max; Time domain ↔RR, ↑SDNN, ↑RMSSD; Frequency domain ↑LF, ↑HF, ↑LF/HF*****; Symbolic analysis ↑0V, ↔1V, ↑2LV, ↑2UV	18 admitted 18 randomized 100% adherence	No
Mutrie *et al.*, 2007	?	NR	NR	+	NR	?	↔BMI; ↔FACT-G, ↑FACT-B, ↔FACT-F, ↔FACT-ES; ↑PANAS; ↔BDI; ↑12-min walk test; ↑Shoulder mobility score	1144 admitted 203 randomized 85.7% adherence	No
Reis *et al.*, 2018	+	NR	NR	+	NR	NR	↔BMI; ↔BPI; ↔PFS*; ↑VO_2max; ↔Sit-and-reach test; ↔HGrip	300 admitted 31 randomized 90.3% adherence	Not reported

Schulz *et al.*, 2017	+	+	+	+	NR	NR	↑BP, ↑LP, ↑LatPD, ↑LegB, ↑LegS strength*****; ↑VO_2peak*****; ↑HADS-D	26 admitted 26 randomized 100% adherence	No
Travier *et al.*, 2015 (PACT trial)	+	+	+	+	NR	NR	Body weight; ↑KFlx, ↑KExt MIPT 60º/sec; ↔KFlx, ↔KExt MIPT 180º/sec; ↔HGrip; ↔VO_2peak; ↔MFI-20*, and ↔FQL; ↔EORTC-QLQ 30 and ↔SF-36	451 admitted 204 randomized 80.3% adherence	No

*, Primary outcome; DR, diminishing returns; IV, initial values; OV, overload; Pr, progression; Rev, reversibility; Sp, specificity; +, Clearly reported; ?, unclear; NR, Not reported. ↑, Significant statistical improve; ↔, No differences; ↓, Significant statistical impairment.

%1-RM, Percentage of 1-repetition maximum; %BF, Percentage of body fat; Abd, Adbominal; AT, Aerobic training; BP, Bench press; BMI, Body mass index; CS, Citrate synthase; CSA, Cross-sectional area; DXA, Dual-energy X-ray absorptiometry; ExtRot, Shoulder external rotation; FM, Fat mass; FwdFlx, Forward flexion; HF, High frequency component; HGrip, Handgrip; HExt, Horizontal extension; HFlx, Horizontal flexion; IntRot, Shoulder internal rotation; KExt, Knee extension; KFlx, Knee flexion; LatPD, Lateral pull-down; LBM, Lean body mass; LE, Leg extension; LegB, Leg bender; LegS, Leg stretcher; LF, Low frequency component; LP, Leg press; MHC, Myosin heavy chain; MIPT, Maximal isokinetic peak torque; MVIC, Maximal voluntary isometric contraction; QoL, Quality of life; RR, Inter-beat interval; RMSSD, Root mean square from SDNN; RT, Resistance training; SDNN, Standard deviation from inter-beat interval.

4.3.4. Effects of resistance training

4.3.4.1. Body composition outcomes

4.3.4.1.1. Body mass

Length of training period, average changes and changes per week

Eight trials were included in this analysis (Kolden *et al.*, 2002; Hutnick *et al.*, 2005; Courneya *et al.*, 2007a; Courneya *et al.*, 2013; T Schmidt *et al.*, 2015; Travier *et al.*, 2015; Mostarda *et al.*, 2017; Mijwel *et al.*, 2018a). The average length of the training period was 15.4±5.7 weeks. The shortest study was 4 weeks and the longest lasted 18 weeks. The mean total change in body weight was 0.4±2.4% (95% CI: -1.33 to 2.05%). The mean body mass change per week 0.04±0.11% (95% CI: -0.05 to 0.12%).

Frequency and volume

The mean frequency of training for body mass changes were 2.6 times a week. Regarding the resistance training volume, included studies prescribed 436.7 ± 162.1 repetitions (95% CI: 324.3 to 549.0 reps) per week. The results are shown in SM Figure S1. Regression analysis resulted in a non-significant relationship between weekly volume and changes in body mass (r^2= 0.12, β=-0.349, p>0.05).

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 70.8 ± 10.6% of 1-RM (95% CI: 63.4 to 78.2% of 1-RM). The results are shown in SM Figure S2. Regression analysis resulted in a non-significant relationship between peak intensity reached and changes in body mass (r^2= 0.04, β= -0.211, p>0.05).

4.3.4.1.2. Body mass index

Length of training period, average changes and changes per week

Four trials were included in this analysis (Hutnick *et al.*, 2005; Mutrie *et al.*, 2007; Mostarda *et al.*, 2017; Reis *et al.*, 2018). The average length of the training period was 13.0±8.2 weeks. The shortest study was 4 weeks and the longest lasted 24 weeks. The mean total change in BMI was -0.98 ± 1.56% (95% CI: -2.51 to 0.54%). The mean BMI change per week -0.05 ± 0.08% (95% CI: -0.13 to 0.03%).

Frequency and volume

The mean frequency of training for BMI changes were 2.7 times a week. Regarding the resistance training volume, included studies prescribed 549.0 ± 140.0 repetitions (CI 95%: 411.8 to 686.2 reps) per week in BMI. In addition, studies that do not report resistance training volume resulted in a decrease of 0.12±0.01% per week. There were no sufficient datapoints for further analysis.

Intensity

Only one study reported resistance training intensity. The study of Hutnick *et al.* (2005) found a decrease of 0.12% in BMI prescribing an intensity that reaches 75% of 1-RM. In addition, studies that do not report resistance training intensity resulted in a decrease of 0.03 ± 0.08% per week in BMI. There were no sufficient datapoints for further analysis.

4.3.4.1.3. Percentage of body fat and absolute fat mass

Length of training period, average changes and changes per week

Five trials were included in this analysis (five trials for %BF, and two trials for absolute fat mass) (Kolden *et al.*, 2002; Hutnick *et al.*, 2005; Bataglini *et al.*, 2007; Courneya *et al.*, 2007a; Courneya *et al.*, 2013). The average length of the training period was 18.9±3.5 weeks for %BF, and 16.6±0.5 weeks for fat mass. The shortest study was 16 weeks and the longest lasted 24 weeks. The mean total change in %BF was -2.34±3.03% (95% CI: -5.0 to 0.32%) and 2.0 ± 0.94% (95% CI: 0.71 to 3.31) in fat mass. The mean %BF change per week was -0.12±0.14% (95% CI: -0.24 to 0.01%), and 0.12±0.05% (95% CI: 0.05 to 0.19%) for fat mass.

Frequency and volume

The mean frequency for %BF changes were 2.8 times a week and 3.0 times a week for fat mass. Regarding the resistance training volume, included studies prescribed 594 ± 54 repetitions (95% CI: 546.7 to 641.3 reps) per week. In addition, studies that do not report resistance training volume resulted in a decrease of 0.10 ± 0.02% per week. There were no sufficient data points for further analysis.

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 70.0 ± 7.1% of 1-RM (95% CI: 63.8 to 76.2% of 1-RM) for %BF and 72.5±3.5% of 1-RM (95% CI: 67.6 to 77.4% of 1-RM) for absolute fat mass. There were no sufficient data points for further analysis.

4.3.4.1.4. Lean body mass

Length of training period, average changes and changes per week

Three trials were included in this analysis (Bataglini *et al.*, 2007; Courneya *et al.*, 2007a; Courneya *et al.*, 2013). The average length of the training period was 18.1±2.5 weeks for lean body mass changes. The shortest study was 16.3 weeks and the longest lasted 21 weeks. The mean total change in lean mass was 2.61 ± 0.27% (95% CI: 2.30 to 2.91). The mean lean mass change per week was 0.14±0.01% (95% CI: 0.14 to 0.15).

Frequency and volume

The mean frequency for absolute lean mass was 2.7 times a week. Regarding the resistance training volume, included studies prescribed on average 594 ± 54.0 repetitions (95% CI: 532.9 to 655.1) per week for lean mass changes. There were no sufficient datapoints for further analysis.

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 68.3 ± 7.6% of 1-RM (95% CI: 59.7 to 77.0% of 1-RM) for lean body mass. There were no sufficient datapoints for further analysis.

4.3.4.2. Muscle strength

4.3.4.2.1. One-repetition maximum

Length of training period, average changes and changes per week

Six trials were included in this analysis (Kolden *et al.*, 2002; Hutnick *et al.*, 2005; Bataglini *et al.*, 2007; Courneya *et al.*, 2007a; Courneya *et al.*, 2013; Schulz *et al.*, 2017). The average length of the training period was 16.7 ± 6.1 weeks. The shortest study was 6 weeks and the longest lasted 24 weeks. The mean total increase in muscle strength was 24.6 ± 10% (95% CI: 19.6 to 29.7 %) for all muscle strength tests. Values

for each 1-RM test are presented in SM Figure S3. The study of Bataglini *et al.* (2007) reported the sum of all 1-RM tests (i.e. leg extension, seated leg curl, lateral pulldown, and seated chest press) and was not included for further analysis of 1-RM strength. The mean strength increases per week for lower and upper-body strength were 2.9 ± 1.6 % (95% CI: 1.6 to 4.2 %) and 2.4 ± 1.9 % (95% CI: 1.1 to 3.7%), respectively.

Frequency and volume

The mean frequency for resistance training was 2.7 times a week. Regarding the resistance training volume, included studies prescribed 514.5±165.0 repetitions (95% CI: 431.0 to 598.0 reps) of resistance training per week. The mean number of weekly total repetitions was 203.0±76.6 (95% CI: 149.9 to 256.0 reps) for upper-body and 198.7±93.2 (95% CI: 124.1 to 273.2 reps) for lower-body exercises. The results are shown in Figure 2. Regression analysis results in a significant negative relationship between weekly volume and upper-body (r^2= 0.97, β=-0.985, p<0.01) and lower-body 1-RM increases (r^2= 0.82, β=-0.904, p<0.05).

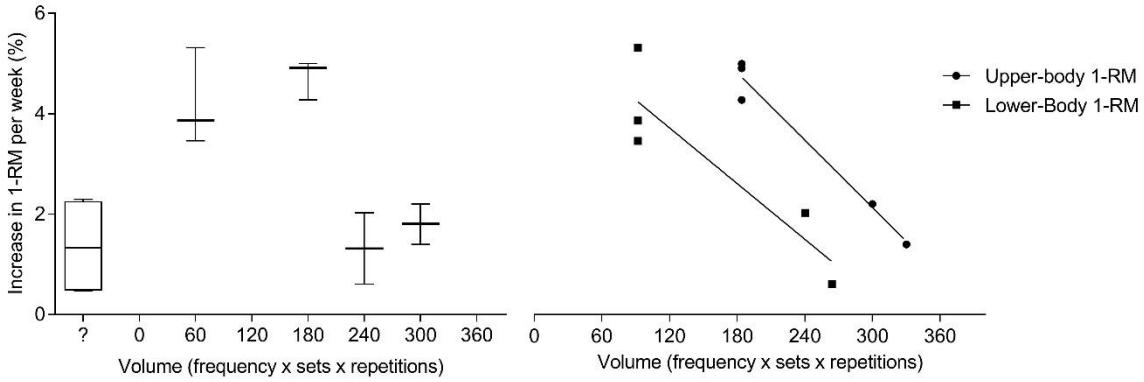

Figure 2. Resistance training weekly volume vs. percentage increase in 1-RM per week (number of study groups= 14). Inspection of the datapoints revealed four identifiable “clusters” in the range of total repetitions. The average rate of increase of strength for each cluster was as follow: 60-119= 4.21±0.97% per week, 180-239= 4.73±0.40% per week, 240-299= 1.31±1.00% per week, and ≥300= 1.80±0.57%. In addition, the unknown resistance training volume (?) resulted in an increase of 1.35±1.00% per week.

