

**Effectiveness of Exercise on Physical Fitness
Attributes in Patients with Breast Cancer undergoing
Neoadjuvant Chemotherapy: preliminary results from
the NEO study**

Dissertação elaborada com vista à obtenção do Grau de Mestre em
Exercício e Saúde

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Abbreviations

AT	Aerobic Training
BC	Breast Cancer
BMI	Body Mass Index
CG	Control Group
CPET	Cardiopulmonary Exercise Test
CRF	Cardiorespiratory Fitness
DNA	Deoxyribonucleic Acid
DXA	Dual-energy X-ray Absorptiometry
FFM	Fat Free Mass
FFMI	Fat Free Mass Index
FM	Fat Mass
FMI	Fat Mass Index
HER2	Human Epidermal Growth Factor Receptor 2
HR_{max}	Maximal Heart Rate
HRR	Heart Rate Reserve
ITTA	Intention-to-Treat Analysis
LSTM	Lean Soft Tissue Mass
MT	Muscle Tissue
NEO-Program	Neoadjuvant Exercise Oncology Program
PPA	Per-Protocol Analysis
RM	Repetition Maximum
RQ_{max}	Maximal Respiratory Quotient
RT	Resistance Training
VO_{2max}	Maximal Oxygen Consumption
VO_{2peak}	Peak Oxygen Consumption
VT₁	First Ventilatory Threshold
VT₂	Second Ventilatory Threshold

Abstract

Purpose: To evaluate the impact of aerobic training (AT) and resistance training (RT) on physical fitness in women newly diagnosed with breast cancer undergoing neoadjuvant chemotherapy.

Methods: A subsample of the NEO study included 33 participants with breast cancer randomly assigned to a control group (CG), AT or RT. The intervention groups engaged in three weekly supervised exercise sessions. Physical fitness outcomes were assessed at baseline and the week before surgery. Data were analyzed using generalized estimating equations.

Results: Of the 33 participants (50.0 ± 8.0 years old), 2 dropped out. A between group effect was found in the AT group on relative VO_{2peak} when compared to other groups (AT vs. CG: $B = 1.24$, $P = 0.005$; AT vs. RT: $B = 1.30$, $P = 0.046$). The same trend was observed for absolute VT_1 (AT vs. CG: $B = 1.69$, $P < 0.001$), absolute VT_2 (AT vs. CG: $B = 1.89$, $P < 0.001$), relative VT_2 (AT vs. CG: $B = 4.36$, $P < 0.001$), peak power (AT vs. CG: $B = 12.27$, $P < 0.001$) and maximal test duration (AT vs. CG: $B = 68.64$, $P < 0.001$). AT and RT showed no significant effects on body composition and muscle strength.

Conclusions: AT had a favorable impact on cardiorespiratory fitness compared to the remaining groups, highlighting its importance in preventing fitness declines during neoadjuvant chemotherapy. Neither AT or RT significantly influenced body composition and muscle strength.

Keywords: cardiorespiratory fitness, muscle strength, body composition, exercise, neoadjuvant chemotherapy

Resumo

Objetivo: Avaliar o impacto do treino aeróbio (AT) e do treino de resistência (RT) na aptidão física em mulheres recentemente diagnosticadas com cancro da mama a realizar quimioterapia neoadjuvante.

Métodos: Uma subamostra do estudo NEO incluiu 33 participantes com cancro da mama aleatoriamente distribuídas por um grupo de controlo (CG), AT ou RT. Os grupos de intervenção realizaram três sessões de exercício supervisionadas por semana. Os resultados ao nível da aptidão física foram avaliados no momento inicial e na semana anterior à cirurgia. Os dados foram analisados utilizando equações de estimativas generalizadas.

Resultados: Das 33 participantes (50.0 ± 8.0 anos), duas desistiram. Observou-se um efeito entre grupos, no grupo AT para o VO_{2pico} relativo em comparação com os outros grupos (AT vs. CG: $B = 1.24$, $P = 0.005$; AT vs. RT: $B = 1.30$, $P = 0.046$). Tendências semelhantes foram observadas no VT_1 absoluto (AT vs. CG: $B = 1.69$, $P < 0.001$), VT_2 absoluto (AT vs. CG: $B = 1.89$, $P < 0.001$), VT_2 relativo (AT vs. CG: $B = 4.36$, $P < 0.001$), potência de pico (AT vs. CG: $B = 12.27$, $P < 0.001$) e duração da prova de esforço (AT vs. CG: $B = 68.64$, $P < 0.001$). AT e RT não demonstraram efeitos significativos ao nível da composição corporal e força muscular.

Conclusões: O AT teve um impacto positivo na aptidão cardiorrespiratória, em comparação com os restantes grupos, destacando a sua importância na prevenção do declínio da aptidão física durante a quimioterapia neoadjuvante. Nenhum dos grupos, AT ou RT, teve efeito significativo na composição corporal e na força muscular.

Palavras-chave: aptidão cardiorrespiratória, força muscular, composição corporal, exercício, quimioterapia neoadjuvante

Chapter 1 – Theoretical Framework

Thesis Overview

In today's world, cancer ranks as the leading cause of disease-related deaths globally (Bray et al., 2018). In 2022, the estimated incidence was 20 million new cancer cases, with projections for 2040 predicting 29.5 million people diagnosed with the disease (Bray et al., 2024). Among the various types of cancer, breast cancer is the most diagnosed worldwide, followed by lung and prostate cancer (Ferlay et al., 2021). These numbers are alarming, and as the projections show, the trend is increasing.

Research in the oncology field has become a priority in the scientific community, not only due to the rising numbers of the disease, but also because of the impact that a diagnosis has on individuals' quality of life. The increase in these numbers appears to be associated with multiple risk factors, both non-modifiable and modifiable and changes in world demographics, such as increased life expectancy and an ever-growing worldwide population (Shah et al., 2014). As for the risk factors, these include age, personal and family history of cancer, genetic predisposition, hormonal changes, and lifestyle factors such as obesity, sedentary behavior, and radiation exposure (Shah et al., 2014). In addition to these factors, the type of treatment, particularly chemotherapy, seems to have a direct impact on the quality of life of cancer patients. Chemotherapy involves the use of anticancer drugs and despite their benefits in combating the disease, such treatments have been shown to have physical and psychological effects that can impact patients' quality of life (Di Nardo et al., 2022; Shien & Iwata, 2020). These effects include fatigue, sleep disturbances, peripheral neuropathy, cognitive changes, ovarian function alteration, and cardiotoxicity (Chen et al., 2019; Dinas, 2020; Jordan et al., 2020; Mock et al., 2000; Sanford et al., 2013; Zamorano et al., 2016).

The current body of literature suggests that exercise can ameliorate many of these detrimental symptoms. Therefore, in the context of cancer treatment, it becomes increasingly crucial to involve patients in a more active lifestyle (Idorn & Hojman, 2016; Irwin et al., 2003). Beyond the biological aspects of cancer related to the well-known hallmarks, factors such as cardiorespiratory fitness, muscle strength, and body composition appear to be evident markers of the changes caused by the disease and its treatment. Increased cardiorespiratory function seems to be associated with a reduced risk of mortality from breast cancer, and it can also impact other factors, such as the prevention of cardiorespiratory diseases and cardiotoxicity, as well as chronic inflammation, immunity, and insulin sensitivity (Bjørke et al., 2020; Ezzatvar et al., 2021; Maginador et al., 2020;

Ross et al., 2016; Schmid & Leitzmann, 2015). On the other hand, optimal levels of muscle strength can have implications related to the reduction of treatment-induced toxicity, fatigue reduction, improved joint mobility, and potentially influencing the prognosis of the disease (Buffart et al., 2020; Courneya et al., 2007; Klassen et al., 2017; Lee et al., 2021). Finally, body composition is a critical outcome in this field, as it is highly influenced by treatment and the hormonal changes often associated with it. Loss of muscle mass, sarcopenia, increased fat mass, and the subsequent development of diseases such as diabetes and cardiovascular diseases are some of the consequences of body composition changes caused by treatment (Bradshaw, 2024; Li et al., 2024; Nissen et al., 2011). In addition to the effects of exercise on patients with cancer, the type of exercise most appropriate has also been a subject of study by experts.

This thesis aims to address some of these shortcomings and is composed of two chapters. The first segment comprises a theoretical review structured in two main blocks: the first provides an overview of the disease from an epidemiological and pathophysiological perspective, concluding with a more specific appreciation of breast cancer; and the second addresses issues related to exercise, physical fitness, and breast cancer, presenting a summary of studies developed in this area. The second section consists of an original manuscript, consisting of a randomized control trial that describes the effects of exercise on physical fitness in patients with breast cancer undergoing neoadjuvant chemotherapy treatment.

Literature Review

1. Cancer

1.1 Epidemiology

Cancer is a noncommunicable disease that ranks as the second leading cause of death worldwide and it is projected to become the primary cause of mortality during this century (Bray et al., 2018). In 2022, noncommunicable diseases were responsible for 74% of worldwide deaths, of which 20% were due to cancer (Bray et al., 2024). Statistical data released by the International Agency for Research on Cancer indicated that approximately 20 million new cancer cases were reported globally, resulting in around 9.7 million deaths attributable to the disease (Bray et al., 2024). In 2040, it is estimated that around 29.5 million people annually will be diagnosed with cancer (Ferlay et al., 2019). Breast cancer (BC) accounts for approximately 50% of cancer-related mortality and is the most diagnosed worldwide, followed by lung and prostate cancers (Ferlay et al., 2021). Besides BC, lung, liver, and stomach cancers are those presenting higher mortality (Ferlay et al., 2021). In Portugal, cancer ranks in second place as the most common cause of death (Lopes et al., 2017), with 7,000 new cases diagnosed annually, equating to 19 new diagnoses per day (Liga Portuguesa Contra o Cancro, 2022). Despite this, the country maintains one of the highest cancer survival rates globally, with a five-year survival rate of 85% following diagnosis, placing it among the top six countries with the best survival outcomes (Fernandes, 2020).

In the next four decades, it is expected that cancer deaths will overcome other known top mortality causes such as cardiovascular diseases (Mattiuzzi & Lippi, 2019). This increase is associated with their incidence, prevalence, and mortality, which derive from an aging population and from an increase in life expectancy. Such changes in cancer prevalence and incidence are usually quantified using disability-adjusted life years, a metric that accounts for both the years lost to premature death and the years lived with disability. In 2015 this number was 527,651 (Lopes et al., 2017). Due to these numbers and to the noticeable impact on lost productivity and the rising cost of treatment, cancer has become a priority at the economic level (Hofmarcher et al., 2020). An investigation aiming to estimate the cost of cancer treatment in Portugal revealed that 565 million euros were spent on anti-cancer therapies, representing 3.91% of the total health expenditure. With the increasing trend of having a higher cancer incidence, as well as higher associated costs, there is a substantial risk of overburdening the national healthcare system, potentially impacting the quality and efficiency of healthcare services (Lopes et al., 2017).

1.2 Cancer Pathophysiology

The etiology of cancer has been a hot topic of investigation over the years. Despite significant scientific advancements, the disease continues to progress due to increased lifespans and shifting patterns of cancer risk factors (Wu et al., 2018), which can broadly be categorized into intrinsic and non-intrinsic risk factors, each with distinct biological implications (Wu et al., 2018). Intrinsic risk factors stem from unmodifiable processes, such as random errors in deoxyribonucleic acid (DNA) replication, while non-intrinsic refers to factors that are partially or totally modifiable. As partially modifiable non intrinsic factors we can consider biologic aging, genetic susceptibility, hormones, growth factors, inflammation, while as fully modifiable ones, we include radiation, chemical carcinogens, virus-related tumors, diet, insufficient physical activity, obesity, alcohol and tobacco smoking (Whiteman & Wilson, 2016; Wu et al., 2018).

The individual cells that constitute our body are endowed with versatility and autonomy, enabling them to grow and divide long after organismic development is complete. This capability allows for the survivability of adult tissues throughout the lifespan. However, some of these cells undergo genomic transformations allowing them to assume roles that are inappropriate for normal tissue maintenance and function (Weinberg, 2014). These genomic mutations result in phenotypic changes that impact cellular proliferation, leading to the appearance of a large group of cells with no similarity when compared with normal tissue, which are named cancer cells (Weinberg, 2014). Most of the cancer cells arise from epithelial tissues and are designated as carcinomas, which are responsible for more than 80% of cancer-related deaths. Carcinomas can be divided into two categories based on the function of epithelial cells: squamous cell carcinomas, which originate from epithelial cells responsible for sealing the cavities or channels that they line and protecting the underlying cell populations (Weinberg, 2014). Further, adenocarcinomas derive from epithelial cells involved in the release of substances into the ducts or cavities (Weinberg, 2014). As for the remaining types of cancer, they originate from non-epithelial tissues; a subset of these cells derives from connective tissues and would be classified as sarcomas; others arise from hematopoietic cells, which are responsible for blood formation; the final subset originates from nervous system cells and are typically referred to as neuroectodermal tumors (Weinberg, 2014).

