

Effects of supervised exercise intervention on cardiorespiratory fitness and health-related quality of life in breast cancer patients during treatment

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KEY WORDS: Quality of Life, Exercise, Breast Cancer, Fatigue.

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List of Abbreviations

EORTC	European Organization Research Treatment of Cancer
HRQOL	Health Related Quality of Life
QOL	Quality of Life
ACSM	American College Sports Medicine
VO_{2max}	Maximal Aerobic Power
VO_{2VE}	Oxygen Consumption at Ventilatory Anaerobic Threshold
FACT	Functional Assessement of Cancer Therapy
CRF	Cancer Related Fatigue
QL	General Quality of Life
PF	Physical Functioning
RF	Role Functioning
CF	Cognitive Functioning
SF	Social Functioning
FA	Fatigue
PA	Pain
BRBI	Body Iagem
BRAS	Arm Symptoms

Abstract

BACKGROUND. With 1.3 million new breast cancer cases reported every year and improved survival, it is important to develop interventions to maintain health related quality of life (HRQOL) during and after cancer treatment. Aerobic and strength training is an intervention that can enhance HRQOL and physical components during treatment.

OBJECTIVES. To examine the effect of 12 weeks of supervised exercise in physical capacity measurement and HRQOL in breast cancer patients during treatment.

METHODS. Breast cancer patients were allocated into an exercise intervention program (EI, n=40) and to a control group (CG, n= 8) that received standard care. The intervention comprised cardiovascular training at 70-85% of VO_{2max} in cycle ergometer, resistance training and specific rehabilitation arm exercises. Patients were trained during 60 minutes, two times per week, during 12 weeks, with progression in time and intensity during the intervention period, with the main goal to achieve, at week 12, thirty minutes at 85% VO_{2max} . Physical capacity and health related quality of life EORTC QLQ-C30 were assessed pre and post intervention. General linear model for repeated measures was used to compare (baseline and 12-week follow-up) with group assignment and time x group interaction included as fixed effects ($p \leq .05$ for significance).

RESULTS. Highly significant increases were achieved with an increase of 17.0% vs. 7.7% in VO_{2max} , and 46,6% vs. 4.9% in power output, respectively, in the intervention group compared to the control group ($p \leq .05$). Gains in strength occurred only in the intervention group with an increase in leg extension by 13.4% ($p \leq .05$). Intervention and control groups improved global health status (10.2 vs. 9.3 points) but emotional status (16.6 vs. 11.0 points) and role function (14.9 vs. -0.1 points) were significantly higher in the intervention group ($p \leq .05$). The fatigue decreased by 16.4 points in the intervention group compared with only 2.7 points in the control group ($p < .001$). A significant decrease in pain was obtained for the intervention group with a reduction by 20.4 points vs. 2.6 points for the control group ($p < .001$).

CONCLUSIONS. A supervised and individualized prescriptive exercise program, results in an improvement in functional ability and HRQOL functions in women with breast cancer.

KEY WORDS: Quality of Life, Exercise, Breast Cancer, Fatigue.

Resumo

INTRODUÇÃO. Com 1.3 milhões de novos casos de cancro todos os anos e com o aumento da taxa de sobrevivência, é importante desenvolver intervenções relacionadas com a qualidade de vida (QOL) durante e depois do tratamento do cancro. O exercício físico pode ser uma estratégia não farmacológica para melhorar a QOL e a capacidade física durante o tratamento da doença.

OBJETIVOS. Avaliar o efeito de um programa de exercício físico supervisionado durante 12 semanas nas alterações físicas, funcionais e a QOL, durante o tratamento, em mulheres com cancro da mama.

MÉTODOS. As mulheres com cancro da mama foram incluídas em dois grupos distintos, sendo que 40 participaram num programa de exercício físico (EF, n=40), enquanto que as restantes integraram o grupo de controlo (GC, n=8). O programa de exercício físico consistiu em treino cardiovascular no ciclo-ergómetro a 70-85% VO_{2max} , treino de resistência de força com bandas terapêuticas e exercícios específicos de reabilitação para os membros superiores. O programa de exercício físico teve a duração de 60 minutos, duas vezes por semana durante 12 semanas. Durante o período de aplicação do programa de exercício físico houve uma progressão no tempo e intensidade com o objetivo de realizar na 12ª semana 30 minutos a 85% VO_{2max} . A capacidade física e a QOL (EORTC QLQ-C30) foram avaliadas antes e depois do programa de intervenção. Para comparar o efeito do programa de exercício físico antes e após a intervenção utilizou-se a Anova de medidas repetidas com a análise da interação tempo x grupo (nível de significância $p \leq .05$).

RESULTADOS. Verificaram-se aumentos significativos de 17.0% vs 7.7% no VO_{2max} e 46,6% vs 4.9% na potência ao VO_{2max} , respectivamente no EF comparado com GC ($p \leq .05$). O aumento da força na leg extension ocorreu apenas no EF 13.4% ($p \leq .05$). Ambos os grupos aumentaram a qualidade de vida geral (10.2 vs 9.3) mas a função emocional (16.6 vs 11.0) e role função (14.9 vs -0.1) foram significativamente mais altos no grupo EF ($p \leq .05$). A fadiga diminuiu cerca de 16.4 pontos no grupo EF comparativamente com 2.7 pontos no GC ($p < .001$). Foi demonstrado um decréscimo significativo da dor apresentado apenas pelo grupo de intervenção com uma redução de 20.4 vs 2.6 pontos para o grupo de controlo ($p < .001$).

CONCLUSÕES. Um programa de exercício físico supervisionado, individualizado e prescritivo durante 12 semanas induziu numa melhoria significativa das capacidades funcionais e QOL em mulheres com cancro da mama.

PALAVRAS-CHAVE – Qualidade de vida, Exercício, Cancro da Mama, Fadiga.

1. Introduction

In the western world, cardiovascular and oncologic diseases are the main causes of premature death (Pedersen & Saltin, 2006). Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The burden of cancer is increasing in economically developing countries as a result population aging and growth as well as, increasingly, an adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and fast food (Jemal et al., 2011). Breast cancer in female and lung cancer in males are the most frequently diagnosed cancers and the leading cause of cancer death for each sex in both economically developed and developing countries except lung cancer is preceded by prostate cancer as the most frequent cancer among males in economically developed countries (Jemal et al., 2011).

Worldwide, 1.3 million new breast cancer cases were reported every year accounting for 23% of the total new cases and 14% (458.000) of the total cancer deaths in 2008 (Jemal et al., 2011). More recent studies in the United States estimate that the 5-year survival rate for all cancers is roughly 62% and represents an approximate total of 9 million cancer survivors. The annual percentage change in the incidence of invasive breast cancers decreased modestly among older women but increased among younger (<40 years) and it has been reported that approximately 25% of breast cancers occur in women less than 50 years of age (e.g. premenopausal) in Europe and in US (Brinton et al., 2008). Early detection and advanced treatment option have led to a steady improvement in 5-year relative survival rate in developed countries where the 5-year relative survival rate is currently 87% (Eheman et al., 2012). Data from 2003 show that 5-year relative survival exceeded 90% for patients with breast cancer and reached levels of about two thirds for patients with colorectal cancer and kidney cancer and patients with non-Hodgkin's lymphoma (Brenner et al., 2007).

This trend has resulted in a growing population of breast cancer survivors who are potentially faced with a number of long-term side effects of cancer and its

treatment (Campbell et al., 2011). Some of these include decrease aerobic capacity and strength, weight gain, fatigue and reduced quality of life.

Treatment is focused on curing the disease and preventing relapse due to metastatic disease (Hoving et al., 2009). This fact accentuates the importance of investigation regarding the development of strategies to improve patients' quality of life, reduce the recurrence risk, the probability of contracting other diseases and prolonging the population's survival (Courneya, 2003).

The quality of life in oncological patients is often affected by the fatigue that they feel. In fact, approximately 70% of the cancerous population reports sensations of fatigue and asthenia during radiotherapy, chemotherapy or after surgery. Furthermore, approximately 30% of the population that survives cancer continues to manifest signs of persistent fatigue (Dimeo, 2001). Therefore, in all the types of cancer, the cancer related fatigue (CRF) severely influences several components of the quality of life since in aggravating symptoms like pain, nausea and dyspnoea, it causes physical, economic and social consequences that are devastating to the patients (Winningham, 2001). Cancer related fatigue (CRF) as a profound, negative impact on daily activities, social activities and overall quality of life (Cella et al., 2002).

Devoogdt et al. (2010) studied the evolution of the total physical activity levels occupational, sport and household activity on breast cancer patients. Physical activity levels are still significantly lower 12 months after treatment for breast cancer than at the pre-operative level. A greater decrease in occupational activities was associated with having a spouse, lymph node stage pN2 or pN3 (versus stage pN0 or pN1) complete axillary dissection (versus sentinel node biopsy), more than 20 lymph nodes dissected (versus less than 10) or undergoing chemotherapy. Moreover, older patients and those smoking before surgery had a higher risk of having a decreased sport activity level 12 months after surgery.

In this study, 1 year after the surgery breast cancer patients showed a 85% reduction from baseline in occupational activities (Devoogdt et al., 2010).

So, cancer patients, and in particular those at risk for a decreases physical activity level and affected by fatigue, should be identified, and encourage to increase their activities with supervised exercise programs. In fact, CRF and decreased physical activity may lead to difficulties in return to work.

Being unable to return to work after cancer treatment, frequent or prolonged work absenteeism, or problems with work performance may impose a significant economic impact on the survivor and her family (Chirikos et al., 2002). Furthermore, it is stated that the longer people are absent from their jobs, the lower the likelihood is that they will ever return to work. Moreover, Whereas loss of occupational identity can be a source of significant anxiety and depression, continuing or returning to the workplace allows many patients to maintain a sense of normalcy or control (Peteet, 2000). Most of the interventions with patients receiving adjuvant treatment show some improvement on quality of life or an other physical and psychological outcomes, such CRF, but do not pay attention to the aspect of work which is considered to be an important contributor to quality of life (Hoving et al., 2009). Some studies investigated return to work following breast cancer surgery. In a systematic review, Hoving et al. (2009) concluded the lack of methodology sound intervention studies on breast cancer survivors with outcome return to work indicating that returning to work programs and vocational rehabilitation for breast cancer survivors should be further developed and evaluated.

At 3 months pos-operative surgery, only 19% of patients working pre-operatively has returned to work and after 12 months the proportion had increased to 60% with patients working in a part-time employment than before surgery (Devoogdt et al., 2010). In other study elaborated in Canada, showed at 12 months, 88% of the breast cancer patients had returned to work (Drolet et al., 2005). There is a high variability among studies about working rates after breast cancer surgery being a possible explanation the difference in health care systems between US, Canada and European countries. In US, after 3 months, 60% of breast cancer patients were working but assistance with transportation, limitation in upper-body strength, and employment in jobs requiring physical activity were needed (Satariano & DeLorenze, 1996).

In light of this information, it is the general purpose of this study is analyse and describe the advantages of the individualized effect of training and exercise, with a clinic purpose, in the alteration of the aerobic/ muscular functions and quality of life outcomes in breast cancer patients during treatment.

2. Review

2.1 Cancer Related Fatigue

Every day people experience fatigue and this symptom is commonly associated with diseases such as depression, multiple sclerosis, arthritis and renal disease, as well as different medical and pharmacological treatments (Schwartz et al., 2001). Patients treated for cancer disease experience a different and more disruptive fatigue. In fact, cancer related fatigue (CRF) is the most prevalent and disturbing side effect of treatment for the majority of cancer patients. CRF is described as being more intense and overwhelming than fatigue before treatment, and exercise is an intervention proposed to reduce fatigue (Adamsen et al., 2004; Dimeo et al., 1999; Lucia et al., 2003; Oldervoll et al., 2003; Watson & Mock, 2004).

Cancer induces an abnormal inflammatory response with a high level of pro-inflammatory cytokines that are responsible for the progression and clinical deterioration of the disease (Winkelman, 2004). Cancer treatment itself contributes to muscular atrophy, through the use of high doses of immunosuppressant drugs such as cyclosporine, cyclophosphamide or glucocorticoids that increase the protein catabolism. The muscular atrophy is essentially the result of the production of tumour necrosis factor-alpha (TNF α) that accentuates the inflammatory response in the musculoskeletal structure (Winkelman, 2004).

Most investigators consider that the origin of CRF is multifactor and not just a result of a single factor (Lucia et al., 2003; Ryan et al., 2007; Stasi et al., 2003; Watson & Mock, 2004); on top of that, the interaction between the various aetiological mechanisms is complex. In fact, fatigue represents just a part of the problem that is the physical incapacity experienced by cancer patients. Fatigue is usually defined as a sensation of lack of physical strength, weakness or loss of energy. However, fatigue becomes a pathological condition when it persists in ordinary daily activities, perseveres during a long period of time, does not improve with rest, or becomes severe enough so that it reduces daily physical activity (Dimeo, 2000). Although surviving cancer is a growing reality, medical intervention is almost always necessary.

2.1.1 Treatments and Toxicity

The most common treatments for cancer are surgery, radiotherapy and chemotherapy. Despite these medical interventions, the patients' quality of life may suffer consequences. Since in 60% of cases of cancer survivors surgery is used, depending on the location and the extent of the operation, a significant morbidity may occur (complications with wounds, infections, loss of function, diminished movement amplitude, diarrhoea, dyspnoea, pain, drowsiness and lymphatic oedema) (Courneya, 2003).

Radiotherapy is used at a certain stage of the treatment in approximately 50% of cancer survivors. Generally, radiotherapy is administered in small fractions repeated over a period of 5 to 8 weeks to maximize the cellular death of the cancerous cells and minimize the damage to normal cells (Courneya, 2003). However, it can induce toxicity in normal cells and depends on the location of the radiation (pain, blistering, reduced elasticity, diminished movement amplitude, nausea, fatigue, pulmonary fibrosis, dry mouth, and cardiomyopathy).

The tumour suppressor protein p-53 is required for most DNA-damage-induced apoptosis. Unfortunately, mutations in the p-53 gene are observed in upwards of 70% of human cancer cases, thus reducing the efficacy of some therapies (63-14). After surgery to remove a tumour (lumpectomy or mastectomy), high levels of ionizing radiation are used to destroy any remaining breast cancer cells in the breast, chest wall, or axillary area. Cell death from radiation therapy occurs primarily during mitosis, when extensive DNA damage makes duplication of the genome impossible (mitotic cell death). P-53 Dependent apoptosis occurs at the G1 checkpoint of the cell cycle and ensures that DNA carrying genomic defects is not replicated. However, in the absence of p53, or when p53 is not functional, the cells become insensitive to low doses of radiation. A high dose of radiation induces necrosis and cytoplasmic constituents being released into the surrounding tissue, which serves as potent inflammatory signals (Bower et al., 2009). Recent data suggest that the fatigue experienced with radiation therapy is associated with the activations of proinflammatory cytokines (Bower et al., 2009).

Systemic therapy is prescribed in several types of cancer. This treatment may be chemotherapy, hormone therapy and immunotherapy. Chemotherapy is administered intravenously or orally, in repeated cycles during 2-4 weeks from 3 to 6 months. Chemotherapy may cause some adverse effects such as fatigue, anorexia, nausea, neutropenia, peripheral neuropathies, ataxia and cardio toxicity. Furthermore, approximately 55% of patients are submitted to adjuvant chemotherapy during the intervention.

Chemotherapy drugs can disrupt the cell cycle at several critical steps and thereby induce apoptosis. *Taxane drugs* work to bind and stabilize cell microtubules to prevent them from separating chromosomes during cell division (anaphase of mitosis), thereby arresting cell cycle; *doxorubicin* (adriamycin) prevents DNA replication by inhibiting the enzymes, topoisomerases, that cut on strand of the DNA to unwind it during replication; and *5-fluorouracil* (5FU, adrucil) inhibits thymidylate synthetase that functions to incorporate the thymine nucleotide into DNA during replication. Some of the more rapidly dividing normal, healthy cells are damaged (e.g. hair follicles, blood cells), subsequent mitosis from resident stem cells can soon replace those lost to chemotherapy or radiation (Clarkson & Kaufman, 2010). Over the past years, different studies have shown that fluorouracil, doxorubicin and cyclophosphamide (FAC) regimen as an adjuvant therapy for early stage of breast cancer is an effective treatment. Moreover, the doxetaxel, doxorubicin and cyclophosphamide regimen (TAC) has recently shown significant improvements in the rates of disease-free and overall survival even more than FAC (Lee et al., 2009). Some studies showed that TAC was more toxic than FAC with respect to neutropenic fever events and many extra hematological side effects such as asthenia, stomatitis, diarrhea and myalgia (Martin et al., 2005). Moreover, breast cancer patients who received TAC as treatment had less QOL scores, compared with FAC after the end of chemotherapy. Nevertheless, these differences gradually disappeared in different scales of QOL lasting for months after finishing chemotherapy (Bastani & Ahmad Kiadaliri, 2011). So, during follow-up period, patients in the TAC group experienced a higher improvement than FAC group.