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 72.0±7.6% of 1-RM (95% CI: 68.2 to 75.8% of 1-RM). The results are shown in Figure 3. Regression analysis results in a non-significant positive trend between peak intensity reached and upper-body (r^2= 0.68, β= 0.823, p>0.05) and lower-body 1-RM test (r^2= 0.49, β=0.699, p>0.05).

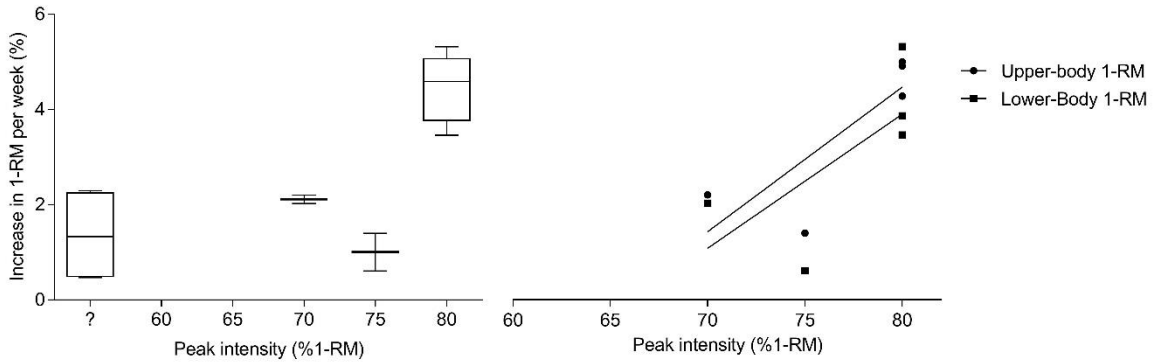

Figure 3. Resistance training peak intensity vs. percentage increase in 1-RM per week (number of study groups= 14). Inspection of the datapoints revealed three identifiable "clusters" in the range of peak intensities. The average rate of increase of strength for each cluster was as follow: 70% of 1-RM= 2.11±0.13% per week, 75% of 1-RM= 1.00±0.56% per week, and 80% of 1-RM= 4.47±0.72% per week. In addition, the unknown resistance training intensity resulted in 1.36±1.00% per week.

4.3.4.2.2. Maximal voluntary isometric contraction

Length of training period, average changes and changes per week

Four trials were included in this analysis (Kilbreath *et al.*, 2012; T Schmidt *et al.*, 2015; Wiskemann *et al.*, 2016; Mijwel *et al.*, 2018a). The average length of the training period was 12.0±3.3 weeks. The shortest study was 8 weeks and the longest lasted 16 weeks. The mean total increase in MVIC was 17.40±10.11% (95% CI: 11.14 to 23.67%) for all muscle strength tests. Values for each MVIC test are presented in SM Figure S4. The mean MVIC increase per week for lower and upper-body MVIC were 0.64±0.30% (95% CI: 0.29 to 0.98%) and 2.22±0.88% (95% CI: 1.57 to 2.88%), respectively.

Frequency and volume

The mean frequency for resistance training was 1.7 times a week. Regarding the resistance training volume, included studies prescribed 306.7±46.2 repetitions (95% CI: 272.4 to 340.9) for upper- and 178.7±51.4 repetitions (95% CI: 120.5 to 236.9 reps) for lower-body per week. There are no sufficient datapoints for further analysis.

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 66.7±15.3% of 1-RM (95% CI: 57.2 to 76.1% of 1-RM). There are no sufficient datapoints for further analysis.

4.3.4.2.3. Maximal isokinetic peak torque

Length of training period, average changes and changes per week

Two trials were included in this analysis (Travier *et al.*, 2015; Wiskemann *et al.*, 2016). The average length of the training period was 15.0±4.2 weeks. The shortest study was 12 weeks and the longest lasted 18 weeks. The mean total increase in isokinetic strength at 60º/sec was 10.05±4.85% (95% CI: 6.68 to 13.41%) for all muscle strength tests. The mean isokinetic strength at 60º/sec increase per week for lower and upper-body were 0.55±0.32% (95% CI: 0.29 to 0.80%) and 1.17±0.02% (95% CI: 1.14 to 1.21), respectively. Regarding isokinetic strength at 180º/sec, the mean total increase was 10.99±3.81% (95% CI: 8.34 to 13.63%) for all muscle strength tests. The mean isokinetic strength at 180º/sec increase per week for lower and upper-body were 0.66±0.20% (95% CI: 0.50 to 0.82%) and 0.95±0.17% (95% CI: 0.72 to 1.19%), respectively.

Frequency and volume

The only prescribed frequency for resistance training was 2.0 times a week. Regarding the resistance training volume, included studies prescribed 102 repetitions for upper- and 34 repetitions for lower-body (Travier *et al.*, 2015), and 360 for upper- and 216 repetitions for lower-body per week (Wiskemann *et al.*, 2016). There are no sufficient datapoints for further analysis.

Intensity

The peak intensity (the highest value reached during a session) was 12RM (~70% of 1-RM) in the study of Wiskemann *et al.* (2016) and 75% of 1-RM in the study of Travier *et al.* (2015). There are no sufficient datapoints for further analysis.

4.3.4.2.4. Handgrip strength

Length of training period, average changes and changes per week

Four trials were included in this analysis (Hutnick *et al.*, 2005; Travier *et al.*, 2015; Mijwel *et al.*, 2018a; Reis *et al.*, 2018). The average length of the training period was 17.5±5.0 weeks. The shortest study was 12 weeks and the longest lasted 24 weeks. The mean total increase in handgrip strength was 9.79±9.80% (95% CI: 3.00 to 16.58%). The mean handgrip strength change per week was 0.65±0.78% (95% CI: 0.11 to 1.19%).

Frequency and volume

The mean frequency for resistance training was 2.5 times a week. Regarding the resistance training volume, included studies prescribed 428.0±263.5 (95% CI: 245.4 to 610.6 reps). The results are shown in SM Figure S6. Regression analysis results in a non-significant relationship between resistance training volume and increases in handgrip strength (r^2= 0.56, β= 0.748, p>0.05).

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 76.7±2.9% of 1-RM (95% CI: 74.7 to 78.7% of 1-RM). Regression analysis results in a non-significant relationship between peak intensity reached and increases in handgrip strength (r^2= 0.07, β= -0.270, p>0.05).

4.3.4.3. Physiological outcomes

4.3.4.3.1. VO_2

Length of training period, average changes and changes per week

Seven trials were included in this analysis (Kolden *et al.*, 2002; Courneya *et al.*, 2007a; Dolan *et al.*, 2010; Courneya *et al.*, 2013; Travier *et al.*, 2015; Mostarda *et al.*, 2017; Schulz *et al.*, 2017; Reis *et al.*, 2018). The average length of the training period was 13.3±5.4 weeks for VO_2. The shortest study was 6 weeks and the longest lasted

18 weeks. The mean total change in VO_2 was 5.47±15.04% (95% CI: -4.95 to 15.89%). The mean VO_2 change per week was 1.10±1.95% (95% CI: -0.25 to 2.45%).

Frequency and volume

The mean frequency for VO_2 was 2.7 times a week. Regarding the resistance training volume, included studies prescribed 377.7±245.9 repetitions (CI 95%: 207.3 to 548.1 reps) per week. The results are shown in SM Figure S3. Regression analysis results in a non-significant relationship between weekly volume and changes in VO_2 (r^2= 0.00, β=0.018, p>0.05).

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 74.0±4.2% of 1-RM (95% CI: 71.1 to 76.9% of 1-RM). The results are shown in SM Figure S4. Regression analysis results in a non-significant relationship between peak intensity reached and changes in VO_2 (r^2= 0.40, β= 0.629, p>0.05).

4.3.4.3.2. Inflammatory markers

Length of training period, average changes and changes per week

Two trials were included in this analysis (Hutnick *et al.*, 2005; ME Schmidt *et al.*, 2016). The average length of the training period was 18.0±8.5 weeks for the different inflammatory markers which were explored. The shortest study was 12 weeks and the longest lasted 24 weeks. The mean total change in IL-6 (39.86±56.38%), IL-1ra (-0.33%), IL-6/IL-1ra (no changes), IFN (29.61%), IFN/IL-6 (21.37%), and SIL-6R (7.66%) were observed. The mean change per week were 1.66±2.35% for IL-6, -0.03% for IL-1ra, no changes for IL-6/IL-1ra, 1.23% for IFN, 0.89% for IFN/IL-6, and 0.32% for SIL-6R.

Frequency and volume

The mean frequency for resistance training was 2.5 times a week. Regarding the resistance training volume, the study Schmidt ME *et al.* (2016) prescribed 480 reps, while the study of Hutnick *et al.* (2005) does not provide information about. There are no sufficient datapoints for further analysis.

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 77.5±3.5% of 1-RM (95% CI: 75.0 to 79.9% of 1-RM). There are no sufficient datapoints for further analysis.

4.3.4.3.3. Immune system markers

Length of training period, average changes and changes per week

Two trials were included in this analysis (Hutnick *et al.*, 2005; T Schmidt *et al.*, 2018). The average length of the training period was 18.0±8.5 weeks for the different immune system which was explored. The shortest study was 12 weeks and the longest lasted 24 weeks. Changes in CD3 (-19.31%), CD4 (-31.97%), CD8 (-10.94%), CD19 (-7.21%), CD16/56 (-1.91%), total CD-4+CD69 (-57.14%), and %CD-4+CD69 (-63.57%) were observed. The mean change per week were -1.61% for CD3, -2.66% for CD4, -0.91% for CD8, -7.22% for CD19, -1.91% for CD16/56, -2.38% for total CD-4+CD69, and -2.65% for %CD-4+CD69.

Frequency and volume

The mean frequency for resistance training was 2.5 times a week. Regarding the resistance training volume, the study of Schmidt T *et al.* (2018) prescribed 400 repetitions, while the study of Hutnick *et al.* (2005) does not provide information about this variable. There are no sufficient datapoints for further analysis.

Intensity

The mean peak intensity (the highest value reached during a session, averaged over the entire period) was 62.5±17.7% of 1-RM (95% CI: 49.4 to 75.6% of 1-RM). There are no sufficient datapoints for further analysis.

4.4. Discussion

In this review, we investigated the components of resistance training studies with breast cancer patients undergoing treatment and its dose-response relation on a range of physical and physiological outcomes. There were four important findings: I) resistance training weekly volume was negatively associated with increases on muscle strength (i.e., dynamic), indicating superior benefits with low-dose of resistance training (i.e., in this case, low-volume); II) no trend linear relationship was found between resistance training volume and intensity, and improvements in body mass, handgrip, and cardiorespiratory fitness, indicating no differences between low- and high-dose of

resistance training (i.e., low- vs. high-volume, and/or low- vs. high-intensity); III) due to limited available (72.2 and 61.1% in volume and intensity, respectively), or insufficient data (<4 data points), no relationship could be explored on BMI, body fat, lean body mass, immune and inflammatory markers, and specific strength measures; and IV) no trial prescribing combined resistance and aerobic exercise, or resistance training alone reported or attended to all key principles of exercise training.

Since the first overview of exercise studies in cancer patients (Galvão & Newton, 2005) reporting only one study with resistance training in breast cancer patients (Kolden *et al.*, 2002), a growing body of literature provided high-level of evidence in important guidelines, all ensuring safety, physical and clinical benefits when a resistance training program is adhered (Schmitz *et al.*, 2010; Rock *et al.*, 2012; Hayes *et al.*, 2019). Nevertheless, it is also well known that the manipulation of resistance training variables such as frequency, volume, and intensity potentialize the effects on specific physiological outcomes in healthy and older people (ACSM, 2009), but this information in people with breast cancer is scarce.