The complexities of neoplastic disease have been elucidated by an organizing principle called the hallmarks of cancer. These hallmarks are acquired capabilities exhibited by cancer cells, often at the molecular, biochemical, and cellular levels during the multistep

development of human tumors (Hanahan & Weinberg, 2000). Currently, fourteen hallmarks may be described:

- 1) Sustaining Proliferative Signaling - Cancer cells can regulate their own growth through autocrine proliferative stimulation, thereby reducing their dependence on proliferative signals from the environment (Hanahan & Weinberg, 2011).
- 2) Evading Growth Suppressors – Cancer cells have the ability to inhibit tumor suppressor genes and modulate the signals that negatively regulate their proliferation (Hanahan & Weinberg, 2011).
- 3) Nonmutational Epigenetic Reprogramming – Occurrence of epigenetic changes in gene expression acts as a form of genome reprogramming (Hanahan, 2022).
- 4) Avoiding Immune Destruction – Cancer cells can evade eradication by developing mechanisms to avoid detection by immune systems (Hanahan & Weinberg, 2011).
- 5) Enabling Replicative Immortality – Cancer cells are capable of undergoing an unlimited number of successive cell growth and division cycles without dying (Hanahan & Weinberg, 2011).
- 6) Tumor-promoting Inflammation – Cancer cells exhibit the capacity to manipulate inflammatory mechanisms, thereby promoting their survival and growth (Hanahan & Weinberg, 2011).
- 7) Polymorphic Microbiomes – Polymorphic variability in microbiomes impacts phenotypes, providing to some microorganisms, such as bacteria, the ability to exert either protective or detrimental effects on cancer development, progression, and response to treatment (Hanahan, 2022).
- 8) Activating Invasion and Metastasis – Tumor cells employ specific mechanisms that enable them to spread into different environments and tissues, invade adjacent tissues and eventually form small nodules of cancer cells, which subsequently develop into macroscopic tumors (Hanahan & Weinberg, 2011).
- 9) Inducing or Accessing Vasculature – Cancer cells have the ability to induce the formation of a tumor-associated neo vasculature through angiogenesis to ensure their sustainability. This process is essential for providing nutrients and oxygen to the tumor, as well as facilitating the removal of metabolic wastes and carbon dioxide (Hanahan & Weinberg, 2011).
- 10) Senescent Cells – Cellular senescence promotes tumor growth by promoting proliferative signaling, avoiding apoptosis, suppressing the immune response, facilitating invasion and metastasis, and inducing angiogenesis (Hanahan, 2022).

- 11) Genome Instability and Mutation – Cancer cells exhibit heightened susceptibility to mutagenic agents, contributing to genetic damage, disrupting cell division regulation and tumor suppression pathways (Hanahan & Weinberg, 2011).
- 12) Resisting Cell Death – Tumor cells assume a variety of strategies to limit apoptosis (Hanahan & Weinberg, 2011).
- 13) Deregulating Cellular Metabolism – Cancer cells are capable of reprogramming their glucose metabolism to promote cell growth and division by assuming a persistent state of “aerobic glycolysis” (Hanahan & Weinberg, 2011).
- 14) Unlocking Phenotypic Plasticity – Tumor cells unlock phenotypic plasticity enabling them to evade or escape from the terminal differentiation state. This plasticity allows them to reverse their cellular state and engage in various forms of disrupted differentiation (Hanahan, 2022).

1.3 Breast Cancer Risk Factors and Classification

Breast cancer is the most prevalent cancer among women worldwide. Among the risk factors generally underlying oncological diseases, this specific type of cancer is influenced by a multifaceted interplay of determinants across multiple domains, including hormonal, environmental, personal, and genetic aspects:

- **Age:** the risk of BC increases with advancing age, with the majority of cases occurring in women aged 50 or older (Shah et al., 2014);
- **Personal history of BC:** an initial diagnosis of ductal carcinoma in situ, stage IIIB, hormone receptor negative cancers, and younger age contribute to the overall risk profile (Shah et al., 2014);
- **Family history:** highest risk associated with increasing number of first-degree relatives diagnosed with BC at a young age (under age 50) (Shah et al., 2014);
- **Genetic predisposition:** 50% of BC predisposition syndromes are associated with mutations in BRCA1 and BCRA2 (Shah et al., 2014).

Investigations also demonstrate that the exposure to endogenous hormones have an impact on the development risk for this disease - early age at menarche, nulliparous women, advanced age at first birth, non-breast feeding, high endogenous sex hormone levels and later onset of menopause are some of the factors that increase this risk (Shah et al., 2014). Evidence suggests a relationship between the use of hormone replacement therapy (HRT) and BC risk – combined estrogen plus progestin in postmenopausal women seems to be linked with higher hormone receptor positive BC - with timing and duration of HRT being considered important moderators of risk calculation. At last, lifestyle factors, as modifiable

risk factors including the excessive use of alcohol, obesity, physical inactivity, and radiation account for 21% of all BC deaths worldwide (Shah et al., 2014).

Upon diagnosis of BC, the disease is classified into a stage based on its progression, i.e., size, lymph nodes, and metastasis. BC staging is firstly categorized as in situ (stage 0) or invasive (stage I to IV). Within the invasive category, further sub-categories are described: localized and regional cancer (stage I to IIIC), which are distinguished by the tumor size and the extent of lymph node involvement, or metastatic (stage IV) (Sharma et al., 2010). Beyond the stage of the cancer, also the biological subtype is an important information to make the best clinical decisions. Through molecular analysis BC can be classified into different subtypes based on the presence or absence of specific receptors and the level of cell proliferation, as follows:

- **Luminal A:** This subtype is positive for estrogen receptor and progesterone receptor, negative for HER2 receptor, and is characterized by a low proliferative index, showing slower tumor growth (Bhushan et al., 2021);
- **Luminal B:** Similar to Luminal A, this one is positive for estrogen and progesterone receptors, negative for HER2 receptor. However, it has a higher proliferative index compared to Luminal A, suggesting more rapid tumor growth (Bhushan et al., 2021);
- **HER2:** This subtype is negative for both estrogen and progesterone receptors, but positive for the HER2 receptor, a protein associated with aggressive tumor behavior. It also exhibits a high proliferative index, indicating faster cell division (Bhushan et al., 2021);
- **Basal-like:** Often referred to as triple-negative breast cancer, this subtype is negative for estrogen and progesterone receptors, and HER2 receptors. It is associated with a high proliferative index (Bhushan et al., 2021);
- **Normal-like:** This subtype is positive for estrogen receptors but negative for progesterone receptors and HER2 receptors. Despite its receptor profile, it is associated with a high proliferative index (Bhushan et al., 2021).

These classifications are essential for tailoring treatment strategies, as receptor status and proliferative index significantly influence prognosis and therapeutic approaches (Bhushan et al., 2021). Refer to Figure 2 for a detailed visual representation of these subtypes:

	Luminal A	Luminal B	HER2	Basal-like	Normal-like
Estrogen Receptor	⊕	⊕	⊖	○	⊕
Progesterone Receptor	⊕	⊖	⊖	○	⊕
HER2 Receptor	⊖	⊖	⊕	⊕	⊖
Proliferative Index	↓	↑	↑	↑	↑
Abbreviations: ⊕ positive, ⊖ negative, ○ absent, ↓ low, ↑ high					

Figure 1 | Subtypes of BC (adapted from (Bhushan et al., 2021))

1.4 Cancer Treatments

Breast cancer is a complex disease, and its optimal management involves collaboration among specialists from various disciplines. Multidisciplinary treatments for patients with BC combine both local and systemic anticancer therapies. Local treatments include surgery and radiation therapy, while systemic treatments encompass a wide range of drugs such as chemotherapy, hormone therapy, targeted therapy, and immunotherapy (Cardoso et al., 2019). The treatment choice should be based on the tumor characteristics – such as location, size, primary tumor site, number of lesions, and the extent of lymph node involvement – as well as biological factors, including pathology, tumor biomarkers, and gene expression profiles. Additionally, patient-specific factors, including age, menopausal status, general health status, and preference must also be considered (Cardoso et al., 2019).

Chemotherapy involves the use of anti-cancer drugs to target cancer cells and it can be administrated as adjuvant therapy, following surgery, or as neoadjuvant therapy, prior to surgery (Shien & Iwata, 2020). Chemotherapeutic agents are classified based on their mechanism of action in the cell cycle:

- **Alkylating agents** like Nitrogen Mustards, Triazenes and Platinum Salts take action directly on DNA by adding an alkyl group to it, resulting in its crosslinking and causing DNA strand breaks, leading to abnormal base pairing and inhibiting cell division, leading to cell death. They are effective during all phases of cell cycle and are used to treat a wide variety of cancers, being more effective in treating slow-growing cancers, such as leukemia (Ralhan & Kaur, 2007);
- **Antimetabolites** like Pyrimidine Analogs, Purine Analogs and Folates Antagonists, are metabolic substances which disturb the biosynthesis or the function of nucleic acids by acting as false substrates during RNA and DNA synthesis. Cells are tricked into taking

in the drugs and then using the antimetabolites instead of their normal building blocks of genetic material, and hence they are unable to copy their DNA and divide into new cells. They take action in the S-phase and are used to treat tumors that are growing quickly such as BC, gastrointestinal adenocarcinomas and squamous cell carcinoma (Mihlon et al., 2010);

- **Topoisomerase Inhibitors I and II** will block the action of topoisomerase I and II enzymes that are responsible for the cleavage and physical stability of DNA strands. This results in DNA strand breaks and blocks on DNA replications and thus, apoptosis. These agents take action during the S phase of cell cycle and are used to treat lymphomas, sarcomas, colorectal, lung, breast and germ cell tumors (Grant & Gourley, 2015);
- **Anti-Mitotic** like Taxanes, Vinka Alkaloids and Eribuli, interfere with microtubules, which are essential components of the cells cytoskeleton and play a critical role in the division of one cell into two identical cells (mitosis). Microtubules are dynamic structures composed of tubulin proteins, and their proper function is necessary for the separation of chromosomes during cell division. They usually take action in the late G2 phase and the M-phase (Chu & Rubin, 2018). Chemotherapy treatments are usually administered in cycles over several months, with each cycle consisting of treatment followed by a respective rest period (Sharma et al., 2010). Chemotherapy is mostly recommended for triple-negative, human epidermal growth factor receptor 2 (HER2) positive BC and in high-risk luminal-like HER2-negative tumors and it shows greater efficacy in ER-negative tumors (Cardoso et al., 2019).

Despite the relevant role that (neo)adjuvant therapies have played in improving survival rates, evidence has demonstrated that the use of different types of drugs can promote different long-term physical, psychological and psychosocial changes, which can have a direct impact on a patients' quality of life (Di Nardo et al., 2022). The most common side effect of chemotherapy is **fatigue**, which can be defined as a subjective sense of physical, emotional and/or cognitive tiredness, and is not proportional to recent activity developed (Mock et al., 2000). Alongside fatigue, **sleep disruption** is another prevalent symptom during and after chemotherapy, which can be explained by feelings of anxiety and physical symptoms, such as pain and vasomotor syndrome (Sanford et al., 2013). Another common side effect is **peripheral neuropathy**, which consists of abnormal sensory experiences like pain, paresthesia or muscle weakness. In severe cases, it can also result in motor and autonomic disfunction (Jordan et al., 2020). **Cognitive impairment**, commonly known as "chemofog", refers to a group of disorders that are frequent in patients treated with

chemotherapy and primarily affect short-term memory, attention, learning, verbal ability, executive functions and motor activities (Chen et al., 2019). Chemotherapy regimens can also impact the **normal ovarian function**, inducing early menopause, and affecting fertility and bone health (early iatrogenic menopause can cause disrupting balance between bone formation and reabsorption) (Dinas, 2020). **Cardiotoxicity** is another significant symptom, encompassing a wide range of clinical conditions such as cardiac dysfunction, ischemia, vascular disorders, endothelial damage and arrhythmias (Zamorano et al., 2016).

2. Exercise, Physical Fitness and Breast Cancer

In the context of cancer, the advantage of involving patients in an active lifestyle, even while facing their illness, is becoming more apparent (Idorn & Hojman, 2016). Women diagnosed with BC typically experience an 11% reduction in physical activity levels, with an even more significant decline of 50% observed in patients undergoing chemotherapy, compared to those who are not receiving treatment. (Irwin et al., 2003). To better understand this, it is crucial to establish the distinction between physical activity, physical exercise and physical fitness – the first encompasses all bodily movements that engage skeletal muscles and require energy expenditure (Dasso, 2019); the second refers to planned, structured, repetitive, and intentional movement aimed at improving or maintaining specific aspects of physical fitness (Dasso, 2019); and the last refers to the state of health and well-being of an individual, as well as their ability to perform physical activities (Caspersen et al., 1985). Physical Fitness can be divided into two main categories, health-related fitness and performance-related fitness, with outcomes such as cardiorespiratory fitness, muscle strength and body composition being included in the first one (Caspersen et al., 1985). Studies have demonstrated that physical exercise is crucial for improving physiological functions, such as cardiorespiratory fitness, muscle strength, and mental health, while also reducing the adverse effects of cancer treatments, including the overall decline in physical performance and the deterioration of psychological well-being (Schmitz et al., 2010). Next chapter will be dedicated to highlighting the evidence of the benefits of exercise on the hallmarks of cancer and more specifically, on BC.

