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REVIEW ARTICLE

Running away from side effects: physical exercise as a complementary intervention for breast cancer patients

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Abstract The number of breast cancer survivors increases every year, thanks to the development of new treatments and screening techniques. However, patients present with numerous side effects that may affect their quality of life. Exercise has been demonstrated to reduce some of these side effects, but in spite of this, few breast cancer patients know and follow the exercise recommendations needed to remain healthy. In this review, we describe the different breast cancer treatments and the related side effects and implications of exercise in relation to these. We propose that exercise could be an integrative complementary intervention to improve physiological, physical and psychological factors that affect survival and quality of life of these patients. For that reason, the main objective of this review is to provide a general overview of exercise benefits in breast cancer patients and recommendations of how to design exercise interventions in patients with different side effects.

Keywords Exercise prescription · Complementary cancer treatment · Specific exercise for breast cancer patients · Global intervention in breast cancer patients

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Introduction

Breast cancer is the most common cancer in women from the Western world, with an incidence of 1.6 million new cancer cases diagnosed in 2012 (25 % of all cancers) [1]. The relative survival over 5 years is above 80 % in most Western countries due to improvements in screening, treatments and diagnostic techniques [2], indicating that this is to a large extent of a disease, which one survives from. Health and oncology associations have developed the term "cancer survivors" for this group, covering people with a long prospected time without cancer disease, but due to their completed cancer, treatment may present with other physiological or psychological problems, needing attention [3]. The estimated number of cancer survivors in 2020 is 11 millions, representing a 42 % increase in just one decade (from 2010 to 2020). In the United States, the costs associated with cancer care are estimated at 173 billions in 2020 [4, 5].

Anti-cancer treatments are associated with several critical side effects, which can affect patients for the rest of their lives [6]. More than 66 % of breast cancer patients present with at least one comorbid condition, and more than 33 % have two or more comorbidities. The most common comorbidities include hypertension, cardiovascular disease, respiratory diseases, obesity and diabetes, and in postmenopausal women, the incidence of hypothyroidism is greatly increasing [7]. In addition, the incidence of comorbidities increases with age in women, and 2 of 3 invasive breast cancers are diagnosed in women aged 55 years or older [8]. Some of these comorbidities can be treated with a range of pharmacological drugs, while others are not readily targetable such as cancer-related fatigue [9].

Exercise has proven an effective, safe and feasible tool to treat the side effects of breast cancer patients [10, 11].

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Studies addressing the effect of exercise on breast-cancer prognosis have found an inverse relationship between exercise and prognosis, with risk reductions ranging between 15 and 67 % for breast-cancer-specific mortality and between 18 and 67 % for all-cause mortality [12]. Other studies have focused on the beneficial effects on physical and psychosocial functioning. In addition, it has been shown that exercise can mitigate treatment-related toxicities among patients receiving adjuvant therapy for early-stage disease [13]. Thus, could exercise be an adequate complementary treatment? At this moment, more than 30 independent studies have been performed in breast cancer patients, showing that exercise is a safe tool to treat different specific aspects that are affected by treatments [14–25].

Only 30–47 % of cancer survivors know and follow the exercise recommendations by American College of Sport Medicine that prescribe at least 150 min of exercise per week, divided into 3–5 sessions, combining aerobic and resistance training [26, 27]. Moreover, around 24–50 % of breast cancer patients actually decrease their postdiagnosis physical activity levels [28]. However, a cancer diagnosis is a possible "teachable moment" [29], where proper counselling and support could help breast cancer patients to maintain or even improve their activity levels.

Yet before designing exercise interventions for breast cancer patients, understanding of their treatment and side effects and which limits this pose on exercise training should be elucidated. Below, we describe the different therapies for breast cancer patients and elaborate on their side effects, which may be of importance for exercise performance. In continuation, we address how exercise programs can be designed and carried out among breast cancer patients.

Breast cancer treatments

Surgery, radiation and systemic therapies, including chemo, endocrine and biological targeted therapies are generally part of standard breast cancer management. The sequence and design of an individualized treatment strategy is usually decided by a multidisciplinary team of specialists to cover the range of therapies [6]. In addition, there are different types of breast cancer, depending on their molecular profile. Generally, BC is classified by immunohistochemistry into three different types: hormone-dependent, HER-2 positive or triple negative [30].

For this reason, treatments are specific for the different subtypes of breast cancer, and side effects are directly related with the specific treatments. Table 1 sums up the principal treatments and the most common side effects.

Treatment side effects and exercise implications

Each breast cancer patient is affected differently by their anti-cancer treatment, first of all because breast cancer patients receive different therapies, and secondly because breast cancer patients are a very heterogeneous population with a large age range and different genetic and environmental background. Here, the most common side effects that should be considered before performing an exercise intervention are described (Table 2).

Physical limitations

Prevalence

It has been estimated that between 2 and 51 % of breast cancer patients present with impairments in the range of motion, between 17 and 33 % report decreased muscle strength and about 12–51 % suffer from chronic pain, after treatments [31]. Between 10 and 60 % of women report at least 1 upper-body symptom at any point from 6 months to 3 years after breast cancer surgery [32]. Even, stiffness in joints and arthralgia are reported in up to 50 % of patients within 6 months after initiation of aromatase inhibitors therapy [33].