The present study provides novel information from an overview of previous studies prescribing resistance training components for this population, given that a superior effect on muscle strength was found with low weekly volume of exercise with changes for body mass, handgrip, and cardiorespiratory fitness outcome between a low and high weekly volume. Thus, it is suggested that for breast cancer patients undergoing primary treatment, a lower-dose of resistance exercise could result in more benefits on muscle strength without hampering body mass or cardiorespiratory fitness adaptations. The reasons for this are still unknown, but it could be related to the immune-related impairments during/after chemotherapy as patients might not fully recover during or after subsequent bouts of exercise and treatment sessions (Martin *et al.*, 2005; Tidball, 2017), especially due to the toxicity of drugs such as taxanes affecting neurosensorial and neuromotor system (Martin *et al.*, 2005; Courneya *et al.*, 2008). Moreover, these results support the design of future phase II and III exercise trials comparing low- vs. high-dose (in this case, low and high volume of resistance training) to test the outcomes of the present review.

The exercise dose-response exploration in cancer patients is an open area for prospective trials. In the WISER Sister trial (Schmitz *et al.*, 2015), the effects of 150min.wk-1 and 300min.wk-1 aerobic exercise were compared to usual care control

in women at high risk for breast cancer during 5-menstrual cycle. It was reported a significant dose-response alteration in favor of higher doses on cardiorespiratory fitness, decreased body fat, and adjusted adipokine levels (Sturgeon *et al.*, 2016), but evidence for it after the diagnosis is still unclear. Contrary, the COURAGE trial (Brown *et al.*, 2016) in stage I-III colon cancer survivors reported superiority for exercise groups vs. usual care control, but no trend linear fashion between doses and responses ($p>0.05$) on prognostic biomarkers such as serum intercellular adhesion molecule-1 (Brown *et al.*, 2018c), metabolic growth factors as fast insulin (Brown *et al.*, 2018b), and circulant tumoral cells (Brown *et al.*, 2018a). However, 150min.wk-1 or plus two to three resistance exercise sessions targeted by physical activity guidelines for cancer patients and abovementioned comparative studies may not be reached, nor represent an appropriate starting weekly dosage to their majority, and therefore, it is reasonable to suggest more investigations about what constitutes a low and upper threshold range of dosage and for whom (Hayes *et al.*, 2019). In this sense, the present review provides important information regarding resistance exercise prescription, indicating no additional benefits for higher doses in breast cancer patients. Nevertheless, considering the individualization and specificity in relation to cancer treatments for its patients, the present review should not be used to set an exercise weekly prescription, but suggest a conservative and appropriate commence allowing gradual progression and modification accordingly comorbidities and treatment-related side effects of breast cancer patients.

As demonstrated in the present and previous reviews (Campbell *et al.*, 2012; Neil-Sztramko *et al.*, 2017), the lack of reporting is one of the main issues of exercise trials in breast cancer patients. Less than 75% of included studies reported the prescribed intensity and/or volume of resistance training indicating the lacking of exercise principles as progression and/or overload. The description of FITT factors or exercise components, in addition to its compliance, is of utmost importance to determine resistance training dose-response and to ensure the delivery of exercise and its expected effects. However, it was not possible to determine whether a higher dose of resistance training (intensity or volume) increase the response on body weight and handgrip strength, given the undetermined features of resistance training such as weekly volume and reached intensity. In addition, the lack of investigations of resistance training components on body composition, immune and inflammatory

markers, and specific strength measures after exercise intervention also hampered further analysis of dose-response in these outcomes. Thus, we suggest that in future trials a best practice in the reporting of exercise prescription and its components, besides a full reporting of prescribed and compliance dose. Such evidence will allow investigating more specific recommendations for this group of patients.

Despite the majority of information for exercise prescription, the present study also provides an important message for oncologists and general physicians. During active treatment, the best practice is to contact and inform clinicians about the exercise prescription and providing the opportunity to open communication, where comments and concerns will enhance patient adherence in an exercise program and reduce possible related side effects (Hayes *et al.*, 2019). In this sense, medical oncologists and radiologists often present concerns regarding the exercise components, mainly about the load. In the present study, our findings reinforce the safety and efficiency of resistance training for breast cancer patients with no concerns on resistance exercise intensity, but impairments on muscle strength related to “doing too much”. Thus, the suggested conservative commences with low-volume of resistance exercise is a promising approach, allowing progression and respecting patients’ individualities (Adams *et al.*, 2018; Newton *et al.*, 2018b; The Lancet *et al.*, 2018; Hayes *et al.*, 2019), besides providing more evidence that other components of resistance exercise (e.g. weekly volume) are also important to be monitoring during treatment and exercise program.

The present review has several strengths and limitations worthy of comment. First, the inclusion of 18 trials, specifically prescribing resistance training as the main or part of the intervention is surprised and maybe the larger review regarding this type of exercise in breast cancer patients. The inclusion of 26 exercise studies by Furmaniak *et al.* (2016), as far as we know, is the last widely review of exercise in breast cancer patients undergoing adjuvant therapy but investigated overall exercise in the management of common side-effects of treatment. Thus, this is the first review specifically examining resistance training dose-response in breast cancer patients. Second, given the lack of reporting and expected heterogeneity of interventions and outcomes, a meta-analytic approach was considered underpowered to demonstrate the moderators of resistance training effect, and due to their inability to investigate covariate interactions. A recent individual patient data meta-analysis by Buffart *et al.*

(2017) approached this issue regarding exercise-related moderators of interventions effect over QoL and physical function. However, the results did not demonstrate the significant moderate effect of FITT factors on these outcomes in cancer patients. It could be argued that such findings are attributable to the use of exercise time per session instead of the resistance training volume (product of sets and repetitions). Future studies should address this issue considering and differentiating the specific features of each exercise type as exercise time per session for aerobic exercise and the volume for resistance exercise. Lastly, the lack of best practices in reporting of outcomes and interventions is widely considered a limitation for further analysis or conclusions in systematic reviews and meta-analyses. In the present review, the description of unknown effects in main outcomes (shown in figures as “?”) is considered an important point and is likely to better identify the current limitations to define dose-response of resistance training in breast cancer patients. It may also encourage the exploration and reporting of these components in future exercise trials.

4.5. Conclusions

In summary, the present review suggests that a low-dose resistance training produces greater changes in muscle strength but similar responses in body weight, handgrip strength and cardiorespiratory fitness compared to higher-doses of training and irrespectively of the exercise intensity prescribed. In addition, we also observed limitations on the reporting of exercise prescription components. We suggest future studies to examine dose-response of resistance training on clinical outcomes in patients undergoing primary treatment.

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4.7. Supplementary material

Table S2. Literature search strategy used for the PubMed database

#1" Search "breast neoplasm"[Mesh] OR breast cancer [title/abstract] OR neoplasm, breast [title/abstract] OR neoplasms, breast [title/abstract] OR tumors, breast [title/abstract] OR breast tumors [title/abstract] OR breast tumor [title/abstract] OR tumor, breast [title/abstract] OR mammary neoplasms, human [title/abstract] OR human mammary neoplasms [title/abstract] OR human mammary neoplasms [title/abstract] OR neoplasm, human mammary [title/abstract] OR neoplasms, human mammary [title/abstract] OR mammary neoplasm, human [title/abstract] OR mammary carcinoma, human [title/abstract] OR carcinoma, human mammary [title/abstract] OR carcinomas, human mammary [title/abstract] OR human mammary carcinomas [title/abstract] OR mammary carcinomas, human [title/abstract] OR human mammary carcinoma [title/abstract] OR cancer, breast [title/abstract] OR cancer of breast [title/abstract] OR mammary cancer [title/abstract] OR malignant neoplasm of breast [title/abstract] OR malignant tumor of breast [title/abstract] OR breast carcinoma [title/abstract] OR cancer of the breast [title/abstract].
#2" Search "resistance training"[Mesh] OR Training, Resistance [title/abstract] OR Strength Training [title/abstract] OR Training, Strength [title/abstract] OR Weight-Lifting Strengthening Program [title/abstract] OR Strengthening Program, Weight-Lifting [title/abstract] OR Strengthening Programs, Weight-Lifting [title/abstract] OR Weight Lifting Strengthening Program [title/abstract] OR Weight-Lifting Strengthening Programs [title/abstract] OR Weight-Lifting Exercise Program [title/abstract] OR Exercise Program, Weight-Lifting [title/abstract] OR Exercise Programs, Weight-Lifting [title/abstract] OR Weight Lifting Exercise Program [title/abstract] OR Weight-Lifting Exercise Programs [title/abstract] OR Weight-Bearing Strengthening Program [title/abstract] OR Strengthening Program, Weight-Bearing [title/abstract] OR Strengthening Programs, Weight-Bearing [title/abstract] OR Weight Bearing Strengthening Program [title/abstract] OR Weight-Bearing Strengthening Programs [title/abstract] OR Weight-Bearing Exercise Program [title/abstract] OR Exercise Program, Weight-Bearing [title/abstract] OR Exercise Programs, Weight-Bearing [title/abstract] OR Weight Bearing Exercise Program [title/abstract] OR Weight-Bearing Exercise Programs [title/abstract].
#1 AND #2

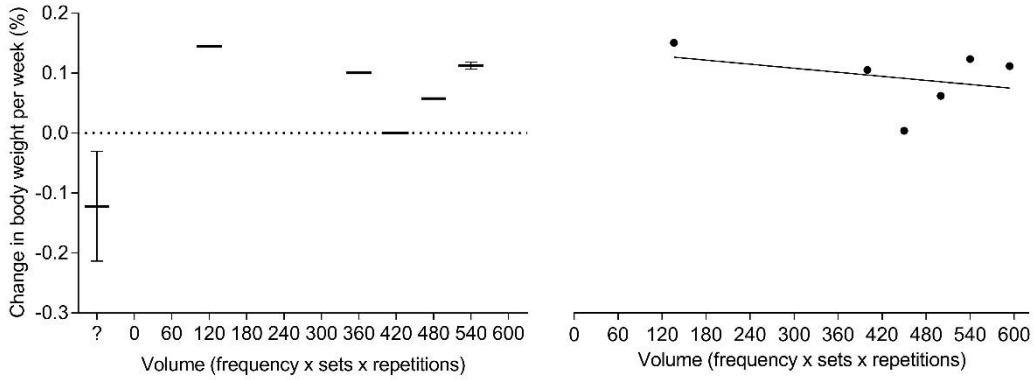

Figure S1. Resistance training weekly volume vs. percentage increase in body mass per week (number of study groups= 8). Inspection of the data points revealed one identifiable "cluster" in the range of total repetitions and single points among the range. The average rate of change of body weight for each range was as follow: 120-179 = 0.14% per week, 360-419 = 0.10% per week, 420-479 = no change, and ≥ 540= 0.11 ± 0.01% per week. In addition, the unknown resistance training volume (?) resulted in a decrease of 0.12±0.13% per week.

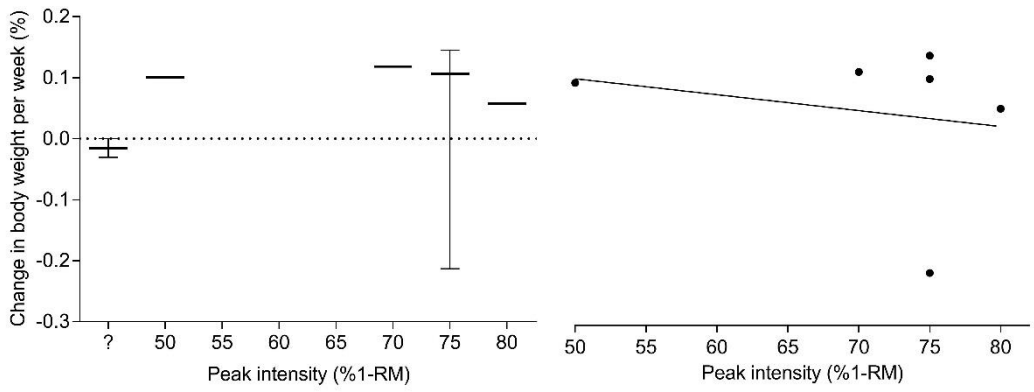

Figure S2. Resistance training peak intensity vs. percentage increase in body mass per week (number of study groups= 8). Inspection of the datapoints revealed one identifiable "cluster" in the range of peak intensities, and single points among the range. The average rate of change of body weight for each cluster was as follow: 50% of 1-RM= 0.10% per week, 70% of 1-RM= 0.11% per week, 75% of 1-RM= 0.01±0.20% per week, and 80% of 1-RM= 0.05% per week. In addition, the unknown resistance training intensity (?) resulted in a decrease of 0.02 ± 0.02% per week.