2.1 Biological Effects

Research has been shown that physical exercise can have several positive effects on cancer patients, with some of them related to the previously mentioned hallmarks (García-Chico et al., 2023):

- 1) Sustaining Proliferative Signaling - Exercise can reduce tumor weight and cell proliferation (de Lima et al., 2011) as well as influence factors associated with that, such

as tumor size reduction (Goh et al., 2013), fewer developed tumors (Malicka et al., 2015), and altered expression of Ki-67 nuclear protein and other proliferation markers (Siewierska et al., 2018). Exercise appears to act as a protective factor against tumor proliferation and development by reducing the expression of estrogen and progesterone receptors (Siewierska et al., 2020).

- 2) **Activating Invasion and Metastasis** - Exercise can influence the onset of metastatic progression and subsequent cancer spread by altering angiogenesis, eliminating circulating tumor cells, and decreasing endothelial permeability (de ten Rye & Deldicque, 2020). Studies also indicate that exercise, when combined with neoadjuvant chemotherapy, results in decreased tumor invasiveness (Jones et al., 2013). Additionally, exercise induces the release of myokines associated with tumor invasion and metastasis (Hojman et al., 2018).
- 3) **Enabling Replicative Immortality** - Exercise plays a pivotal role by influencing cancer development and its dependence on genetic alterations in chromosomes, DNA methylation, miRNA expression and chromatin structures (Grazioli et al., 2017). Additionally, exercise can mitigate telomere attrition and help in maintaining a balance with oxidative stress and inflammatory status, which inversely impacts telomere length (Arsenis et al., 2017).
- 4) **Inducing or Accessing Vasculature** - Exercise can enhance the maturity of tumor vessels and increase microvessel density (Betof et al., 2015). This results in the creation of an unfavorable environment for cancer progression and improves drug delivery, thereby improving the response to anticancer treatment (Magnussen & Mills, 2021). Different types of exercise appear to modulate the expression of vascular endothelial growth factor-A (VEGF-A), which is the main hypoxia-inducible angiogenic stimulator (Faustino-Rocha et al., 2016).
- 5) **Resisting Cell Death** - Exercise improves apoptosis and reduces BC resistance to programmed cell death by downregulating anti-apoptotic proteins and upregulating the expression of pro-apoptotic factors (Kim et al., 2020).
- 6) **Deregulating Cellular Metabolism** - Exercise can contribute to changes in glucose synthesis and utilization (Hojman et al., 2018). Investigations conducted in animals have demonstrated that after exercise, there is a reduction in tumor mass (Aveseh et al., 2015) and a shift in macronutrient oxidation, primarily favoring carbohydrate oxidation (Vulczak et al., 2020).
- 7) **Avoiding Immune Destruction** - Exercise may potentially amplify the abundance and activity of immune system cells (Jurdana, 2021).

- 8) Tumor-promoting Inflammation - Exercise appears to decrease the levels of pro-inflammatory markers such as IL-6, while simultaneously enhancing the expression of anti-inflammatory factors like IL-10 and adiponectin (Hooshmand Moghadam et al., 2021).

2.2 Breast Cancer and Cardiorespiratory Fitness

Cardiorespiratory Fitness refers to the capacity of the human body to capture, fix, transport, and use oxygen from the atmosphere to cells and the physiological processes utilized during physical activity (Ross et al., 2016). Evaluating this physical fitness component involves assessing an individual's functional capacity and analyzing associated intrinsic processes such as pulmonary ventilation and diffusion, right and left ventricular function (both systole and diastole), ventricular-arterial coupling, the efficiency of blood vessels in receiving and transporting blood from the heart to meet oxygen requirements, and the ability of muscle cells to utilize the oxygen and nutrients delivered by the blood. The communication of these metabolic needs to the cardiovascular control center is also considered (Ross et al., 2016).

Upon being diagnosed with BC, individuals often adopt a sedentary lifestyle, most of the time related to treatment outcomes such as chemotherapy and radiotherapy. In such cases, these treatments can induce physical alterations and yield side effects, such as fatigue, cardiotoxicity, insomnia, nausea, neuropathy, and strength impairment (Ficarra et al., 2022). Evidence shows that a 31% impairment in cardiorespiratory fitness is caused by treatment side effects (Ficarra et al., 2022; Maginador et al., 2020). Additionally, lower levels of physical activity are further emphasized by rest prescriptions, which are common because medical protocols do not always prioritize exercise for cancer patients (Ficarra et al., 2022; Maginador et al., 2020).

Based on research, several strong indicators highlight the importance of developing cardiorespiratory fitness. Firstly, higher levels of cardiorespiratory fitness are associated with a reduced risk of mortality from BC (Ezzatvar et al., 2021; Schmid & Leitzmann, 2015). The beneficial impact of cardiorespiratory fitness may influence insulin sensitivity, chronic inflammation, steroid hormone levels, growth factor production, innate immunity, antioxidant capacity, DNA repair, and cell proliferation and apoptosis (Schmid & Leitzmann, 2015). Another crucial factor is that low cardiorespiratory fitness levels are linked to a higher risk of cardiovascular disease (Ross et al., 2016). Data also indicate that a poor maximal oxygen consumption (VO_{2max}) is associated with a lower quality of life and treatment-induced cardiotoxicity (Maginador et al., 2020). Conversely, normal VO_{2max} levels are related to

higher physical activity levels, better daily functioning, and fewer toxic effects from various treatments on the cardiovascular, respiratory, and skeletal muscle systems (Bjørke et al., 2019). Furthermore, evidence suggests that optimizing cardiorespiratory fitness before surgery can improve outcomes, including reduced surgical risk, mortality and improved function during the postsurgical period (Ezzatvar et al., 2021). With that said, exercise appears to be an effective strategy to help patients with BC manage symptoms, improve their physical fitness, and especially their cardiorespiratory fitness, with important effects on the patients' quality of life during and after treatment (Bjørke et al., 2019; Grazioli et al., 2017).

As far as the type of exercise is concerned, evidence suggests that combined exercise may have beneficial effects on VO_{2max} and oxygen consumption peak power output at ventilatory threshold (Travier et al., 2015). Furthermore, both continuous and interval aerobic training have been shown to be effective in increasing VO_{2max} (Buchheit & Laursen, 2013). Additionally, low intensity aerobic exercise showed nonsignificant effects (Segal et al., 2001), while moderate to vigorous aerobic exercise were effective in improving the VO_{2max} (Al-Majid et al., 2015; Ma Z., 2018; Maginador et al., 2020; Mowafy Z.M.E. et al., 2016; Van Waart et al., 2015).

2.3 Breast Cancer and Muscle Strength

Muscle Strength is defined as the capacity of a muscle to produce force to overcome an applied load (Montaño-Rojas et al., 2020). It is closely related to an individual's performance in daily activities, as more challenging tasks require greater effort relative to their muscle capacity (D. X. M. Wang et al., 2020).

In the context of BC diagnosis, due to treatment side effects, individuals often adopt a more physically inactive lifestyle (Schneider et al., 2007). This behavior leads to a reduced daily energy expenditure during therapy, which is associated with muscle mass loss (Klassen et al., 2017). BC treatments have acute and chronic effects on physiological systems, including the muscular system (Silva et al., 2022). For instance, chemotherapy induces both structural and biochemical changes in muscle tissue, causing oxidative stress (Klassen et al., 2017) and mitochondrial dysfunction (Buffart et al., 2020). These changes result in: a decreased cross-sectional area of muscle fibers as a result of a loss of myofibrils and myofilament; a shift of muscle fibers with a transition to a more glycolytic phenotype (Klassen et al., 2017); loss of muscle extensibility; and a decline in proteins necessary for metabolism, resulting in a diminished oxidative capacity of the muscle (Schneider et al.,

2007). Altogether, these deleterious alterations promote muscle weakness and mobility impairments, heighten the risk of sarcopenia, and compromise the quality of life (Schneider et al., 2007) with implications for multiple clinical outcomes, such as treatment toxicities or time-to-tumor progression (Klassen et al., 2017), as well as in BC patients' daily living (Silva et al., 2022).

Therefore, enhancing or at least preserving muscle strength in BC population should be a primary therapeutic goal (Silva et al., 2022). Exercise-induced adaptations and improved muscular performance can mitigate cancer-related toxicities, potentially enhancing prognosis, quality of life, and long-term survival (Courneya et al., 2007, 2014; Klassen et al., 2017). The current body of literature for other types of cancer suggests that combined strength and cardiorespiratory exercise can preserve or even improve the contractile properties of type II muscle fibers, which is paramount to preventing fatigue during chemotherapy (Buffart et al., 2020). Further, strength training has been shown to benefit the musculoskeletal system, improve joint mobility, and reduce fatigue, highlighting the importance of including muscle strength exercises in training programs for this population (Lee et al., 2021; McGovern et al., 2022; Montaña-Rojas et al., 2020). Additionally, moderate-intensity exercise can improve muscular performance, and enhance both physical and psychological well-being in cancer survivors (Schneider et al., 2007).

2.4 Breast Cancer and Body Composition

Body Composition refers to the chemical and physical elements that collectively constitute the mass of an organism, organized systematically (Stewart, 2010). A five-component model of body composition is proposed – body mass is considered as five distinct and separate yet integrated levels of increasing complexity (Z. M. Wang et al., 1992). The five levels, which are atomic (I), molecular (II), cellular (III), tissue-system (IV), and whole body (V), are unique, non-overlapping, and the combined total of all the components at each level of analysis equals the body mass (Z. M. Wang et al., 1992). Providing a brief description of these five levels, the atomic level considers that atoms or elements serve as the basic blocks of the human body assuming 11 major elements, with six of those (oxygen, carbon, hydrogen, nitrogen, calcium, and phosphorus) making up more than 98% of body mass (Snyder et al., 1984); the molecular level includes five major components: water, protein, carbohydrates, minerals and lipids (Z. M. Wang et al., 1992); the cellular level model consists of three components which are cell mass, extracellular fluid and extracellular solids (Heymsfield et al., 1997); at last, the tissue-system level components are adipose-tissue, skeletal muscle, bone, visceral organs, and brain (Heymsfield et al., 1997).

Throughout the treatment, BC patients experience body composition changes that might be, in part, explained by factors such as sedentary behavior, emotional stress, depression, anxiety, and premature menopause linked to treatment (Joaquim et al., 2022). Beyond these factors, the treatment itself seems to be the main reason for body composition modifications (Joaquim et al., 2022). Sarcopenia, described as the progressive degeneration of muscle mass and strength, along with decreased physical activity, has emerged as a crucial factor influencing survival and treatment-related complications in BC patients (Roberto et al., 2024). In cancer patients, malnutrition and chronic inflammation can impair muscle tissue, promoting muscle loss and acting as a trigger for sarcopenia (Roberto et al., 2024). Chemotherapy-induced weight gain is yet another significant alteration that can impact both health and quality of life for patients by increasing their body fat. Importantly, it may lead to later recurrence of BC and even death (Li et al., 2024), as it also contributes to other high-burden comorbidities such as diabetes and cardiovascular disease (Bradshaw, 2024). Studies indicate that chemotherapy-induced weight gain follows a pattern of sarcopenic obesity, involving weight gain with concurrent lean mass loss (Nissen et al., 2011). Ovarian failure during chemotherapy treatment can also be related to weight gain, since it may impact hormonal levels and promote changes in taste and smell that can affect dietary eating patterns (Berg et al., 2017). Another important factor is the influence that body composition has on the completion of the treatment. Toxicities due to chemotherapy can be challenging since they can cause systemic symptoms, which can result in treatments being delayed or even ceased early, and thus reduce the therapeutic effects (Lewis et al., 2024; Pin et al., 2018). Evidence shows that the ability of individuals to metabolize and eliminate drugs from the body can vary, and is often linked to body composition, with lean body mass better predicting drug distribution and clearance (Fraser et al., 2022; Ryan et al., 2019). In this case, sarcopenia along with low muscle density was significantly associated with a higher risk of chemotherapy toxicities (Aleixo et al., 2019).

Regular physical exercise plays a crucial role in controlling body weight and preventing negative changes in body composition. Exercise is associated with weight reduction and a lower body mass index (Soares Falcetta et al., 2018). Evidence suggests that it benefits waist circumference reduction (Singh et al., 2018) and overall reduction in body fat (Boing et al., 2020). Additionally, exercise can attenuate the loss of lean mass (Ikeda et al., 2022; Li et al., 2024; Parker et al., 2021; Zylstra et al., 2022).