Hormone therapy is administered orally and can have several side effects such as weight gain, loss of muscular mass, accumulation of fat mass in the torso

and face, osteoporosis, fatigue and increased susceptibility to infections (Demark-Wahnefried et al., 2012). Lastly, immunotherapy is a recent form of treatment that maximizes the effect of other drugs as well as the defence mechanisms against cancerous cells. However, currently, in several clinical cases a combination of various types of treatment is being applied. In this situation, the timing and the treatment sequence depends on the staging and type of cancer. Consequently, it is possible that some cancer survivors may be treated on several occasions with different forms of treatment (Courneya, 2003). The supply of oxygen to the mitochondrion is a critical factor in the regulation of energy production. An adequate supply of energy to the cells requires the integrity of all the stages in the capture cascade, transport and use of oxygen. Anatomical and functional alterations due to the treatment of cancer can affect cells' oxygen supply. On the other hand, the treatment itself, in inducing cardiovascular toxicity, can cause a dysfunction of the left ventricle (indicated by diminished systolic volume), ventricular contractility alterations and consequently diminished cardiac debt. Furthermore, pulmonary toxicity resulting from the treatment may cause a reduction of the lung's full capacity, diminished vital capacity, a reduction of the inspiratory and diffusion capacities which, in its turn, compromise O₂ and CO₂ gas exchanges (Schneider et al., 2007). Moreover, diminished pulmonary volume due to illness (pulmonary metastases and pleural effusion) or as a sequel of the treatment (lobotomy, pulmonary fibrosis after radiotherapy) may alter the ventilation-perfusion ratio, causing difficulty to the saturation of haemoglobin (Lucia et al., 2003).

Therefore, the treatment of cancer can reduce O₂ transport capacity through the aerobic path by the different path of physiological mechanisms (Dimeo, 2000; Lucia et al., 2003).

This toxicity is often observed in women with breast cancer during and after treatment. However, these negative effects can be attenuated through the intervention of an exercise programme. By means of an exercise intervention of 3 weekly training sessions over a period of 6 months, between 45-75% HR_{max}, Schneider et al. (2007) observed, in breast cancer survivors, improved systolic arterial pressure (-2.6%), diastolic arterial pressure (-3.4%), and cardiac frequency at rest (-4.0%), while pulmonary capacity assessed by vital capacity

improved (+2.8%), as did maximum oxygen consumption (+15.1%). In the specific case of chemotherapy, the marrow may be affected, which consequently diminishes the production of red blood cells. Cardiotoxic cytostatic agents, such as anthracycline and cyclophosphamide, can reduce blood flow to the musculo-skeleton (Dimeo, 2000).

The loss of muscular function induced by a prolonged period of bed rest can result in a substantial loss of muscular mass, plasmatic volume and reduced cardiac output that impairs energetic efficiency (Levine et al., 1997). This clinical status is very similar to being bedridden, since 6 weeks in this condition was enough to induce diminished left ventricular mass in $8.0 \pm 2.2\%$ and is connected to reduced final diastolic volume on the second week in $14 \pm 1.7\%$ (Perhonen et al., 2001). Furthermore, treatment with high doses of corticosteroids results in diminished muscular mass. Inducing immunosuppression using cyclosporine (CsA) may result in mitochondrial myopathy, loss of capillary density and, consequently, loss of physical capacity (Zbreski et al., 2006). CsA is an immunosuppressant commonly used in organ transplants. This drug acts as a cytosolic phosphatase protein inhibitor in T-Killer lymphocytes. In the Zbreski et al. (2006) study, the administration of CsA resulted in muscular atrophy, inducing a 22% decrease in fiber cross-sectional area. These last occurrences are clinically indistinguishable from alterations caused by detraining or by reducing physical activity.

The majority of breast cancers are estrogen receptor-positive, although estrogen receptor negative disease is more frequent in premenopausal (37%) than postmenopausal women (21%) (Anderson et al., 2002). Breast cancers that occur in younger women are of concern because these cancers are often hormone receptor negative (estrogen receptor [ER]- and progesterone receptor [PR]-), are high grade, and are diagnosed at advanced stages (Klauber-DeMore, 2005). Current treatment guidelines recommend that premenopausal women with hormone receptor-negative disease receive adjuvant chemotherapy, and that those with hormone-positive disease receive adjuvant endocrine therapy (tamoxifen +/- ovarian function suppression) with or without adjuvant chemotherapy based on the biology and extent of the primary tumor within the breast and regional lymph nodes (Burstin et al., 2010). Among the

adjuvant therapy options for premenopausal patients with breast cancer, both endocrine therapy (ovarian suppression or tamoxifen) and chemotherapy can result in substantial bone loss from suppression of estrogen levels (Headley et al., 1998; Nikander et al., 2012).

Women who have premature menopause as a result of chemotherapy due to breast cancer are at an increased risk of bone loss and may be at risk for early development of osteoporosis (Headley et al., 1998). Moreover, women who became permanently amenorrheic as a result of chemotherapy had 14% lower bone mass density than women who maintained menses after chemotherapy (Headley et al., 1998). Rates of bone loss occurring with cancer therapy can be up to tenfold higher than normal (Guise, 2006).

Nikander et al. (2012) examined the impact of aerobic exercise training (3x/week) in bone structural strength and observed a positive training effects on bone structural traits (1.2%), physical performance (~3-4%) and body composition (~1-3%) in breast cancer patients. However, resistance training is more effective in maintaining bone density (Schwartz et al., 2007). Knobf et al. (2008) conducted 12-24 week supervised weight-loaded aerobic intervention with women with breast cancer who were 3 year from completing breast cancer treatment. Bone remodeling was measured by serum biomarkers and no significant changes in serum osteocalcin, or lean muscle mass were observed. However, women at high risk for weight gain and bone loss maintained their weight and bone mass. A home-based strength training intervention, in postmenopausal breast cancer survivors with osteopenia or osteoporosis, resulted in improvements on bone mineral density with a significant increase in muscle strength for hip flexion, hip extension, and knee flexion, and BMD of the spine and hip (Waltman et al., 2003). A controlled pilot trial was carried out to assess the feasibility and efficacy of an aerobic exercise in enhancing physical performance of breast cancer patients after adjuvant treatments. Aerobic and step training during 12 weeks and the magnitude of the load during training sessions, which seemed to be sufficiently high to increase bone mass in different patients, suggest that this kind of vigorous training regimen is feasible among breast cancer survivors and could have a potential to prevent bone loss from the adjuvant treatments of breast cancer. To prevent bone loss, intense

aerobic exercise appeared to be well-tolerated and an effective training mode among breast cancer survivors who had recently completed heavy adjuvant treatments such as chemotherapy (Nikander et al., 2007).

As cancer treatment regimens evolve, patients live longer but, sometimes, with the unwanted complication of anaemia. Anemia is a common haematologic manifestation in cancer and can increase the disease's aggressiveness, causes fatigue and reduces quality of life (QOL) and can also limit the treatment (Straus et al., 2006).

One of the many causes of CRF is anemia which comes with the disease and its treatment. Although it is not the only cause of CRF, anemia is the easiest to document using standard complete blood count haemoglobin (Hgb) levels for mild (10.00-11.99 g/dL), moderate (8.00-9.90 g/dL), and severe (<8.00 g/dL) anemia. These clinical definitions allow us to establish *criterion* of anemic cancer patients who can be tested for levels of self-reported fatigue and its impact on function (Cella et al., 2002).

Moreover, it has been demonstrated that a state of anemia is an indicator of a disease's independent prognosis (Ludwig & Strasser, 2001). It has also been demonstrated in cancer patients that a state of mild or moderate anemia (Hb values 10-12g/dL and 8-10g/dL, respectively) is significantly associated with a low survival rate (Ludwig & Strasser, 2001). In cancer patients, the incidence of chronic anemia depends on the type of malignancy, the staging and duration, and also type and intensity of treatment (Ludwig & Strasser, 2001).

A multinational study, comprising Europe, carried out by the European Cancer Anaemia Survey (ECAS) documented the prevalence, incidence and severity of anemia in a numerous and representative sample of the European cancerous population (Ludwig et al., 2004). In this study it was demonstrated that anemia was more frequent in patients with gynaecologic cancers (81,4%), lung cancer (77,0%) and lymphoma/myeloma (72,9%). Some authors report that the prevalence of anemia is particularly high in patients with lung carcinoma (50%-60% with Hb <11 g/dL) (Kosmidis & Krzakowski, 2005; Ludwig et al., 2004), especially when compared to less prevalence in colorectal and breast carcinoma (approximately 10-20%); the total incidence of anemia was 53,7%. In this case, patients that had been submitted to chemotherapy had a higher

incidence of anemia (63,7%) compared to concomitant chemo-radiotherapy (41,9%) or radiation therapy (19,5%) (Ludwig et al., 2004).

In the case of lung cancer, cytotoxic chemotherapy is one of the main factors that contribute to the probability of developing or aggravating pre-existing anemia (Dowlati et al., 1997). Therefore, the incidence of anemia depends on the chemotherapy treatment that is used. The combination of cisplatin and *etoposide*, commonly used in the treatment of small cell lung carcinoma (SCLC) is associated with severe anemia in 16-55% of patients (Itri, 2000). In advanced non-small lung cell carcinoma (NSCLC), one of the firstly used treatments is paclitaxel and platinum therapies. However, the combination of these two drugs can induce anemia in approximately 78% of patients and, approximately 33% of patients can develop severe anemia (Langer et al., 1995). In these cases, the mechanism involved in chemotherapy-induced anemia includes direct myelosuppression and, in some cases, loss of renal function. These data are reinforced by the ECAS study since chemotherapy treatment induced mild to moderate anemia in 8-100% of patients suffering from NSCLC and 0-87% in those with SCLC (Ludwig et al., 2004). Moreover, severe anemia (Hb < 8 g/dL) and life-threatening anemia (Hb < 6.5 g/dL) occurs in 0-40% of patients with NSCLC and 0-55% in those suffering from SCLC (Groopman & Itri, 1999). Because of this, approximately 43% of patients with lung carcinoma were given blood transfusions, while patients suffering from breast carcinoma receiving blood transfusions did not exceeded 19% (Kosmidis & Krzakowski, 2005). Therefore, we can conclude that platinum compounds (like cisplatin or carboplatin) seem to particularly induce myelosuppression.

Generally speaking, the hemoglobin values in the ECAS study are categorized between 10,0 and 11,9 g/dL. Nevertheless, the longer chemotherapy is used the higher is the risk of developing anemia. This fact was confirmed by progressive proportion of patients with low levels of hemoglobin (i.e. <10,0 g/dL) as the cycles increased (Ludwig et al., 2004). In fact, anemia was observed in 19,5% of patients in the first cycle with an increased incidence to 56,7% on the fifth cycle of chemotherapy. If baseline hemoglobin level is approximately 15 g/dL and subsequently these values are reduced by 2 g/dL during the first 3/4 weeks of chemotherapy, 49% of patients are going to require a blood

transfusion to treat anemia at a certain stage during treatment. On the other hand, if a similar Hb decrease from a 11 g/dL baseline level occurs during the first cycle of treatment, practically all patients will need a transfusion (Langer et al., 2002). Therefore, it is necessary to determine the optimal cut-off value for the treatment of anemia, which is a critical criterion to maximize quality of life and possibly other outcomes in cancer patients. The ASH/ASCO guidelines recommend that treatment using erythropoietin starts when hemoglobin values decrease to <10,0 g/dL (Rizzo et al., 2002). Besides, when patients are symptomatic due to anemia and hemoglobin values are between 10 g/dL and 12 g/dL, the decision of implementing the start of the treatment is at the doctor's discretion (Ludwig et al., 2004).

Furthermore, the ECAS study revealed that patients with lower hemoglobin values also had lower WHO Performance Scores when compared to those with higher hemoglobin values. 50,7% of patients with <8,0 g/dL hemoglobin had 2-4 WHO scores, as did 40% of those with 8.0-9.9 g/dL hemoglobin. On top of which, almost a quarter (24,8%) of patients with 10,0-11,9 g/dL hemoglobin had 2-4 WHO scores (Ludwing et al., 2004). These results can lead to a better understanding of anemia when associated with cancer therapy, thus optimizing the patient's treatment and improving quality of life during that period. These results are reinforced by the Cella study that analyzed the use of Functional Assessment of Cancer Therapy (FACT) to assess the impact of fatigue or anemia in cancer patients' QOL. Patients with Hb > 12 g/dL (defined as non anemic) felt less fatigue, better wellbeing and higher general levels of QOL, when compared to those who were not anemic (Cella, 1997).

Moderate physical exercise can be a strategy to increase hemoglobin. In the specific case of breast cancer, women who undergo radiation therapy are prone to diminished erythrocyte levels during the months after treatment. As previously analyzed, this erythrocyte decrease appears to be associated to complications that include fatigue, anemia, depression and reduced physical functioning (Lucia et al., 2003). Furthermore, diminished erythrocyte levels seem to be connected to a decrease in the survival rate in some types of cancer. Drouin et al. (2006) studied the influence of moderately intense aerobic exercise and its positive effect in hemoglobin (HB), haematocrit (HCT) and red

blood cells (RBC) in women with breast cancer in stages 0 to 4 (Tis, N0, M0; to T0-4, N3-M0) subjected to a 7-week radiation therapy regimen (Drouin et al., 2006). The exercise intervention consisted of walking 3 to 4 times a week, at an intensity between 50% and 70% CF_{max} . Through this research, investigators observed that moderately intense aerobic exercise during radiation therapy in breast cancer prevented the reduction of erythrocyte levels when compared to control group. Moreover, the authors verified a positive correlation between the peak of aerobic capacity and the final erythrocyte evaluation, corroborating the concept of the connection between erythrocyte level and improved physical capacity (Drouin et al., 2006).

2.1.2 Peripheral Fatigue and Central Fatigue

The main mechanisms of fatigue have been categorized in two principal components: peripheral fatigue and central fatigue. Peripheral fatigue is a result of the neuromuscular system's inability to carry out a task in response to central stimulation. Two recent studies have analysed the effect of radiotherapy in neuromuscular fatigue. Monga et al. (1997) observed in prostate cancer patients diminished neuromuscular efficiency (*a muscular function parameter*) in the anterior skeletal muscle tibia's fast fibres. The patients were submitted to a radiation treatment protocol with 68 to 70Gy in 34 to 38 fractions during a period of 7 to 8 weeks. However, when the effect of radiotherapy was studied, using certain psychometric scales, to ascertain the psychological and emotional state, and sleep parameters, no association was made between radiotherapy and clinical fatigue (Monga et al., 1997). Moreover, the same patients did not have diminished VO_{2max} , assessed by modified Bruce protocol, which led to the conclusion that neuromuscular instead of cardiorespiratory factors contribute mostly to increased muscular fatigue. Therefore, 68 to 70Gy of ionizing radiation in the pelvic area of patients who are undergoing treatment for prostate cancer, emphasizes neuromuscular fatigue. In the majority of patients, the fatigue persisted 5 to 6 weeks after radiotherapy had ended, which may indicate that the nature of the fatigue presumably resulted from subtle lesions in the muscular structure. Authors speculate that ionizing radiation may have altered the integrity of the sarcolemma, sarcoplasm and/or the integrity of the

mitochondrial membranes (Monga et al., 1997). This alteration causes a disruption in the strength producing mechanisms and/or a calcium abduction by the sarcoplasm and by the Ca-ATPase, which entails a deficiency in the excitation-contraction process (Bigland-Ritchie et al., 1995). Furthermore, this alteration in the cytoskeleton can cause an electrolyte gradients' imbalance in the cellular membranes, thus inducing a K^+ accumulation in the extracellular medium (plasma). In the Agroyannis et al. (1992) study, it was observed that in 21 patients with malignant tumours (lung, breast, endometrium and prostate), 36 to 60Gy of radiation during 20 to 30 fractions of radiotherapy caused a significant increase in the release of seric transferrin and TNF- α .

On the other hand, central fatigue affects the central nervous system and is the result of a progressive failure in the transmission of stimuli by the motoneuron. A study on patients with chronic fatigue syndrome demonstrated that a plasmatic free tryptophan increase can potentially lead to a high level of cerebral serotonin (5-HT) (Castell et al., 1999). The tryptophan and the branched-chain amino acids (BCAAs) compete to enter the brain through the same transport – albumin (Ryan et al., 2007). Several protocols that use exercise as a way to induce fatigue reveal that the increase of cerebral 5-HT levels during exercise is the result of a reduction of BCAAs, which allows the tryptophan to enter the brain through the hematoencephalic barrier. On top of which, exercise increases the concentration of plasmatic free fatty acids that bind with the albumin, causing an increase of free tryptophan in the plasma. Supporting this, research on animal models has demonstrated that concentrations of cerebral 5-HT increase during exercise, reaching the highest concentration at the point of fatigue (Ryan et al., 2007).

2.1.3. Exercise and cancer related fatigue

More recently, exercise has been tested in the treatment/reduction of cancer-related fatigue (Dimeo, 2001; Winningham, 2001). Schwartz et al. (2001) showed that fatigue was significantly reduced on exercise days compared with non-exercise days. Furthermore, the amount of exercise, measured by the number of minutes of actual practice, was significantly associated with fatigue

levels. There is growing evidence that aerobic exercise programs can reduce fatigue in cancer patients receiving chemotherapy (Adamsen et al., 2004; Adamsen et al., 2006; Dimeo et al., 2003; Dimeo et al., 1999; Quist et al., 2006; Schwartz et al., 2001; Winningham et al., 1989).

Mock et al. (2001) studied the effect of home-based exercise at least 90 min per week for three or more days in women with breast cancer who reported significantly less fatigue and emotional distress as well as higher functional ability and QOL than the women who were less active during treatment.