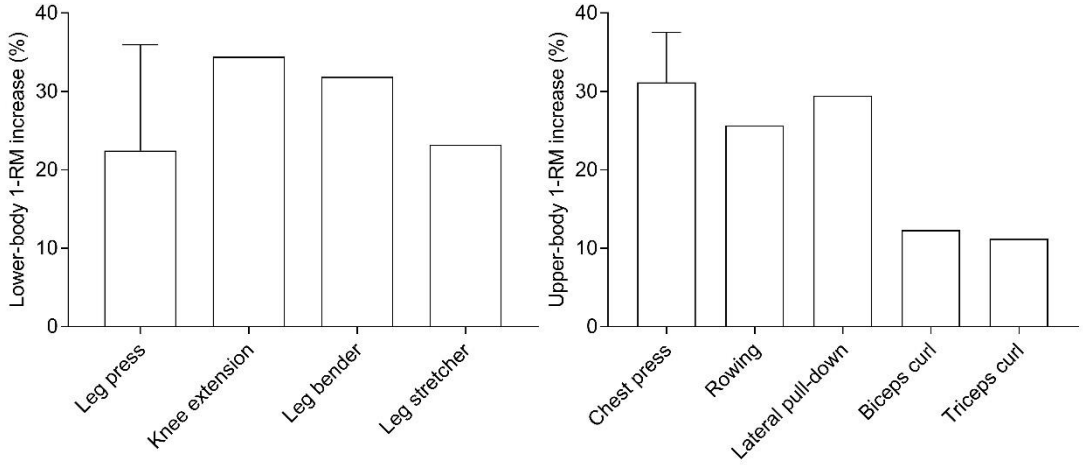

Figure S3. Increases in maximal strength measured by 1-RM after resistance training. For lower and upper-body 1-RM test the mean total increase were 26.14±10.15% (leg press: 22.45±13.49%; knee extension: 34.42%; leg bender: 31.89%; leg stretcher: 23.18%) and 25.42±9.58% (chest press: 31.16±6.37%; rowing: 25.66%; lateral pull-down: 29.45%; biceps curl: 12.34%; triceps curl: 11.21%), respectively. Data were presented as mean, and SD when available.

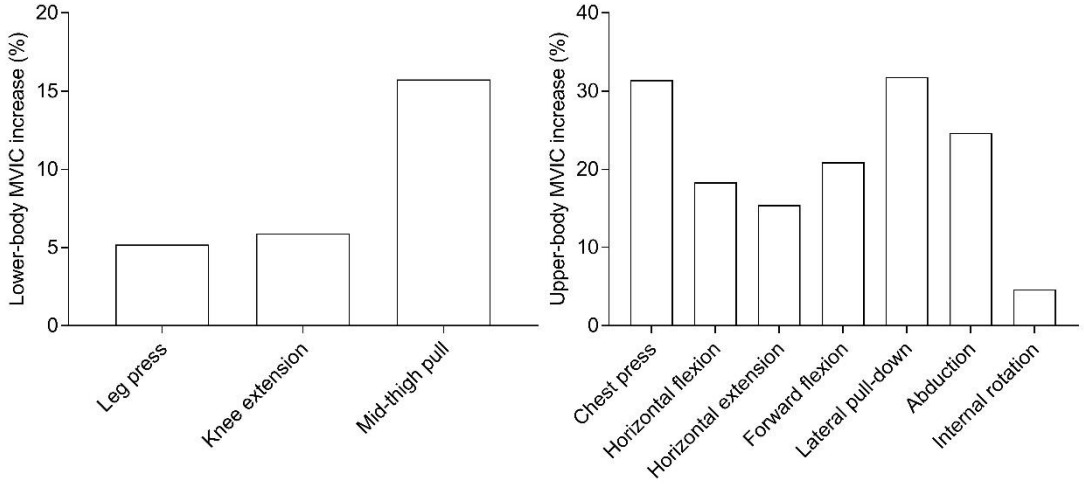

Figure S4. Increases in maximal strength measured by maximal voluntary isometric contraction (MVIC) after resistance training. For lower and upper-body MVIC test the mean total increase were 8.95±5.90% (leg press: 5.18%; knee extension: 5.91%; and mid-thigh pull: 15.75%) and 21.02±9.52% (chest press: 31.42%, horizontal flexion: 18.32%, horizontal extension: 15.43%, forward flexion: 20.87%, lateral pull-down:

31.81%, abduction: 24.67%, and internal rotation: 4.65%), respectively. Data were presented as mean, and SD when available.

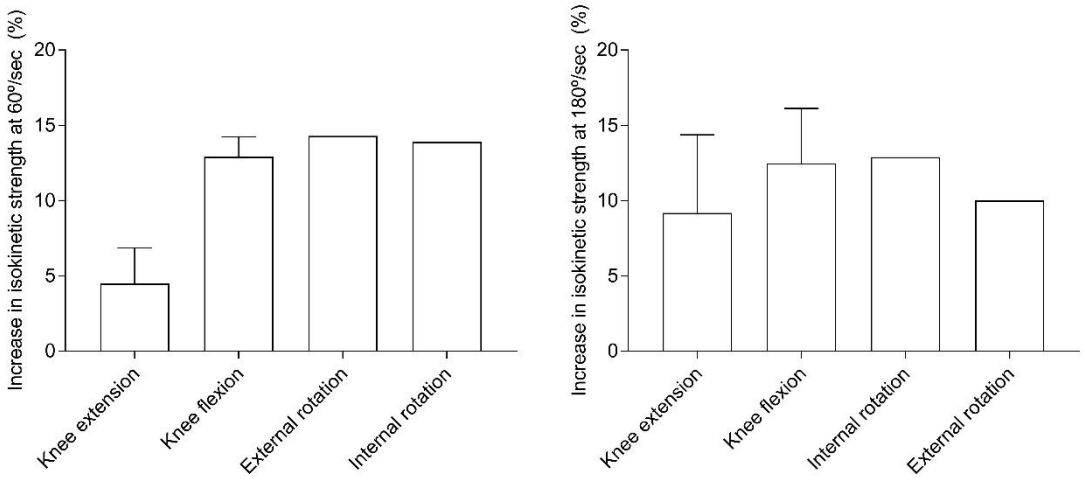

Figure S5. Increases in maximal strength measured by isokinetic contractions at 60 and 180º/sec after resistance training. For lower- and upper-body isokinetic strength at 60º/sec the mean total increase was 8.70±4.92% (knee extension: 4.48±2.37%, and knee flexion: 12.91±1.32%), and 14.09±0.28% (internal rotation: 13.89%, and external rotation: 14.29%), respectively. Data were presented as mean, and SD when available. Regarding lower- and upper-body isokinetic strength at 180º/sec, the mean total increase was 10.83±4.40% (knee extension: 9.18±5.20 and knee flexion: 12.48±3.65%), and 11.45±2.05% (internal rotation: 12.90% and external rotation: 10.00%), respectively. Data were presented as mean, and SD when available.

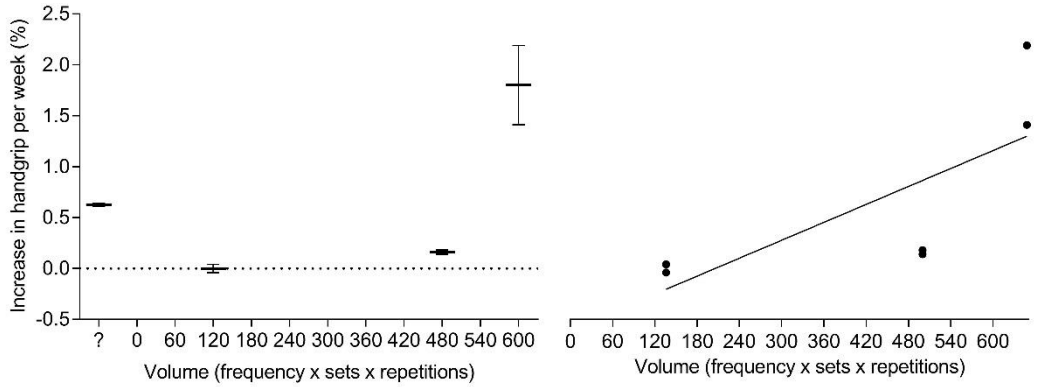

Figure S6. Resistance training weekly volume vs. percentage increase in handgrip strength per week (number of study groups= 8). Inspection of the datapoints revealed three identifiable “clusters” in the range of total repetitions. The average rate of change

of handgrip strength for each cluster was as follow: 120-179= no change per week, 480-539= 0.16±0.03%, and ≥600= 1.80±0.55%. In addition, the unknown resistance training volume resulted in an increase of 0.63±0.02% per week.

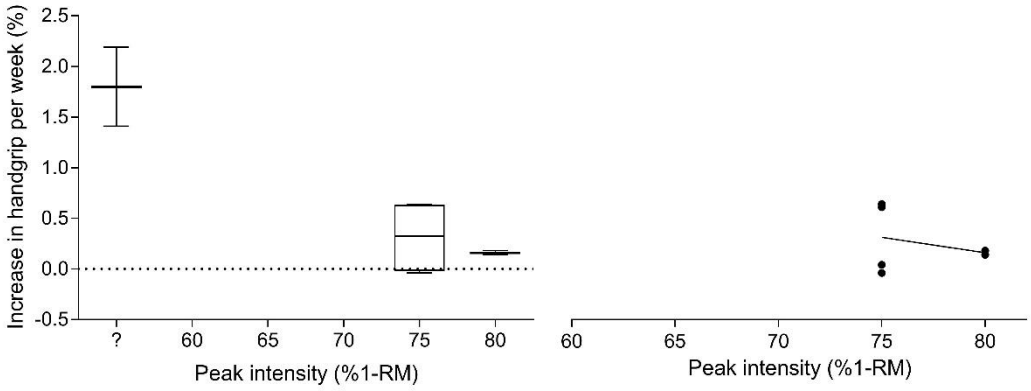

Figure S7. Resistance training peak intensity vs. percentage increase in handgrip strength per week (number of study groups= 8). Inspection of the datapoints revealed two identifiable "clusters" in the range of total repetitions. The average rate of change of handgrip strength for each range was as follow: 75% of 1-RM= 0.31±0.36% per week, and 80% of 1-RM= 0.16±0.03% per week. In addition, the unknown resistance training volume resulted in an increase of 1.80±0.55% per week.

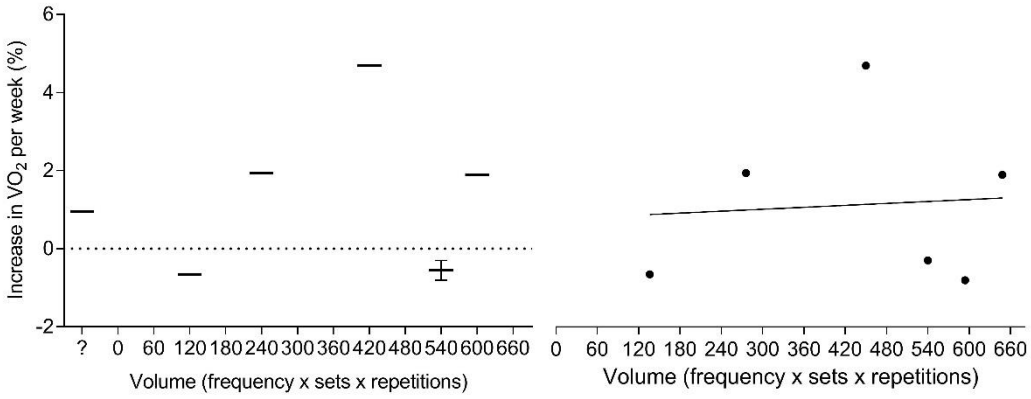

Figure S8. Resistance training weekly volume vs. percentage increase in VO_2 (peak or maximum when available) per week (number of study groups= 7). Inspection of the datapoints revealed one identifiable "clusters" in the range of total repetitions and single points among the range. The average rate of change of VO2 for each cluster was as follow: 120-179= -0.65% per week, 240-299= 1.93%, 420-479= 4.68%, 540-

599= -0.55±0.35%, and ≥600= 1.89%. In addition, the unknown resistance training volume resulted in an increase of 0.94% per week.