Causes

All these complications are often associated with surgery, especially mastectomies or lymph node dissections. These interventions may damage the intercostal brachial or thoracodorsal nerve, being the cause of axillary paresthesia, muscle dysfunction and pain. Yet, radiotherapy can also cause physical limitations through chronic scaring and fibrosis in the treated area. In addition, breast reconstruction after mastectomy may use tissue from other parts of the body (dorsal muscle or abdominal tissue), which can change body perception and movement. Related to arthralgia, multifactorial aspects are described, such as loss of muscular mass, weight gain or menopause and the reduction of oestrogens levels [34].

Implications

The restriction in physical movement has important implications in daily life of these women. Nerve injury that is not treated may change muscle recruitment pattern and flow-on effects to surrounding musculature, and the use of the arm may be permanently altered. Radiotherapy damages diminish joint mobility and foster short and potentially long-term postural changes. The alterations in the use and function of the upper body is associated with psychosocial and social implications, influencing all aspects of

Table 1 Principal treatments in breast cancer and their more common acute and chronic effects

Treatments	Procedure	Acute side effects	Chronic side effects
Local therapy			
Surgery	There are two possible options of surgery: breast cancer conserving (only tumour bulk is resected) and total mastectomy (mammary gland is extirpated completely) [30]	Pain Functional limitations	Fatigue Lymphedema
	Sentinel lymph node biopsy and pathology analysis. If tumour cells are present in the lymph node biopsy, additional lymph nodes are removed (lymph node dissection) [30]		
Radiation therapy	Radiation is applied at the thorax and the armpit and can be given in the adjuvant setting independent of chemotherapy. Could be external radiation, using a machine outside the body or internal radiation or brachytherapy where radioactive seeds or pellet are placed directly into the beast tissue, next to the cancer. If breast-conserving surgery was done, an extra boost of radiation is given to the area in the breast where the cancer was removed to prevent relapse	Pain Functional limitations Impaired immune function Gastrointestinal toxicity Skin changes	Fatigue Lymphedema Cardiovascular damages Pulmonary changes Cognitive changes Second cancers
Systemic therapy			
Chemotherapy	Cytotoxic or cytostatic drugs, which can be administered before surgery (neoadjuvant therapy), but most commonly after surgery (adjuvant therapy). Common chemotherapeutics in breast cancer include anthracyclines (doxorubicin and epirubicin) and taxanes (paclitaxel and docetaxel). These may be used with other drugs like fluoracil and cyclophosphamide [143]	Peripheral neuropathy Impaired immune function Reproductive changes Body weight changes Fat mass increases Lean mass losses Gastrointestinal toxicity	Fatigue Cardiovascular damages Cognitive changes Second cancers
Endocrine therapy	By blockade of female sex hormone signalling, the growth of oestrogen-receptor-positive tumours can be inhibited. Different drugs are used for pre- or postmenopausal women		
	Tamoxifen is often given to patients with hormone-dependent breast cancer who are pre-menopausal [30]. It could be used in postmenopausal depending on their individual profiles or comorbidities [144]	Body weight changes Articular pain Fat mass increase Lean mass losses Impaired immune function Gastrointestinal toxicity Second cancer	Fatigue
	Postmenopausal women obtain oestrogen from fat tissue through an enzyme called aromatase and an aromatase inhibitor is used to block hormone effect in this patients [27]	Body weight changes Articular pain Fat mass increase Lean mass losses Impaired immune function Osteoporosis	Fatigue
Biological therapy	It is used in HER2 positive tumours. Monoclonal antibody therapy is a cancer treatment that uses antibodies made in the laboratory from a single type of immune system cells. It can identify substances on cancer cells or normal cells that may help cancer cells grow [30]	Cardiovascular damages Impaired immune function	Fatigue

patients' daily life and hence quality of life [5, 31, 35]. Joint pain is one of the principal reasons for patients to discontinuate aromatase inhibitors therapy [36].

Exercise implications

Gentle articular movements in all range of shoulder joint mobility and stretching will increase the range movement of the joint [37]. In fact, patient education to identify positions or activities that alleviate the symptom is important for self-care management. They have to be developed in a gradual and progressive plan, always avoiding pain. This exercise, during and after treatments, enhances tissue extensibility, promotes normal range of mobility [38] and prevents muscle contractures and alterations in mechanics of shoulder [39]. Resistance exercise of arms and legs increases resistance to musculoskeletal injury and muscular strength, improves range of motion, decreases weight and body fat as well as systemic inflammation levels. All of these have special influence in

reducing of joint pain and physical limitation, increasing quality of life [34, 40].

Lymphedema

Prevalence

Lymphedema is a common problem, affecting between 6 and 43 % of breast cancer patients, in particular patients, who have had lymph node resection, where 30–50 % of the women are affected.

Causes

Lymphedema risk factors are radiation with treatment on the dominant side, body composition and physical activity levels.

Implications

Lymphedema causes swelling, tightness and heaviness in the affected arm and includes cosmetic and functional problems, pain, infections and cellulitis [41, 42].

Exercise implications

Previous studies have shown that resistance training does not induce lymphedema [43–45] and is now been accepted by the American College of Sport Medicine as a safe intervention [27]. In fact, progressive exercise planning has been proven as effective treatment to reduce lymphedema in breast cancer patients [46, 47], suggesting that exercise may prevent the development of lymphedema [45]. It may be related to the fact that lymphedema is more associated with subfascial lymphatic system than with epifascial lymphatic system and functional improvements in the subfascial lymphatic system may produce improvements in lymphedema. Based on these findings, improvements in muscle strength, gained by resistance exercise, produce improvements in subfascial lymphatic system, as has been observed in previous studies [48, 49].

Physical capacity reduction

Prevalence

Breast cancer patients' physical capacity is consistently around 30 % below that of age- and sex-matched sedentary individuals without a history of cancer [50, 51].