The literature describes exercise as having potential importance in the quantitative reduction of fatigue. The qualitative data in this study highlight the experience of cancer patients having a comfortable sense of fatigue while simultaneously improving their physical form and increasing their strength. Data from Adamsen et al. (2004) describe different forms of fatigue in cancer patients. The sensation of fatigue which results from exercising (i. e. exercise induced fatigue) is experienced as a positive and natural tiredness and is furthermore associated with an after-effect of improved physical well-being, tranquillity, release, relaxation, and, for some, typically improved sleep (Cella et al., 2002). It is a sense of fatigue that is desirable because the after-effects are familiar as they were experienced during sports activities prior to their illness (Watson & Mock, 2004). This contrasts with fatigue induced by chemotherapy which can be characterized as negative because of its connection with the experience of physical discomfort. It is not a sense of fatigue that is desired but rather is imposed on the body from the outside through medication, and usually leads to a passive physical state. Adamsen et al. (2004) showed that cancer patients can transform the nature of fatigue – from a negative chemotherapy induced fatigue into a positive exercise induced fatigue.

The impact of exercise on fatigue was significant and reflects the effectiveness of low to moderate intensity regular exercise in maintaining functional ability and reducing fatigue in patients with breast cancer. Exercise was consistently associated with reducing fatigue the day of exercise and one day afterward over the first two cycles of chemotherapy in breast cancer patients (Schwartz et al., 2001). However, current level of fatigue increased when exercise exceeded 60

minutes, probably due to changes in nutrition and hydration states (Schwartz et al., 2001).

In short, physical inactivity induces an accentuated loss of muscular mass and loss of cardiorespiratory capacity. Therefore, lack of physical activity causes a tendentiously perpetual condition of diminished activity leading to fatigue and vice-versa (Figure 1). This mechanism may explain persistent fatigue and physical performance impairment in several patients, even years after ceasing of treatment (Dimeo, 2000; Lucia et al., 2003).

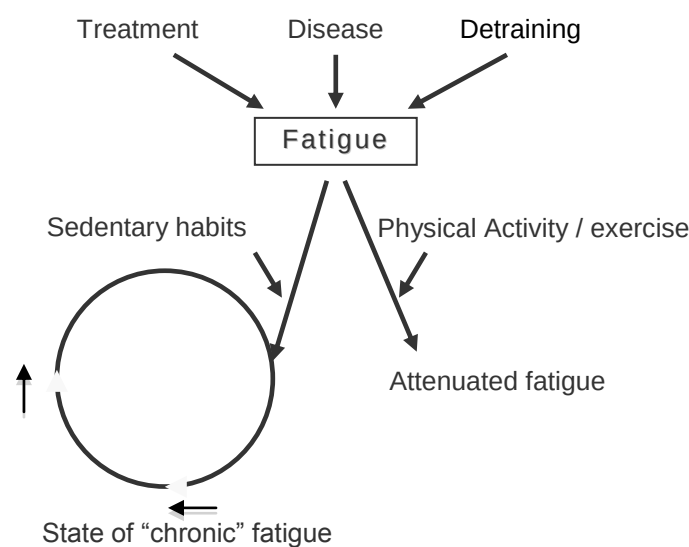


Image 1: Effect of treatment, disease and detraining in Cancer Related Fatigue (Adapted from Rundle, (Rundle, 2005).

In a cross sectional study, 3 years after breast cancer treatment, persistent pain and sensory disturbances remain clinically significant problems among 47% breast cancer patients who received surgery (Gartner et al., 2009). In fact, fatigue and pain overlap, and both seem to be additionally associated with mental health (Gartner et al., 2009).

The cause of pain in cancer patients and in general, remains unclear. A 4 year follow-up showed an increase in pain symptoms in those women taking tamoxifen at baseline; in those reporting depression or stressful life events during the first 12 months after enrolment. Nevertheless, exercise at baseline had a beneficial effect on pain recovery (Rief et al., 2011). So, pain should be a major outcome in evaluations of cancer treatment and rehabilitation programs.

In 2009, with support from Siteman Cancer Centre and the Oncology Nursing Society, the ACSM convened an expert roundtable to review the literature on exercise in cancer survivors and issue guidelines for activity, along with recommendations on exercise testing and prescription (Schmitz et al., 2010). The ACSM guidelines for cancer survivors emphasis on returning to normal daily activities as quickly as possible after surgery and continuing these activities as much as possible during any adjuvant treatments (Wolin et al., 2012).

Low to moderate exercise interventions of variable duration seem to be the standards applied across existing studies. Predominantly, those studies have examined the effects of a single activity, e.g. cardiovascular training on stationary bicycles, rather than resistance to the exercise as the one of modality (Galvao & Newton, 2005). More studies are needed to provide evidence of whether specific patient groups, at different stages of the disease and/or with different diagnoses and treatments, can benefit from exercise. So, due to the lack of evidence, no recommendations can be issued at present (Lucia et al., 2003).

A multidimensional 6 weeks high intensity exercise training design intervention in cancer patients with different types of solid tumours and haematological malignancies undergoing chemotherapy, increased VO_{2max} in 16% and dynamic strength of 40%. Furthermore, it was observed a significant reduction in treatment-related symptoms and significantly improved their general well-being and quality of life specifically with a reduction of fatigue and pain (Adamsen et al., 2006). In accordance with these results, Kolden et al. (2002) verified through a supervised 16 week program involving cardiovascular, resistance and flexibility training, 1h three times a week in 40 sedentary women with breast cancer, an increase in strength of 36% and in cardiovascular capacity of 15%. These results suggest that cancer patients undergoing chemotherapy may benefit from a multidimensional exercise interventions.

Knutsen et al. (2006) reported any adverse effects such as unintentional physical reactions, cardiac, or respiratory arrest, or hypotension during VO_{2max} and 1RM strength test in cancer patients undergoing chemotherapy. The study

showed that patients felt significantly safer in performing the maximum physical capacity tests and in using their bodies in a 6 week high intensity training.

2.2. Cancer, exercise and quality of life

Investigation regarding exercise in cancer survivors began in the early 80's but published articles became consistent in the late 90's only. The Alberta University in Edmonton, Canada, by means of investigator Kerry Courneya, has been a driving force in clinical trials in this area (Courneya, 2003; Courneya et al., 2008; Courneya & Friedenreich, 2011).

The positive effect and the advantage of exercise in cancer patients were described for the first time by (Winningham et al., 1989).

Physical exercise is one of the foremost areas of research in cancer control with potential to improve the lives of cancer; the context "cancer survivor" indicates any person who has or had cancer, from the time of diagnosis onward (Ingram & Visovsky, 2007). The psychological and physical symptoms resulting from cancer and its treatments (e.g., pain, fatigue, nausea, vomiting, depression) will contribute to excessive patterns of rest and also contribute to immobility. Bed rest will precipitate muscle weakness, atrophy, and functional impairment (Ingram & Visovsky, 2007).

Evidence of the benefits of exercise for cancer survivors has mounted steadily over the past in the areas of psychology and quality of life outcomes. Recently, improvements in physical functioning, body weight and composition, muscle strength and endurance (Quist et al., 2006), and immune function have been reported.

The exercise interventions are low to moderately intense (exercise intensity between 55% and 85% HR_{max}) with very similar protocols throughout the various studies (Courneya & Friedenreich, 1999; Dimeo et al., 1999). These rules are in accordance with ACSM guidelines, that state that 6 to 7 weeks of training are enough to obtain significant muscular hypertrophy gains. As to the frequency of training, two to three weekly training sessions are sufficient to promote the desired adaptations (Garber et al., 2011).

Several clinical trials have studied the relationship between clinical exercise, quality of life and psychosocial parameters in cancer survivors. The exercise programs in the trials consisted mainly of 3 weekly sessions of moderate and vigorous exercise, with a duration that increased progressively up to 45` over a period of 3 to 4 months. These studies demonstrated that exercise reduced anxiety, depression, improved self-esteem and diminished fatigue-related symptoms (Herrero et al., 2006; Quist et al., 2006).

One of the best direct indicators of cardio respiratory capacity is VO_{2max} . This variable is an excellent indicator of a person's health condition and an independent mortality predictor in healthy or unhealthy individuals (Garber et al., 2011). Initially, some authors alerted to the possibility that vigorous exercise, including maximal physical evaluation tests, could impair the cancer patient's health during chemotherapy due to the administered drugs' adverse effects. However, contrary to what was expected, the study carried out by Knutsen et al. did not observe adverse effects such as hypotension, cardiac or respiratory arrests, during the assessment of aerobic and muscular functions following maximum protocols (Knutsen et al., 2006).

Obesity is a risk factor for some of the most common cancers in the western world, such as post menopausal breast cancer and colorectal cancer. This is one of the reasons why cancer patients are overweight or obese at the time of diagnosis (Brown et al., 2003). Furthermore, there is strong evidence that excessive weight increases the recurrence risk in several cancers, as well as increased mortality risk (Eheman et al., 2012). At present, the International Agency for Research on Cancer estimates that 25% of cancer cases are caused by excessive weight, obesity and a sedentary life (Ahlberg et al., 2003). The current tendency of increasing number of adults and children that are overweight or obese and, simultaneously, have low levels of physical activity makes the connection of their lifestyle with cancer a matter of public health (Campbell & McTiernan, 2007). Therefore, exercise has been used as a mean to reduce obesity and to promote a healthy lifestyle.

Empirically, strength training is generally inappropriate for people with an illness as well as for cancer survivors, and for this reason there is still little investigation on the potentials of this type of training. However, several studies have

observed improved quality of life in cancer patients even when the exercise program is discontinued for a period of time due to a specific reason (anemia, infections and demotivation). An 8-week exercise program of aerobic training combined with strength exercises, with 3 weekly 90 minute sessions, in women with breast cancer, significantly increased muscular mass and reduced fat mass and these improvements were linked to an improved quality of life (EORTC QLQ-C30) (Herrero et al., 2007). On top of that, in breast cancer survivors, even after an 8-week detraining period QOL was not diminished, as were not dynamic force and specific functional tasks of muscular capacity. However, the same period of detraining reduced cardio respiratory capacity by $\sim 6 \text{ ml} \cdot \text{Kg}^{-1} \cdot \text{min}^{-1}$ ($\text{VO}_{2\text{peak}}$) (Herrero et al., 2007). Therefore, cardiorespiratory adaptations are quickly lost. Nevertheless, strength training should be integrated as a component in a training program since it attenuates muscular atrophy induced by treatment and sedentary habits in cancer survivors (Inui, 2002). In this case, ACSM guidelines recommend that 6 to 7 weeks of training are enough to obtain significant muscular hypertrophy gains. As far as frequency is concerned, 2 to 3 weekly training sessions are sufficient for both men and women (Schmitz et al., 2010). In fact, aerobic and strength training improves quality of life in a way that is practically unparalleled in patients with various types of cancer, that is to say, an increase of almost 43% in dynamic muscular force accompanied by a 21% increase in the improvement of QOL after 18 weeks of aerobic and strength training (De Backer, Van Breda, et al., 2007).

In another recent study, during the hospitalization of patients submitted to high-dose chemotherapy, an exercise program of aerobic resistance that consisted of pedaling for 30 minutes on a reclined cycle ergometer, reduced fatigue and loss of physical performance. On the other hand, chemotherapy-related complications, namely aplasia (quantity of neutrophils $< 500/\text{mL}$ and platelets $< 20,000/\text{mL}$) and duration of hospitalization, were significantly inferior in the trained group, when compared to the control group (Dimeo et al., 1999).

In the specific case of prostate cancer treatment, the deprivation of androgens can cause an adverse effect – bone mineral density loss, progressing to osteoporosis. It is described that this bone mineral density loss, of 3 to 5% in the first years of treatment, results in a higher incidence of fractures

(Friedenreich, 2001). Therefore, not only has exercise an important role in preventing prostate cancer but it also prevents the adverse effects that can occur during therapy (Campbell & McTiernan, 2007).

Since approximately 60% of cancer survivors are 65 years old or more, there has been an interest in studying the potentials of exercise in these ages. In fact, since aging is connected to a decline in neuromuscular function and diminished capacity to synthesize proteins, the scientific community questions whether the elderly are subject to physical exercise's positive adaptations. Besides, studies in the last decades have demonstrated that the elderly revealed improved physiologic function and positive adaptations such as those that were observed in younger adults (Drouin, 2004). Exercise, in this type of population, requires some precautions in several situations due to some contraindications.

Psychological factors also have an important function in the aetiology of cancer-related fatigue's genesis. In this particular case, depression is considered a contributing factor to fatigue in cancer patients. The effect of physical activity is not limited to improved muscular and cardiovascular functions. In fact, improved physical performance can increase a patient's sensation of control, independence and self-esteem; this improved self-esteem can result in better social interaction, reduced anxiety and fear (Dimeo, 2000).

Segal et al. (2001) did not observe any effect of structured exercise on aerobic fitness and in HRQOL in breast cancer patients during treatment. These results are, to some extent, in line with (Thorsen et al., 2005) who did not observed any beneficial effect on fatigue, mental distress and HRQOL parameters of the 14-week supervised home-based training program intervention shortly after chemotherapy. The fact that patients performed multiple supervised activities by themselves could represent additional stress for them. However, VO_{2max} increased by $6.4 \text{ ml/kg/min}^{-1}$ in the patients in the interventions group and only $3.1 \text{ ml/Kg/min}^{-1}$ in the patients in the control group corresponding to 23% and 10%, respectively) showing a beneficial effect on CRF in young and middle-aged cancer patients. Opposite to this findings Segal et al. (2003) demonstrated a positive effect of a 12-week supervised strength-training program on fatigue and overall HRQOL in men receiving androgen deprivation for prostate cancer.

Dimeo, Fetscher, et al. (1997) observed a positive effect of an interval exercise, using a cycle ergometer in bed, on fatigue and psychological distress in cancer patients during hospitalization.

Courneya et al. (2003) reported a positive effect on fatigue and in overall HRQOL in breast cancer patients several months after treatment.

Burnham and Wilcox (Burnham & Wilcox, 2002) observed a significantly higher overall HRQOL improvement in the exercise group compared with the control group but mental distress between groups was the same.

Mock et al. (1997) demonstrated a positive effect of a 6-week individualized self-paced progressive walking program on fatigue and anxiety in breast cancer patients during radiotherapy. However, there were no significant differences between the exercise group and the control group in depression.

The magnitude of changes in mental distress, fatigue, and HRQOL parameters in trials in this area are not consistent. It is not clear enough whether these differences of outcome are the result of differences in the patients characteristics and/or the type and the timing of the intervention or if these variations are explained by different methods of assessment (Thorsen et al., 2005).

The application of the principles of exercise training (specificity, overload, progression, initial values, reversibility and diminishing returns) in a design of an exercise prescription ensures the most appropriate type and dose of exercise to promote the desired outcome (Campbell et al., 2011).

De Backer et al. (2009) conducted a systematic review to summarize the research of previous studies that used resistance training with cancer patients. The duration of the resistance training programs ranged from 3 to 24 weeks, with an average of 12 weeks and most of them prescribed two or three sessions per week. Furthermore, most of the studies applied resistance with aerobic training. Few studies described the number of sets and repetitions, and among 10 of them, intensities ranged from 30-60 to 60-85% of 1RM. With regard to aerobic exercises, treadmill walking and stationary cycling were the most frequently prescribed sessions. Intensities of aerobic exercises varied from 40% to 90% of heart rate maximum. Studies incorporating resistance training prescribed either exercises using machines or resistance bands (Spence et al.,

2010). As outcomes measures, most of the studies assessed muscle strength (1RM), endurance tests (maximal number of repetitions at 60-75% of 1RM), hand grip tests. The results demonstrate that increases in muscular strength occur in women with breast cancer who receive resistance training (Loprinzi & Cardinal, 2012).

Evidence suggests that health professionals might encourage breast cancer's patients to increase physical activity in a consistent way during treatment, because regular practice of exercise, as soon as possible after surgery and during treatment, may reduce secondary effects.

Patients with breast cancer should start to increase gradually their physical activity to a 150 minutes per week within an moderate intensity or to a 75 minutes per week at a vigorous intensity as soon as they finish their chemotherapy or radiotherapy treatments; as well as patients reaching progressively the minimum exercise guidelines, should be persuaded to increase their physical activity level to 180 minutes per week of moderate intensity up to vigorous intensity, because these activity levels are necessary to prevent the recurrence of breast cancer (Holmes et al., 2005).

3. Objectives

The main objective of the study was to examine the effect of 12 weeks of supervised exercise in physical capacity, lower and upper body strength and QOL, in breast cancer patients, during treatment.

Primary outcome was measured through the change in cardiovascular fitness and strength and the evaluation of health related quality of life, between baseline and post intervention.

A secondary objective of the study was to assess the feasibility of supervised exercise program and respective effects upon cancer related fatigue, in breast cancer patients, during treatment.

Secondary outcome was assessed through the change VO_{2max} , power output and in pain and fatigue symptoms between baseline and post intervention program. Results were compared with a control group.

Another second objective of this study was to examine aerobic and muscle functional changes, induced by a 12 weeks combined aerobic and endurance exercise program, in breast cancer patients and compares it with healthy women.

This outcome was assessed through the changes in physical components between baseline and post intervention program, using health results as reference.

4. Material and Methods

Research Design

This study examines the effects of exercise during cancer treatment on physical fitness (primary outcome). Secondary outcomes will be the effects on improvement of health related quality of life, reduction of pain and fatigue. This study is designed as a pragmatic randomised controlled trial, with two study arms: a group of voluntary patients with an exercise program in addition to usual care; a control group receiving usual care and maintaining their normal physical activity. The supervised exercise program is a 12-week progressive intensity programme.

Measurements were made at baseline and repeated 12 weeks later - follow-up measurements. Moreover, at baseline and after the intervention program the results from the breast cancer patients are compared with a healthy group.