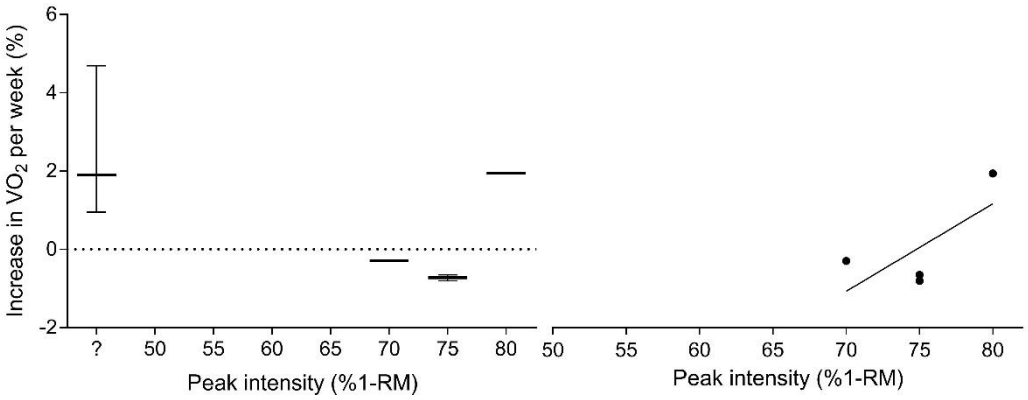

Figure S9. Resistance training peak intensity vs. percentage increase in VO_2 (peak or maximum when available) per week (number of study groups= 7). Inspection of the datapoints revealed one identifiable "cluster" in the range of peak intensities, and single points among the range. The average rate of change of VO_2 for each range was as follow: 70% of 1-RM= -0.29% per week, 75% of 1-RM= -1.45±0.11% per week, and 80% of 1-RM= 1.94% per week. In addition, the unknown resistance training intensity resulted in an increase of 2.51±1.94% per week.

Appendix 1. Checklist of items to include when reporting a systematic review or meta-analysis

SECTION/TOPIC	#	CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	30
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	30
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	31-32
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	32
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-

SECTION/TOPIC	#	CHECKLIST ITEM	REPORTED ON PAGE #
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	33
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	33
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	33 and 71
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	37
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	35
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	33
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	33
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-

SECTION/TOPIC	#	CHECKLIST ITEM	REPORTED ON PAGE #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	33-35
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	33-35
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	37
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	38
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	44-49
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	39-58
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	46-48

SECTION/TOPIC	#	CHECKLIST ITEM	REPORTED ON PAGE #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) (see Item 16).	39-58
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	58-59
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	61-62
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	62
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

5. DOSE-RESPONSE EFFECTS OF RESISTANCE EXERCISE IN BREAST CANCER PATIENTS UNDERGOING PRIMARY TREATMENT: A PILOT STUDY FROM A RANDOMIZED CONTROLLED TRIAL

Abstract

Purpose: Breast cancer chemotherapy causes several side-effects in patients undergoing primary treatment. In this context, exercise has been considered one of the most powerful adjunct therapy to alleviate these side-effects, improve physical fitness and quality of life, in addition, to act independent and synergistically with other therapies in tumor biology. However, little is known about its respective dose-response, mainly regarding resistance exercise.

Patients and Methods: We conducted a three-arm randomized controlled trial between 2017 and 2019 that randomly assigned 22 breast cancer patients initiating adjuvant chemotherapy to traditional resistance training plus aerobic exercise (TRT), low-dose resistance training plus aerobic exercise (LRT), or usual care control (UC) for the duration of 12 weeks. Our primary endpoint was maximal strength. Our secondary endpoints were cardiorespiratory fitness, body composition, fatigue, and quality of life.

Results: In this preliminary report, adjusted analysis indicated no superiority of TRT compared to LRT in all outcomes. At 3 months, maximal strength was significantly improved in LRT group compared to UC ($P<0.05$), while no changes were observed in cardiorespiratory fitness ($P=0.345$). Regarding body composition, pronounced effect in fat mass was observed for TRT group ($P=0.01$), while differences in total fat and lean mass at 3 months were not. In addition, TRT promoted a significant reduction in patient-rated fatigue ($P=0.03$), but not in fatigue physical assessment ($P=0.327$ – 0.894) at 3 months. Lastly, changes in QoL were more pronounced in LRT ($P=0.016$).

Conclusion: Both doses of resistance combined with aerobic exercise had comparable effects on improving physical fitness, fat mass, patient-rated fatigue, and QoL after 3 months. In these preliminary results, low-dose resistance exercise, in terms of minimal-dose approach, would have important practical application given its time efficiency and less discomfort related to exercise practice.

5.1. Introduction

The mainstream treatments for breast cancer involve systemic (i.e., hormone and chemotherapy) and loco-regional procedures (i.e., surgery and radiation) clinically defined in accordance with the stage and course of the disease (Runowicz *et al.*, 2016). Despite its success in eliminating the tumor cells and improve 5-year survival rate (Miller *et al.*, 2016), breast cancer patients face a wide range of short- and long-term adverse effects that are unpredictable by the warranty of survival. In the case of chemotherapy, for example, it is well-established the impacts on musculoskeletal and cardiovascular systems (Jones *et al.*, 2007), and body composition worsening (Demark-Wahnefried *et al.*, 2001) that can fully impact the quality of life and physical function in breast cancer patients during and after adjuvant and neoadjuvant treatments. Thus, due to the higher incidence of disease and use of chemotherapy as the first line therapy (Torre *et al.*, 2017), alternative adjunct treatments are of utmost importance to help avoid and attenuate chemotherapy-related side effects in breast cancer treatment.

The use of exercise as a medicine for cancer management is supported by worldwide organizations as *American College of Sports Medicine* (Schmitz *et al.*, 2010), *Exercise and Sports Science Australia* (Hayes *et al.*, 2019), and *Clinical Oncology Society Australia* (Cormie *et al.*, 2018) considering the several findings in 20 years of *exercise oncology*, in addition to their independent and synergistically effect with other therapies (Koelwyn *et al.*, 2017; Ashcraft *et al.*, 2018). However, its overall application was still looked with a certain skepticism due to the lack of evidence whether exercise positively affects cancer survival (phase III trial), and some suggestions of a “single metric” to suit all patients (The Lancet, 2018; Newton *et al.*, 2018). Generic physical activity recommendations, also approached in previous editorials (Hardcastle & Cohen, 2017; Adams *et al.*, 2018), has been considered unfit to cancer patient’s needs due to their challenging inability to meet 150min.wk^{-1} of unsupervised physical activity (Nelson *et al.*, 2019). In this context, where patients are prone to cardiovascular and metabolic comorbidities in addition to all common chemotherapy side-effects (Jones *et al.*, 2007; Srokowski *et al.*, 2009), new strategies are required to improve exercise attendance and practicability to beyond a unique dose and type. Nevertheless, considering the individualization and specificity in relation to breast cancer treatments for its patients, conservative and appropriate commence

information could improve appropriate progression and modification accordingly patient needs (Hayes *et al.*, 2019).

Few investigations regarding exercise dose-response were proposed in patients with cancer. Different doses' prescription of aerobic exercise (150 vs. 300min.wk^{-1}) were explored in women at risk for breast cancer (Schmitz *et al.*, 2015), and colon cancer survivors (Brown *et al.*, 2016), but restricted to this type of exercise, and precluding any assumption for other exercise types or cancer patients. Considering the benefits of resistance training and its potent anabolic and neural stimulus for breast cancer patients (Schmitz *et al.*, 2010), its investigation becomes clinically necessary as well as their respective dose to reach relevant improvements on clinical outcomes during primary treatment. In older women, for example, promising results were found as similar improvements on maximal strength, muscle hypertrophy, and body composition after short- and long-term resistance training performing single- or multiple-sets (Galvão & Taaffe, 2005; Radaelli *et al.*, 2014; Cunha *et al.*, 2018). These findings, if translated for breast cancer patients, may help to improve physical function and tolerance to treatment with time-efficiency and safety (Galvão & Taaffe, 2005). Thus, whether a lower-dose of resistance training is found to be equally efficient as well as higher-doses, benefits such as the increase of physical activity levels and reduced systemic acute impacts (e.g. exercise-induced muscle damage) would improve adherence and minimize respective barriers during physical exercise interventions (Courneya *et al.*, 2008a).

Considering the aforementioned, here, we report preliminary results from the *Adaptations Regarding Exercise and Breast Cancer* (ABRACE - NCT03314168) trial, designed to compare the possible effects of a 12-week combined low- (i.e., single-sets) or a traditional-dose (i.e., multiple-sets) resistance training with aerobic exercise on maximal strength, body composition, muscle thickness, cardiorespiratory fitness, fatigue, and quality of life in breast cancer patients receiving primary treatment. Because of the well-known cardiovascular side-effects, and most effective format of exercise program for women with breast cancer (Schmitz *et al.*, 2010), combined resistance and aerobic exercises were prescribed in order to maintain and attenuate further impairments on cardiovascular function during treatment (Jones *et al.*, 2013). In this three-arm clinical trial, we hypothesized that both doses of resistance training

combined with aerobic exercise would be equally superior to usual care in these respective outcomes.

5.2. Patients and Methods

5.2.1. Settings and Participants

Two hundred-nineteen patients with breast cancer were screened for participation from September 2017 to February 2019 at two different cancer institutes (Porto Alegre, RS, Brazil) and their progress through the study is shown in Figure 1. Patients were eligible for the study if they were nonpregnant women aged 18 years or older with stage I to III breast cancer initiating adjuvant or neoadjuvant chemotherapy. Women were excluded if they had uncontrolled hypertension, cardiac illness, or psychiatry illness, or if they otherwise were not approved by their oncologist. In addition, any musculoskeletal, neurological, or cardiovascular disorder that might compromise their involvement in an exercise training program. All participants obtained medical clearance from their physician. The trial received ethical approval from all involved centers and written informed consent from all potential participants.

5.2.2. Design and Procedures

This was a three-armed prospective randomized controlled trial. Potential participants were identified by their treating oncologist, nurse, and nutritionist before chemotherapy, and referred to the study team to confirm eligibility, describe the study, and obtain inform consent. Interested participants completed a questionnaire, physical fitness tests (maximal strength and aerobic fitness), muscle-ultrasound assessment, and dual x-ray absorptiometry scan. Further information about each method was described above, and in their respectively supplementary material (SM) section.

5.2.3. Random Assignment

After the completion of the baseline assessment, participants were randomly assigned to the three arms: traditional resistance training + aerobic exercise (TRT), low-dose resistance training + aerobic exercise (LRT), or usual care control (UC) in a ratio of 1:1 using a computer random assignment program by an independent researcher, blinded to the details of the study. The allocation sequence was concealed from the trial team and exercise physiologists involved. Control participants could undergo the training after the assessment period had been completed.