Causes

Physical capacity depends on an integrated physiological system, including the cardiovascular system to transport oxygen and nutrients and skeletal muscles to perform external work. Anti-cancer treatment is associated with impairments in the cardiovascular system by acute reductions in red blood cells and cardiotoxicity after treatment with anthracyclines (more permanent) or trastuzumab (reversible). Moreover, many breast cancer patients lose muscle mass due to physical inactivity and cancer treatments such as chemotherapy [52].

Implications

Physical capacity is a powerful predictor of mortality in both healthy and diseased populations [53–55]. Moreover, VO_{2peak} is an important predictor of anthracycline and trastuzumab-induced left ventricular dysfunction and cardiovascular diseases risk profile as well as global quality of life and fatigue in patients with solid malignancies [56–59].

Exercise implications

Physical activity and aerobic and resistance training produce a complex cascade of metabolic adaptations, producing changes in both acute and adaptive response to exercise. The main objective of the physical adaptations is the maintenance of homeostasis and resistance of fatigue during exercise, producing complex genetic, molecular and physiological adaptation with important metabolic changes, which improve VO_2max and physical capacity [60–62].

Cardiac dysfunction

Prevalence

Radiotherapy at the left side increase cardiovascular mortality by 25 % 15 years after diagnosis compared with women irradiated in right side [63]. Of the chemotherapeutics, between 13 and 39 % of breast cancer patients treated with anthracyclines present with cardiac events at some point in their life [64].

Causes

Anthracycline-mediated cardiotoxicity can occur in an acute or subacute fashion; however, the majority of cases are late-onset, occurring at least 1 year after completion of therapy, and tends to be irreversible. It is related to the cumulative anthracycline dose and may reflect a variety of intracellular mechanisms including free radical formation. Monoclonal antibody therapy such as tratuzumab may lead to cardiac dysfunction during the time of medication administration and are generally reversible during a pause in anti-cancer therapy if treated with cardiac medication [6, 65, 66].

Table 2 Summary of exercise management suggestions and possible responsible mechanisms

Side effect	Exercise management	Exercise mechanisms
Physical limitations	Soft articular movements stretching	Enhances tissue extensibility and promotes normal range of mobility avoiding muscles contractures and alterations in mechanics of shoulder
	Progressive muscle strength training in both, upper-body limbs and legs	Resistance exercise increases muscular strength, improves range of motion, and decreases weight, body fat and systemic inflammation levels
Lymphedema	Stretching to reduce pain	Stretching improve tissue extensibility
	Resistance exercise	Subfascial lymphe system is improved by resistance exercise and muscle strength
Physical capacity	Aerobic exercise with intensity changes	Intensity changes in aerobic exercise and resistance training improve muscle cells adaptation in both senses, molecular and physiological, as well as cardiovascular adaptation to increase peripheral blood flow
	Resistance exercise	
Cardiac dysfunction	Aerobic exercise	Reduction of global inflammation
	Resistance exercise	Cardiac capacity and strength of cardiac muscle are increased with a combined training program
		Increase of peripheral blood vessels
Weight gain	Aerobic exercise	Increased of calories waste and metabolism
	Resistance exercise	Increased of muscle mass, preventing sarcopenia obesity
Bone loss	Upper-body resistance exercise to recover spine bone mass	Resistance and impact exercise promotes bone regeneration decreasing osteoporosis levels
	Impact aerobic exercise to recover hip-bone mass	
Cognitive impairments	Aerobic exercise	Improving cerebral plasticity
Cancer-related fatigue	Combining exercise: aerobic and strength	Moderate to high intensity presented the best results reducing cancer-related fatigue, due to improvement in muscle mass, reduction in global inflammation and increased of cardiovascular capacity
Psychological problems	Group and guide exercise	Training with people in the same situation may reduce these side effects

Implications

Treatment-induced cardiac dysfunction increase cardiac mortality in breast cancer patients even 15 years after diagnosis [31] and is related to the reduction in physical capacity [67].

Exercise implications

Aerobic exercise practised at low intensity in low level of aerobic threshold increases left ventricle volume, as well as contractility and elasticity of the cardiac muscle. Another main implication is that exercise improves muscle cardiac irrigation with a high number of vases [68]. In addition, exercise reduces global low-grade inflammation, which is related with cardiovascular diseases as previously described.

Weight gain

Prevalence

Weight gain is a major problem during breast cancer treatment and is shown to affect more than 68 % of breast cancer patients with a mean weight gain of 3.9 kg, ranging between 0.1 and 27 kg [69], even in patients undergoing diet control [70]. These weight gains are exclusively caused by an increase in body fat. Seventy-four percentage of women gained body fat in a range of 0.1–15.0 % [69].

Causes

The causes of weight gain are multifactorial, including factors such as changes in activity level, menopausal status, supportive medication, in particular, glucocorticoids endocrine manipulation, metabolism change and mood [71]. In postmenopausal women, it is particularly important to control fat mass because the oestrogens are primarily produced by fat mass after menopause, so high level of fat mass decreases the survival rates of these patients [11].

Implications

In case of induced menopause and postmenopausal women, fat mass produces high levels of pro-inflammatory cytokines and pro-tumour genesis proteins, which are related with a poor quality of survival [10, 72]. It has been shown

that overweight women exhibit a 30–40 % increased risk of death [73]. In addition, weight gain is related with an increase of diabetes and cardiovascular disease risk [52].