Thesis purpose

Despite the increase in the current body of literature on the effects of exercise on cardiorespiratory fitness, muscular strength, and body composition in breast cancer patients, the findings remain limited and inconclusive regarding a definitive cause-effect relationship. Additionally, the current evidence does not clearly examine the potential influence of exercise type, intensity, and volume in such programs, which continues to be a topic of debate among experts. Furthermore, there is a notable scarcity of studies conducted during the neoadjuvant period, as most research focuses on survivors or those who have undergone adjuvant treatment. Therefore, the aim of this dissertation is to provide preliminary data on the effectiveness of different types of exercise on physical fitness in breast cancer patients undergoing neoadjuvant treatment. We hypothesize that higher levels of exercise during neoadjuvant treatment will lead to improved cardiorespiratory capacity, muscle strength, and body composition.

Chapter 2 – Theoretical Framework

Effectiveness of Exercise on Physical Fitness Attributes
in Patients with Breast Cancer undergoing Neoadjuvant Chemotherapy:
preliminary results from the NEO study

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Abstract

Purpose: To evaluate the impact of aerobic training (AT) and resistance training (RT) on physical fitness in women newly diagnosed with breast cancer undergoing neoadjuvant chemotherapy.

Methods: A subsample of the NEO study included 33 participants with breast cancer randomly assigned to a control group (CG), AT or RT. The intervention groups engaged in three weekly supervised exercise sessions. Physical fitness outcomes were assessed at baseline and the week before surgery. Data were analyzed using generalized estimating equations.

Results: Of the 33 participants (50.0 ± 8.0 years old), 2 dropped out. A between group effect was found in the AT group on relative VO_{2peak} when compared to other groups (AT vs. CG: $B = 1.24$, $P = 0.005$; AT vs. RT: $B = 1.30$, $P = 0.046$). The same trend was observed for absolute VT_1 (AT vs. CG: $B = 1.69$, $P < 0.001$), absolute VT_2 (AT vs. CG: $B = 1.89$, $P < 0.001$), relative VT_2 (AT vs. CG: $B = 4.36$, $P < 0.001$), peak power (AT vs. CG: $B = 12.27$, $P < 0.001$) and maximal test duration (AT vs. CG: $B = 68.64$, $P < 0.001$). AT and RT showed no significant effects on body composition and muscle strength.

Conclusions: AT had a favorable impact on cardiorespiratory fitness compared to the remaining groups, highlighting its importance in preventing fitness declines during neoadjuvant chemotherapy. Neither AT or RT significantly influenced body composition and muscle strength.

Keywords: cardiorespiratory fitness, muscle strength, body composition, exercise, neoadjuvant chemotherapy

Introduction

According to GLOBOCAN statistics, in 2022 the incidence for breast cancer (BC) was set on 20 million new cases per year, leading to a total of 9.7 thousand deaths worldwide (Bray et al., 2024). BC ranks as the most frequently diagnosed cancer and is a leading cause of morbidity and mortality among women (Sung et al., 2021). Consequently, it is important to have pharmacological and non-pharmacological strategies to prevent, treat and control this disease.

Exercise has increasingly been recognized as a valuable tool for improving physical fitness, with its role in cancer management gaining attention in recent years. High physical fitness levels offer extensive health benefits, including improved quality of life, reduced mortality rates, and better cardiometabolic and inflammatory responses (HHS, 2018). Research suggests that physical activity positively influences key physiological functions, such as cardiorespiratory capacity, muscular strength, and mental health (Schmitz et al., 2010). In fact, women often experience a notable decline in physical activity, with an average reduction of 11%, and chemotherapy patients show even greater decreases of up to 50% compared to those untreated (Irwin et al., 2003). For individuals with breast cancer, maintaining higher physical fitness levels is associated with more favorable treatment outcomes, including better therapy tolerance, enhanced quality of life, and lower cancer-related fatigue, as demonstrated in multiple studies (Malveiro et al., 2023; Schmidt T et al., 2015; Scott et al., 2018). Exercise is especially valuable during the neoadjuvant phase since it may support patients in handling the physical demands of their therapy regimens (Ehlers et al., 2020).

Research has examined the effects of various exercise types, notably resistance and aerobic training, on physical fitness outcomes for breast cancer patients undergoing neoadjuvant and adjuvant therapy (Courneya et al., 2007, 2013; Mijwel et al., 2019; Schmidt T et al., 2015; Travier et al., 2015).

Although sparse, exercise interventions show encouraging results, though findings vary. While aerobic exercise reliably enhances cardiorespiratory fitness, its effects on muscle strength and body composition are often less pronounced compared to resistance training (Mijwel et al., 2019). Additionally, combining aerobic and resistance training may yield more holistic benefits to physical fitness, though further studies are necessary to confirm these effects (Segal et al., 2017).

In view of the encouraging yet varied preliminary findings, additional research is essential to identify the most effective exercise protocols for optimizing physical fitness during this

phase of treatment and for this type of population. Therefore, this study aims to assess the impact of aerobic and resistance training on cardiorespiratory fitness, muscle strength, and body composition in breast cancer patients, particularly early in the treatment timeline, soon after diagnosis, thereby allowing for earlier therapeutic intervention. It also underscores the importance of community-based exercise initiatives within healthcare settings, which may help mitigate treatment-related adverse effects and improve the overall quality of life for this population.

Material and Methods

1. Sample Recruitment

The current study is part of the Neoadjuvant Exercise Oncology Program (NEO Program) (ClinicalTrials.gov Identifier: NCT05297773), which is embedded within an ongoing clinical trial. Recruitment was conducted at Champalimaud Clinical Center Breast Unit/Champalimaud Foundation. The inclusion criteria of this study were as follows: histologically confirmed hormone-responsive/HER2 negative BC (stage 0-III); scheduled for neoadjuvant chemotherapy; treated in Champalimaud Clinical Center; women aged ≥ 18 years, non-pregnant; no involvement in any structured exercise program in the past 6 months; medical approval to participate in the study; and willingness to attend exercise sessions. The exclusion criteria were: treatment for any cancer in the past 5 years (except basal cancer or cervix cancer); uncontrolled heart disease (heart failure, uncontrolled coronary heart disease, uncontrolled hypertension, cardiac disease); diabetes mellitus; lung condition (chronic obstructive or restrictive pulmonary disease); psychological disorders (Dementia, Alzheimer, and Parkinson disease); severe disability, or other medical conditions that prevents from exercise training; alcohol or drugs abuse.

Power and sample calculations (G-Power, Version 3.1.9.2) were based on an effect size of 0.25 for KI-67 while using ANOVA – repeated measures within-between interactions, a power of 0.80, a significance of 0.05, and an expected dropout of 40%. The calculation yielded a total sample size of 120 participants (60 undergoing chemotherapy: 20 participants per group per treatment). For this particular study, the sub-sample comprised a total of 33 participants. This study was approved by the Ethics Committee of the Faculty of Human Kinetics and was developed in accordance with the Declaration of Helsinki as well as with the Convention on Human Rights and Biomedicine. Written informed consents were obtained from all participants prior to the beginning of the study.

2. Study Design

Participants were enrolled in a randomized controlled trial (The Neoadjuvant Exercise Oncology Program – The NEO-Program) conducted at the Champalimaud Foundation from December 2022 to June 2024 (Figure 3). The study spanned the entire neoadjuvant therapy period (from BC diagnosis to surgery) on a total of 16 weeks, with participants divided into three groups: 1) Aerobic Training (AT); 2) Resistance Training (RT); 3) Control Group (CG). This specific study is a preliminary analysis based on the currently available data, as sample collection is still ongoing. To allocate participants, a researcher not involved in the project utilized a computer-generated random number list, following an allocation ratio of 1:1:1. In this particular study the outcomes of interest were body mass index (BMI), fat mass index (FMI), absolute and relative fat mass (FM), fat free mass index (FFMI), absolute fat free mass (FFM), lean soft tissue mass (LSTM), muscular tissue (MT), absolute and relative peak oxygen consumption (VO_{2peak}), first ventilatory threshold (VT_1), second ventilatory threshold (VT_2), peak power, maximal respiratory quotient (RQ_{max}), maximal heart rate (HR_{max}), test time, exercise time, maximum strength, right and left handgrip.

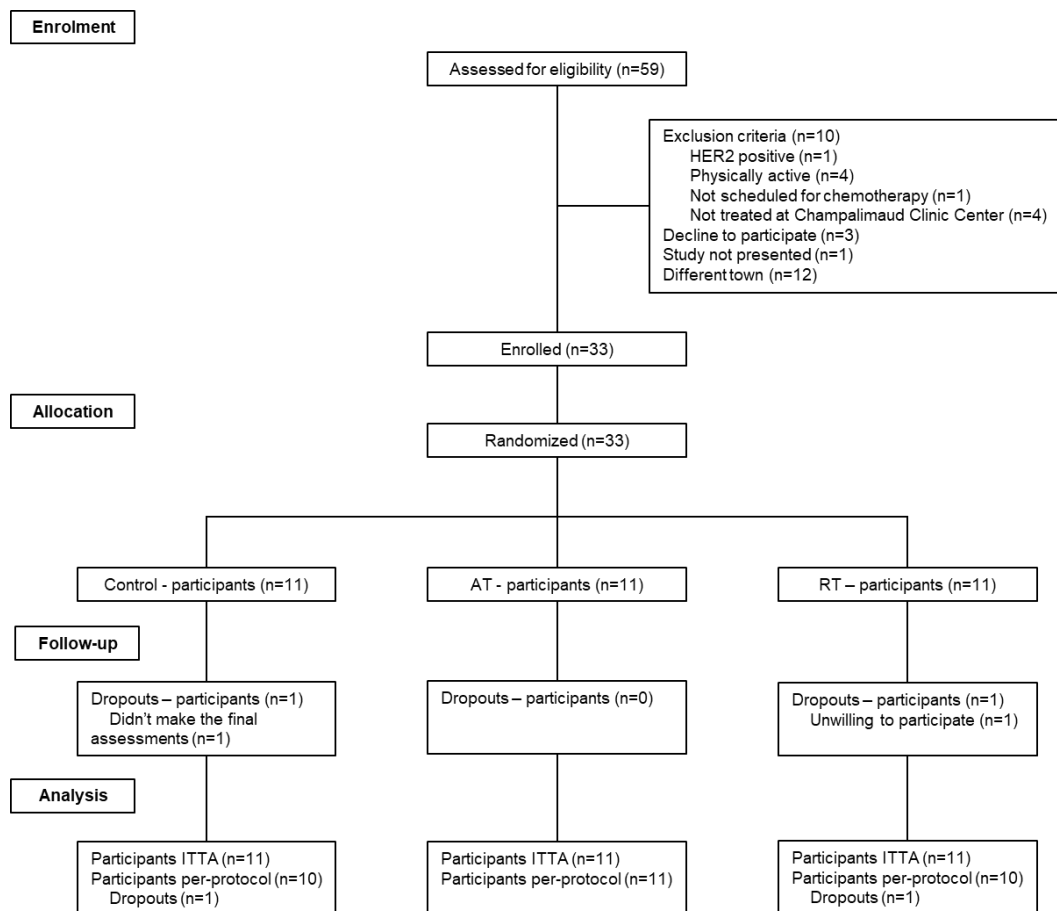


Figure 2 | Study Flow Chart

2.1 Intervention Protocol

The intervention spanned the entire neoadjuvant therapy period on a total of 16 weeks and was designed to ensure equal energy expenditure across exercise sessions in both exercise groups, with a weekly target of 10 kcal/kg. The exercise session duration was determined based on the weekly energy expenditure target and individual VO_{2peak} levels. Each week, the session duration was adjusted according to body weight, without altering the weekly target of 10 kcal/kg. Each training group completed three exercise sessions per week and the control group completed one session per week. Each exercise session consisted of three components: 5 minutes of warm-up, the specific exercise modality (duration according to the previously listed adjustments, on average 45 minutes), and 5 minutes of cool down. All exercise sessions were supervised by exercise professionals.

2.1.1 Aerobic Training

For the AT group, participants initially engaged in continuous cycling at 30%-35% of their heart rate reserve (HRR) – estimated using the resting heart rate and the maximum heart rate values - for one month (phase 1: adaptation phase). Following this, the intensity gradually increased every 4-5 weeks, reaching up to a maximum of 80% of HRR (moderate intensity), based on participant tolerance. An individualized equation, which establishes the relationship between heart rate, oxygen consumption, and power output, was determined during the cardiorespiratory fitness assessment and used to set the exercise intensity. Predicted training frequency was also established.

2.1.2 Resistance Training

Initially, during the first two weeks of the adaptive phase (1 month), the RT group performed two sets of 12-15 repetitions (40%-RM, rate of perceived exertion: 9-11) for 8 exercises targeting both the upper and lower body (leg press, leg extension, leg curl, deadlift (glute bridge, plank, dead bug, seated row, shoulder press). After the adaptive phase, participants progressed to three sets of each exercise (70%-RM, rate of perceived exertion: 14-15). Throughout the ST program, load will be adjusted in order to keep the perceived exertion of the participant at, at least, 14-15 and according to individual tolerance.