5.2.4. Exercise Training Program

Participants undertook combined progressive resistance and aerobic training twice a week for 12 weeks. The resistance exercises included leg extension, chest press, leg curl, lat pull down, unilateral biceps curl, calf raises, triceps extension, shoulder external rotation, and curl-ups. The resistance exercise program was designed to progress from 60 to 80%1-RM performed with single- (one set per exercise) in LRT and multiple-sets (three sets per exercise) in TRT group for leg extension and bench press (1-RM reassessed at every 4 weeks) ranging from 12 to 8 repetitions. In the remaining exercises, 1-RM was not reassessed due to time constraints, and therefore, the training load was adjusted using autoregulation (i.e., self-determine load at each session collaboratively with the supervising exercise physiologist) through the Omni scale (Mann *et al.*, 2010; Fairman *et al.*, 2017; Newton *et al.*, 2018). The aerobic component of the training program included 20 to 25 minutes of cycling at 80 to 90% of the heart rate at the second ventilatory threshold, obtained in the incremental exercise protocol. Sessions were conducted in small groups of one to four participants under the direct supervision of exercise physiologists. Details about the combined progressive resistance and aerobic training were described in the SM section.

5.2.5. Primary and Secondary Study Endpoints

Study outcomes were assessed at baseline (1 to 2 weeks after starting chemotherapy), and after the intervention (1 to 2 weeks after 12 weeks). The primary endpoint, muscle strength, was determined for the leg extension using the three-repetition maximum. The maximum weight and number of repetitions were used to estimate the one-repetition maximum (1-RM).

Objective measured outcomes were assessed at baseline and after the intervention. Whole body lean mass, fat mass, and percent fat were assessed by DXA (GE Healthcare Lunar, model Lunar Prodigy Madison, USA). Muscle thickness was assessed using B-mode ultrasound (Nemio XG, Toshiba, Japan) at quadriceps femoris. Aerobic fitness was evaluated using a maximal incremental exercise protocol on a cycle ergometer. Expired gases were analyzed continuously, breath-by-breath, using an open-circuit spirometry system (Quark CPET, Cosmed, Italy). Peak oxygen consumption was determined by independent visual inspection and analyzing the values close from participants exhaustion, with its respective time to reach it (time to

peak). Muscular fatigue was determined by the calculation of the peak torque decline at $60^{o}.s^{-1}$ in knee extensors of the right leg assessed obtained in an isokinetic dynamometer (Cybex Norm, New York, USA). Therefore, we used the muscular fatigue index: FI%= [(peak torque of 2, 3, and 4^{th} repetitions – peak torque of 8, 9, and 10^{th})/ peak torque of 2, 3, and 4^{th} repetitions] x 100. In addition, cancer-specific quality of life and fatigue were assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) C30 and its module BR23, and the Piper Fatigue Scale, respectively, at baseline and after the intervention.

5.2.6. Statistical Analyses and Sample Size Calculation

To achieve 80% power at an α level of 0.05 (two-tailed), 15 participants per group would be required to detect a mean difference in change for leg extension maximal strength of 8.2 kg (standard deviation of 8.0 kg) (Courneya *et al.*, 2007) and a non-inferiority hypothesis, at the end of the 12-week intervention. To account for dropout, our goal was to recruit 54 in total. With 22 participants randomized, this pilot study had the respective power to detect a difference in change maximal strength of 12.0 kg on the leg extension exercise, with a two-tailed $\alpha \leq 0.05$, and no adjustment for multiple testing. Baseline comparisons were performed using univariate analysis of variance (ANOVA), and X^2 analyses for categoric variables. Repeated measures ANOVA was used to model each outcome measure at two time points and compare the differences over time and groups. Adjusted analyses were performed controlling for baseline values of the outcome. It was provided descriptive data and 95% confidence intervals (95% CI), F and P-values for all possible comparisons and its respective adjusted mean changes. For all analyses, it was used the intent-to-treat principle using maximum-likelihood imputation of missing values (expectation maximization). Data were analyzed using SPSS (version 22.0, SPSS Inc, Chicago, IL) statistical software package.

5.3. Results

5.3.1. Participants characteristics

Recruitment was from September 2017 to February 2019 (Figure 1). In the present pilot study, 22 participants (32.8%) were recruited from 67 eligible patients. The most common reasons for refusal were lack of interest (n=4). We obtained the follow-up data from 20 (90.9%) of 22 participants. The reason for loss to follow-up was lack of interest. On average, participants in LRT and TRT attended 59.7% (86 of 144

sessions) and 43.0% (62 of 144 sessions) of their exercise sessions, respectively, with no reported adverse events during this period.

Participants had a mean age of 49.0±13.6 years, 72.7% had a college or university degree, and 63.6% are married or living together. Exercise and nutritional status were not changed during follow-up (P>0.05). Half participants had stage I/IIa or IIb/IIIa breast cancer, and almost all women were receiving adjuvant treatment (83.3%). Baseline characteristics were balanced across groups as presented in Table 1.

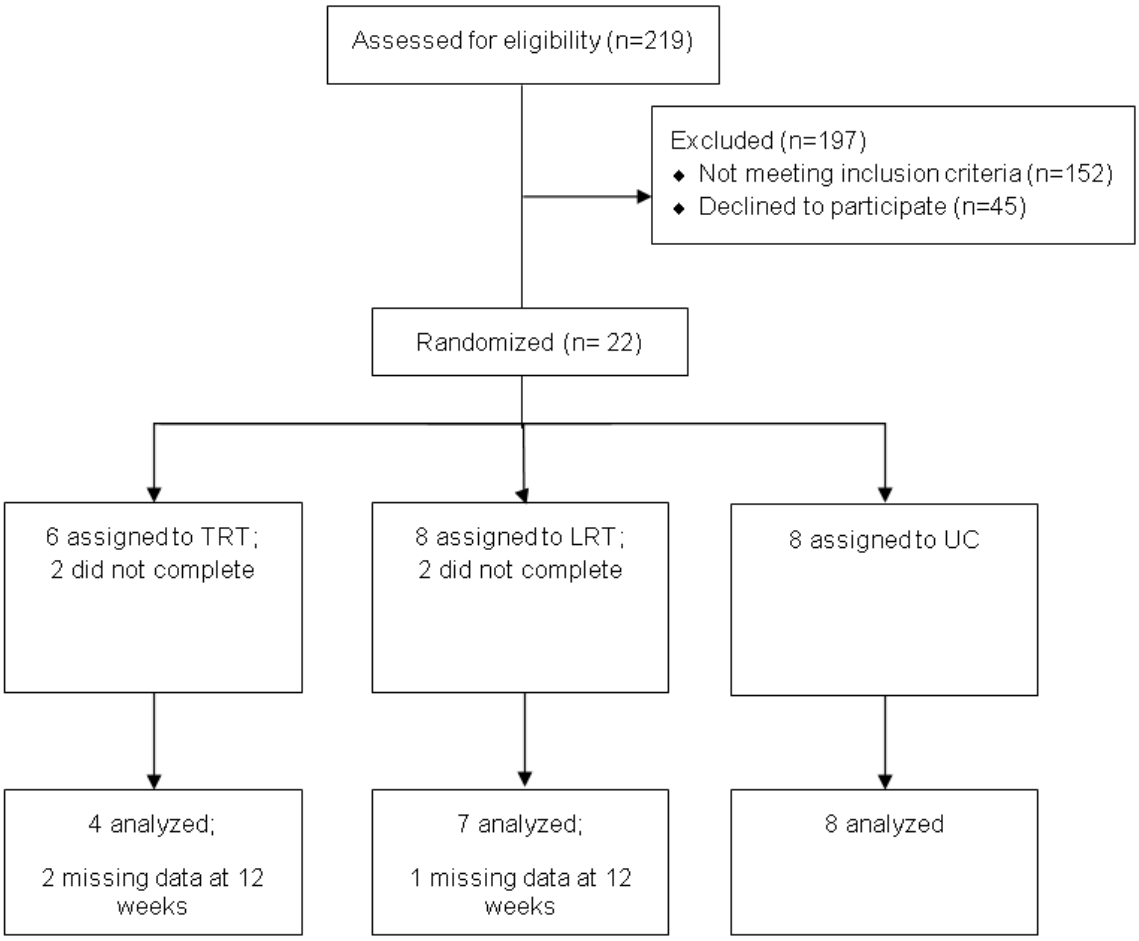

Figure 1. Study flow chart.

Table 1. Baseline demographic, medical, and behavioral profile of overall participants and by its group assignment.

	Overall (n=22)		UC (n=8)		LRT (n=8)		TRT (n=6)		
Variable	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**P**
Demographic profile									
Age, years	49.4±14.3		46.9±14.5		49.4±12.5		51.5±15.7		.831
Married/ Living together	14	63.6	6	75.0	6	75.0	2	33.3	.195
Completed university	16	72.7	7	87.5	6	75.0	3	50.0	.174
Medical profile									
Weigth, kg	64.4±13.0		59.7±5.8		60.9±8.2		75.3±19.3		.046
BMI, $kg.m^{-2}$	24.5±4.5		22.4±2.3		23.9±3.8		28.2±5.8		.044
Obese	4	18.2	0	0	1	12.5	3	50.0	.049
Disease stage									
I/ IIa	8	44.4	2	33.3	3	50.0	3	50.0	.566
IIb/ IIIa	7	38.9	3	50.0	3	50.0	1	16.7	
Surgical protocol									
Breast conservation	7	38.9	1	16.7	3	37.5	3	50.0	.116
Behavioral profile									
Physically active	8	44.4	2	33.3	2	33.3	4	66.7	.772

5.3.2. Changes in maximal strength and cardiorespiratory fitness

There were no significant differences between groups at baseline for leg extension maximal strength (P=0.161), and absolute and relative VO_2 (P=0.632 – 0.830). Leg extension muscle strength was significantly different between groups (P=0.041), with the LRT group presenting an adjusted mean difference of 14.0 kg (95% CI, 1.5 – 26.5; P=0.033) at 3 months higher than UC group (+7.2 kg; 95% CI, 0.2 – 14.2; P=0.043). In addition, no differences were found between groups at 3 months for relative VO_2 (P=0.345), supported by no significant changes in absolute VO_2 (P=0.252). Table 2 provides further information.

Table 2. Effects of low-dose and traditional resistance training on physical fitness in breast cancer patients undergoing primary treatment.

	Baseline		3 months		Adjusted mean change		Between-groups
	Mean	SD	Mean	SD	Mean	95% CI	F and P values
Maximal strength							
Leg extension 1-RM, kg							
UC	66.9	11.4	65.5	12.2	-1.4	-5.9 to 3.0	
LRT	57.4	11.2	71.4	16.3	14.0*#	1.5 to 26.5	F=3.8; P=.041
TRT	74.9	25.6	81.5	24.2	6.6	-5.7 to 18.9	
Cardiorespiratory fitness							
Relative VO_2, ml.kg.min^{-1}							
UC	24.1	3.1	23.7	3.3	-0.3	-2.5 to 1.9	
LRT	22.7	7.0	24.3	5.9	1.6	-0.8 to 3.9	F=1.1; P=.345
TRT	20.7	8.8	23.2	6.0	0.5	-1.2 to 2.1	
Absolute VO_2, ml.min							
UC	1427.0	169.9	1422.1	236.7	-4.9	-163.9 to 154.1	
LRT	1355.1	332.5	1457.4	255.3	102.3	-0.9 to 205.5	F=1.5; P=.252
TRT	1440.7	350.1	1397.8	453.1	-42.9	-182.2 to 96.4	

Abbreviations: SD, standard deviation; 1-RM, one repetition maximal; VO_2, peak volume of oxygen uptake; UC, usual care; LRT, low-dose resistance training; TRT, traditional resistance training.

* Within-group significant change after repeated measures ANOVA adjusted by baseline value.

Between-group significant change after repeated measures ANOVA adjusted by baseline value, compared to UC group.