Exercise implications

Exercise intervention has been shown to control weight gain in pre- and postmenopausal women [74, 75]. In postmenopausal women, exercise reduce waist–hip ratio, which may be associated with a change in serum estradiol levels and reduce body fat mass, causing a reduction in serum estradiol and inflammatory biomarkers levels [75, 76]. Exercise and training increase muscle mass, which is associated with a higher basal metabolism, calories waist [77] and irisine production, which promotes changes in body fat mass, transforming white fat mass (which maintains body temperature) into brown fat mass (responsible for producing energy), raising fat mass waste [78].

Bone loss

Prevalence

Around 78 % of females cancer patients present with elevated rates of osteoporosis compared with the general population. In addition, osteoporosis was found in 16 % of cancer patients in complete remission and osteopenia in 44 % of them (these rates were not statically different among various cancer types) [79].

Causes

Chemotherapy reduces bone mass density (BMD) by around 4 % in lumbar spine after 6 months of treatment. Aromatase inhibitors cause a 4–6 % reduction in BMD in lumbar spine, or premature menopause is associated with a 11 % reduction in BMD after 1 year [80–82]. The reductions in circulating estradiol levels that occur at menopause are associated with a rapid deterioration in bone mass by as much as 3 % per year for the first 5 years after menopause.

Implications

It has significant health consequence, such as an increased risk of fracture and a reduction in physical daily activities [83].

Exercise implications

Exercise promotes bone regeneration and thereby decreases osteoporosis levels. However, not all types of exercise could produce this effect. Winters-Stone et al. [84] carefully studied this, showing that the best exercise to get this bone prevention was by combining upper-body resistance exercise, which maintains and recovers bone spine density through tension produced by muscle insertion and impact exercise [85] where body weight is sustained by legs, which activates hip and femur bone recovery.

Cognitive impairments (chemo-brain)

Prevalence

Some recent reviews estimate that 75 % of women who receive chemotherapy will experience a decrease in cognitive function within 2 years of treatment. The cognitive problems in those who receive chemotherapy are more severe than in those who only receive loco-regional therapy [6]. These disturbances in the cognitive domains are diverse and include memory, processing speed, attention and executive function.

Causes

At this moment, the biological mechanism has not been completely elucidated, and there are multiple hypotheses for the physiological changes in the brain that might underlie these cognitive impairments, including disruption of hippocampal cell proliferation and neurogenesis, chronic inflammation, increased oxidative stress, white matter disruption and long-term changes in cerebral blood flow and metabolism [86].

Implications

The cognitive dysfunction is a source of serious concern and anxiety for breast cancer survivors [6], and in addition, it has an important influence on the adherence to treatments, as well as negatively impact activities of daily living, such as work performance [87], access to medical and other health service and caring for and socially interacting with family members [87].

Exercise implications

It has been observed that voluntary exercise may produce cerebral plasticity when physical activity is promoted [88]. It may increase brain-derived neurotrophic factor [89], which supports the survival and growth of many neuronal subtypes, including glutamatergic neurons [90, 91], emerging as a key mediator of synaptic efficacy, neuronal connectivity and use-dependent plasticity [92–95]. In addition, some kind of exercise may increase memory and attention, such as dance choreographies or learning about new technical movements, stimulating attention to the body. Few researches have pursued this area, so there is a

lack of information about the power of exercise as a complementary therapy for cognitive impairments.

Cancer-related fatigue

Prevalence

Approximately 48 % of patients with cancer report cancer-related fatigue manifest as an experience of tiredness or exhaustion not necessarily precipitated by activity. Fatigue is considered pathological when it persists for several months, and it is not relieved by rest and may be worsened with rest.

Causes

A direct relationship between muscle mass and cancer-related fatigue has been observed [96], stressing that a reduction in muscle mass decreases energy [97], a theory which is further supported by the fact that fatigue is reduced with physical activity [98]. Other biological factors, such as low haemoglobin, elevated levels of inflammatory cytokines and insulin resistance, could be related with this problem [97–99].

Implications

The discomfort associated with persistent fatigue leads to a decrease in daily activity level during cancer treatment, resulting in a lower tolerance for exercise. The patients may become too tired to participate fully in the roles and activities that make life meaningful and losing motivation, which precipitate depression and negatively impact their quality of life [100].

Exercise implications

A recent meta-analysis has found that exercises have beneficial effect in fatigue in cancer patients both during and after cancer treatments and regardless of the program duration. In addition, more effects were observed in moderate or vigorous intensity, than in mild intensity [101]. The physiological mechanisms that produce this decrease in fatigue levels are multifactorial, including increase in muscle mass, reduction in body fat and hormonal and immune adaptations [101].

Psychological problems

Prevalence

Around 22 % of cancer patients present with moderate to high levels of depression, and 38 % of patients report moderate to high anxiety [102].

Causes

The main cause related to psychological problems is the diagnosis of cancer and its subsequent treatments, since its high probability of experiencing side effects, which may results in a reduction in quality of life [103, 104]. Radical treatments produce side effects, which influence in body image, anxiety and depression due to the weight gain, body composition changes or –cancer-related fatigue [105, 106].

Implications

The presence of side effects has the potential to impact overall quality of life. Some previous studies have shown that, 2 years posttreatment, women with breast cancer presented a significant deterioration in the psychological dimension [107], and it may be maintained until 5 years after treatments [108]. These psychological disorders may produce mental adverse reactions in the patients, leading them to discontinue the treatment, which can negatively influence in treatment outcomes [109, 110].