Patients

This clinical prospective study was conducted from October 2011 to May 2012. Participants were recruited in Mama Help - Support Centre for Breast Cancer Patients. A total of 51 breast cancer patients, aged from 32 to 67 years, receiving adjuvant treatments (chemotherapy, radiotherapy, endocrine therapy, or their combination) participated in this 12 week, controlled exercise intervention. All patients were operated previously submitted to surgery (either mastectomy or breast conserving surgery with sentinel lymph node biopsy, or axillary dissection).

Patients participating in the study met the following eligibility criteria: female gender, women with confirmed stages I-III breast cancer, aged 30 - 70 years and not fulfilling the current American College of Sports Medicine guidelines for adequate physical activity (<150 min per week) (Garber et al., 2011). Furthermore, patients should also have received at least one cycle of chemotherapy. Exclusion criteria were stage IV disease, the absence of systemic adjuvant therapy, pregnancy or lactation, severe cardiac disease (NYHA class III or more), myocardial infarction within 2 months, uncontrolled hypertension (blood pressure > 160/90 mm Hg), verified osteoporosis, other

serious illness or medical condition, which could contraindicate exercise, patients not capable of training (severe knee arthrosis, ligament or cartilage injuries at lower extremities), severe anemia (<8 g/dL) or platelet count lower than $50 \cdot 10^9/\mu\text{L}$. The Karnofsky performance status (KPS) was used as an observer-rated measure of functional ability (Brown et al., 2005). The patients had a Karnofsky performance status of 60 or higher.

All patients signed an informed consent. Participants were stratified by treatment and then randomly assigned into exercise and control groups (figure 2). Subjects were also informed that participation in the study was voluntary, all data would be confidential, and that they were free to abandon the study at any time without incurring changes in their usual cancer treatment.

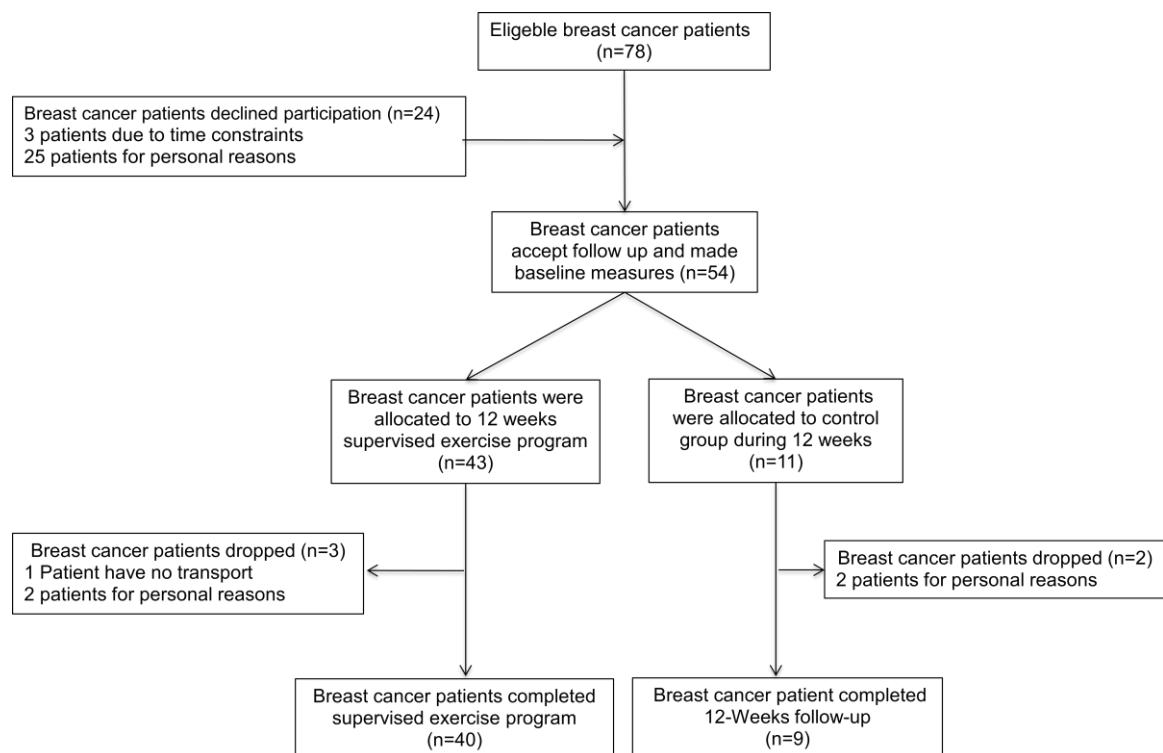


Figure 2: Flow of breast cancer patients through the study.

The Healthy control group (n= 15) was essentially a convenience sample, selected to match the anticipated age and gender profile of the patients with breast cancer. These women were not known to have cancer.

The ethical committee of Sports Faculty of University of Porto and the Ethical committee of Mama Help - Support Centre for Breast Cancer Patients approved the study protocol. The project was carried out in accordance with Helsinki Declaration.

Measurements made at baseline and at follow-up after the 12-week period

Patient Function

The Karnofsky performance status (KPS) was used as an observer-rated measure of functional ability.

Body composition

Fat mass percentage was calculated through bioelectrical impedance analysis (InBody 230 Biospac, Seoul, Korea). Body mass index (BMI) was calculated as weight (kg) / height (m)².

Handgrip performance

Maximal grip strength and fatigue resistance were measured using a mechanical handgrip dynamometer (Grip-D TTK5401, Tokyo, Japan). The elbow joint angle was flexed at a 90° angle with the wrist as close to 0° as possible. Trials were performed in an alternating bilateral sequence for a total of six attempts (three with each arm), and a rest period of 30 seconds was required between each trial to standardize test procedures. The patient was given clear instructions when to start and stop the contraction and was encouraged during the test to squeeze the handgrip as hard as possible. The mean of the three trials was calculated and averaged for each patient. We nominated the arm where the surgery was performed as the *handrip C* and the opposite as *handrip D*.

Functional muscle performance

Functional muscle performance was determined using a sit-stand test. For this test, we used a straight-backed chair (40cm high) and asked each subject to sit and stand, at their fastest pace, during 30 seconds with their arms folded across the chest. The final test score is the number of times that the patient rises to a full stand from the seated position with arms folded within 30 seconds.

Maximal isometric leg extension

Maximal leg extension was measured using a strain gauge (Globus, Codogne, Italy). In a seated position, in a chair with a knee angle joint at 90° and arms folded across the chest, patients realized at a command signal, maximal strength with quadriceps up to force reached maximum values. Trials were conducted with three attempts with an interval of two minutes between them; the average of the three tests was used as reference value.

Health-related quality of life

The assessment of HRQOL was performed by using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QLQ-C30), which is a psychometrically instrument designed to be applicable to a broad range of cancer patients (Aaronson et al., 1993). The instrument has been evaluated with regard to both validity and reliability (Fayers, 2001). QOL was measured using the questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC): the EORTC QLQ-C30 (third version 3.0).

The EORTC QLQ-C30 comprises five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, pain, nausea and vomiting), and six single items assessing additional symptoms commonly reported by cancer patients. It also includes two questions on patients overall quality of life and overall health condition, providing a global quality-of-life score. In the present study, the dimension of physical function, emotional function, role function, cognitive function and global quality of life were considered. Furthermore, symptoms of fatigue and pain were also analyzed. These scales

were transferred to a 0 to 100 scale, which was calculated by using the scoring manual provided by the EORTC (Fayers, 2001). For the physical function, emotional function, role function, cognitive function and global quality-of-life scales, a higher score indicates better level of functioning, whereas increasing values on the fatigue and pain scale indicate more symptoms.

The breast cancer module is meant for use among patients varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy and hormonal treatment). The module comprises 23 questions assessing disease symptoms (arms symptoms and breast symptoms), side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective. In the present study, for the BR23 questionnaire the arm symptoms and body image were considered. The scoring approach for the QLQ-BR23 is identical in principle to that for the function and symptom scales.

Cardiorespiratory fitness

All cardiorespiratory exercise tests were performed under similar environmental conditions (temperature ~20 °C; relative humidity 45 – 55%; barometric pressure – 720mmHg) on an electrically braked cycle ergometer (BH Fitness Tesis, Barcelona, Spain). After a warm-up period, of 5 min with no load, power output was increased from an initial value of 20 W by 10W·min⁻¹. The cadence monitor was placed in view of the subject during each test, and an exercise cancer physiologist insured that they maintained the required pedalling cadence throughout the duration of the test. The test was terminated upon volitional exhaustion and/or when cadence could not be maintained at a minimum of 60 rev.min⁻¹. (Herrero et al., 2006) Subjects refrained from performing physical activity during the 24h-period before the tests.

Expired respiratory gas fractions were measured using an open circuit breath – by-breath automated gas-analysis system (Cortex, Metalyzer, 3B, Leipzig, Germany). Before each test, flow, volume and gases were calibrated. HR was measured and recorded every 5 seconds using a HR monitor (Vantage NV,

Polar Electro, Kempele, Finland) that was connected with the gas-analyzer system.

Maximal oxygen uptake (VO_{2max}) and peak respiratory exchange ratio (RER_{peak}) were recorded as the highest value obtained for any continuous 20-second period. The workload eliciting the VO_2 at ventilatory threshold (VO_{2VT}) was determined using the criteria of an increase in both ventilatory equivalent oxygen ($VE.VO_{2-1}$) and end tidal pressure of oxygen ($P_{et}O_2$), with no increase in the ventilatory equivalent of carbon dioxide ($VE.VCO_{2-1}$).

Description of the Exercise Intervention Program

The patients in the intervention group received written information about some simple principles of training physiology. The exercise objectives, specified for breast cancer patients were set by literature search (Campbell et al., 2011; Herrero et al., 2006; Knutsen et al., 2006; Schmitz et al., 2010; Velthuis et al., 2010) and by seeking advices from cancer caregivers. Moreover, the exercise methods were developed in close cooperation with physiotherapists experienced in reahabilitation programs for cancer. Based on results from medical and cancer history, physical examination, and initial physiological and psychological assessment, an individualized exercise prescription was developed. Before each training session, a cancer exercise specialist, asked each participant a series of questions that would clarify the need to alter the exercise intervention, if necessary. Questions focused on how the patient felt after the last exercise session, if patient had muscle soreness or specific problems that would affect training (Schneider et al., 2007). Each exercise program was individualized according to baseline health and fitness levels. Patients trained in groups of four to six members and each session was supervised by the same experienced investigator. The patients in the exercise group trained two times per week for a 60 minutes period. The 60 minutes exercise program include a warming up (5 minutes), aerobic and muscle strength (50 minutes) and a cooling down (5 minutes).

The exercise program was composed of combination of cardiovascular training (cycle-ergometer), strength training, balance and core training, patient-specific rehabilitation and flexibility which were classified as either high or low intensity. Heavy resistance training and stationary bicycling who rise significantly the heart rate were categorized as high-intensity activities whereas patient-specific rehabilitation and flexibility, requiring lower energy expenditure, were termed lower intensity activities. The program was conducted in in specially designed workout room located in Mama Help - Support Centre for Breast Cancer Patients.

High intensity training

At the beginning of the program, aerobic training consisted of pedaling on a cycle-ergometer for a 15 minutes at 70% of maximal heart rate (HR_{max}), during the first four weeks, observed during the pre-training cardiorespiratory test. After week 4, we increased 5 minutes per week to allow patients to complete 30 minutes of continuous pedaling. For subjects with poorer physical condition, it was sometimes necessary to divide the first sessions into shorter time intervals to complete the 15 or 20 minutes workout in stationary bicycle (e.g., bouts of 5 minutes). The aerobic training was intended to be near to the anaerobic threshold but mostly aerobic. Nevertheless, individual anaerobic threshold could have been exceeded temporarily during the training.

Resistance training included exercise engaging major muscle groups (chest press, leg squat, leg calf rise, leg extension, adductor / adductor, abdominal crunch, arm extension, arm curl, dorsal). All exercises were performed through the full range of motion normally associated with the correct technique for each exercise. During the first 6 weeks, patients performed one and two set of exercises for large (e.g., Leg Squat) and small muscle groups (e.g. arm extension), respectively, and all sets were performed at a resistance that allowed 12 – 15 repetitions. Thereafter, the resistance used was individually adjusted and increased to allow the completion of 8-10 repetitions for four sets for large muscle groups and 3 sets for small muscle groups. Abdominal and lower back exercises were performed in 15-20 repetitions.

Steps aerobics exercises were also used in resistance training and consisted of several, typical step movements resulting in a total of 150-200 jumps (Thorsen et al., 2005). Moreover, Circuit-training consisted of 5 to 6 different vigorous exercises such as abdominal, squats, leg extension, chest press and leg calf rise. Duration of each circuit training movement varied from 30 to 40 seconds with half resting period between consecutive movements. During training sessions, the training intensity was occasionally monitored with heart rate measurements to ensure the consistency between self-rated and actual exertion levels.

Furthermore, patients were advised to maintain their exercise intensity comparable to a level between 12 and 14 (slightly strenuous to strenuous) of the Borg scale, a numerical scale used to rate perceived exertion (Borg et al., 1985).

Low intensity training

The exercise sessions concluded with an extremely low-intensity cool down that targeted all major muscle groups, as flexibility or balance exercises. Flexibility comprised some exercises that emphasized all major muscle groups.

Contraindications

In accordance with the guidelines and safety precautions defined by Dimeo et al. (1999), pre-exercise screening and monitoring was performed. Patients undergoing chemotherapy or radiotherapy and with one of the following criteria were instructed to interrupt physical training on the specific day: leukocyte $<0.5 \times 10^9/L$, hemoglobin $<6\text{mmol/L}$, thrombocyte concentration $<20 \times 10^9/L$, respiratory frequency >20 , pulse at rest <100 bpm, and temperature above 38°C . In cases of infection, a pause in training was recommended until the patient had been asymptomatic for a day and then training can be slowly resumed (Pedersen & Saltin, 2006).

Control Group

Patients assigned to the control group received usual care, i. e., no exercise intervention. They will be asked to maintain their habitual physical activity pattern but after completion of the present study, control subjects were offered participation in a rehabilitation programme for cancer patients (Schmitz et al., 2010).

Statistical Analyses

Characteristics of the patients at baseline and after 12-weeks intervention were expressed either as means and standard deviations or proportions. Baseline differences in each characteristic between intervention group and control group were tested with unpaired sample t-tests and Pearson chi-squares tests. Paired sample t-tests were used to compare each characteristics over time (baseline and 12-week follow-up). General linear model (GLM) for repeated measures was used to compare each characteristic over time (baseline and 12-week follow-up) with group assignment and time x group interaction included as fixed effects. For each characteristic analyzed, change scores were calculated as the difference between baseline and 12-weeks values; the difference was then divided by the initial value to estimate percentage or relative change. None of the measures showed significant deviations from a normal distribution (Shapiro-Wilk test). Significance level in all analyses was set at 0.05. Statistical analyses were conducted using SPSS version 20.0.

5. Results

Compliance and adherence to exercise program.

The flow of participants through the study is illustrated in figure 2. Briefly, 82 breast cancer patients were assessed for eligibility when contacted personally, and 54 accepted to participate in the study. Forty three of the 54 were allocated in exercise intervention program and 11 on the control group. Despite the demanding nature of this exercise intervention, 40 of 43 patients (93%) were able to complete a 12-week exercise program, which indicates a high level of compliance. Three patients with breast cancer did not go onward within the exercise programme, after the baseline evaluation (7%): two of them justified with personal reasons, and the other one had no regular transport from home to the place where the program was being monitored. Within the control group, nine from the eleven patients who realized the baseline evaluation (81.8%) did execute the follow-up, and they concluded the evaluation in week 12. Demographic, anthropometric, body composition and descriptive characteristics are shown in Table 1. There are no significant differences between groups in any baseline characteristic except in treatment. Control group has, on average, a higher weight and BMI than the exercise intervention group.

Table 1: Baseline demographic characteristics, diagnosis and treatment according to group.