5.3.3. Changes in body composition, and muscle thickness

There were no significant differences between groups at baseline for percent of fat, fat and lean mass (P=0.077 – 0.345). Total body fat, and lean mass were not changed after 3 months (P=0.733 – 0.926; Table 3). The TRT group presented a significant adjusted mean change after 3 months for total fat mass (-1.8kg; 95% CI, -3.1 – -0.5; P=0.017), but not different than other groups (P=0.926). Regarding muscle thickness, no significant differences were observed at baseline for QF_{MT} (P=0.084), in addition to no significant differences during the study period (P=0.885).

Table 3. Effects of low-dose and traditional resistance training on body composition, and muscle thickness in breast cancer patients undergoing primary treatment.

	Baseline		3 months		Adjusted mean change		Between-groups
	Mean	SD	Mean	SD	Mean	95% CI	F and P values
Body composition							
Total body fat, %							
UC	35.1	5.4	33.8	5.5	-1.3	-3.0 to 0.3	
LRT	37.1	8.1	36.3	7.5	-0.8	-2.4 to 0.7	F=0.3; P=.733
TRT	40.7	7.3	39.2	6.1	-1.5	-3.2 to 0.1	
Total fat mass, kg							
UC	20.4	4.0	19.7	4.6	-0.6	-2.2 to 1.0	
LRT	22.5	7.6	21.8	6.3	-0.7	-1.8 to 0.4	F=0.1; P=.926
TRT	31.1	13.0	29.2	11.1	-1.8*	-3.1 to -0.5	
Total lean mass, kg							
UC	37.6	4.4	38.4	4.6	0.8	-0.4 to 2.0	
LRT	37.0	3.8	37.6	4.0	0.5	-0.9 to 2.0	F=0.1; P=.897
TRT	42.5	6.8	43.0	7.1	0.5	-1.5 to 2.4	
Muscle thickness							
Quadriceps femoris, mm							
UC	55.7	5.3	58.5	6.8	2.8	-1.7 to 7.4	
LRT	59.2	7.4	60.4	10.2	1.2	-4.8 to 7.2	F=0.1; P=.942
TRT	68.9	11.7	71.6	10.8	2.7	-1.5 to 6.8	

Abbreviations: SD, standard deviation; UC, usual care; LRT, low-dose resistance training; TRT, traditional resistance training.

* Within group significant change after repeated measures ANOVA adjusted by baseline value.

5.3.4. Changes in fatigue and quality of life

There were no differences between groups at baseline for Piper Fatigue Scale, time to peak on aerobic fitness test, and muscular fatigue index (P=0.443 – 0.763). No differences between groups were observed in Piper Fatigue Scale, time to peak, and muscular fatigue index after 3 months (P=0.233 – 0.307; Table 4). The TRT group was the only presenting a significant adjusted mean difference for Piper Fatigue Scale after 3 months (-1.3 pts; 95% CI, -2.3 – -0.2; P=0.03), while no other difference was observed within and between groups.

At baseline, no differences were observed in EORTC-QLQ C30 and its module BR23 (P=0.778 – 0.853). For EORTC QLQ C30 and BR23 module, no differences between groups were also observed after 3 months (P=0.128 – 0.280; Table 4). The LRT group was the only to present a significant adjusted mean difference of 10.7 pts (95% CI; 5.3 – 16.2; P=0.003) for EORTC QLQ C30 after 3 months, while no other difference was observed.

Table 4. Effects of low-dose and traditional resistance training on fatigue and quality of life in breast cancer patients undergoing primary treatment.

	Baseline		3 months		Adjusted mean change		Between-groups
	Mean	SD	Mean	SD	Mean	95% CI	F and P values
Fatigue							
Piper fatigue scale, pts							
UC	3.4	1.6	3.2	1.1	-0.1	-1.2 to 0.9	
LRT	2.9	0.9	2.4	1.0	-0.5	-1.3 to 0.3	F=1.3; P=.307
TRT	3.9	1.7	2.6	1.0	-1.3*	-2.3 to -0.2	
Muscular fatigue index, %							
UC	11.3	2.5	13.5	3.2	2.2	-0.4 to 4.8	
LRT	12.2	5.5	12.9	5.3	0.7	-2.1 to 3.6	F=1.6; P=.233
TRT	12.9	2.4	12.1	2.4	-0.8	-2.2 to 0.7	
Time to peak, sec							
UC	466.9	113.8	448.9	79.3	-18.0	-61.3 to 25.3	
LRT	431.4	82.3	455.5	74.9	24.1	-16.6 to 64.9	F=1.3; P=.288
TRT	462.8	82.5	436.3	100.6	-26.8	-86.6 to 33.0	
Quality of life							
EORTC QLQ C-30, pts							
UC	81.0	17.7	86.1	6.2	5.0	-0.3 to 10.4	
LRT	80.9	6.7	91.6	5.8	10.7*	5.3 to 16.2	F=2.3; P=.128
TRT	77.6	8.8	84.4	8.0	6.8	-1.6 to 15.2	
EORTC QLQ BR23, pts							
UC	81.0	10.5	82.5	8.5	1.5	-5.9 to 8.9	
LRT	84.1	8.0	86.8	7.9	2.7	-4.4 to 9.8	F=1.4; P=.280
TRT	83.0	7.4	80.8	6.6	-2.2	-10.6 to 6.2	

Abbreviations: SD, standard deviation; UC, usual care; LRT, low-dose resistance training; TRT, traditional resistance training.

* Within group significant change after repeated measures ANOVA adjusted by baseline value.

5.4. Discussion

In the present study, we examined the dose-response effects of resistance combined to aerobic exercise on physical fitness, body composition, muscle thickness, fatigue, and quality of life in breast cancer patients undergoing primary treatment. Despite the lack of some significant interactions and small sample size, four important findings were found: I) a low-dose of exercise present a superior effect on maximal strength when compared to UC, and a similar effect to TRT on cardiorespiratory fitness; II) exercise may affect fat mass, but its effects were more pronounced in TRT group, while no changes were observed in total fat and lean mass, and muscle thickness; III) a higher-dose of exercise may promote significant reduction in fatigue assessed by Piper Fatigue Scale after 3 months, but not in the physical assessment of fatigue; and IV) LRT reached higher changes on quality of life assessed by QLQ C30, but not pronounced in BR23 when compared to TRT and UC after 3 months.

Neural and cardiovascular toxicities are common during primary treatment of breast cancer (Gilchrist *et al.*, 2019; Lacourt & Heijnen, 2017). The use of taxanes-based chemotherapy is related to higher rates of anemia, neurosensory and neuromotor effects (Mamounas *et al.*, 2005), in addition to the use of corticosteroids promoting muscle catabolism during treatment. In a subanalysis of Supervised Trial of Aerobic versus Resistance Training (START) the use of taxanes moderated an adjusted mean difference of 5.1 kg (95% CI, 2.3 – 7.9 kg), while nontaxane regimen resulted in 10.3 kg (95% CI, 8.4 – 12.1 kg) after resistance training intervention (Courneya *et al.*, 2007; 2008b). In our sample, all patients were submitted to taxanes regimens, and participants reached similar values to Courneya *et al.* (2008) in the TRT group. However, it was observed an unexpected trend to larger gains in LRT group at 3 months (2-fold more than TRT), different than previous literature (Galvão *et al.*, 2005; Radaelli *et al.*, 2014; Cunha *et al.*, 2018) demonstrating similar, but larger improvements in higher-doses group compared to lower- (16-21% vs. 9-16%, respectively). Our preliminary results indicating a superior effect for lower-dose may be attributed to the less mechanical and metabolic stress imposed by this dose of exercise, suggesting preservation of immune system and its recovery during or for subsequent bouts of exercise (Tidball, 2017) in patients during chemotherapy. In addition, it is also important to note that a low-dose of resistance training combined with aerobic exercise prescription does not hamper further adaptations in

cardiorespiratory fitness. Thus, based on our current sample, it is possible to suggest that lower-doses of resistance exercise combined to 20-30 min aerobic exercise would be feasible and safe to reach relevant gains in physical fitness after 3 months of exercise and reducing risk for future cancer-related comorbidities as cardiovascular and metabolic diseases (Newton & Galvão, 2008; Scott *et al.*, 2018), but future reports with larger sample will be necessary to elucidate this data.

Changes in body composition after exercise interventions remains challenging for breast cancer patients as reported as inconsistent evidence level in the last ACMS *Roundtable in Cancer Survivors* for fat and lean mass (Schmitz *et al.*, 2010). In fact, the expected changes in lean and fat mass after resistance and aerobic exercises, respectively (Courneya *et al.*, 2007), is not clearly observed when both types of exercise are combined in breast cancer patients (Battaglini *et al.*, 2007; Courneya *et al.*, 2013). Unexpectedly, our results indicate a possible effect of exercise for fat mass, restricted to TRT, while lean mass and muscle thickness seem to be not changed at 3 months. In this sense, changes in fat mass may occur dependent of resistance exercise dose when combined with aerobic exercise, and for now, the present results provide a potential benefit using higher-doses of exercise in patients undergoing primary treatment. On the other hand, the expected anabolic benefits of exercise, i.e., increases in lean mass, and/or hypertrophy, was not observed independent of dose, in addition to a resistance- aerobic exercise order prioritizing muscular adaptations within combined training (Wilson *et al.*, 2012; Eddens *et al.*, 2018). Thus, it is possible to hypothesize that gains in muscle mass could need longer periods of intervention such as the observed after all primary treatment (Courneya *et al.*, 2007) because of an impaired hormonal- and immune-related muscle adaptation in patients undergoing taxane-based chemotherapy (Tidball, 2017); while the time-course for fat mass loss seems to be dependent of more exercise and earlier in this type of exercise.

Counteract cancer-related fatigue is the primary endpoint of many exercise oncology studies (Courneya *et al.*, 2007; Furmaniak *et al.*, 2016; Mijwel *et al.*, 2017) given its strong incidence and report among cancer patients, in addition to its repercussion in physical activity levels, and mental health (Oh & Cho, 2018; Lavallée *et al.*, 2019), during and even after treatment. The larger meta-analysis for this outcome (Furmaniak *et al.*, 2016) presents an exercise effect of -0.28 (95% CI, -0.41 – -0.16) considering aerobic, resistance, or combined exercises (n=19 studies), but its

respective dose was not assessed. In the present report, a higher-dose of exercise shown a superior effect in Piper Fatigue Scale at 3 months, but not for the physical assessment of fatigue. As far as we know, fatigue physical assessment is not so widespread in exercise oncology literature, while subjective scales are widely used. However, if associations between them exist, are still unclear. The reports of BEST trial (Klassen *et al.*, 2014; 2016) presented significant differences in maintenance of knee extension maximal strength (-24.0 vs. -12.3%, respectively), and cardiorespiratory parameters between breast cancer patients and healthy women. Taking altogether, the impairments in self-perception of fatigue (Oh & Cho, 2018) and fatigue physical assessment after chemotherapy (Klassen *et al.*, 2014; 2016), we may suggest that a higher dose of exercise may affect more the subjective domain of fatigue through psychological aspects as well-being during its practice than specific muscular and peripheral endurance adaptations. However, studies should attempt the associations between different aspects of cancer-related fatigue and determining the possible mediators of this outcome in breast cancer patients, besides the possible benefits of exercise in longer interventions or during all period of treatment.

In the last 20 years of exercise oncology, cumulative findings support the benefits of exercise to improve or maintain quality of life in cancer patients (Cormie *et al.*, 2018a). In breast cancer, the START reports shown 5.9 pts (95% CI, 0.6 – 11.2 pts) improvements on QoL assessed by Functional Assessment of Cancer Therapy (FACT) in resistance training group (Courneya *et al.*, 2007), in addition to a moderation by preference, where patients with allocation and preference for resistance training improved more than allocated to UC or aerobic exercise (11.6 – 16.8 pts of superiority) (Courneya *et al.*, 2008b). In the present study, despite the fact that patients were prone and volunteer for an exercise trial, it is not possible to observe a type preference since participants were partially contemplated by either resistance or aerobic exercise. In this sense, our results demonstrated a superior effect for LRT group (10.7 pts; 95% CI; 5.3 – 16.2) assessed by EORTIC-QLQ C30, indicating that a lower dose of exercise may also promote this benefit in a short-term period, regardless of a possible preference within a combined exercise. Some factors could corroborate for this superior effect such as I) less time spent to exercise practice; II) more tolerance to chemotherapy with a low-dose of exercise; and III) less acute discomforts provoked by exercise-induced muscle damage. Furthermore, differences in BR23 module were not

observed, indicating that a short-term intervention which not be enough to significantly reduce perception of symptoms, but attenuate further impairments, and larger samples and longer interventions could provide powered analysis in this endpoint.