Exercise implications

In a recent meta-analysis, it was observed that aerobic exercise reduced symptoms in dose-response fashion such that as weekly minutes of aerobic exercise were increased, cancer survivors engaged in supervised exercise experience less-depressive symptoms than those who engaged in unsupervised exercise [111]. Another meta-analysis showed that exercise interventions improved depression, body image and anxiety [112]. Multiple factors could lead to psychological disorders in breast cancer patients; however, it is important to know which of them could be treated or could be led to exercise prescription.

The combination of some or all of these side effects has a repercussion in breast cancer survivors' quality of life. It contributes directly to their psychosocial functioning, reducing their social life [113, 114]. However, exercise has been proved as a possible complementary treatment in some of these side effects. Now the question is: Which kind of exercise could be the best to breast cancer patients depending on their side effect or to prevent them?

Breast cancer biomarkers and exercise effect

Some studies have found relationship between some biomarkers and survival of patients. Some of these biomarkers have shown sensibility to exercise programs, which promote the global effect of exercise. These biomarkers that have shown sensibility to exercise intervention are sex hormones levels [74, 75], insulin levels [115],

Table 3 Breast cancer biomarkers and exercise evidence about their changes

Cancer biomarkers	Cancer relationship	Exercise evidence
Sex hormones	Elevated endogenous estradiol and androgen levels are associated with poor survival in breast cancer patients with hormone-positive receptors, whereas increased sex hormones-binding globulin (SHBG) levels are associated with decreased risk	Postmenopausal women: aerobic exercise decreases serum estradiol and increases sex hormones-binding globulin (SHBG) levels in postmenopausal women, mainly, due to the weight loss, as during menopause, oestrogen is produced from their body fat mass
		Pre-menopausal women: it has been shown that high-intensity aerobic exercise reduced total oestrogen levels by 18.9 %, due to a reduction in luteal phase levels although length of this phase was unchangeable
		Although these trials have not been developed in breast cancer patients, changes in sex hormone levels can be obtained in pre-and, in particular, postmenopausal women
Insulin	Insulin can stimulate the growth of normal and malignant breast epithelial cells in vitro, and high-fasting insulin levels are related with poorest survival in breast cancer patients	Aerobic exercise with intensity changes produces better metabolic adaptation in muscle cells and decrease IGF-1 levels and increase IGFBP-3 levels
		Combined exercise (strength and aerobic) decreases plasma insulin levels and increases sensitivity of muscle tissue to insulin
		Resistance exercise improves lean and reduces fat body mass
Immune cell function	Immune function is affected by cancer treatments, associated with leukopenia. However, an adequate blood immune function is positively associated with progression-free and overall survival	Moderate aerobic exercise increases immune cell function by increasing percentage NK cell-specific lysis by 9.4 %
Inflammatory cytokines	Low-grade inflammation is a risk factor for breast cancer recurrence and mortality. Specifically, Interleukine-6 (IL-6), TNF-α and C-reactive protein (CRP). CRP is an acute phase protein is widely accepted as a sensitive and reliable biomarker of systemic inflammation and IL-6 and TNF-α are inflammation-responsive and pro-inflammatory cytokines, respectively, that influence CRP production. IL-6 and TNF-α are commonly found in adipose tissue, as it is infiltrated with immune cells, which produce these cytokines	The metabolic changes with aerobic exercise intervention are not fully understood, but may be related to fat mass reduction and the promotion of anti-inflammatory environment, producing a decrease in C-reactive protein

inflammation levels [76, 116–118] and immune function [15]. All of these must be taken into account to prescribe exercise, due to the importance that they have shown in breast cancer survival (Table 3). In addition, the effect of exercise on these biomarkers has been investigated in randomized controlled trials, which are summarized in Table 4.

Exercise intervention

Above, we described the common side effects and physiological limitations in breast cancer patients. It should be stressed that none of these side effects contraindicate exercise in breast cancer survivors, if the intensity and duration of the prescribed exercise take into account the physical function of the patient individualizing exercise prescription according to a cancer survivor's pre-treatment aerobic fitness, medical comorbidities, response to treatment and the immediate or persistent negative effects of treatment that are experienced at any given time [27] (Fig. 1).

Below, we address the different practical considerations, such as where, when, what and how much, as well as describe the different training modalities, which must be taking into considerations when designing a good exercise intervention.

Practical considerations before initiating an exercise intervention

For any exercise intervention to be successful, one must select training forms, which the patients are motivated for. Yet, keeping this in mind, there are several aspects, which ought to be fitted into the preferred training. For instance, selecting activities involving leg support of the body weight (impact activity) will promote bone regeneration in order to prevent osteoporosis [119]. Thus, if patients like cycling or swimming, they should be encouraged to combine these with any impact activity [31, 120]. Another

Table 4 Summary of RCT in breast cancer survivals and principle biomarkers in breast cancer. (PE = primary endpoint)