Variables	Intervention Group (n=40) ³	Control Group (n=9) ³	p	Healthy Group (n=15)
Age, y	48.9 (8.7)	49.7 (8.4)	0.805 ¹	46.8 (9.1)
Height, cm	159.3 (16.5)	163.9 (4.7)	0.418 ¹	161.9 (4.9)
Weight, Kg	63.3 (11.1)	70.9 (10.4)	0.073 ¹	59.3 (8.1)
IMC (kg/m ²)	24.2 (4.0)	26.5 (4.3)	0.122 ¹	22.6 (3.0)
Percentage of fat	32.3 (7.6)	35.0 (8.5)	0.346 ¹	18.7 (7.8)
Karnofsky performance status	73.8 (12.9)	75.6 (7.3)	0.688 ¹	100
Smoking			0.263 ²	
Smokers, n (%)	5 (12.5)	0 (0)		1 (6.7%)
Lymphnode dissection			0.881 ²	NA
Yes, n (%)	32 (80.0)	7 (77.8)		
No, n (%)	8 (20.0)	2 (22.2)		
Type of surgery			0.815 ²	NA
Breast conserving surgery, n (%)	14 (35.0%)	3 (33.3)		
Mastectomy, n (%)	26 (65.0%)	6 (66.7)		
Treatment			<0.001 ²	
Chemotherapy, n (%)	7 (17.5)	2 (22.2)		NA
Radiation therapy, n (%)	6 (15.0)	1 (11.1)		NA
Endocrine therapy, n (%)	27 (67.5)	6 (66.7)		NA
Physical function				
VO _{2max} (ml/kg/min ⁻¹)	21.2 (3.5)	19.4 (3.3)	0.192 ¹	NA
Power Output (W)	63.1 (11.7)	67.2 (19.5)	0.411 ¹	NA
Ventilation (L/min)	38.3 (9.6)	42.7 (15.0)	0.261 ¹	NA
VO ₂ VE (ml/kg/min ⁻¹)	17.2 (3.2)	16.7 (2.2)	0.620 ¹	NA
Handgrip right (kg)	24.7 (4.3)	23.4 (4.2)	0.403 ¹	NA
Handgrip left (kg)	24.3 (3.8)	22.0 (3.7)	0.092 ¹	NA
Sit-stand (#)	18.1 (5.1)	16.8 (3.6)	0.457 ¹	NA
Leg Extension (kg)	34.9 (11.8)	32.0 (5.0)	0.484 ¹	NA
Quality of life function				
Global Health Status	62.7 (17.4)	58.3 (19.9)	0.510 ¹	NA
Physical Function	76.8 (13.5)	71.8 (16.9)	0.344 ¹	NA
Role Function	69.2 (26.2)	53.7 (31.0)	0.130 ¹	NA
Emotional Function	65.6 (24.3)	55.5 (30.9)	0.290 ¹	NA
Cognitive Function	70.8 (28.9)	66.7 (27.6)	0.697 ¹	NA
Social Function	65.4 (24.3)	51.8 (26.9)	0.144 ¹	NA
Quality of life symptoms				
Fatigue	40.3 (22.2)	51.9 (26.1)	0.146 ¹	NA
Pain	30.4 (25.0)	40.7 (18.8)	0.251 ¹	NA
BR-23				
Body Image	73.3 (21.5)	69.4 (25.0)	0.636 ¹	NA
Arm Symptoms	23.3 (21.5)	27.1 (11.3)	0.610 ¹	NA

¹ independent t-test² Chi-square test³ Data presented as average (standard deviation)

Table 2. Baseline and follow-up muscle strength and cardiorespiratory fitness components of breast cancer patients in supervised exercise program.

Measures	Increase, n (%)	Decrease, n (%)	No change, n (%)	Baseline ¹	12-Week ¹	%Δ ²	p
VO _{2max} (ml/kg/min ⁻¹)	36 (90.0)	1 (2.5)	3 (7.5)	21.2 (3.5)	24.8 (4.9)	17.0	<0.001
Power Output (W)	37 (92.5)	1 (2.5)	2 (5.0)	63.1 (11.7)	92.5 (18.9)	46.6	<0.001
Ventilation (L/min)	35 (87.5)	5 (12.5)	0 (0)	38.3 (9.6)	46.0 (10.5)	20.1	<0.001
VO ₂ VE (ml/kg/min ⁻¹)	29 (72.5)	7 (17.5)	4 (10.0)	17.2 (3.2)	19.9 (4.1)	15.7	0.001
Handgrip right (kg)	32 (80.0)	8 (20.0)	0 (0.0)	24.7 (4.3)	25.6 (3.9)	3.6	0.072
Handgrip left (kg)	22 (55.0)	17 (42.5)	1 (2.5)	24.3 (3.8)	24.1 (4.0)	-0.8	0.565
Sit-stand (#)	36 (90.0)	2 (5.0)	2 (5.0)	18.1 (5.1)	22.6 (5.3)	24.8	<0.001
Leg extension (kg)	35 (87.5)	3 (7.5)	2 (5.0)	34.9 (11.8)	39.6 (13.9)	13.4	0.003

¹Data presented as average (standard deviation)

²Data presented as percentage of change

Table 3. Baseline and follow-up health-related quality of life subscales (EORTC QLQ-C30/BR23) of breast cancer patients in the control group.

Measures	Increase (%)	Decrease (%)	No change (%)	Baseline ¹	12 week ¹	% ²	P
EORTC QLQ-C30							
Global Health Status	23 (57.5)	7 (17.5)	10 (25)	62.7 (17.4)	72.5 (14.9)	9.8	0.001
Physical Function	25 (62.5)	6 (15.0)	9 (22.5)	76.8 (13.5)	84.2 (10.5)	7.4	<0.001
Role Function	21 (52.5)	3 (7.5)	16 (40)	69.2 (26.2)	85.8 (17.9)	16.6	<0.001
Emotional Function	26 (65.0)	7 (17.5)	7 (17.5)	65.6 (24.3)	80.4 (15.3)	14.8	0.001
Cognitive Function	22 (55.0)	4 (10.0)	14 (35.0)	70.8 (28.9)	82.9 (17.1)	12.1	0.001
Social Function	25 (62.5)	5 (12.5)	10 (25.0)	65.4 (24.3)	82.9 (20.3)	17.5	<0.001
Fatigue	29 (72.5)	3 (7.5)	8 (20.0)	40.3 (22.2)	23.9 (19.1)	-16.4	<0.001
Pain	35 (87.5)	0 (0.0)	5 (12.5)	30.4 (25.0)	10.0 (14.0)	-20.4	<0.001
BR23							
Body Image	30 (75.0)	2 (5.0)	8 (20.0)	73.3 (21.5)	82.5 (18.6)	9.2	0.003
Arm Symptoms	25 (62.5)	2 (5.0)	13 (32.5)	23.3 (21.5)	19.2 (17.4)	-4.1	0.012

¹Data presented as average (standard deviation)

²Data presented as score change.

Changes in Muscle and in Cardiovascular Fitness with 12 weeks supervised exercise

Changes in muscle strength and physiological characteristics are shown in table 2 and figure 3. The majority of physical components increased significantly after 12 weeks supervised exercise ($p < 0.05$) (VO_{2max} : +17.0%, Power output: +46.6%; Ventilation: +20.1%; VO_2 at ventilatory threshold: +15.7%; Sit-stand: +6.1%; Leg extension: 13.4%). No significant changes in handgrip in the arm where the surgery was performed ($p = 0.565$) and in the opposite arm ($p = 0.072$) were found. After the intervention, more than seventy percent (VO_2 at ventilatory threshold: 29/40), eighty percent (Ventilation: 35/40; Leg extension: 35/40) and ninety percent (VO_{2max} : 36/40; power output: 37/40; sit-stand: 36/40) of breast cancer patients exhibited an improvement in these physical components (figure 3).

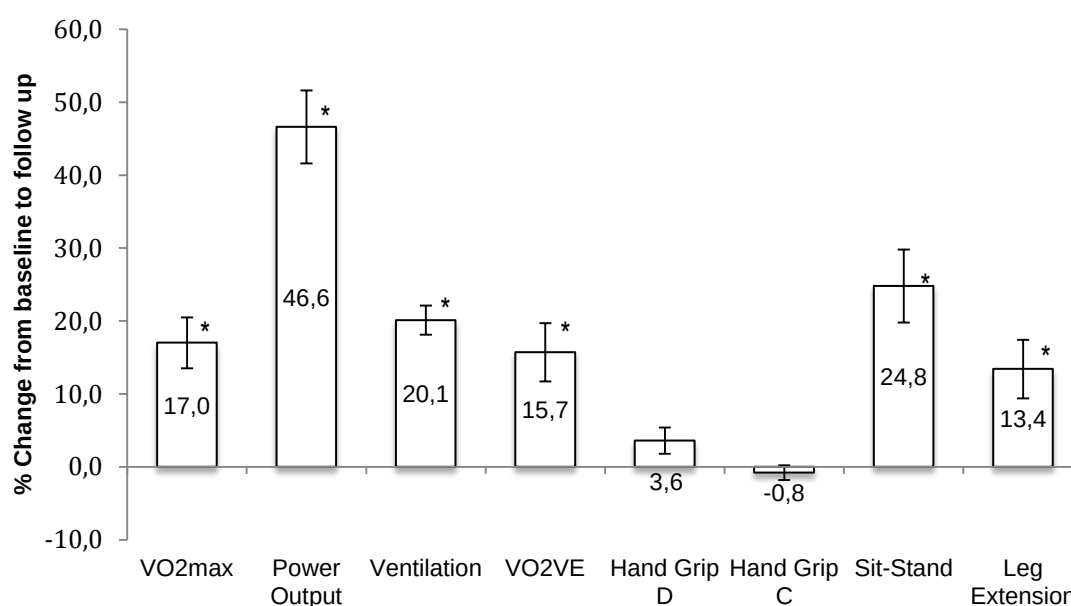


Figure 3: Percentage of change from baseline to 12 week in VO_{2max} , power output, ventilation, anaerobic threshold, handgrip, sit-stand test and leg extension in breast cancer patients. *Statistically significance difference ($p < 0.005$).

Changes in HRQOL with 12 weeks supervised exercise

From baseline to 12 weeks supervised training (table 3 and figure 4), significant increases were observed in health-related quality of life measures (EORTC-QLQ-C30) ($p < 0.05$), with score changes rang from -20.4 to 17.5% (Table 3). Breast cancer patients showed significant changes in pain and fatigue ($p < 0.01$)

with a decrease of 20.4-points (67.1%) and 16.4-points (40.7%) respectively. After the intervention, more than fifty percent (global health status: 23/40; role function: 21/40; cognitive function: 22/40), sixty percent (physical function: 25/40; emotional function: 26/40; social function: 25/40; arm function: 25/40) and seventy percent (body image: 30/40) of breast cancer patients increased their health-related quality of life measurements. It is noticeable that more than seventy percent (Fatigue: 29/40) and eighty percent (Pain: 35/40) of the participants reported, respectively, less fatigue and pain. After the intervention, while 7.5% (3/40) exhibited more fatigue, none of the patients reported more pain.

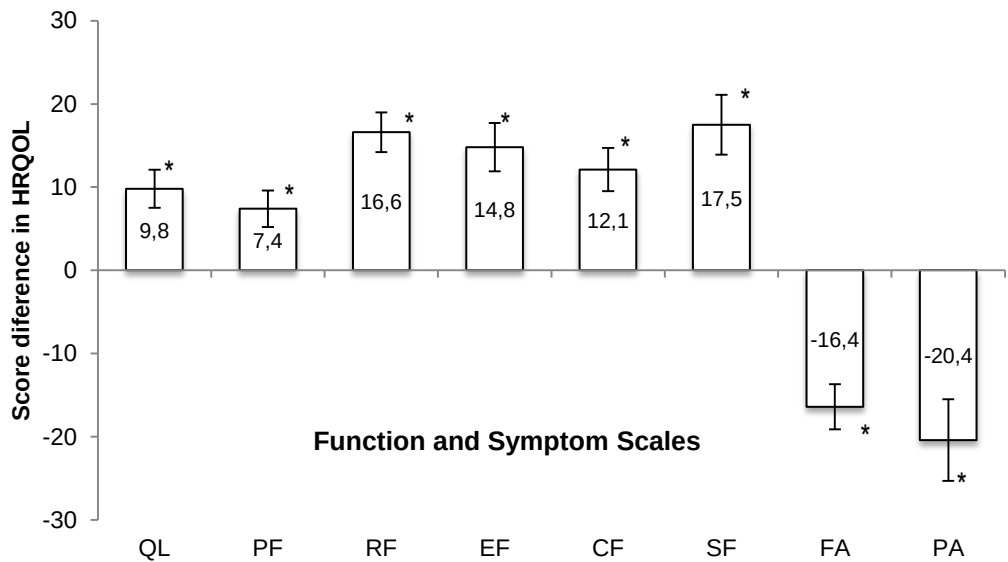


Figure 4: Score change from baseline to 12 week in quality of life, physical function, role function, emotional function cognitive function, fatigue and pain in breast cancer patients. *Statistically significance difference ($p < 0.005$).

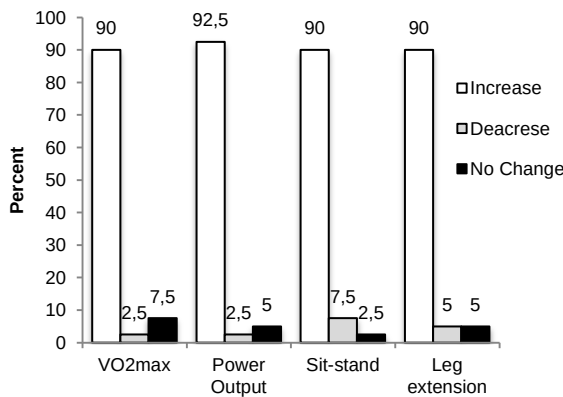


Figure 5. Percent of patients that increased, decreased, or did not change in VO2max, power output sit-stand and leg extension, from baseline to 12 weeks of supervised exercise.

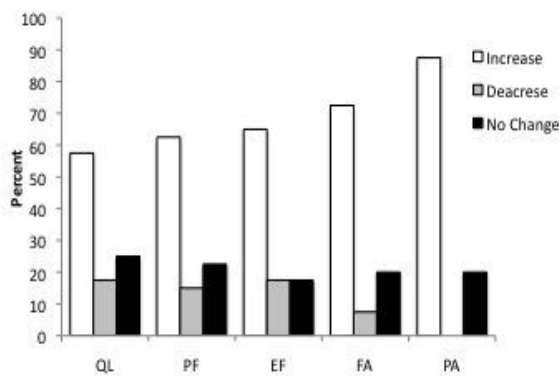


Figure 6. Percent of patients that increased, decreased, or did not change in global QOL, physical function, emotional function, fatigue and pain, from baseline to 12 weeks of supervised exercise.

Table 4. Baseline and 12-week muscle strength and cardiorespiratory fitness components in intervention group and control group.

Intervention group				Control group			GLM repeated measures		
Measures	Baseline ¹	12-week ¹	%Δ ²	Baseline ¹	12-week ¹	%Δ ²	Time ³	Group ³	Time*Group ³
VO _{2max} (ml/kg/min ⁻¹)	21.2 (3.5)	24.8 (4.9)	17.0	19.4 (3.3)	20.9 (3.4)	7.7	<0.001	0.045	0.007
Power Output (W)	63.1 (11.7)	92.5 (18.9)	46.6	67.2 (19.5)	70.5 (19.4)	4.9	<0.001	0.096)	<0.001
Ventilation (L/min)	38.3 (9.6)	46.0 (10.5)	20.1	42.7 (15.0)	44.4 (14.9)	3.9	<0.001	0.705	0.026
VO ₂ VE (ml/kg/min ⁻¹)	17.2 (3.2)	19.9 (4.1)	15.7	16.7 (2.2)	17.4 (2.6)	4.1	0.027	0.141	<0.001
Handgrip right (kg)	24.7 (4.3)	25.6 (3.9)	3.6	23.4 (4.2)	22.9 (4.8)	2.1	0.734	0.163	0.265
Handgrip left (kg)	24.3 (3.8)	24.1 (4.0)	-0.8	22.0 (3.7)	21.1 (3.5)	- 4.1	0.244	0.053	0.481
Sit-stand (#)	18.1 (5.1)	22.6 (5.3)	24.8	16.8 (3.6)	19.0 (3.7)	13.0	<0.001	0.147	<0.001
Leg extension (kg)	34.9 (11.8)	39.6 (13.9)	13,4	32.0 (5.0)	32.0 (4.8)	0	0.147	0.209	0.001

¹Data presented as mean (standard deviation)

²Data presented as percentage of change

³Data presented as p values

Table 5. Baseline and 12-week health-related quality of life subscales (EORTC QLQ-C30/BR23) in intervention group and control group.

Intervention group				Control group			GLM repeated measures		
Measures	Baseline ¹	12-week ¹	S.Change	Baseline ¹	12-week ¹	S.Change	Time ²	Group ²	Time*Group ²
EORTC QLQ-C30									
Global Health Status	62.7 (17.4)	72.5 (14.9)	9.8	58.3 (19.9)	67.6 (19.7)	9.3	0.002	0.401	<0.001
Physical Function	76.8 (13.5)	84.2 (10.5)	7.4	71.8 (16.9)	74.8 (12.8)	3.0	0.025	0.087	<0.001
Role Function	69.2 (26.2)	85.8 (17.9)	16.6	53.7 (31.0)	70.4 (27.4)	16.7	0.001	0.705	<0.001
Emotional Function	65.6 (24.3)	80.4 (15.3)	14.8	55.5 (30.9)	55.4 (39.6)	-0.1	0.117	0.022	<0.001
Cognitive Function	70.8 (28.9)	82.9 (17.1)	12.1	66.7 (27.6)	75.9 (31.3)	9.2	0.005	0.511	<0.001
Social Function	65.4 (24.3)	82.9 (20.3)	17.5	51.8 (26.9)	64.8 (25.9)	13.0	0.001	0.033	<0.001
Fatigue	40.3 (22.2)	23.9 (19.1)	-16.4	51.9 (26.1)	48.2 (28.4)	-3.7	0.003	0.021	<0.001
Pain	30.4 (25.0)	10.0 (14.0)	-20.4	40.7 (18.8)	37.1 (29.8)	-3.6	0.002	0.009	<0.029
BR23									
Body Image	73.3 (21.5)	82.5 (18.6)	9.2	69.4 (25.0)	76.8 (20.8)	7.4	0.021	0.484	0.801
Arm Symptoms	23.3 (21.5)	19.2 (17.4)	-4.1	27.1 (11.3)	23.4 (13.0)	-3.7	0.041	0.541	0.901

¹Data presented as mean (standard deviation)

²Data presented as p values

Changes in muscle strength, cardiorespiratory fitness and HRQOL between intervention group and control group

At follow-up, a significant main effect for time and a significant time by group interaction effect were evident for the majority of muscle strength and cardiorespiratory fitness measures (Table 4). From baseline to 12-weeks, there was a statistical significant increase in VO_{2max} , power output, ventilation ($p<0.001$) and sit and stand ($p<0.001$). The significant results suggest that the time effects in the muscle strength and cardiorespiratory fitness measurements were different between intervention group and control group (Figure 7). In the intervention group, mean values significantly improved ($p<0.05$). In the control group values remained rather constant at follow-up ($p>0.05$). In fact, from baseline to after 12-weeks, intervention group showed significantly greater changes in VO_{2max} (17.0% versus 7.7%), power output (46.6% versus 4.9%), ventilation (20.1% versus 4.9%), VO_2 at ventilatory threshold (15.7% versus 4.1%), sit-stand (24.8% versus 13.0%) and leg extension (13.4% versus 0%) compared to control group. No significant intervention effects were observed for handgrip measures.