The present study has several strength and limitations worthy of comment. First, given the sound justification for exercise as an important part of therapy (Schmitz *et al.*, 2010; Rock *et al.*, 2012; Cormie *et al.*, 2018; Hayes *et al.*, 2019), but lack of phase III exercise trials and respective dose-response in breast cancer patients (The Lancet, 2018; Cormie *et al.*, 2018; Adams *et al.*, 2018), the present study fills an important avenue regarding dose-response, and was the first trial to address this issue in resistance exercise for patients undergoing primary treatment. Secondly, the present results demonstrate similar-to-superior benefits of lower-dose of resistance in combination with aerobic exercise compared to traditional resistance exercise prescriptions on most part of the current outcomes, and despite the small sample size, our preliminary results support the continuation and highlight the benefits of LRT on important investigated outcomes. Third, it is important considering that patients were volunteers for an exercise trial and as such may not be representative of all patients with breast cancer undergoing chemotherapy. Finally, we were only able to recruit a ~third of 54 patients originally planned. However, this is a very challenging trial given the difficult and absence of support to implement exercise in a clinical setting, besides the inactivity or sedentary behavior among patients. Moreover, among the 19 registered trials about exercise and breast cancer this is the first to attempt patients undergoing primary treatment in Brazil.

In conclusion, both doses of resistance combined with aerobic exercise had comparable effects on improving physical fitness, fat mass, patient-rated fatigue, and QoL at 3 months. In these preliminary results, low-dose resistance exercise, in terms of minimal-dose approach, would have important practical application given its time efficiency, besides its similar enhancement when compared to traditional doses of resistance training in breast cancer patients. In addition, besides the safety and feasibility, a low-dose resistance training is also likely to provide clinically meaningful benefits in breast cancer patients undergoing primary treatment.

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5.6. Supplementary material

5.6.1. Materials and methods

5.6.1.1. Exercise Training Program

The combined progressive resistance and aerobic exercise prescription was provided in Table S1. The resistance exercises were designed to progress from 60 to 80%1-RM for 12 to 8 repetitions performed with single- in LRT and multiple-sets in TRT group for leg extension and bench press. In these exercises, 1-RM was reassessed at every 4 weeks for further load adjustment, while in the remaining exercises, the load was adjusted to progress from 6 to 8 in the Omni scale (i.e., autoregulation concept). In addition, both exercise groups rested 1-2min between sets and/or exercises. Regarding the aerobic component, 20 to 25 minutes of cycling at 80-90% of the heart rate at the second ventilatory threshold was prescribed. Sessions were conducted in small groups of one to four participants under the direct supervision of exercise physiologists.

Table S1. Exercise program for low-dose (LRT) and traditional resistance training (TRT) throughout 12 weeks of intervention.

	Resistance exercise				**Aerobic exercise**	
	LRT group	TRT group	Overall		Overall	
Weeks	Volume	Volume	Intensity	Rest	Volume	Intensity
1-4w	1 set 10-12 reps	3 sets 10-12 reps	60%1-RM 6 OMNI's scale	~1min b/w sets and/or exercises	20min	80%HR of VT 2
5-8w	1 set 8-10 reps	3 sets 8-10 reps	70%1-RM 7 OMNI's scale	~1.5min b/w sets and/or exercises	25min	85%HR of VT 2
9-12w	1 set 8 reps	3 sets 8 reps	80%1-RM 8 OMNI's scale	~2min b/w sets and/or exercises	25min	90%HR of VT 2

%1-RM, Percentage of 1-repetition maximum; HR, Heart rate; VT 2, second ventilatory threshold.

5.6.1.2. Main outcomes evaluation

Maximal Strength

The maximal strength was measured using bilateral leg extension three-repetition maximum (3-RM) test (KonnenGym, China). Before the maximal test, participants performed 10 repetitions of the estimated 1-RM as a warm-up. Thereafter, the resistance was increases until no additional weight could be lifted using proper technique and range of motion (recorded by a customized device). The 3-RM was defined as the maximum weight that participant could move through a full range of motion three times. The movement started at 90º of knee flexion (0º = knee fully extended) to full extension which was individualized for each participant. The maximum weight and number of repetitions were used to estimate the one-repetition maximum (1-RM). The subject's maximal strength was determined with no more than five attempts, with a 3-min rest between attempts.

Aerobic fitness

VO_2 peak was determined by the breath-by-breath method using an open-circuit spirometry system (Quark CPET, Cosmed, Rome, Italy) on a cycle ergometer (ERGO-FIT, Pirmasens, Germany). The 3-min warm-up consisted of cycling at 20W and was followed by increases of 20W/min until exhaustion, with 3-min recovery at 20 W. Time to reach the peak value (time to peak) and peak work rate were also registered, while heart rate was measured continuously via chest belt telemetry (Cosmed, Rome, Italy). VO_2 peak and ventilatory thresholds (VT1 and VT2) data were obtained through a visual inspection of the graphs. Participants were verbally encouraged to perform at maximum effort during physical tests.

Body composition

The percent of fat, fat mass, and lean mass of the total body were obtained by imaging with dual energy X-ray absorptiometry - DXA (GE Healthcare Lunar, model Lunar Prodigy Madison, USA). The assessments were performed by an experienced assessor using standardized measurement procedures in accordance with the manufacturer's recommendations. The equipment was calibrated once a day before the evaluation. The individuals wore light clothing, and they were instructed to remove any metal material and to wear clothes without zippers, buttons or any similar

accessory. In addition, the participants were positioned in a supine position, lying still for approximately 8 min, while the arm of the equipment scanned the individual's body in the head-to-toe direction. The presented values were automatically calculated by the equipment's software (Encore version 14.1, Lunar Prodigy Madison, USA).

Muscle ultrasound

B-mode ultrasound images were obtained with a 30 and 60-mm, 9.0-MHz linear-array probe (image depth: 70 mm, 90-dB general gain, time gain compensation at neutral position) using ultrasound (Nemio XG, Toshiba, Japan). Participants rested in the supine position with the lower limbs extended and relaxed during 5 min before images acquisition (Lopez *et al.*, 2019). Similar to previous study, transverse images of the lower-limbs were acquired (Lopez *et al.*, 2019). The lower-limbs muscle thickness was the assessed through the sum of quadriceps femoris muscles as previously proposed (Lopez *et al.* 2017; 2019). The measurement for the vastus lateralis (VL) was taken midway between the lateral condyle of the femur and greater trochanter, whereas the measurement vastus medialis (VM) was taken at 30% of the distance between the lateral condyle of the femur and the greater trochanter. Rectus femoris (RF) and vastus intermedius (VI) were measured as 50% of the distance from the iliac crest to the upper edge of the patella.

Three images of the VL, RF-VI and VM were taken in that respective order, and images were exported to a personal computer for further analyses that were performed by the same investigator. Image analyses were performed using ImageJ 1.42q software (National Institutes of Health, Bethesda, MD, USA). Muscle thickness was determined as the distance of the adipose tissue-muscle interface for VL, RF and VM. Whole quadriceps femoris muscle thickness (QF_{MT}) was obtained as the sum of the four individual heads of the quadriceps ($QF_{MT}=VL_{MT} + RF_{MT} +VM_{MT}$). Given the difficult to obtain VI_{MT} in participants with a higher subcutaneous layer, this muscle was retained for further analysis. The coefficient of variation and standard error mean for muscle thickness in our laboratory were 1.3% and 0.61mm, respectively.

Muscular fatigue

Maximal isokinetic peak torque was tested for the right knee extensors at the angular velocities of $60°.s^{-1}$ on an isokinetic dynamometer (Cybex Norm, USA), calibrated according manufacture’s instruction before tests. Participants were seated

with the hip flexed at 85° (0°= anatomic position), and the lateral femoral condyle of the right leg was aligned with the dynamometer' axis of rotation. An initial warm up of 10 submaximal isokinetic knee extension/flexion at 120° s-1 was performed and one minute after warm up participants performed one submaximal MIVC. Then, two 3-s and one 15-s knee extension maximal isometric voluntary contraction attempts at knee angle of 60° (0° = knee fully extended) were performed with a rest periods of 120s between attempts (data not presented). After 3 min, a pre-test of 3 submaximal repetitions for angular velocity familiarization, the maximal isokinetic knee extension peak torque was measured during one set of 10 repetitions at the angular velocity of $60°{\cdot}s^{-1}$. The test was performed in a 90° range of motion (i.e., 0° - full extension).

Muscular fatigue was determined by the calculation of the peak torque decline at 60°/s in knee extensors of the right leg. Therefore, we used the muscular fatigue index: FI% = [(peak torque of initial three repetitions-peak torque of final three repetitions)/peak torque of initial three repetitions] × 100 to define the ability of the participants to maintain a level of performance. A high FI% value indicates that muscles fatigue quickly. The peak torque of the 1st repetition overall was markedly lower than that of the 2nd repetition, and it was omitted from further analysis (Pinto *et al.*, 2017).

Breast cancer-specific quality of life and fatigue

Quality of life (QoL) was assessed using the Brazilian version of the 30-item EORTC QLQ-C30 (version 3.0) (Aaronson *et al.*, 1993; Michels *et al.*, 2013). Scores were derived and scaled from 0 to 100 according to the EORTC scoring manual (Fayers *et al.*, 2001) considering global QoL score, five multi-item functional scales (physical, emotional, role, cognitive and social function), and eight multi-item symptoms scales, with higher scores indicating better QoL. In addition, the 23-item breast cancer specific module (EORTC QLQ-BR23) was also applied and scored as well. Cancer-related fatigue was assessed using the Brazilian version of the 22-item Piper Fatigue Scale (PFS) which has been validated in the Brazilian population (Piper *et al.*, 1998; Guarda Korelo *et al.*, 2019), covering four dimensions of fatigue: behavioral/daily life (6 items), sensory/physical (5 items), cognitive (6 items), and affective/emotional meaning (5 items). Each item is composed of a scale from 0 to 10, with zero indicating "no fatigue." Scores were calculated according to recommended scoring procedures.

5.6.2. References

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6. SUMMARY OF FINDINGS

In the present thesis, both the fourth and fifth chapters were driven to examine the dose-response relationship of resistance training in breast cancer patients undergoing primary treatment, in addition to the depth literature review supporting why to investigate this issue. Is noteworthy and potentially the results of these two studies that provide the first line of evidence regarding resistance exercise dose-response in this clinical population. Initially, our systematic review provides an exploratory approach suggesting no trend for superiority between low- and high-dose of resistance training over body composition, cardiorespiratory fitness, and immune markers, but an unexpected higher benefit in maximal strength for lower-volume of resistance training. Thereafter, our experimental study comparing low- and higher-volumes of resistance training in combination with aerobic exercise tested this hypothesis. The results demonstrating similar-to-superior benefits on physical fitness, body fat, fatigue, and quality of life to single-sets compared to a traditional dose of resistance training. These findings, despite the lack of sufficient sample size, are promising given the possible benefits with less time spent and common discomforts related to resistance training practice. Thus, the present thesis providing evidence to a possible minimal-dose approach of resistance exercise in breast cancer patients undergoing primary treatment, besides indicating that is possible training with less volume of resistance exercise and reaching physical and clinical benefits as well, considering the individualization, conservative and appropriate commence accordingly patient needs (Hayes *et al.*, 2019).

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