RCT	*N*	Moment of Intervention	Participant characteristics	Intervention	Endpoints	Conclusions
Fairey et al. [115][a]	52	Posttreatment (≥6 months)	Stage I–IIIB Non-smoker Postmenopausal With or without current tamoxifen or anastrozole treatment Cardiac disease, diabetics or women with mental illness were excluded	*Duration* 15 weeks/3 times per week *Exercise prescription* cycle hergometer 15 min/s 1–3 weeks. +5 min every week 3 week to 35 min for 13–15 weeks *Intensity* 70–75 % of VO_2 peak	(PE) Reduction in fasting Insulin Glucose Insulin resistance IGF-I, IGF-II, IGFBP-1 and IGFBP-3 IGF-I/IGFBP-3	IGF-I decreases with exercise IGFBP-3 increases with exercise IGF-I/IGFBP-3 decreases with exercise
Fairey et al. [15][a]	52	Posttreatment (≥6 months)	Stage I–IIIB Non-smoker Postmenopausal Current tamoxifen or anastrozole treatment Cardiac disease, diabetics or women with mental illness were excluded	*Duration* 15 weeks/3 times per week *Exercise prescription* Cycle hergometer 15 min/s 1–3 weeks. +5 min every week 3 weeks to 35 min for 13–15 weeks *Intensity* 70–75 % of VO_2 peak	(PE) NK cell cytotoxic activity Neutrophil function Blood mononuclear cell phenotypes Cytokine	Exercise increases natural killer cell cytotoxic activity and improves blood immune function in postmenopausal breast cancer survivors
Fairey et al. [76]	52	Posttreatment (≥6 months)	Stage I–IIIB Non-smoker Postmenopausal Current tamoxifen or anastrozole treatment Cardiac disease, diabetics or women with mental illness were excluded	*Duration* 15 weeks/3 times per week *Exercise prescription* Cycle hergometer 15 min/s 1–3 weeks. +5 min every week 3 weeks to 35 min for 13–15 weeks *Intensity* 70–75 % of VO_2 peak	(PE) C-reactive protein Lipids Heart rate variables Peak oxygen consumption	C-reactive protein decreases with exercise Exercise increases VO_2 peak consumption Exercise increases HR reserve Exercise decreases triglycerides
Irwin et al. [23][b]	68	Posttreatment (≥6 months)	0–IIIA stage Inactive Postmenopausal Non-smoker Not diabetics Not women with recurrence or second cancer	*Duration* 6 months/5 times per week *Exercise prescription* A combined supervised aerobic training program at a local health club designed sessions 3 times per week and a home aerobic training program 2 days per week 15–30 min *Intensity* Moderate intensity (from 50 to 80 % maximal heart rate)	(PE) Fasting insulin levels IGF-1 IGFBP-3	Exercise decreases IGF-1 and increases in IGFBP-3 Fat-free mass were positively correlated with changes in IL-6 and negatively correlated with changes in IL-2

Table 4 continued

RCT	*N*	Moment of Intervention	Participant characteristics	Intervention	Endpoints	Conclusions
Janelsin et al. [145]	21	Posttreatment (>1 and <30 months)	Primary diagnosis 0–IIIB Not vigorous-intensity exercise more than 1 day per week Not mental disorders Not users of psychotropic drugs were exclude	*Duration* 12 weeks/3 times per week *Exercise prescription* Tai Chi Chuan sessions. 60 min *Intensity* moderate intensity	(PE) Reduce insulin levels IGF-I IGFBP-3	Exercise decreases blood insulin levels. IGF-I and increases IGFBP-1* Pro-inflammatory cytokines IL-2 and IFN-γ decreases with exercise* IGF-I and IGFBP-1 were inversely correlated; IGF-I and IFN-γ were positive correlated; insulin and IFN-γ were positively correlated; and fat-free mass were positively correlated with changes in IL-6 and negatively correlated with changes in IL-2
Jones et al. [146][b]	68	Posttreatment (≥6 months)	0–IIIA stage Inactive Postmenopausal Non-smoker Not diabetics Not women with recurrence or second cancer	*Duration* 6 months/5 times per week *Exercise prescription* A combined supervised aerobic training program at a local health club designed sessions 3 times per week and a home aerobic training program 2 days per week 15–30 min *Intensity* Moderate intensity (from 50 to 80 % maximal heart rate)	(PE) to examine changes in proinflammatory biomarkers concentration (IL-6, CRP and TNF-α)	Six months moderate exercise not decreased C-reactive protein level, IL-6 and TNF-α concentration* A borderline correlation between change in percentage body fat and change in CRP was observed in exercise group*
Ligibel et al. [147]	82	Posttreatment (≥3 months)	I–III stage Postmenopausal Not corticosteroids Body mass index >25 or fat percentage >30 % Baseline exercise <40 min per week Hormonal therapy allowed	*Duration* 16 weeks/3–5 times per week *Exercise prescription* Two supervised strength training (50 min each session) and home-based aerobic training protocol (90 min per week). Not changes in dietary habits *Intensity* Moderate intensity	(PE) reduce insulin concentration Glucose Insulin resistance Hip–waist circumference BMI Body composition	Exercise decreases insulin levels and improves insulin resistance Exercise decreases hip circumference and waist circumference
Payne et al. [148]	20	Posttreatment (time after treatment is not described)	Postmenopausal with complains of fatigue Hormonal therapy Karnofsky performance ≥80 Age 55 years or older No mental diseases No neuromuscular deficits	*Duration* 12 weeks/4 times per week *Exercise prescription* Home-based walking intervention. Walking 20 min *Intensity* Moderate intensity	(PE) Fatigue, sleep disturbance, and depression Cortisol Serotonin Interleukin-6 Bilirubin	Serum serotonin levels were significantly different between groups and across time Sleep disturbance was significantly lower in exercise group than control group and also over time

Table 4 continued

RCT	*N*	Moment of Intervention	Participant characteristics	Intervention	Endpoints	Conclusions
Schmitz et al. [77]	81	Posttreatment	Hormonal treatment allowed Physician permission for weight training Not morbidly obese Not hypertensive Not weight loss plan Non-smoker Sedentary to moderate physically active Body weight stable	*Duration* 12 months/2 times per week *Exercise prescription* strength training. 6 months of follow up exercise and 6 free months 60 min *Intensity* Moderate to vigorous intensity	Body fat percentage and lean body mass Fasting blood glucose Glucose levels Insulin Insulin resistance IGF-axis protein BMI Strength	Strength exercise decreases in IGF-1 and increases in IGFBP-3 Strength exercise increases lean mass and decreases body fat percentage

* Not significant changes were found

[a,b] Publications from the same study

example stresses the need to train in the free movements to get a minimum of muscle body tone. Such can be obtained with, for example, aerobics or other dancing activities.