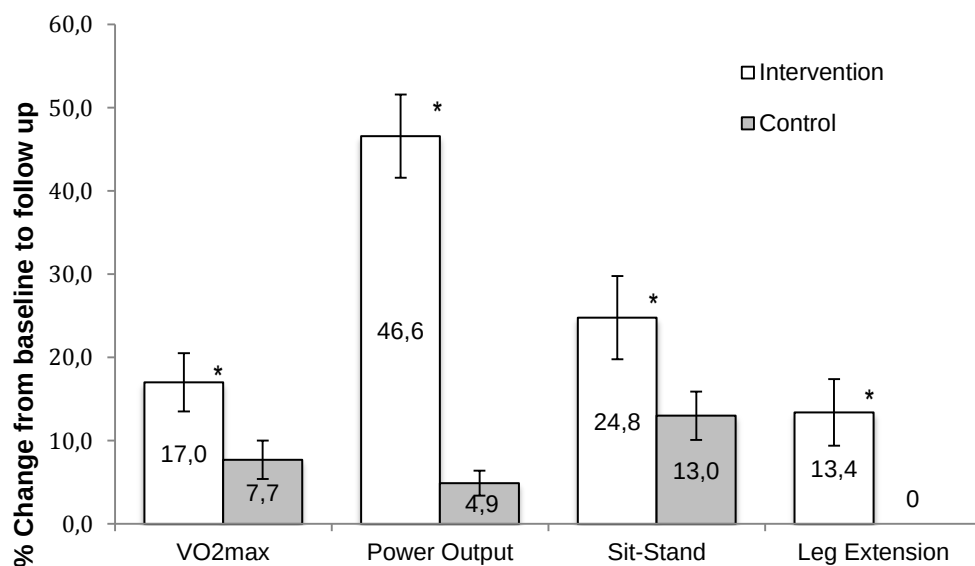


Figure 7. Percentage of change from baseline to 12 week in VO_{2max} , power output, sit-stand test and leg extension from exercise program and control group of breast cancer patients. *Statistically significance difference ($p<0.005$).

Regarding quality of life measures, from baseline to 12 weeks, a significant main effect for time and group and a significant time by group interaction effect

was evident for the majority of measurements. Across the intervention, there was a statistical significant increase in all values. Intervention group had a significantly higher increase in global health status (9.8 versus 9.3 points), physical function (7.4 versus 3.0 points), emotional function (14.8 versus -0.1 points), cognitive function (12.1 versus 9.2 points), social function (17.5 versus 13.0 points), body image (9.2 versus 7.4 points) and arm symptoms (-4.1 versus -3.7 points) than control group. It was also observed a significant higher decrease in fatigue (-16.4 versus -3.7 points) and pain (-20.4 versus -3.6 points). The significant interactions suggest that the time effects in the quality of life differed between intervention group and control group (Figure 8). Among intervention group, mean values significantly improved with the intervention ($p < 0.05$), whereas they remained rather constant at follow-up in control group ($p > 0.05$).

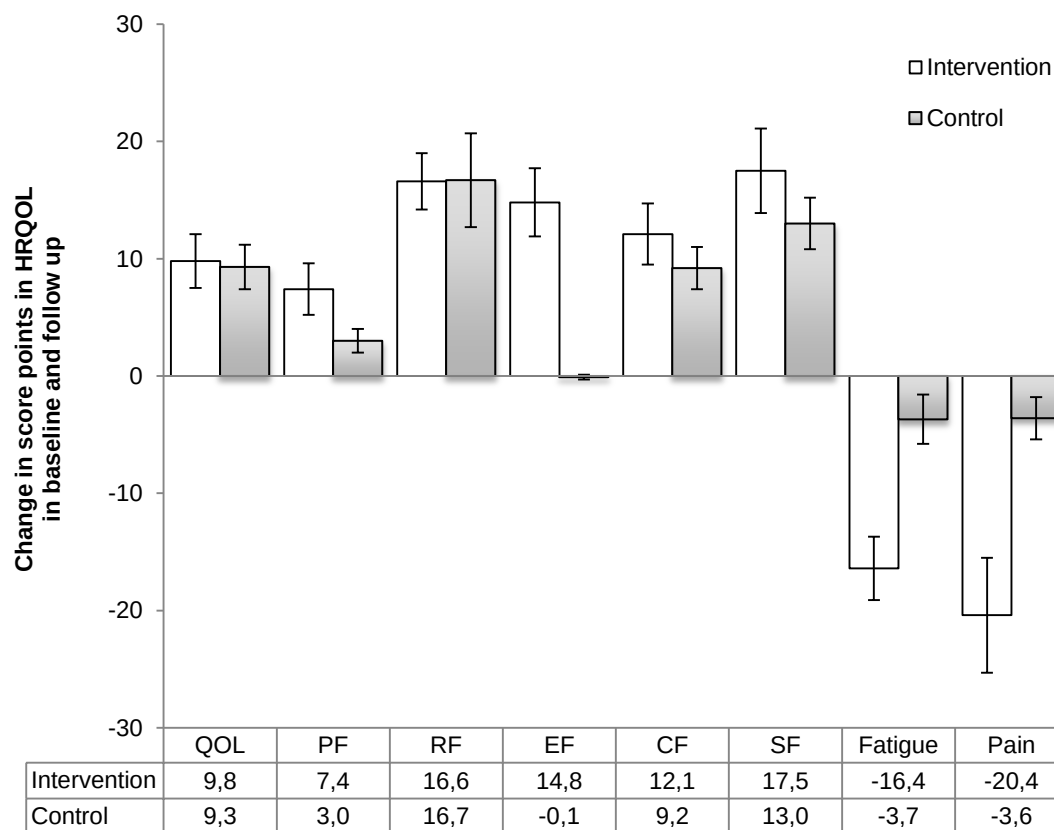


Figure 8: Score change from baseline to 12 week in quality of life, physical function, role function, emotion function, cognitive function, social function, fatigue and pain in breast cancer patients intervention group and control group.

Table 6. Baseline and 12-week muscle strength and cardiorespiratory fitness components in intervention group and healthy group.

Measures	Healthy group	Intervention group		Baseline differences		12-week differences	
		Baseline	12-week	Difference ¹ (%)	p ²	Difference ³ (%)	p ⁴
VO _{2max} (ml/kg/min ⁻¹)	30.7 (4.0)	21.2 (3.5)	24.8 (4.9)	9.5 (30.9%)	<0.001	5.9 (19.2%)	<0.001
Power Output (W)	114.6 (20.4)	63.1 (11.7)	92.5 (18.9)	51.5 (44.9%)	<0.001	22.2 (19.3%)	<0.001
Ventilation (L/min)	63.2 (11.8)	38.3 (9.6)	46.0 (10.5)	24.9 (39.4%)	<0.001	17.2 (27.2%)	<0.001
VO ₂ VE (ml/kg/min ⁻¹)	23.7 (2.9)	17.2 (3.2)	19.9 (4.1)	6.5 (27.4%)	<0.001	3.7 (16.0%)	0.002
Handgrip right (kg)	29.2 (3.5)	24.7 (4.3)	25.6 (3.9)	4.5 (15.4%)	0.001	3.6 (12.3%)	0.003
Handgrip left (kg)	28.5 (2,7)	24.3 (3.8)	24.1 (4.0)	4.2 (14.7%)	<0.001	4.4 (15.4%)	<0.001
Sit-stand (#)	27.4 (5.2)	18.1 (5.1)	22.6 (5.3)	9.3 (33.9%)	<0.001	4.8 (17.5%)	0.04
Leg extension (kg)	48.9 (10.2)	34.9 (11.8)	39.6 (13.9)	14.0 (28.6%)	<0.001	9.3 (19.0%)	0.022

¹ Difference between baseline intervention group values and healthy group values, then dividing each result by baseline intervention group values.

² p values obtained from the independent t-tests comparing baseline intervention group and healthy control group mean values.

³ Difference between 12 week intervention group values and healthy group values, then dividing each result by 12 week intervention group values.

⁴ p values obtained from the independent t-tests comparing 12-week intervention group and healthy control group mean values.

Changes in muscle strength and in cardiorespiratory fitness

Table 6 displays muscle strength and cardiorespiratory fitness components in intervention group at baseline and 12-weeks and compares each time with healthy group values. As expected, at baseline and 12-weeks, independent t-tests showed significant differences in all measures favoring healthy group ($p<0.05$). At baseline the differences between both groups were approximately from 31% to 40% in cardiorespiratory components and from 34% to 28% in muscle strength measures. However, 12 weeks of supervised exercise intervention, resulted in significant improvements in strength and aerobic capacity in breast cancer patients (see table 2; except handgrip measures) and consequently resulted in a lower difference compared to the healthy group. The data collected after the 12-weeks, showed approximately 20% to 27% lower cardiorespiratory fitness in the intervention group. Regarding muscle strength measures, the differences compared to the healthy group were from 15% to 19%.

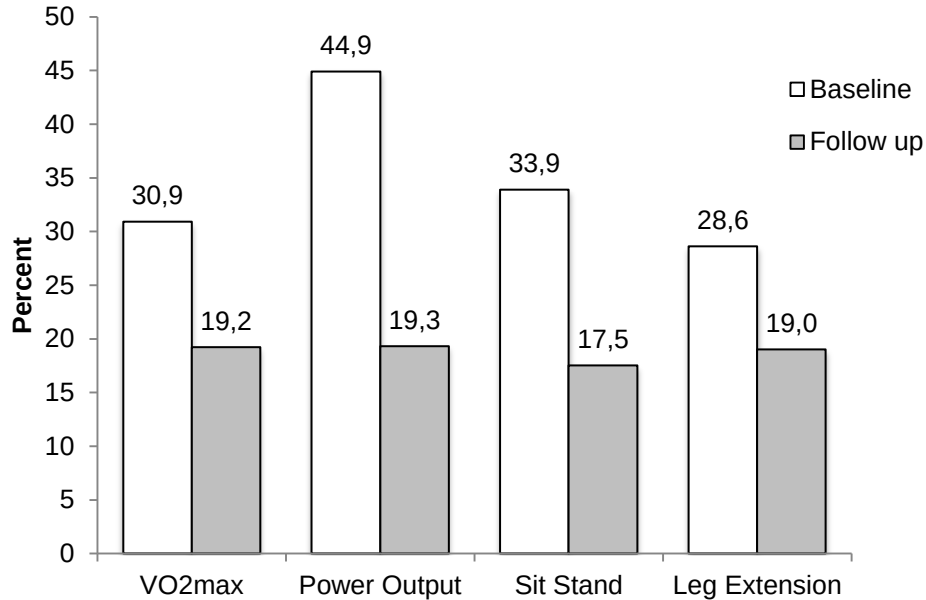


Figure 9: Comparison of percent of change decrease in VO_{2max} , power output, sit stand test and leg extension from baseline to week 12, between healthy group and breast cancer patients in intervention exercise program.

6. Discussion

Despite the demanding nature of this exercise intervention, 40 of 43 patients (93%) were able to complete a 12-week exercise program, which indicates a high level of compliance, very similar to previous studies comprising breast cancer patients (Cheema et al., 2008; Courneya et al., 2003; Nikander et al., 2007). Moreover, the compliance is higher when compared to other studies involving patients with different diagnosis (Quist et al., 2006). The combination of a training facility at the Mama Help- Support Centre for Breast Cancer Patients with professional supervision, was crucial, to convince patients that the exercise program was a complement to the ongoing medical treatment. No major adverse effects and no major health problems were noted in the subjects of both groups, over the 12-week period.

The number of studies examining the benefits of exercise for breast cancer patients, has tremendously increased, in recent years. However, the majority of published works show inadequacies in design regarding principles of exercise training, and also lack detailed exercise prescription and report of patients adherence to the programme (Campbell et al., 2011). Therefore, there is shortage of information for developing specific exercise prescription to reduce side effects of cancer treatment. As far as exercise intensity is concerned, it has been reported that exercise dose and reported adherence rate were significantly and inversely correlated ($r=-0.62$, $p=0.002$ for weekly dose; $r=-0.82$, $p<0.001$ for total dose) implying that lower prescribed dose of intervention presented greater adherence rate (Carayol et al., 2012).

Our study shows that a 12-week planned supervised training program, combining resistance and cardio respiratory exercises, brings positive changes to cardiorespiratory components, strength, muscle function, and quality of life outcome in breast cancer patients. These results are important, as cancer related fatigue decreases the QOL, which can be maintained, even after treatment, in 30% of patients with cancer (Stasi et al., 2003).

Several studies have shown that exercise may improve cancer patients' physical fitness and well-being (Cheema et al., 2008; Herrero et al., 2006; Nikander et al., 2007; Schneider et al., 2007; Schwartz et al., 2001). However,

most of these studies (Mustian et al., 2009; Saarto et al., 2012) were home-based exercise, with little control over the amount and intensity of exercise undertaken, making results difficult to compare (Quist et al., 2006). Some studies involving exercise were randomized-controlled trials, with cancer patients undergoing chemotherapy (Adamsen et al., 2006; Courneya et al., 2007; Dimeo, Fetscher, et al., 1997), radiotherapy (Karvinen et al., 2011) and specifically breast cancer patients on adjuvant chemotherapy (Carayol et al., 2012; Courneya et al., 2007; Winningham et al., 1989). Most of the studies applied low-to-moderate exercise interventions (intensity between 55% and 85% of maximal heart rate), which appears to be standard, across existing studies (Ingram & Visovsky, 2007). Resistance training is an important component of any training program (Lucia et al., 2003). It is still difficult to assess which categories of patients (stage of illness, diagnosis and treatment) would best benefit from exercise, at what intensity, and in which form (Quist et al., 2006). In our study, breast cancer patients with different stages of the disease and with different cytostatic treatments, were included in a program combining aerobic training with resistance training.

Our results for VO_{2max} are in accordance with studies of MacVicar et al. (1989) and Kolden et al. (2002) who found that an aerobic interval training cycle ergometer program, over a 10-week period, in 45 patients receiving chemotherapy for breast cancer, leads to significant improvement in VO_{2max} . Similar increases (improvement of 17.4%) in VO_{2max} were found in 53 postmenopausal breast cancer survivors, who trained in cycle ergometer during 3 weeks (Courneya et al., 2003). Quist et al. (2006) studied the effect of high-intensity resistance and cardiovascular training during a 9h weekly intervention, during 6 weeks, in cancer patients undergoing chemotherapy. The results showed a 41.3% increase in muscular strength and 14.5% in aerobic fitness demonstrating that high-intensity workout is well tolerated and beneficial to cancer patients undergoing chemotherapy. Cancer patients in advanced stage, profited, significantly, from the heavy resistance training of larger muscle groups – 3 series of five to eight repetitions at 85-90% of 1RM, 3 times weekly. The

aerobic training of 10 minutes of intense periods on stationary bicycles, equivalent to the average of 85.1% of each patient's maximum heart rate, led to a significant increase in VO_{2max} .

Furthermore, low to moderate intensity training (40-50% HRmax), seems to induce improvements in aerobic function, compared to a control group (Burnham & Wilcox, 2002).

In our study, we verified an increase in in the VO_{2max} of 17.5%, that is quite similar to the study of Thorsen et al. (2005) in which, during 14 training weeks, twice a week, for 30 minutes, at 60-70% of HRmax, VO_{2max} improved by 23%, comparatively to the control group, who had an increase of only 10%. However, our results differ from this last study, since in Thorsen et al. (2005) the control group had a more evident reduction of fatigue (17.0 points), comparatively to the exercise group, in which the decrease was of (5.8 points) - EORCT QLQ C-30.

VO_{2max} attained during a graded maximal exercise, is considered the single best indicator of aerobic physical fitness (De Backer, Schep, et al., 2007). When expressed relative to body mass, VO_{2max} is also an indicator of health status and predictor of mortality (Blair et al., 1996). In our study, the average values of VO_{2max} were clearly below 30 ml/kg/min⁻¹, which reflects the poor physical condition and the need for breast cancer patients and survivors to engage in exercise training programs, to improve their VO_{2max} values, and thus their overall health status (Schmitz et al., 2010).

On the other hand, after 12 weeks of training, the increase in VO_{2max} of 17.5% in the intervention group translated into a decrease in VO_{2max} in a diminishing from from 44.8% to 23.7%, comparing to the healthy group. The implication of the alteration of the VO_{2max} in the aerobic function, in survival, is not yet known. However, a prospective study with 6.213 patients with cardio vascular disease, showed that the increase of 1-MET in cardio respiratory capacity, increased survival by 12% (Myers et al., 2002).

Exercise training counteracts negative effects of cancer treatments and can improve cardiovascular efficiency, increase cardiac output and stroke volume,

decrease resting heart rate, lower exercise heart rate, and improve ventilation and transport of oxygen from the environment to the cell (Noakes, 2000).