2.1.3 Control Group

Participants were invited to an orientation session and participated in a 45-minute stretching and relaxation session per week.

2.1.4 Training sessions monitoring

At the start of each week, participants were weighed. Participants were evaluated based on their perceived exertion and enjoyment using the Borg Scale of Perceived Exertion (6-20) (Borg, 1982) and the Feeling Scale (Hardy & Rejeski, 1989), after the warm-up and before the cool-down. Additionally, all sessions were monitored with a heart rate monitor (H10, Polar). All measurements were documented on an individual training sheet.

3. Outcomes Assessments

Baseline assessments were carried out during the week prior to initiation of the intervention and the start of neoadjuvant treatment. Post-intervention assessments were carried out in the week after the last neoadjuvant treatment.

3.1 Cardiorespiratory Fitness

Cardiorespiratory Fitness was assessed through an incremental supervised cardiopulmonary exercise test (CPET) conducted on a cycle ergometer (Monark). Before the test, participants were familiarized with the protocol and the Borg Rating of Perceived Exertion Scale. Three minutes of resting metabolic data were collected before starting the exercise. The assessment began at 20 Watts, with the workload increasing by 10 Watts per minute based on the participant's cardiopulmonary response during the first minute, continuing until volitional exhaustion or symptom limitation. Participants were instructed to pedal at a rate of 60-70 rpm. The data collected were absolute and relative $\text{VO}_{2\text{peak}}$, VT_1 , VT_2 , peak power, RQ_{max} , HR_{max} , test time and exercise time, and were all recorded using Omnia software. Both VT_1 and VT_2 were determined using the threshold equivalent method through graphical analysis of the relationship between oxygen uptake (VO_2) and carbon dioxide output (VCO_2). VT_1 was identified by analyzing the inflection point where a noticeable change occurred in the slope of the $\dot{\text{VO}}_2/\dot{\text{VCO}}_2$. VT_1 was identified by the inflection point where the rate of VCO_2 increase accelerated more steeply than VO_2 , marking the transition from predominantly aerobic to early anaerobic metabolism. VT_2 was determined by a second, more pronounced change in the slope, characterized by a sharp increase in VCO_2 , while VO_2 continued to rise at a relatively constant rate, reflecting a greater reliance on anaerobic pathways. After calibration, inspired and expired gases were continuously analyzed on a breath-by-breath basis using a non-portable gas analyzer (QUARK RMR w/CPET, version 9.1, Cosmed, Rome, Italy). Participants exercised until at least two of the following criteria were met: (1) volitional fatigue; (2) respiratory exchange ratio of 1.1 or higher; (3) predicted HR_{max} reached; (4) no increase in oxygen uptake despite increasing workload. Peak oxygen uptake was determined as the highest 20-second average recorded

during the final minute of exercise and will be referred to as cardiorespiratory fitness (CRF) hereafter. After stopping, participants remained seated on the cycle ergometer while recovery measures were taken. Recovery heart rate (heart rate at peak effort minus heart rate after exercise) was determined at 60- and 120-seconds post-test.

The CPET was conducted at baseline and post-intervention, with each assessment taking approximately 30 minutes. The test was performed in the morning. This procedure carried minimal risk of injury related to exercise practice.

3.2 Muscle Strength

The handgrip strength test and mid-thigh pull test were conducted under isometric conditions to evaluate upper and lower limb strength, respectively. For the handgrip test, a hydraulic calibrated hand dynamometer (JAMAR) was used following the guidelines of the American Society of Hand Therapists. Before the assessment, participants performed a 3-minute warm-up, which included 2 familiarization handgrip repetitions. The test was conducted in a seated position without arm rests, with feet fully on the floor, hips as far back as possible, and hips and knees at 90°, as confirmed by a goniometer. The shoulder was instructed to be adducted and neutrally rotated, the elbow flexed at 90°, and the forearm in a mid-prone neutral position. Participants performed three 3-second isometric repetitions with 1-minute recovery intervals between each. The average of the three trials were calculated, and verbal encouragement was given.

Lower limb strength was assessed with an isometric mid-thigh pull test, while using a force sensor (Chronojump Boscossystem 2.2.1, Version 2.25). Prior to the assessment, a 5-minute warm-up was performed, which included 3 repetitions for familiarization with the mid-thigh pull. After a countdown, participants completed three maximal voluntary repetitions for 4-5 seconds each, with verbal encouragement and a 3-minute recovery period between trials. The bar was positioned near the thigh, with the knees at 120°, as confirmed by a goniometer. Participants were instructed to pull the bar "as hard and as fast as possible" (Sousa-Santos & Amaral, 2017).

Muscle strength was assessed at baseline and post-intervention, with each assessment taking approximately 15 minutes. The procedure carried minimal risk of injury associated with exercise practice.

3.3 Body Composition

3.3.1 Anthropometric

For height and weight procedures participants were weighed on an electronic scale (Seca, Hamburg, Germany) without shoes and wearing minimal clothing, with measurements recorded to the nearest 0.01 kg. Height was measured using a stadiometer (Seca, Hamburg, Germany) to the nearest 0.1 cm, following standardized procedures (Lohman, 1988). BMI was calculated as the ratio of weight (kg) to the square of height (m). Body weight and height were measured at baseline and post-intervention, with participants wearing minimal clothing and no shoes.

3.3.2 Dual-energy x-ray absorptiometry (Champalimaud Foundation's Protocol)

Dual-energy X-ray Absorptiometry (DXA) equipment (GE Lunar Prodigy Primo, Hologic, Wisconsin, USA) was used to estimate absolute and relative FM, FMI, FFM, FFMI and LSTM. TM was estimated using an equation involving DXA variables (J. Kim et al., 2004). A whole-body scan was conducted, measuring the attenuation of X-rays pulsed between 70 and 140 kV in sync with the line frequency for each pixel of the scanned image.

DXA scans were conducted at baseline and post-intervention. Participants were assessed in the morning following overnight fasting, while wearing minimal clothing and after removing any metal props.

4. Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics version 28.0.0.0 (2021) for Windows (SPSS Inc., an IBM Company, Chicago, IL, USA). Descriptive statistics for the sample were expressed as mean and standard deviation (mean $\pm$ SD) for all primary and secondary outcome variables. Normality was evaluated with the Shapiro-Wilk test and confirmed by examining Q-Q plots. Group differences were analyzed using One-Way ANOVA with Tukey's post hoc test for pairwise comparisons, or the Kruskal-Wallis test for non-parametric data. Generalized estimating equations were used to estimate between-group and within-group effects on various physical fitness outcomes, while controlling for potential confounders, such as age. A linear relationship for the response variable was assumed, and an autoregressive correlation structure was applied to the data. For both primary and secondary outcomes, an intention-to-treat analysis (ITTA) was conducted, incorporating all participants who were initially randomized. Additionally, a per-protocol analysis (PPA) was carried out on a subgroup of participants who completed the study, as

well as those in the intervention groups who demonstrated at least 70% adherence to the total number of training sessions.

Results

The baseline descriptive characteristics of the participants organized by intervention group and for the total sample are presented in Table 1. The overall sample comprised 33 women, with a mean age of 50.0 ± 8.0 years. The average BMI was approximately 24.7 kg/m^2 , with 24.2% of the participants classified as obese, 24.2% as overweight, and 51.5% as having normal weight. In terms of cancer type, 57.6% were diagnosed with Luminal A and 43.3% with Luminal B. Tumor stage information was not available for three participants, while the majority were primarily at stage II (56.7%). Most participants were premenopausal (66.7%).

No dropout rates were observed in the AT group, whereas dropout rates of 9% were observed for the RT and control groups (Figure 3). The mean adherence percentages for participants who met the per-protocol criteria were 92% for the AT group and 74% for the RT group. We did not find significant trends relating compliance to the protocol. We observed no group differences at baseline for the different descriptive variables ($P \geq 0.05$).

Table 1 | Baseline characteristics of the participants

	Baseline			All sample (N = 33)	p value
	CG (n= 11)	AT (n = 11)	RT (n = 11)		
Age (y)	50.0 ± 18.0	49.0 ± 5.0	50.0 ± 15.0	50.0 ± 8.0	0.388
Cancer Subtype (%)					
Luminal A	63.6	54,5	54,5	57.6	0.887
Luminal B	36.4	45.5	45.5	42.4	
Tumor Stage (%)					
II	70	72.7	22.2	56.7	0.049 ^a
III	30	27.3	77.8	43.3	
Menopause Status (%)					
Premenopause	54.5	81.8	63.6	66.7	0.396
Postmenopause	45.5	18.2	36.4	33.3	
Height (cm)	160.1 ± 6.2	162.7 ± 4.9	161.9 ± 6.8	161.5 ± 5.6	0.583
Weight (kg)	70.8 ± 8.8	68.0 ± 12.3	64.6 ± 11.7	67.8 ± 11.0	0.425
BMI (kg/m ²)	26.0 ± 6.9	23.8 ± 8.3	24.1 ± 5.4	24.7 ± 6.5	0.170
FMI (kg/m ²)	11.3 ± 3.1	9.3 ± 2.9	9.0 ± 3.0	9.8 ± 3.1	0.172
FFMI (kg/m ²)	15.6 ± 1.8	14.9 ± 2.3	15.5 ± 2.7	15.5 ± 2.1	0.783
VO _{2peak} (mL kg ⁻¹ min ⁻¹)	21.0 ± 4.1	22.8 ± 4.3	21.5 ± 5.1	21.8 ± 4.5	0.626
Maximum Strength (N)	491.4 ± 168.8	495.4 ± 136.9	424.0 ± 179.2	469.6 ± 160.6	0.524
Handgrip Right Hand (kg)	25.6 ± 4.9	28.4 ± 3.7	26.8 ± 8.2	26.9 ± 5.8	0.541
Handgrip Left Hand (kg)	23.7 ± 4.9	25.8 ± 4.6	25.2 ± 7.0	24.9 ± 5.5	0.658
SB (min/day)	579.3 ± 51.2	544.7 ± 51.2	553.1 ± 40.3	559.7 ± 48.8	0.242
MVPA (min/day)	17.1 ± 18.7	18.7 ± 18.5	17.2 ± 25.0	17.9 ± 15.9	0.880
Attendance (%)	N/A	92	74	83	0.660

Abbreviations: BMI, body mass index; FMI, fat mass index; FFMI, free fat mass index; SB, sedentary behavior; MVPA, moderate-to-vigorous physical activity; N/A, not applicable.

^aDifferences between group baseline values (P < 0.05)

Table 2 presents results related to body composition, CRF, and muscle strength profiles at baseline and final assessment, as well as the between-group and within-group effects for the ITTA analysis (AT vs. RT vs. CG). For the body composition variables, no between-group effects was found ($P > 0.05$) in the ITTA for both the AT and RT intervention groups. Regarding cardiorespiratory variables, we identified between-group effects in relative $\text{VO}_{2\text{peak}}$, absolute VT_1 , absolute VT_2 , relative VT_2 , peak power, test time and exercise time. For instance, there were between-group effects for relative $\text{VO}_{2\text{peak}}$, between AT group and CG ($B = 1.24$, $P = 0.005$), and between AT and RT ($B = 1.30$, $P = 0.046$) groups. Much of these results were driven by a within-group effect on relative $\text{VO}_{2\text{peak}}$, where both the CG ($P < 0.001$) and RT group ($P = 0.032$) decreased their values from baseline to follow-up.

For absolute VT_1 , a similar between-group effect was observed for AT group and CG ($B = 1.69$, $P < 0.001$) and for the AT and RT groups ($B = 1.13$, $P = 0.033$). Significant within-group effects were found for the CG ($P = 0.008$) and the AT group ($P = 0.023$). In absolute VT_2 , between-group effect was found for AT group and CG ($B = 1.89$, $P < 0.001$) and for AT and RT groups ($B = 0.95$, $P = 0.034$). Significant within-group effects were found in both CG ($P = 0.003$) and the AT group ($P = 0.022$) at the final assessments. For relative VT_2 , significant between-group effects were observed between the AT group and CG ($B = 4.36$, $P < 0.001$) and between RT and CG ($B = 3.68$, $P = 0.029$).

In peak power, significant between-group effects were found between all groups: AT and CG ($B = 12.27$, $P < 0.001$), RT and CG ($B = 7.73$, $P = 0.002$), and AT and RT ($B = 4.56$, $P = 0.014$). Within-group effects were also significant for CG ($P < 0.001$) and the AT group ($P = 0.017$). Finally, between-group effects were found for both test time and exercise time in the CPET. For test time, effects happened between the AT group and CG ($B = 68.64$, $P < 0.001$), and AT and RT groups ($B = 34.55$, $P = 0.022$). Significant within-group effects occurred in CG ($P < 0.001$) and the AT group ($P = 0.015$). For exercise time, significant between-group effects were found between all groups: AT and CG ($B = 68.64$, $P < 0.001$), RT and CG ($B = 41.36$, $P = 0.009$), and AT and RT ($B = 27.27$, $P = 0.008$). Within-group significant effects were also noted for CG ($P < 0.001$) and the AT group ($P = 0.005$).