On the practical side, studies have shown that patients prefer exercise counselling during their treatments. Exploring this preference, consultations with trained physiologists at a point during the cancer trajectory could be a good option for promoting the beneficial effects of training [121] as some technical aspects have to be demonstrated; a combined informative and practice exercise session would be an ideal option in order to get a behavioural change in patients after treatments [122].

Studies also show that group-based interventions are popular as these give the patients an opportunity to meet training partners in the same situation, helping them both to maintain training and manage psychological implications [123] through interactions with other patients, possibly experiencing similar problems. Such group-based exercise interventions have indeed shown significant reductions in anxiety or depression symptoms, improving the quality of life of patients [101].

Along the lines of group-based training, the physical setting of the training also plays an important role. Supervised training intervention performed in the hospital setting or sport facilities have proven most efficient in mediating physiological and psychological improvements. Yet, these studies are costly and resource consuming. At the other end of the spectrum, home-based training studies have showed that this training setting also improves physiological outcomes, but that it is harder to keep the motivation going in this setting.

Finally, the time aspect might be a significant barrier for some patients. The general recommendation of physical activity is 150 min of exercise in 3–5 days of moderate intensity or 70 min of high-intensity exercise, combining 2 days of resistance exercise and 3 days of aerobic exercise [27]. But this can be varied, for instance patients might work less time in each session and then do more days because it helps to start gradually and avoid a high tiredness after the first sessions [32]. The start has to be progressively in order to get an adequate progression and adaptation to exercise.

Selecting exercise modality and intensity

For the more formal design of an exercise intervention, the first objective is to know whether the women present any cardiac damage or other comorbid conditions, because it could lead to the intensity of the prescription and the way they have to train [27]. The second point that one should take into account is the control of the intensity. During endurance training, a heart rate monitor is a feasible option to monitor intensity as the heart rate is controlled at the

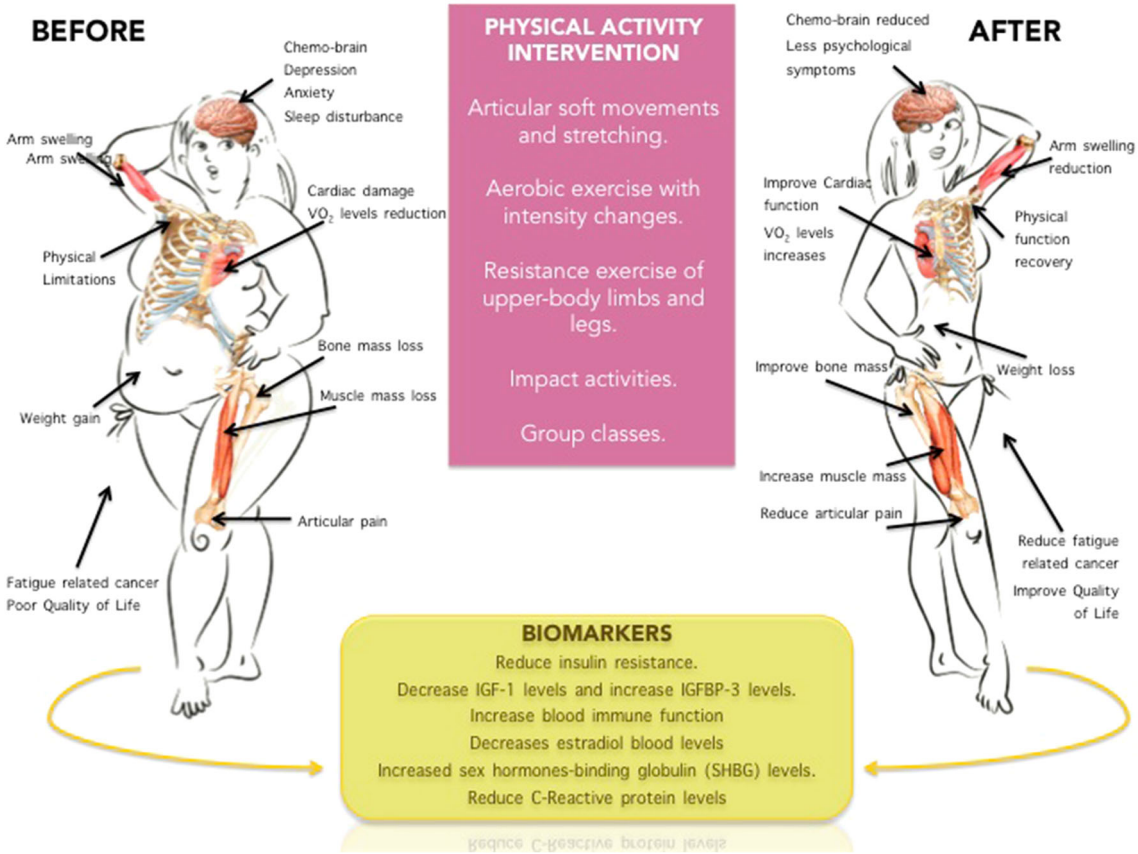

Fig. 1 Outline the effect of exercise on the breast cáncer treatments side effects

same time. Using the Karvonen equation, one could prescribe exercise intensity by heart rate reserve percentage [124]. In case of resistance training with elastic bands, repetitions of the exercise are the way to control the intensity. Once patients start with strength machines, 1 maximal resistance (1RM) test could be performed to adapt the intensity related to their maximum [27]. Some patients do not present with any cardiac dysfunctions, and in that case, subjective perception of effort might be useful to the intensity control, that is, Borg scale [125].