Hayward et al. (2004) found that exercise training preserved intrinsic cardiovascular function after treatment with various chemotherapeutics agents. These protective effects were associated with an exercise induced increase in endothelial nitric oxide syntheses, myocardial heat shock protein content, a prevention of chemotherapy-induced myocardial lipid per oxidation, and reduced mortality after treatment (Hayward et al., 2004). However, despite aerobic training, in 70 women with HER2-positive tumors, short course of adjuvant trastuzumab was associated with left ventricular dilation and decreased systolic function (Haykowsky et al., 2009). In addition, power output and VO_{2max} were not different after training (Haykowsky et al., 2009). However, participants attended only 59% of prescribed sessions during 4 months, which is an insufficient number of sessions to achieve beneficial training adaptations.

On the other hand, the VO_{2max} increase in postmenopausal women may be more skeletal-muscle related, considering that the oxygen consumption may increase with training, without eccentric left ventricle hypertrophy capacity increases (Spina et al., 2000). Adaptations of skeletal-muscle with training, are partially due to the increase of (i) oxidative capacity increase, (ii) capillary density, (iii) glycogen storage capacity and also (iv) in the skeletal muscle of fibres type I (Lucia et al., 2003).

Magnitude of change in cardiopulmonary function after treatment can be considerably larger than those found in other studies in breast cancer patients during treatment (Courneya et al., 2003). Courneya et al. (2003) surmised that perhaps the differences in outcomes were the result of differences in methodologies between investigations, or perhaps breast cancer survivors' responded better to exercise after treatment. Nevertheless, breast cancer survivors respond differently to exercise, depending on where they are on the cancer phase of treatment (Schneider et al., 2007). So, it is important that exercise be individualized to specific needs of the cancer survivor, who already has a compromised system, to prevent exacerbation of physiological and

psychological toxicities that occur as a result of cancer treatments (Schneider et al., 2007).

During chemotherapy, some studies show different results in cardiorespiratory exercise effects. Segal et al. (2001) show increases only in the VO_{2max} 3.5 ml/kg/min⁻¹ in patients who were not under chemotherapy treatments. *However, in the current study we observed an increase of 15.4% in VO_{2max} in breast cancer patients undergoing chemotherapy*, which are in line with the results of Quist et al. (2006) who found an increase of 14% in aerobic fitness after a 9-h weekly training program over 6 weeks. Moreover, during 6 months of aerobic training with a pace of 2 to 3 weekly sessions, women with breast cancer undergoing chemotherapy, with a maximum HR between 40 and 75%, improved time of VO_{2max} by 17.8%, while the group of women who finished their treatments, improved time of VO_{2max} by 28.0% (Schneider et al., 2007). Furthermore, moderate intensity reduced fatigue during and after treatment in breast cancer patients (Schneider et al., 2007).

Besides the increase in VO_{2max} , a significant observation of the results of this study is the outstanding increase in power output. It can be argued that an improvement in the cycle endurance time, may be more clinically relevant than an improvement in VO_{2max} (Laviolette et al., 2008; Ong et al., 2004). Ong et al. (2004) analysed several outcomes in chronic obstructive pulmonary disease through several exercise protocols. After an intervention of 6 weeks of supervised exercise power output increased by 30% and endurance time by 144% ($p<0.001$).

In our study, lower body strength, evaluated by leg extension, increased significantly by 13.4% ($p<0.001$), which demonstrated that this is a lower increase than the one found in the study of Ohira et al. (2006) who verified an increase of 38% in leg press ($p<0.001$). However, our results are comparable with those obtained by Kolden et al. (2002) which involved supervised, structural group exercise program using resistance bands, dumbbells, and variable resistance machines. Contrary to our results, Nikander et al. (2012) did not observe any improvement in leg extension strength, which may be

explained by the fact that the present intervention did not include resistance training but aerobic impact only. On the other hand, functional tests may be more applicable than maximum force tests (1RM), as used in some studies (Adamsen et al., 2006; Quist et al., 2006) since the increase of dynamic maximum force may not be clinically relevant for those who survive, or cancer patients (Herrero et al., 2006), opposite to what we often verify with athletes. Due to this fact, the study of muscular functionality was put into practice using the sit-stand test, already validated for use in patients with cancer (Herrero et al., 2006). After follow-up and in accordance to these authors, we found a significant increase in sit-stand test by 24.8% ($p < 0.001$). Winters-Stone et al. (2008) verified that sit-stand 30s test, age and (self-reported) physical activity, were independent factors in fatigue prediction.

Individual reaction to training charges is one of the effects in the exercise adaptation. Some individuals can increase, significantly, from baseline to week 12, independently of their age (Quist et al., 2006). Sometimes, low baseline values are justified by surgery procedures, a long stay in hospital and/or treatments (e.g. cytotoxic treatments >12 months). In our study, we achieved increases in strength of 100%, as was observed in other studies (Quist et al., 2006). In the study of Quist et al. (2006),

In our study, we did not find differences in upper-member strength, through the handgrip evaluation. In opposition to our results, weight training twice a week, for 6 months, improved body composition and 63% upper body strength (1-RM test in bench press), with improvements in physical global scores, in breast cancer survivors (Ohira et al., 2006).

Furthermore, McKenzie & Kalda (2003) estimated the effect of 8-week combined aerobic in Monark Rehab Trainer arm-ergometer and resistance exercises, on QOL, and arm components with unilateral upper extremity lymphodema, secondary to treatment. Their results showed that an improvement in QOL and lymphedema was not affected by upper-body strength training exercises. Intense aerobic exercise, for 12 weeks, appeared to be well tolerated, as well as an effective training mode in breast cancer survivors, who

had recently completed heavy adjuvant treatments, such as chemotherapy. The mechanism by which weight training may be a sense of return to feeling in control of their bodies, that may translate into feeling greater efficacy in other areas of their lives (Ohira et al., 2006).

The low intensity change in our training program for upper body may have influenced the fact no significant differences had been found in strength follow up, through the handgrip. On the other hand, the fact that we did not apply an evaluation strength test of the upper body, with the Bench Press, was a limitation of this study.

Additional studies should take place in this area, to determine the optimum training program, to enhance upper body strength. Some studies, with breast cancer patients with lymphedema, are excluded, since the investigators are concerned that it could affect performance and training (Herrero et al., 2006; Nikander et al., 2007). Moreover, there is a compelling evidence for the safety and benefits of exercise to decrease lymphedema risks, reduce symptoms, and increase strength (Schmitz et al., 2009).

Besides, handgrip performance is not a consistent predictor as a credit to evaluate CRF (Kilgour et al., 2010). Maximal grip strength reflects the capacity of the muscles to generate a large force in a very short time (Bautmans et al., 2007). Muscle performance is important during daily activities that need sustained activity (i.e. to lift, to carry or to manipulate objects), grip work might be the best test, which reflects the functional capacity, resulting from the development of a certain strength level, in relation to the time it can be maintained (Bautmans et al., 2007). The association between fatigue and maximum strength through the handgrip, looks weak but, when fatigue protocols are used, the association may increase (Stone et al., 2000). Therefore, for physical functioning, maximal strength and grip work (eventually corrected for body weight) might be the best parameter to measure the physical evaluation (Bautmans et al., 2007). Some discrepancies among studies could be partially explained by the variety of different types of tumours in studies, as well as age or body weight (Bautmans et al., 2007; Kilgour et al., 2010; Stone et al., 2000).

During radiation therapy for breast cancer, muscles of the chest wall may be irradiated, and a typical radiation dose used in breast cancer treatment is 1.8-2.0 Gy/day, 5 days/week, over 6 weeks (total of about 54-60 Gy). These muscles include pectorals (major and minor), subclavius and anterior serratus. Depending on the irradiation treatment area, muscles of the back, particularly the rhomboid layer and underlying deep muscles, may be exposed to radiation as well. Common resistance exercises, like bench press, push ups and lat pull-downs, involve chest wall and back muscles (Clarkson & Kaufman, 2010) and may be eventually affected due to side effects of radiotherapy.

In our study, the muscle function values, handgrip and sit stand test, are clearly inferior to those of the Healthy control group, which, in a certain way, may be one of the reasons why, in baseline, the intervention and control group showed persistent fatigue and pain signs. In the study elaborated by Kilgour et al. (2010), upper and lower body muscle strength, had significant predictors of CRF. In a study with advanced lung cancer patients, when compared to healthy ones, it was found beyond correlation between fatigue and strength in leg extension, the best parameters which related to CRF were the 30s-timed sit-stand tests and the KPS ($p < 0.001$), showing that a lower functionality translates into a higher fatigue score (Brown et al., 2005).

Considering the quadriceps muscle function in the several tests used to evaluate the functional performance in patients with cancer (e.g. sit-stand test, timed up and go, and 6-min walk test), there is, clearly, a necessity for studying the lower members strength in order to understand functional adaptations of a training program in patients with cancer (Kilgour et al., 2010). These elements demonstrate the intervention of efficacy in this study, as it was verified that 12 weeks of training reduced the difference in leg extension from 40.1% to 23.5%, and, in the sit-stand test, the result varied from 51.3% to 21.2% comparing to the Healthy group.

Intervention exercise time is a factor that may influence results. In a specific study about intervention time, cardio respiratory capacity parameters as well as those of QOL, were compared, using from 3 to 6 months interventions (Sprod et al., 2010). It was demonstrated that 3 months of training improved

cardiovascular endurance, fatigue and depressing symptoms, in women with breast cancer. However, only the group of patients with cancer who trained for 6 months, showed an improvement of lung function, evaluated by FVC and FEV1, when comparing to the control group. On the other hand, although 3-month training is considered to be sufficient to improve strength in leg press, 6 months of training allowed to increase strength even more (Sprod et al., 2010).

Although in our study the intervention group had an increase in lower body strength of 13.4% ($p < 0.001$), Drouin et al. (2006) found increases of 38% after 6 months of training. So, we can speculate that if our exercise program was extended in time, we could find even more significant improvements in muscular function.

Identically Sprod et al. (2010) verified that after 12 weeks of training, fatigue was substantially reduced, demonstrating that 12 weeks of training is an enough time period to promote decreases in fatigue. In a study by Herrero et al. (2006), sixteen breast cancer patients were randomly assigned to a training or to a non-exercise group. The results from patients in the exercise group were compared to those in a control group, over a short period of 8-week exercise program. The program consisted of 3 weekly sessions of 90 minutes, with resistance and aerobic training. VO_{2max} improved by $3.9 \text{ ml/kg/min}^{-1}$ and performance in leg press improved (17.9Kg), demonstrating that a short exercise program improves fitness and QOL in women with breast cancer.

In our study, outcomes related to quality of life, improved significantly after exercise intervention. We verified a difference of more than 10 points, in global health status, role, emotional, cognitive and social function, as well as in fatigue and pain. Besides, physical function improved by 7 points. In these cases, an increase of 20 points on what concerns fatigue and more than 15 points in pain reflects a very high increase. Since the control group had daily health care support during the intervention period, this group also improved the global quality of life and social functioning.

However, in agreement with our study, patients in the intervention group had a slightly better outcome for some HRQOL dimensions than patients in the control

group (Courneya et al., 2003; Mock et al., 2001). These findings are consistent with Naumann et al. (2012), who reported an increase of more than 10 points in QOL, in individual home-based and group-based training, in breast cancer survivors, after 9 weeks of exercise.

Contrary to our study, Thorsen et al. (2005) verified a slightly better outcome for some HRQOL dimensions in the control group than in patients in the intervention group. The magnitude of changes in mental distress, fatigue, and HRQOL parameters in trials in this area, are not consistent. It is not clear whether these disparities of outcome are the result of differences in patient characteristics and/or the type and timing of intervention, or whether these variations can be explained by different methods of assessment.

The most frequently reported symptom, resulting from treatment, is fatigue, which may last months and years after treatment (Bower et al., 2009; Erickson, 2004; Ryan et al., 2007; Stasi et al., 2003). Cardiovascular toxicity can result in left ventricular dysfunction evidences, by an increase time to peak filling of the left ventricle, lower left ventricular ejection fraction, abnormal left ventricular contractility, reduced cardiac output and stroke volume, weak lead to lower oxygen and nutrition delivery (Brockstein et al., 2000; Gianni et al., 2001). Furthermore, pulmonary toxicity can occur as a result of cancer treatments and lead to shortness of breath, decrease of total lung capacity, vital capacity, inspirable capacity and decreased diffusion capacity, which, in turn, can compromise oxygen delivery and carbon dioxide removal (Brockstein et al., 2000). With the increasing prevalence of cancer fatigue and treatment toxicities on the quality of life, determining how to manage and promote efficacious strategies for overcoming these alterations should be investigated during and after cancer treatment (Schneider et al., 2007).

In the present study, exercise induced a pronounced decrease in fatigue and pain symptoms, which is in line with literature results referring that exercise may help to manage fatigue during and after treatments (Adamsen et al., 2004; Dimeo, Stieglitz, et al., 1997; Dimeo et al., 1999; Mock et al., 2005; Mock et al., 2001; Stricker et al., 2004). However, the alteration of this symptom should be interpreted with some prudence. We use the symptom scale fatigue from

EORTC QLQ C-30 but, probably, it is important the use of a domain-specific instrument when fatigue is the primary outcome. Knobel et al. (2003) validated the fatigue scale in EORTC QLQ C-30 against the Fatigue questionnaire, the latter measuring both physical and mental fatigue. The analysis demonstrated that the fatigue scale in EORTC QLQ C-30 correlated higher with the physical fatigue scale ($r=0.67$ to 0.75) than with mental fatigue scale ($r= 0.49$ to 0.61). Fatigue measured by EORTC QLQ-C30 does not differentiate between acute and chronic fatigue (Thorsen et al., 2005). So, these authors recommend for studies with fatigue as defined end point,, a domain-specific instrument, which is more suitable to evaluate fatigue (Stone et al., 1998). Besides, in patients with advanced lung cancer, a correlation between FACT-Fatigue questionnaire and EORTC QLQ C-30 fatigue scales ($r=0.712$; $p<0.001$) was verified, showing that the questionnaire which was used in this study may help to understand the fatigue intensity in our work.

In our program, patients in the intervention program reported less fatigue than patients in the control group, suggesting that exercise may reduce fatigue. Nevertheless, in the healthy control group, fatigue was not evaluated. After radiotherapy, Smets, Visser, Willems-Groot, Garssen, Oldenburger, et al. (1998) concluded that fatigue in breast cancer patients increased by 46% compared to a healthy control group.

Moreover, after 9 months in disease-free patients, 26% of patients worried about their fatigue and, patients' overall quality of life was negatively related to fatigue ($r = -0.46$) and was significantly associated with gender, physical distress, pain rating, sleep quality, functional disability, psychological distress and depression, but not with medical or treatment-related variables (Smets, Visser, Willems-Groot, Garssen, Schuster-Uitterhoeve, et al., 1998). On the other hand, Geinitz et al. (2001) observed an increase in fatigue during 5 weeks of adjuvant radiotherapy in patients with breast cancer. Nevertheless, fatigue returned to pretreatment levels 2 months after treatment. No evidence was found about anxiety, depression, serum levels of IL-1beta, IL-6, tumor necrosis factor-alpha, or declining hemoglobin levels being responsible for the treatment-

induced fatigue. Fatigue is common in depression, and both fatigue and depression are common in cancer patients (Stone et al., 1998). In some studies, consistent associations were found between fatigue and psychological distress (Stone et al., 2000). Moreover, Stone et al. (2000) found an association between fatigue severity and global quality of life suggesting that fatigue is an important contributor to quality of life in both health and disease, and has a high impact on the well-being among cancer patients.

Contrary to our study, Thorsen et al. (2005) did not observe any beneficial effect on fatigue, mental distress and HRQOL parameters from the 14-week supervised home-based program training intervention shortly after chemotherapy. The fact that patients themselves performed multiple supervised could represent additional stress. However, VO_{2max} increased by 6.4 ml/kg/min⁻¹ in patients in the intervention group and only 3.1 ml/Kg/min⁻¹ inpatients in the control group, corresponding to 23% and 10%, respectively), showing a beneficial effect on CRF in young and middle-aged cancer patients.

The dose-effect relationship of exercise with fatigue needs more investigation. Nevertheless, some results revealed that a greater decrease in fatigue and an increase in QOL were observed with weak targeted exercise doses, <12MET h/week, as well as with long duration interventions (>18weeks) for QOL (Carayol et al., 2012). These findings generate the hypothesis that the prescription of a 20-week exercise program targeting 8-10 MET h/week could be well adapted for patients with breast cancer receiving adjuvant therapy (Carayol et al., 2012). In this case, combined aerobic and resistance (2 sessions of moderate intensity aerobic exercise and one resistance session for principal muscular groups) during 30-45 minutes is recommended (Carayol et al., 2012). In our program, each exercise session had a limit time of 60 minutes, because the fatigue state may be aggravated by longer sessions (Schwartz et al., 2001). The reason for this is unclear, perhaps prolonged exercise provokes muscular fatigue and the feeling of fatigue associated with changes in nutrition and hydration states can increase the sensation of the current level of fatigue.

Determining the optimal dose of exercise to reduce fatigue is elusive. In our study, women were instructed to exercise at an intensity of 70-85% of VO_{2max}

but it was important that intensity was symptom limited. This exercise intensity was acceptable for breast cancer patients and did not worsen their symptoms during exercise. Schwartz et al. (2001) showed that fatigue was significantly reduced on exercise days compared with non-exercise days. Furthermore, the amount of exercise, measured as the number of minutes exercised, was significantly associated with fatigue levels. In a meta-analysis, the authors observed a positive relationship, meaning that larger amounts of targeted aerobic activity were associated with substantial QOL improvements, but the studies included various cancer sites, both controlled and uncontrolled trial and mixed intervention periods with most of the studies involving post adjuvant therapy intervention (Ferrer et al., 2011).