Regarding muscle strength variables, no between-group effects were found.

Table 3 summarizes results for the PPA analysis. When considering PPA, a similar ITTA trend effect was observed for body composition and strength variables. For cardiorespiratory fitness variables, same between and within-group effects were found for

–relative $\text{VO}_{2\text{peak}}$, absolute first ventilatory threshold (VT_1), peak power, test time and exercise time. For absolute and relative VT_2 , different between-groups effects were found. In absolute VT_2 , between-group effects were observed for all groups: AT group and CG ($B = 2.22$, $P < 0.001$), AT and RT group ($B = 0.98$, $P = 0.039$) and RT group and CG ($B = 1.23$, $P = 0.049$). Significant within-group effects were found in both the CG ($P < 0.001$) and the AT group ($P = 0.022$) at the final assessments. For relative VT_2 , between-group effects were found for the AT group and CG ($B = 4.64$, $P < 0.001$) as well as between RT and CG ($B = 4.14$, $P = 0.028$).

Table 2 | Body composition, cardiorespiratory fitness and muscle strength profile at baseline and final assessment: Within and between group changes using the intention-to-treat analysis

Outcome	CG (n= 11)		AT (n = 11)		RT (n = 11)		AT ^a Control	RT ^a Control	AT ^a RT
	Baseline	Final	Baseline	Final	Baseline	Final	B (95% CI)	B (95% CI)	B (95% CI)
Weight (kg)	70.8 ± 8.8	70.2 ± 9.9	68.0 ± 12.3	67.8 ± 11.0	64.6 ± 11.7	65.0 ± 11.4	-0.16 (-1.47; 1.77)	0.49 (-0.84; 1.81)	-0.33 (-1.63; 0.97)
BMI (kg/m ²)	26.0 ± 6.9	26.0 ± 4.9	23.8 ± 8.3	24.3 ± 6.6	24.1 ± 5.4	24.2 ± 5.7	0.079 (-0.56; 0.71)	0.22 (-0.32; 0.75)	-0.14 (-0.63; 0.36)
FMI (kg/m ²)	11.3 ± 3.1	11.2 ± 3.3	9.3 ± 2.9	9.5 ± 2.6	9.0 ± 3.0	8.7 ± 2.9	0.09 (-0.34; 0.53)	-0.12 (-0.55; 0.30)	0.22 (-0.14; 0.82)
FM (kg)	28.5 ± 6.2	28.5 ± 6.9	24.5 ± 7.6	24.9 ± 6.5	23.5 ± 7.6	22.8 ± 7.5	0.198 (-0.88; 1.28)	-0.34 (-1.39; 0.72)	0.53 (-0.41; 0.57)
FM (%)	40.8 ± 4.6	41.1 ± 4.5	36.4 ± 5.0	37.2 ± 4.6	36.2 ± 6.6	35.3 ± 7.7	0.27 (-0.62; 1.16)	-0.61 (-1.82; 0.61)	0.87 (-0.36; 2.11)
FFMI (kg/m ²)	15.6 ± 1.8	15.7 ± 2.0	14.9 ± 2.3	15.6 ± 1.9	15.5 ± 2.7	15.5 ± 2.4	0.05 (-0.21; 0.32)	0.26 (-0.15; 0.67)	-0.21 (-0.66; 0.82)
FFM (kg)	40.7 ± 4.1	40.1 ± 4.3	41.0 ± 5.2	41.5 ± 5.9	40.0 ± 5.0	40.7 ± 6.1	1.33 (-0.55; 0.82)	0.63 (-0.39; 1.65)	-0.50 (-1.64; 0.24)
LSTM (kg)	38.9 ± 4.0	38.4 ± 4.2	39.7 ± 5.1	39.4 ± 5.6	38.1 ± 4.7	38.8 ± 5.9	0.13 (-0.56; 0.81)	0.65 (-0.38; 1.67)	-0.52 (-1.67; 0.63)
MT (kg)	17.2 ± 2.2	16.8 ± 2.7	17.7 ± 2.6	17.4 ± 3.0	16.8 ± 2.7	17.1 ± 3.5	0.10 (-0.37; 0.57)	0.39 (-0.27; 1.06)	-0.29 (-1.01; 0.43)
VO _{2peak} (mL kg ⁻¹ min ⁻¹)	21.0 ± 4.1	17.9 ± 2.9^b	22.8 ± 4.3	22.9 ± 4.4	21.5 ± 5.1	18.9 ± 4.8^b	1.24 (0.38; 2.10)^a	-0.055 (-1.39; 1.28)	1.30 (0.02; 2.57)^a
VO _{2peak} (mL min ⁻¹)	1340.0 ± 386.0	1185.0 ± 468.0^b	1523.0 ± 357.0	1494.0 ± 327.0	1379.0 ± 544.0	1127.0 ± 559.0^b	57.01 (-17.94; 132.03)	41.05 (-19.20; 101.29)	16.00 (-55.11; 87.11)
VT ₁ (mL kg ⁻¹ min ⁻¹)	12.0 ± 2.4	10.4 ± 1.7^b	12.7 ± 1.4	14.5 ± 3.3^b	12.4 ± 2.1	12.0 ± 2.9	1.69 (0.72; 2.66)^a	0.56 (-0.33; 1.44)	1.13 (0.09; 2.17)^a
VT ₁ (%)	59.2 ± 8.8	60.3 ± 5.8	56.4 ± 6.6	62.8 ± 7.3	59.1 ± 11.0	60.8 ± 9.6	0.08 (-0.56; 0.71)	0.22 (-0.32; 0.75)	2.37 (-1.79; 6.52)
VT ₂ (mL kg ⁻¹ min ⁻¹)	16.2 ± 4.5	13.7 ± 2.4^b	17.5 ± 2.8	18.7 ± 2.8^b	17.3 ± 4.1	16.6 ± 4.3	1.89 (0.89; 2.895)^a	0.94 (-0.17; 2.05)	0.95 (0.07; 1.83)^a
VT ₂ (%)	80.0 ± 7.0	78.0 ± 4.0	77.0 ± 6.0	82.0 ± 9.0	81.0 ± 15.0	86.0 ± 12.0	4.36 (1.98; 6.74)^a	3.68 (0.37; 6.995)^a	0.68 (-2.11; 3.48)
Peak Power (Watts)	107.3 ± 26.5	89.1 ± 25.9^b	111.8 ± 17.8	118.2 ± 17.2^b	96.4 ± 25.4	93.6 ± 24.6	12.27 (7.38; 17.17)^a	7.73 (2.86; 12.59)^a	4.56 (0.90; 8.19)^a

RQ _{max} (bpm)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 1.1	1.2 ± 0.1	0.01 (-0.03; 0.05)	-0.01 (-0.05; 0.04)	0.02 (-0.03; 0.06)
HR _{max} (bpm)	159.6 ± 19.6	160.9 ± 15.3	167.3 ± 12.6	168.1 ± 13.6	153.6 ± 25.4	150.3 ± 28.1	-0.27 (-3.796; 3.25)	-2.36 (-6.49; 1.76)	2.09 (-1.67; 5.86)
Test Time (sec)	960.0 ± 171.6	860.9 ± 157.8^b	995.5 ± 102.6	1033.6 ± 102.4^b	905.5 ± 153.7	874.6 ± 172.1	68.64 (36.48; 100.79)^a	34.09 (-3.73; 71.91)	34.55 (5.07; 64.02)^a
Exercise Time (sec)	583.6 ± 163.0	484.6 ± 154.2^b	614.6 ± 104.1	652.7 ± 101.4^b	526.4 ± 149.4	510.0 ± 148.9	68.64 (38.18; 99.09)^a	41.36 (10.28; 72.45)^a	27.27 (7.27; 47.28)^a
Maximum Strength (N)	491.4 ± 168.8	494.2 ± 211.4	495.4 ± 136.9	549.0 ± 128.8^b	424.0 ± 179.2	476.1 ± 143.1^b	15.86 (-16.32; 48.03)	15.12 (-13.95; 44.18)	0.74 (-31.16; 32.63)
Handgrip Right Hand (kg)	25.6 ± 4.9	23.7 ± 4.5^b	28.4 ± 3.7	29.0 ± 3.4	26.8 ± 8.2	26.2 ± 6.3	1.28 (-0.10; 2.66)	0.68 (-0.695; 2.06)	0.599 (-0.79; 1.99)
Handgrip Left Hand (kg)	23.7 ± 4.9	22.8 ± 5.9	25.8 ± 4.6	26.8 ± 5.0	25.2 ± 7.0	23.7 ± 5.1	0.92 (-0.59; 2.43)	-0.36 (-1.71; 0.98)	1.28 (-0.33; 2.90)

Abbreviations: BMI, body mass index; FMI, fat mass index; FM, fat mass; FFMI, free fat mass index; FFM, free fat mass; LSTM, lean soft tissue mass; VT₁, first ventilatory threshold; VT₂, second ventilatory threshold; RQ, respiratory quotient; HR, heart rate.

Betas are presented as unstandardized coefficients with the respective 95% confidence intervals.

^aBetween-group changes significant at P < 0.05.

^bWithin-group changes significant at P < 0.05.

Table 3 | Body composition, cardiorespiratory fitness and muscle strength profile at baseline and final assessment: Within and between group changes using the per protocol analysis

Outcome	CG (n= 10)		AT (n = 11)		RT (n = 10)		AT ^a Control	RT ^a Control	AT ^a RT
	Baseline	Final	Baseline	Final	Baseline	Final	B (95% CI)	B (95% CI)	B (95% CI)
Weight (kg)	71.0 ± 9.2	70.2 ± 10.5	68.0 ± 12.3	67.8 ± 10.95	64.94 ± 12.2	65.4 ± 11.9	0.28 (-1.41; 1.96)	0.63 (-0.81; 2.07)	-0.35 (-1.69; 0.98)
BMI (kg/m ²)	26.2 ± 7.6	25.97 ± 5.6	23.8 ± 8.3	24.3 ± 6.6	23.7 ± 6.8	24.2 ± 6.6	0.13 (-0.54; 0.79)	0.27 (-0.31; 0.34)	-0.15 (-0.65; 0.36)
FMI (kg/m ²)	11.5 ± 3.2	11.5 ± 3.4	9.3 ± 2.9	9.5 ± 2.6	8.9 ± 3.1	8.6 ± 3.0	0.09 (-0.37; 0.56)	-0.14 (-0.60; 0.33)	0.23 (-0.15; 0.86)
FM (kg)	28.9 ± 6.4	28.8 ± 7.2	24.5 ± 7.6	24.9 ± 6.5	23.3 ± 8.0	22.6 ± 7.9	0.20 (-0.95; 1.35)	-0.37 (-1.53; 0.79)	0.57 (-0.41; 0.60)
FM (%)	41.3 ± 4.6	41.6 ± 4.5	36.4 ± 4.95	37.2 ± 4.6	35.7 ± 6.7	34.6 ± 7.8	0.25 (-0.68; 1.19)	-0.67 (-2.00; 0.67)	0.92 (-0.40; 2.24)
FFMI (kg/m ²)	16.0 ± 2.2	15.7 ± 2.1	15.8 ± 1.8	15.6 ± 1.9	15.4 ± 1.6	15.7 ± 2.4	0.06 (-0.21; 0.33)	0.29 (-0.16; 0.74)	-0.22 (-0.70; 0.86)
FFM (kg)	40.6 ± 4.3	39.9 ± 4.5	41.8 ± 5.2	41.5 ± 5.9	40.5 ± 4.9	41.3 ± 6.1	0.17 (-0.54; 0.86)	0.70 (-0.42; 1.82)	-0.53 (-1.76; 0.69)
LSTM (kg)	38.8 ± 4.2	38.2 ± 4.3	39.7 ± 5.1	39.4 ± 5.6	38.5 ± 4.7	39.3 ± 5.96	0.16 (-0.54; 0.85)	0.71 (-0.41; 1.84)	-0.56 (-1.79; 0.26)
MT (kg)	17.2 ± 2.3	16.7 ± 2.8	17.7 ± 2.6	17.4 ± 3.0	17.0 ± 2.7	17.4 ± 3.5	0.13 (-0.36; 0.61)	0.43 (-0.30; 1.16)	-0.31 (-1.08; 0.47)
VO _{2peak} (mL kg ⁻¹ min ⁻¹)	21.4 ± 4.2	17.9 ± 3.1^b	19.95 ± 4.3	22.9 ± 4.4	21.9 ± 5.2	19.1 ± 5.0^b	1.55 (0.65; 2.44)^a	0.12 (-1.31; 1.56)	1.42 (0.07; 2.78)^a
VO _{2peak} (mL min ⁻¹)	1345.0 ± 524.0	1156.0 ± 517.8^b	1523.0 ± 357.0	1494.0 ± 327.0	1389.0 ± 476.0	1389.5 ± 476.0^b	76.56 (-0.20; 153.31)	56.44 (-7.97; 120.85)	20.11 (-52.74; 92.96)
VT ₁ (mL kg ⁻¹ min ⁻¹)	12.7 ± 1.99	10.6 ± 1.7^b	12.7 ± 1.4	14.5 ± 3.3^b	12.6 ± 2.1	12.6 ± 2.1	1.91 (0.90; 2.93)^a	0.76 (-0.23; 1.74)	1.16 (0.07; 2.24)^a
VT ₁ (%)	60.2 ± 8.6	61.4 ± 4.7	56.4 ± 6.6	62.8 ± 7.3	58.4 ± 6.0	58.4 ± 6.0	2.67 (-0.95; 6.30)	0.39 (-3.92; 4.70)	2.28 (-2.13; 6.68)
VT ₂ (mL kg ⁻¹ min ⁻¹)	17.5 ± 3.8	14.0 ± 2.3^b	17.5 ± 2.8	18.7 ± 2.8^b	17.7 ± 3.95	17.7 ± 3.95	2.22 (1.13; 3.30)^a	1.23 (0.004; 2.46)^a	0.98 (0.05; 1.92)^a
VT ₂ (%)	81.8 ± 5.8	77.7 ± 6.3	77.0 ± 4.1	82.1 ± 7.1	81.3 ± 6.0	81.3 ± 6.0	4.64 (1.98; 7.29)^a	4.14 (0.46; 7.83)^a	0.50 (-2.51; 3.50)
Peak Power (Watts)	108.0 ± 27.8	88.0 ± 27.0^b	111.8 ± 17.8	118.2 ± 17.2^b	99.0 ± 25.1	96.0 ± 24.6	13.18 (8.28; 18.09)^a	8.50 (3.49; 13.51)^a	4.68 (0.87; 8.50)^a
RQ _{max} (bpm)	1.2 ± 0.1	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	0.01 (-0.03; 0.05)	-0.01 (-0.06; 0.05)	0.01 (-0.03; 0.06)

HR _{max} (bpm)	161.2 ± 18.5	159.6 ± 15.5	167.3 ± 12.6	168.1 ± 13.6	157.3 ± 23.5	157.3 ± 23.5	-0.33 (-4.35; 3.70)	-2.59 (-7.34; 2.18)	2.26 (-1.74; 6.26)
Test Time (sec)	965.0 ± 180.0	856.0 ± 165.4^b	995.5 ± 102.6	1033.6 ± 102.4^b	918.0 ± 155.98	884.0 ± 178.3	73.59 (40.46; 106.72)^a	37.50 (-2.71; 77.71)	36.10 (4.60; 67.58)^a
Exercise Time (sec)	589.0 ± 170.8	480.0 ± 161.8^b	614.6 ± 104.1	652.7 ± 101.4^b	540.0 ± 150.0	522.0 ± 151.2	73.59 (42.28; 104.91)^a	45.50 (12.90; 78.10)^a	28.10 (7.03; 49.15)^a
Maximum Strength (N)	493.1 ± 178.94	506.8 ± 233.5	495.4 ± 136.91	548.97 ± 128.8^b	418.8 ± 188.0	476.2 ± 150.8^b	10.74 (- 26.28; 47.75)	12.60 (- 22.59; 47.79)	-1.87 (-34.66; 30.93)
Handgrip Right Hand (kg)	25.2 ± 4.9	23.4 ± 4.7	28.4 ± 3.7	29.0 ± 3.4	26.7 ± 8.6	26.1 ± 6.6	1.18 (-0.26; 2.61)	0.55 (-0.95; 2.05)	0.63 (-0.83; 2.09)
Handgrip Left Hand (kg)	23.4 ± 5.1	23.0 ± 6.2	25.8 ± 4.6	26.8 ± 4.95	25.5 ± 7.3	23.8 ± 5.3	0.69 (-0.80; 2.18)	-0.67 (-2.07; 0.73)	1.36 (-0.32; 3.03)

Abbreviations: BMI, body mass index; FMI, fat mass index; FM, fat mass; FFMI, free fat mass index; FFM, free fat mass; LSTM, lean soft tissue mass; VT₁, first ventilatory threshold; VT₂, second ventilatory threshold; RQ, respiratory quotient; HR, heart rate.

Betas are presented as unstandardized coefficients with the respective 95% confidence intervals.

^aBetween-group changes significant at P < 0.05.

^bWithin-group changes significant at P < 0.05.

Discussion

This study aimed to investigate the impact of an exercise intervention on physical fitness attributes in patients diagnosed with BC undergoing neoadjuvant treatment. The main findings from this preliminary study showed a between-group effect for some cardiorespiratory variables such as relative $\text{VO}_{2\text{peak}}$, absolute VT_1 , absolute VT_2 , relative VT_2 , peak power, test time and exercise time. No between-group effects were found for body composition and muscle strength variables.

To date, most randomized controlled trials investigating the benefits of exercise in cancer patients have been conducted during the adjuvant treatment period or post-treatment (Courneya et al., 2014; Soares Falcetta et al., 2018), or in other types of cancer (Malveiro et al., 2023) rather than specifically in breast cancer. The growing understanding of how exercise can positively impact this population from the point of diagnosis may help prevent and mitigate the effects of treatment in breast cancer patients. Cardiorespiratory fitness is considered a strong predictor of mortality and cardiovascular disease risk in BC patients (Schmid & Leitzmann, 2015). Given the nature of the study and the timeframe in which it is conducted, it is important to emphasize that CRF values may also serve as prognostic markers for surgical risk and postoperative recovery (Ezzatvar et al., 2021). This component of physical fitness is commonly represented by $\text{VO}_{2\text{max}}$ or $\text{VO}_{2\text{peak}}$ with the literature showing that lower VO_2 values are associated with a reduced quality of life, increased cardiotoxicity from treatment, and higher mortality risk (Maginador et al., 2020).

The preliminary results from this suggest a between group effect, between those in the AT group and the other two groups, CG and RT, concerning CRF levels. This effect indicates that CRF values in the AT group were maintained or increased by the end of chemotherapy, while the other two groups experienced a significant decline. These findings align with previous studies regarding the influence of exercise on CRF. Most of previous studies examining the relationship between cancer, exercise, and CRF have demonstrated a strong positive correlation between these factors. From those studies, and analyzing the ones similar to ours, a study conducted across seven hospitals in the Netherlands, with women with breast cancer diagnosed and scheduled for chemotherapy (neoadjuvant or adjuvant) investigated the effects of an 18-week aerobic and resistance exercise intervention, consisting of two weekly sessions supervised by a physiotherapist (Travier et al., 2015). The results demonstrated that the exercise intervention had beneficial effects on VO_2 at the ventilatory threshold, showing significant differences in favor of the intervention group, but

showed no between group effects in VO_{2max} (Travier et al., 2015). Conversely, a study conducted in Stockholm aimed to investigate and compare the effects of exercise interventions through a 16-week program involving two supervised exercise sessions per week, in breast cancer diagnosed women who planned to receive adjuvant chemotherapy, didn't show entirely clear results about CRF changes (Mijwel et al., 2019). These inconclusive results are consistent with findings from a study that examined the effects of aerobic and resistance exercise on health-related fitness in breast cancer patients undergoing adjuvant chemotherapy, where participants exercised three times per week for the duration of their chemotherapy (Courneya et al., 2014). When comparing the results from these previous studies with ours, several methodological differences were identified that may account for some observed variations. First, although all studies included breast cancer patients, none were exclusively focused on those undergoing neoadjuvant chemotherapy (Courneya et al., 2014; Mijwel et al., 2019). In fact, there is a scarcity of studies examining this specific treatment modality and timing. Additionally, none of these studies listed pre-diagnosis high physical activity levels as an exclusion criterion, despite some noting this as a potential source of bias (Travier et al., 2015). Moreover, several studies used combined exercise interventions without assessing the separate benefits of aerobic versus resistance training (Travier et al., 2015). Regarding exercise prescription, two studies utilized high-intensity training (Mijwel et al., 2019; Travier et al., 2015). Another notable difference was the sample size, which was significantly larger in all other studies (Courneya et al., 2014; Mijwel et al., 2019; Travier et al., 2015). Lastly, adherence to the exercise program appeared to be as high as in our study, and, where described, the cardiopulmonary test was consistently used as the optimal assessment method (Travier et al., 2015).

On a different note, we also observed that the effects of the two types of exercise differ, with results only evident in the AT group. Evidence suggests that although the benefits of AT surpass those of RT in terms of cardiorespiratory capacity, RT also impacts this capacity through mechanisms such as the improvement of muscle oxidative capacity and muscle function, enabling the handling of greater workloads and thereby increasing oxygen demand during exercise, indirectly affecting VO_{2max} (Brellenthin et al., 2019; Collins et al., 2021). The evidence further indicates that the effectiveness of resistance training on cardiorespiratory capacity depends on the intensity, volume, and type of training applied, with combined training being the most recommended approach (Gao & Yu, 2023; Ozaki et al., 2013). Thus, based on our methodology, our CRF results could be attributed to the management of AT compared to RT. Our RT methodology was designed to promote hypertrophy, which

required progressive loading throughout the study. However, this progression was not feasible for all participants, often due to chemotherapy side effects such as muscle pain and fatigue, which hindered consistent progression. Additionally, training volumes varied more within the RT group, resulting in greater heterogeneity in both duration and intensity among participants. This difference in training volume was also significant when compared to the AT group.

Previous studies have demonstrated that patients undergoing cancer treatments, particularly chemotherapy, often experience a decline in cardiorespiratory fitness (Peel et al., 2014). In fact, in our study both the CG and RT group experienced a decrease in CRF as observed by the within group effect. These results may justify the between group interaction favoring the AT group, which was able to maintain its values across the exercise intervention. The underlying cause of this decline is likely multifactorial, involving various components of the oxygen transport system. Most of the time this results in left ventricular dysfunction, indicating abnormal cardiac function, which, due to the biology of the disease, is directly linked to a reduction in VO_{2max} (Howden et al., 2019). In contrast to the detrimental effects of cancer on VO_{2max} , exercise induces physiological adaptations that enhance VO_{2max} . These adaptations include improved cardiac function, increased blood volume, enhanced mitochondrial density, and increased capillary density (Vasankari, 2020). Despite the differences in CRF levels at the final assessment, the study revealed that after the intervention, ventilatory thresholds increased in the AT group compared to the CG group, which showed a decrease. No significant differences were found in the RT group. According to the evidence, it is possible to improve the ventilatory threshold without a significant increase in VO_{2max} (Tomescu et al., 2016). Long-duration continuous aerobic training, as cycling or running for periods ranging from 30 minutes to 2 hours, performed at moderate intensities, enhances the body's capacity to uptake and distribute oxygen (Tomescu et al., 2016). Over time, this adaptation results in a shift of the ventilatory threshold to higher exercise intensities, allowing the individual to sustain more intense physical exercise before lactate accumulation occurs (Sihite et al., 2023). Additionally, improvements in muscle oxidative capacity shift the lactate threshold upwards, enabling individuals to exercise at a higher percentage of their VO_{2max} without accumulating lactate as quickly (Amani-Shalamzari et al., 2019). For this reason and considering the observed behavior of participants in terms of CRF values and the methodology of AT, our results for the ventilatory threshold align with what was expected. Following the logic of the events described above, the results presented regarding peak power and time duration further reinforce the theory established so far. (Amani-Shalamzari et al., 2019; Sihite et al., 2023). In clinical

populations, such as cancer patients undergoing treatment, this improvement is associated with better functional capacity and health-related quality of life (Tomescu et al., 2016).