In our study, women did not show an increase in body weight (not an outcome measure of our study). Nevertheless, besides being a quality of life contributor, exercise may also be a strategy for weight control since weight gain is common in both pre and postmenopausal women after diagnosis (Demark-Wahnefried et al., 2000) as well as during and after adjuvant treatments (Harvie et al., 2004; Sestak et al., 2012) and during the five-year follow-up (Makari-Judson et al., 2007). Furthermore, the weight gains also tend to be linked to an increase in fat mass and the recent findings of Winters-Stone et al. (2008) showed that higher percentage of body fat reported more fatigue compared to leaner women. Moreover, using separate correlation analysis, using lean mass and fat mass, the later was significantly and positively associated with fatigue rather than lean mass (Winters-Stone et al., 2008). Upon diagnosis, and as a consequence of receiving treatment, being overweight or obese elevates risk up to 4-fold of developing multiple other diseases such type II diabetes, asthma, chronic back pain, osteoarthritis and cardiovascular disease (Rock & Demark-Wahnefried, 2002). A meta-analysis included 43 studies that enrolled women diagnosed with breast cancer between 1963 and 2005 with a sample size ranged from 100 to 42 4168. demonstrated that obesity is associated with poorer overall and breast cancer-specific survival (Protani et al., 2010). Weight gain is critical to patients,

as it relates to body image, but it is also a risk factor for impairment and poorer outcomes of treatment (Demark-Wahnefried et al., 2012).

Weight control in women with breast cancer is important because the weight (BMI > 25.0) may increase the lymphedema probability. In the study of Swenson et al. (2009), through the multivariable analysis, axillary radiation, more extensive surgery, chemotherapy were predictive of lymphedema but, the only factor significantly associated with lymphedema, was overweight ($p = 0.022$). Being overweight is an important modifiable risk factor for lymphedema. Furthermore, the results indicate a lower lymphedema incidence in women with breast cancer who were submitted to resistance training strength (Swenson et al., 2009).

The main strengths of the present study are the several measurements of physical performance and HRQOL. Opposite to other intervention studies of exercise, we chose a multi-structured exercise program, supervised in clinical context. We pretended to adequate the individuality of the exercise and to apply the principles of training in each exercise sessions, as the answer to exercise and to treatment varies among patients with breast cancer. The exercise program also intended to reduce the drop out percentage and to increase motivation for physical exercise practice, during and after treatment.

A high adhesion to the program was evident, which also confirms that women with breast cancer are able to tolerate high intensity aerobic exercises. To our knowledge, this is one of the first studies which analyses and compares the muscle and aerobic fitness through a multidisciplinary exercise program using a healthy control group. These results may be important for future studies with the outcome of returning to work since a poor physical condition may impair the productivity.

The main limitation of the study is the small sample size and the heterogeneity of the case group due to variations in adjuvant treatments. A larger sample would also allow the possibility to access the relationship between the amount and intensity of exercise and respective changes in outcome. Using a fatigue specific questionnaire as the FACT-Fatigue, would help to have a better

understanding of the different fatigue categories and show a more solid analysis of the fatigue changes during the intervention. Using a fatigue protocol will probably give more information about the effect of a training program in breast cancer patients, with the aim to evaluate the strength of the upper members.

The results of this study demonstrate the importance of exercise to reduce fatigue in women with breast cancer during treatment. Although in opposition to standard practice, it appears that women with breast cancer who are regular exercisers should be encouraged to continue their exercise program and women who are not regular exercisers should be given guidance and instruction to begin an exercise program.

7. Conclusion

In conclusion, the results of the current study suggest that exercise supervised intervention program during 12 weeks increase cardiorespiratory fitness, strength and health related quality of life in breast cancer patients. Among the several physical components, the most responsive index, as measured by the percentage of change from baseline, was power output. The patients experienced a significant reduction in treatment-related fatigue and pain symptoms and significantly improved physical function. The observed changes in questionnaire scores with 12 weeks supervised exercise reached clinical significance in several dimensions scores. The exercise was important to enhance both emotional and social functioning on top of physical improvements.

Supervised aerobic training combined with strength training in this study support the potential that exercise is a safe, effective and a beneficial intervention strategy for improving physical fitness and health related quality of life in breast cancer patients during treatment.

Ours findings also suggest that multidimensional exercise training should be recommended for breast cancer patients during treatment.

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9. Attachments

Termo de Consentimento
Programa de Exercício em Mulheres com Cancro da Mama

No âmbito do Doutoramento em Ciências do Desporto na Faculdade de Desporto da Universidade do Porto, está a decorrer uma investigação sobre o efeito do exercício físico na qualidade de vida em Mulheres com cancro da mama.

O conhecimento das alterações funcionais e estruturais dos pacientes com cancro durante e após o tratamento, torna-se fundamental para o desenvolvimento de programas de prevenção da fadiga relacionada com o cancro.

Este trabalho tem como objectivo geral analisar e descrever o efeito individualizado do treino e exercício, com finalidade terapêutica, nas alterações da função aeróbia e muscular, durante e após o período de tratamento em pacientes com cancro.

Para se conseguir executar esta fase do trabalho é necessário avaliar a qualidade de vida, a função muscular e aeróbia através da avaliação em ciclo ergómetro com espirometria.

Para o efeito, **apela-se à colaboração de pessoas para integrarem a amostra do estudo**, pelo que, se solicitam algumas informações e obtenção de consentimento informado.

Nome _____ **Idade** _____

Data de Nascimento _____ **B.I.** _____

Declaro, por meio deste termo, que concordo em participar na pesquisa de campo referente a este trabalho sobre "O efeito do exercício em pacientes com cancro", desenvolvido pelo aluno de Doutoramento, Eduardo Oliveira, sob orientação do Prof. Doutor José Soares e colaboração da Prof. Doutora Maria João Cardoso, Presidente do Centro MamaHelp.

Fui informada da garantia de anonimato, de ser submetido(a) a um inquérito sobre Qualidade de Vida através de um questionário bem como ser submetido a um inquérito sobre a História Clínica e Estilo de Vida

Declaro que fui informada que serei pesado numa balança de bio-impedância para determinar a composição corporal. A respectiva medição terá de ser realizada sem sapatos e sem meias.

Declaro ter sido informada sobre a medição da frequência cardíaca de repouso e da variabilidade da frequência cardíaca. O protocolo desta medição consiste em avaliar a frequência cardíaca em decúbito dorsal durante dez minutos.

Declaro ter sido informada sobre o protocolo da medição da força de preensão da mão e medição da força dos membros inferiores nomeadamente do quadríceps. A medição da força é realizada pela capacidade de produzir força com máxima intensidade durante três segundos com recurso a um dinamómetro portátil.

Declaro que fui informada sobre a medição da aptidão cárdio-respiratória que é realizada através de uma prova de esforço numa bicicleta estática com um protocolo de exercício que aumenta progressivamente a intensidade. Para esta avaliação é necessário colocar uma

máscara que envolve a boca e o nariz com o objectivo de se avaliar os gases inspirados e expirados. Para além disso será colocado um aparelho no peito para registar a frequência cardíaca durante a prova de esforço e monitorizar a intensidade de exercício.

Declaro que fui informada que os custos de deslocação MamaHelp serão por mim assumidos (nome) _____.

Declaro que fui esclarecida que caso haja necessidade de realizar um hemograma, os custos serão suportados pelo projecto que está a decorrer.

Declaro que fui informada que o protocolo de exercício terá a duração de 12 semanas (3 meses) com uma frequência de 2 vezes por semana. Cada sessão de exercício terá a duração de 45 minutos. O programa de exercício poderá ser realizado de duas formas. A primeira possibilidade é realizar o exercício físico no MamaHelp com ajuda de profissionais especializados. A segunda possibilidade é realizar o programa de exercício no domicílio. Neste caso, os exercícios serão explicados previamente no MamaHelp. O protocolo de exercício será constituído por exercícios de reforço muscular. O meio utilizado para se melhorar a funcionalidade muscular será através do recurso a elásticos. Este material será fornecido sendo os custos suportados pelo respectivo projecto.

Declaro que fui esclarecida que o protocolo de avaliação terá dois momentos de avaliação com uma distância temporal de 12 semanas entre eles. O primeiro momento de avaliação corresponde à avaliação inicial e segunda e última avaliação corresponde ao término do programa de exercício (semana 12).

Afirmo que aceito participar por minha própria vontade, sem receber qualquer incentivo financeiro e com a finalidade exclusiva de colaborar para o sucesso deste trabalho.

_____, ____ de Outubro de 2011

(Assinatura)

Muito obrigado pela colaboração!

História clínica

Nome _____ Data _____

Morada _____

Código Postal _____ - _____ Localidade _____

Telefone _____ Data Nascimento _____ Idade _____

Email _____

Tipo de cancro: _____ Data do Diagnóstico: _____

Localização Específica: _____ (p. ex. Lado dir/esq do peito)

Cirurgia: ____ Sim ____ Não Data da cirurgia: _____

Tipo de Cirurgia: _____

Outras Cirurgias: _____

Sintomas: _____

_____ (sintomas que teve que originaram o diagnóstico de
cancro: fadiga, náuseas, etc.)

Tratamento pós cirurgia (quimioterapia, radioterapia): _____

Duração do tratamento: _____

Data do último tratamento: _____

Actualmente realiza quimioterapia? ____sim ____ não

Se sim, qual a data último tratamento? _____

Actualmente realiza radioterapia? ____sim ____ não

Se sim, qual a data último tratamento? _____

Tomas algum tipo de medicação? ____sim ____ não

Se sim qual? _____

Estilo de Vida / Avaliação da Actividade Física

Nome: _____ Data: _____

Tabagismo

1. Alguma vez já fumou? _____
2. Fuma actualmente? _____ Quantidade por dia/semana _____
3. Com que idade começou a fumar? _____
4. Com que idade deixou de fumar? _____

Ingestão de bebidas alcoólicas

1. No último mês, quantos dias por semana ingeriu bebidas alcoólicas? _____
2. No último mês, qual a quantidade de ingerida apenas numa ocasião? _____

Sono

1. Durante a última semana, qual foi a média de horas de sono durante a semana (segunda a sexta feira)? _____
2. Qual foi a média de horas de sono aos fins de semana (Sábado e Domingo)? _____

Exercício

1. Realiza exercício de uma forma regular? _____
2. Que tipo de exercícios realiza de uma forma regular? _____
3. Quantos dias por semana realiza exercício de uma forma regular? _____
4. Qual o tempo dispendido numa única sessão de exercício (minutos)? _____
5. Considera o seu exercício de baixa, moderada ou elevada intensidade? _____
6. Assinale o seu tipo de ocupação profissional:
_____ Inactivo(a) (p.ex. trabalho numa secretária)
_____ Trabalho ligeiro (p.ex. trabalhos em casa, jardinagem)
_____ Trabalho intenso (p.ex. carregar objectos pesados)
7. Que tipo de actividade física o(a) motiva mais? _____
8. Que tipo de material/equipamento tem disponível para a prática de exercício?

9. A sua actividade física alterou-se durante o último ano? _____

Estilo de Vida / Avaliação da Actividade Física

Dieta

1. Neste momento, está satisfeito(a) com o seu peso? _____
2. Qual o peso que gostaria de ter? _____
3. Em adulto, qual foi a sua pesagem mais alta? _____
4. Em adulto, qual foi a sua pesagem mais baixa? _____
5. Se já tentou perder peso, que métodos é que abordou? _____

Registo de actividades diárias

1. Tem dificuldade em realizar algumas das seguintes actividades?

___ Carregar as compras	___ Rotinas de jardinagem
___ Guardar compras / louça	___ Conduzir
___ Lavar roupa / pôr roupa a secar	___ Fazer a cama
___ Passar a roupa a ferro	___ Pegar nos filhos

___ Outra _____

2. Responda se anteriormente assinalou alguma resposta,
 - a. A dificuldade que referiu começou a manifestar-se antes ou após o tratamento do cancro? _____
 - b. Se conhecida, descreva a causa de ter a respectiva dificuldade. _____



EORTC QLQ-C30 (version 3)

Gostaríamos de conhecer alguns pormenores sobre si e a sua saúde. Responda você mesmo/a, por favor, a todas as perguntas fazendo um círculo à volta do número que melhor se aplica ao seu caso. Não há respostas certas nem erradas. A informação fornecida é estritamente confidencial.

Escreva as iniciais do seu nome:

--	--	--	--	--

A data de nascimento (dia, mês, ano):

--	--	--	--	--	--	--	--	--	--

A data de hoje (dia, mês, ano):

31

--	--	--	--	--	--	--	--	--	--

	Não	Um pouco	Bastante	Muito
1. Custa-lhe fazer esforços mais violentos, por exemplo, carregar um saco de compras pesado ou uma mala?	1	2	3	4
2. Custa-lhe percorrer uma <u>grande</u> distância a pé?	1	2	3	4
3. Custa-lhe dar um <u>pequeno</u> passeio a pé, fora de casa?	1	2	3	4
4. Precisa de ficar na cama ou numa cadeira durante o dia?	1	2	3	4
5. Precisa que o/a ajudem a comer, a vestir-se, a lavar-se ou a ir à casa de banho?	1	2	3	4

Durante a última semana :

	Não	Um pouco	Bastante	Muito
6. Sentiu-se limitado/a no seu emprego ou no desempenho das suas actividades diárias?	1	2	3	4
7. Sentiu-se limitado/a na ocupação habitual dos seus tempos livres ou noutras actividades de lazer?	1	2	3	4
8. Teve falta de ar?	1	2	3	4
9. Teve dores?	1	2	3	4
10. Precisou de descansar?	1	2	3	4
11. Teve dificuldade em dormir?	1	2	3	4
12. Sentiu-se fraco/a?	1	2	3	4
13. Teve falta de apetite?	1	2	3	4
14. Teve enjoos?	1	2	3	4
15. Vomitou?	1	2	3	4

Por favor, passe à página seguinte

Durante a última semana :

	Não	Um pouco	Bastante	Muito
16. Teve prisão de ventre?	1	2	3	4
17. Teve diarreia?	1	2	3	4
18. Sentiu-se cansado/a?	1	2	3	4
19. As dores perturbaram as suas actividades diárias?	1	2	3	4
20. Teve dificuldade em concentrar-se, por exemplo, para ler o jornal ou ver televisão?	1	2	3	4
21. Sentiu-se tenso/a?	1	2	3	4
22. Teve preocupações?	1	2	3	4
23. Sentiu-se irritável?	1	2	3	4
24. Sentiu-se deprimido/a?	1	2	3	4
25. Teve dificuldade em lembrar-se das coisas?	1	2	3	4
26. O seu estado físico ou tratamento médico interferiram na sua vida <u>familiar</u> ?	1	2	3	4
27. O seu estado físico ou tratamento médico interferiram na sua actividade <u>social</u> ?	1	2	3	4
28. O seu estado físico ou tratamento médico causaram-lhe problemas de ordem financeira?	1	2	3	4

Nas perguntas que se seguem faça um círculo à volta do número, entre 1 e 7, que melhor se aplica ao seu caso

29. Como classificaria a sua saúde em geral durante a última semana?

1 2 3 4 5 6 7

Péssima

Óptima

30. Como classificaria a sua qualidade de vida global durante a última semana?

1 2 3 4 5 6 7

Péssima

Óptima



EORTC QLQ - BR23

Às vezes os doentes relatam que tem os seguintes sintomas ou problemas. Por favor, indique em que medida sentiu estes sintomas ou problemas durante a semana passada.

Durante a semana passada:

	Não	Um pouco	Bastante	Muito
31. Sentiu seca na boca?	1	2	3	4
32. A comida e a bebida souberam-lhe de forma diferente da habitual?	1	2	3	4
33. Os olhos doeram-lhe, picaram ou choraram?	1	2	3	4
34. Caiu-lhe algum cabelo?	1	2	3	4
35. Só responda a esta pergunta se teve quedas de cabelo: Ficou preocupada com as quedas de cabelo?	1	2	3	4
36. Sentiu-se doente ou indisposta?	1	2	3	4
37. Teve afrontamentos?	1	2	3	4
38. Teve dores de cabeça?	1	2	3	4
39. Sentiu-se menos atraente fisicamente devido à doença e ao tratamento ?	1	2	3	4
40. Sentiu-se menos feminina por causa da doença e do tratamento?	1	2	3	4
41. Teve dificuldade em olhar para o seu corpo, nua?	1	2	3	4
42. Sentiu-se pouco satisfeita com o seu corpo?	1	2	3	4
43. Preocupou-se com o seu estado de saúde no futuro?	1	2	3	4

Durante as últimas quatro semanas:

	Não	Um pouco	Bastante	Muito
44. Até que ponto sentiu desejo sexual?	1	2	3	4
45. Até que ponto esteve sexualmente activa? (com ou sem relações sexuais)	1	2	3	4
46. Só responda a esta pergunta se esteve sexualmente activa: Até que ponto as relações sexuais deram-lhe prazer?	1	2	3	4

Por favor, passe para a página seguinte

Durante a última semana:

	Não	Um pouco	Bas- tante	Muito
47. Teve dores no braço ou no ombro?	1	2	3	4
48. Teve o braço ou a mão inchados?	1	2	3	4
49. Teve dificuldade em levantar o braço ou fazer movimentos laterais com ele?	1	2	3	4
50. Sentiu dores na área da mama afectada?	1	2	3	4
51. A área da mama afectada inchou?	1	2	3	4
52. Sentiu a área da mama afectada muito sensível?	1	2	3	4
53. Teve problemas de pele na área ou à volta da área da mama afectada? (por exemplo, comichão, pele seca, pele a escamar)	1	2	3	4