In the case of muscle strength, evidence indicates that due to the sedentary behavior adopted during the treatment period - related to the treatment's side effects - there is a tendency for a decrease in muscle mass (Klassen et al., 2017; Schneider et al., 2007). Moreover, chemotherapy specifically has the capacity to induce structural and biochemical changes in muscle tissue, promoting muscle weakness, fatigue, and mobility impairments, thereby increasing the risk of sarcopenia and compromising patients' quality of life (Buffart et al., 2020; Klassen et al., 2017; Schneider et al., 2007; Silva et al., 2022). Our results did not show significant changes in muscle strength parameters. Overall, there were no between group effects in strength variables. Previous studies have revealed that resistance training can have beneficial effects in this population, as it acts on various biological mechanisms, such as hormonal regulation, inflammation reduction, and appetite stimulation, which lead to improvements in muscle metabolism, better control of fatigue and muscle wasting, as well as improved nutrition supporting muscle recovery (Misiąg et al., 2022; Segal et al., 2017). Studies similar to ours, which used resistance training in cancer patients, consistently demonstrate a favorable impact on strength outcomes (Mijwel et al., 2019; Schmidt T et al., 2015; Travier et al., 2015; Van Waart et al., 2015). The study by Travier et al. (2015) which investigated the effects of an 18-week aerobic and resistance exercise intervention in women diagnosed with breast cancer and scheduled for chemotherapy treatment (neoadjuvant or adjuvant), demonstrated significantly higher muscle strength in the intervention group for both leg flexion and extension compared to the control group, while no significant changes were observed in handgrip strength. In another 16-week intervention study (Mijwel et al., 2019), women diagnosed with breast cancer who were planned to receive adjuvant chemotherapy observed significant lower-limb strength gains in both exercise groups compared to the control group, with handgrip strength gains also being reported by Mijwel et al. (2019). The Physical Exercise During Adjuvant Chemotherapy Effectiveness Study, a randomized, controlled, multicenter trial for breast and colon cancer patients undergoing adjuvant chemotherapy, compared two programs: Onco-Move (a low-intensity, self-managed physical activity program) and OnTrack (a moderate- to high-intensity combined resistance and aerobic exercise program (Van Waart et al., 2015). The results showed that physical fitness (muscle strength and CRF) levels were maintained after chemotherapy in the OnTrack group but declined in the control and Onco-Move groups (Van Waart et al., 2015). While no improvements in fitness levels were observed during chemotherapy, the intervention helped stabilize or slow the

decline (Van Waart et al., 2015). In another prospective randomized controlled trial, 12-week supervised resistance training (RT) and endurance training (ET) were compared with standard care (SC) in women with primary moderate- or high-risk breast cancer during adjuvant chemotherapy. Both RT and ET led to significantly improved total strength, with the largest gains observed in the RT group, showing statistically significant differences compared to SC (Schmidt et al., 2015).

Our findings contrast with those previously reported. When comparing these studies with ours, several differences emerge that may help explain these discrepancies. In terms of sample composition, no other studies included participants with simultaneous breast cancer diagnoses undergoing neoadjuvant chemotherapy. Additionally, unlike our study, the exclusion criteria in these studies did not account for pre-diagnosis physical activity levels. Regarding sample size, three out of the four studies had significantly larger samples than ours (Mijwel et al., 2019; Travier et al., 2015; Van Waart et al., 2015). Only one study used the same assessment method as ours (Mijwel et al., 2019), while the others employed different devices for measuring lower body strength: a Cybex dynamometer (Travier et al., 2015), a microFET hand-held dynamometer (Van Waart et al., 2015) and the M3 Diagnos (Schmidt T et al., 2015). All studies used handgrip measurements for upper limb strength. Concerning intervention protocols, load intensity was prescribed using the one-repetition maximum (1RM) method across studies. However, several studies implemented higher load intensities than our protocol suggested, working above 70% of 1RM (Mijwel et al., 2019; Travier et al., 2015; Van Waart et al., 2015). Furthermore, some studies incorporated combined training, including both resistance and aerobic exercise, rather than focusing exclusively on one modality (Travier et al., 2015; Van Waart et al., 2015). Our findings can be attributed to various methodological issues. First, regarding the parameters of the exercise program, although the criteria for load progression were initially established, it is important to note that the subjective evaluations of the patients, derived from the Borg scale, were considered in this progression. Also, the initial set timelines and the intensity of each set were not always adhered to, as treatment side effects, such as muscle pain and fatigue, hindered this adherence. Finally, the effectiveness of the mid-thigh pull test depends heavily on achieving the correct joint angles, particularly in the hip, knee, and ankle. Small deviations in these angles can significantly affect force production and complicate the standardization of the test across different individuals (Guppy SN et al., 2018). This variability can introduce error and reduce the test's reliability. The mid-thigh pull may also exhibit a learning curve, where participants become more proficient in producing maximal force with repeated trials, especially if they are unfamiliar with the test (Guppy SN et al.,

2018). This could result in variations in test outcomes that are more reflective of skill improvement rather than true strength gains. Furthermore, improper execution or pre-existing injuries could exacerbate issues in the lower back, hips, or knees during the mid-thigh pull test (Guppy SN et al., 2018).

Regarding body composition, the literature review describes that oncology patients undergoing chemotherapy experience alterations due to both the disease itself and the effects of treatment. Chemotherapy tends to reduce physical activity levels, elevate inflammation, and increase muscle protein breakdown, all contributing factors to the reduction in muscle mass, referred to etiologically as sarcopenia (Roberto et al., 2024). Additionally, the direct cytotoxic effects of chemotherapy drugs on muscle tissue exacerbate muscle atrophy (Roberto et al., 2024). On the other hand, the sedentary behavior associated with metabolic and hormonal changes induced by treatment promotes fat storage, leading to an increase in fat mass (Li et al., 2024). Conversely, there is a decline in lean body mass, a predictor of long-term health consequences (Li et al., 2024). Chemotherapy can also alter fat distribution, increasing the tendency for visceral fat accumulation, which is linked to a higher risk of metabolic diseases such as diabetes and cardiovascular disease (Bradshaw, 2024). Lastly, there is also a greater tendency for fluid retention during treatment, which can result in edema, potentially masking actual losses in muscle mass or increases in fat (Bradshaw, 2024). In contrast, exercise can lead to a reduction in body fat, particularly visceral fat, which is crucial for lowering the risk of metabolic diseases and reducing inflammation, a key factor in cancer progression (Soares Falcetta et al., 2018). Additionally, exercise promotes the preservation of muscle mass by inducing muscle protein synthesis, counteracting the effects of muscle atrophy and sarcopenia (Ikeda et al., 2022). It also enhances metabolic health by improving insulin sensitivity and lowering inflammatory markers, thereby preventing weight gain associated with treatment and supporting a healthy body composition, including both fat mass and lean mass ratios (Parker et al., 2021). Furthermore, exercise improves circulation and lymphatic flow, potentially reducing the impact of edema, which is common among cancer patients undergoing chemotherapy (Battaglini et al., 2014).

Our preliminary findings have shown no between-group effects of the intervention arms in any of the body composition outcomes, when compared to the control group. Similar studies that aimed to understand the impact of an exercise program on body composition in patients with BC have shown mixed results (Courneya et al., 2007, 2013; Mijwel et al., 2019; Travier et al., 2015). A multicenter randomized controlled trial in Canada assigned breast cancer

patients starting adjuvant chemotherapy to usual care, or supervised resistance and aerobic exercise (Courneya et al., 2007). While neither intervention prevented weight gain, the aerobic exercise group prevented fat gain, and the resistance exercise group increased lean body mass (Courneya et al., 2007). Similarly, Mijwel et al. (2019), who compared the effects of different exercise interventions on cancer outcomes in women diagnosed with breast cancer who planned to receive adjuvant chemotherapy, showed that after a 16-week exercise program, women in the aerobic high-intensity interval training group displayed reduced body mass, with significant differences compared to the usual care group that gained weight during chemotherapy. Contrarily, a Canadian multicenter trial that included supervised exercise sessions three times weekly during adjuvant chemotherapy in women with breast cancer, reported no significant changes in body composition between groups (Courneya et al., 2013). Likewise, the study by Travier et al. (2015), which evaluated an 18-week aerobic and resistance exercise program in women diagnosed with breast cancer and scheduled for chemotherapy treatment (neoadjuvant or adjuvant), showed that body weight similarly increased in both exercise and control groups at 18 and 36 weeks.

Compared to our findings, several methodological factors may account for the differences observed between our study and those referenced above. First, regarding sample size, all four studies included larger sample sizes than ours (Courneya et al., 2007, 2013; Mijwel et al., 2019; Travier et al., 2015). Additionally, none of these studies exclusively focused on breast cancer patients undergoing neoadjuvant chemotherapy. In terms of assessment methods, only two of the four studies utilized DXA scanning, as we did (Courneya et al., 2007, 2013). Regarding exercise prescription, one study compared aerobic exercise at different intensities with combined exercise (Courneya et al., 2013), one implemented combined exercise alone (Travier et al., 2015) and two studies used aerobic versus resistance exercise protocols, as in our study (Courneya et al., 2007; Mijwel et al., 2019). Concerning exercise intensity, two studies incorporated higher intensities: one used high-intensity interval training (HIIT) for both aerobic and resistance training (Mijwel et al., 2019), and the other employed combined training with interval-based aerobic segments and resistance exercises at loads exceeding 70% of maximum strength (Travier et al., 2015). The remaining two studies applied intensities like ours (Courneya et al., 2007, 2013). As in our study, none of the referenced studies included dietary interventions (Courneya et al., 2007, 2013; Mijwel et al., 2019; Travier et al., 2015). Our findings align with the existing literature, which remains unclear on this topic. Several factors could explain these results. Firstly, as previously discussed in the muscle strength section, the sample size was not ideal, with only 11 participants per group, while recommendations typically suggest a

sample size ranging from 20 to 30 (Mijwel et al., 2018; Schoenfeld et al., 2021). Another factor that could explain these findings is related to the participants' diets. In this case, there was no control over the type of diet the participants followed during the program. Nutrition plays a critical role in body composition changes so when dietary intake is not controlled or monitored, differences in caloric intake, protein consumption, or nutritional quality between participants could have influenced the results (Basen-Engquist et al., 2020; Pérez-Bilbao et al., 2023).

Overall, the study results indicate that, in the presence of exercise, the deterioration of various components of physical fitness - expected due to both the disease and its associated treatment, as supported by the evidence previously discussed - was reduced or, in some cases, did not occur at all. Even in cases where no significant effects were observed, which essentially reflects the preservation of the patients' physical profiles, these outcomes are favorable for the participants' overall health.

Strengths and Limitations

Beyond these findings, it is also important to highlight that this is one of the few studies that explores the interaction between physical exercise and physical fitness in such a specific population, and with such specific design – randomized control trial during the neoadjuvant period treatment. Achieving positive indicators during neoadjuvant treatment could potentially result in better outcomes from the time of diagnosis and improved management of treatment-related side effects. Furthermore, the high adherence to the exercise program described above is a positive indicator (92% for AT group and 74% for RT group), as it not only helps improve quality of life during treatment but also positively impacts the overall health of the patient.

However, this study has a few limitations. Firstly, the fact of being preliminary results from a larger study led to a small sample size which may have limited the statistical power to detect significant changes. In terms of methodology, the assessment of lower limb muscle strength may have been biased due to the known issues related with the method itself. Additionally, other sources of inter-individual variability may have some heterogeneity to the exercise program outcomes (e.g. nutrition).

Conclusion

Based on our preliminary results, this study provides an important foundation for understanding the impact of an exercise intervention on physical fitness outcomes in women with breast cancer undergoing neoadjuvant treatment. Our findings highlight the

significant impact of the treatment on CRF, emphasizing the benefits of aerobic exercise in counteracting these negative effects. The aerobic training group also improved other cardiorespiratory fitness indicators, such as ventilatory thresholds, endurance during physical exercise, and tolerated workload during exertion. Regarding body composition and muscle strength, our data didn't reveal significant changes in any of the intervention arms, underlining the need for further research in this area.

In summary, this study underscores the importance of investing in exercise programs aimed at preserving physical fitness in breast cancer patients undergoing neoadjuvant treatment. It highlights the benefits of promoting cardiorespiratory fitness, muscle strength, and body composition, while minimizing the adverse effects of treatment and disease in newly diagnosed patients.

Future Work

Based on our hypothesis regarding the influence of exercise on physical fitness in BC patients undergoing neoadjuvant treatment, our findings pave the way for future studies exploring this relationship on other health-related outcomes. Future research should prioritize larger sample sizes and, if possible, include patients undergoing varied treatment types, allowing for the development of strategies that cover a broader spectrum of the BC population (e.g. triple negatives). Additionally, similar exercise interventions should be explored in other cancer types, while also addressing their long-term effects.

Furthermore, exploring interindividual variability in response to the intervention program is essential. Given the complex nature of cancer and its treatment, responses to exercise can be influenced by a variety of factors. Identifying responders and non-responders and understanding the factors contributing to these differences could have important implications for improving the effectiveness of exercise programs for all patients. By investigating potential predictors of response - such as genetic markers, baseline fitness levels, and comorbidities - researchers can develop more targeted and individualized exercise prescriptions that optimize outcomes for each patient.

The study has revealed some differences between AT and RT. These differences should be explored further in future research, testing various exercise combinations. It may also be beneficial to investigate whether these advantages are present in non-sedentary populations. Given the unclear results regarding body composition, potentially due to the lack of dietary control, future studies that incorporate a combined approach of diet and

exercise could offer new insights. Moreover, the high adherence to the program observed in this study suggests a promising future for the integration of such exercise interventions in the BC population. The exercise sessions also functioned as a support group during treatment, highlighting the psychosocial benefits of such programs, an area worth exploring further. Lastly, due to the complex relationships established in this study, the development of multidisciplinary studies involving healthcare professionals - such as oncologists, nutritionists, psychologists, and exercise physiologists - could result in methodologies that are more tailored to the individual needs of participants, potentially increasing the efficiency of the interventions.

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