Aerobic exercise

Aerobic training involves training of the cardio-vascular system under aerobic conditions. Benefits of aerobic exercise are related to improvements in cardiac function [126], with an increase of physical capacity [14], a reduction in weight gain [127] and a good management of fatigue and depression [128, 129] in breast cancer patients. Training at moderate intensity facilitate such improvements in breast cancer survivors [26]. For this reason, patients should work above 60 % in order to get physiological improvements [10, 125]. Variation and progression in the training program should be obtained, so the body does not get used to the activity and stops improving, and interval training with periods of high intensity (e.g. 85 % of heart rate) followed by low-intensity intervals can provide such progression. This will improve the strength, physical capacity and reduce insulin resistance of muscles. It is an effective way to avoid diabetes, as the body keeps going burning calories after exercise cessation. In addition, this kind of training has been demonstrated to be a safe way to train in patients with cardiac damage or cancer patients, getting better results than normal training [130–134].

Resistance exercise

Strength training is essential to rebuild muscle mass and improve functional limitations [5, 44]. However, surgery and lymphedema risk might scare some women from initiating strength training. Yet, several studies show that strength training does not induce lymphedema [5, 27, 135]. First time, early assessment and intervention postsurgery, by way of education and shoulder exercise, are important to correct subtle treatments-related changes in scapulae position, and stability that left untreated may lead to upper-body symptoms and impairments. Then, movement repetitions without resistance give the muscles the necessary

tone to do more intense exercise, with the objective to improve the range movement and activate the tissues that have been damaged by radiation and surgery. When movements are developed comfortably, training with elastic bands could be initiated, always taking care with the body positions. Between 10 and 15 repetition of each exercise in 2 sets, 2 times per week is enough in order to maintain muscle tone with this method [125]. The best way is to start with more repetitions and less resistance and gradually increase the resistance at the same time that the repetitions are reduced. Global strength and neurological muscle aspects are improved. Muscle mass will not increase as much when muscle adaptations become apparent after some months of training with elastic bands. Strength machines will be the next step. Specialist management is important to control the main aspects of them: posture, charges or the initial test to individualize resistance training. It is important to remember that exercise never must produce pain.

Stretching

At the end of a training, introduce a whole body stretching routine, in order to relax muscle and mind, and improve flexibility and the joint range mobility [125]. The most efficient relaxation of muscle mass is through maintaining each stretch between 20 and 30 s. Arm–shoulder stretching has been proved as an effective intervention to recover physical functioning and mobility [136]. It is important to focus on muscles that have been used during the session, but in breast cancer survivors, it is equally important to stretch the deltoid, pectoral, dorsal and all arm muscles to avoid stiffness in the upper limbs. It is also the moment to work the lymphedema exercise that some hospitals provide to patients such as elevate the arm as far as the patient can or try to touch as far as you can in your back [43].

Lymphedema exercise

It is important to note that lymphedema has to be treated by a specialist. However, there are tips that could be taken into account during this process:

1. Insist that women go as soon as possible to a specialist if she notes warm, sore muscles, redness or pain in her arm.
2. The patients should receive exercises to do at home. The effect will be greatest if she repeats the exercises every day.
3. To start, gentle range of motion exercise to warm up the area is indicated, including, at least, waist, shoulder, elbow, wrist and neck. It is better if you include whole joints in order to get a global relax.
4. It is recommended to stretch the whole body every day, including specific stretching of shoulder in order to avoid cordons or other lymphedema complications. Stretching orders should be starting from head to feet, and when exercise is done, they should be at the end of the session.
5. The patients have to be invited to ask to her care provider the strength exercise specific to improve her position, reduce lymphedema and recover nerve function [137] and not to forgot to highlight to use the compression garment following the specialist suggestions.

Cost-effectiveness of exercise: a possibility to explore

One of the possible benefits that needs further exploration, is the impact in public health economy system. Although an investment in infrastructures and qualified personal should be taken into account for a quality exercise plan in cancer survivors, there are indirect data taken from the cost of the comorbidities that potentially could be avoided with exercise and that orientate to a potential cost-effectiveness of this treatment. Specifically, the weight gain that usually leads in over-weight or obese women, which has been defined as an important risk factor for multiple serious health problems in adults (heart failure, diabetes, high cholesterol, high blood pressure, certain types of cancer, stroke, diabetes, muscle and bone disorders), is related to 26 % higher cost than normal weight people, in Spain [138]. In addition, it is estimated that diabetes-related healthcare cost per patients is €667 per month after 1 year of treatment [139]; in patients with heart failure, costs are ranged from €885 to €1,422 per patient per year [140], and some Catalonian hospitals data showed that the direct cost of osteoporosis to the healthcare system was around €5,943.4 per patient per year [141]. World Health Organization established that around 30 % of heart failures and 27 % of diabetes could be prevented with an active life style. In addition, exercise is the most effective treatment to prevent weight gain, and it is essential in weight loss programs to maintain the results [142]. In addition, after initial introduction, the patients can perform the exercise alone, reducing the costs for rehabilitation. However, this suggestion comes from an indirect analysis, so further studies will be developed in a future to know the exercise cost-effectiveness in a mid and long term.

Conclusion

A cancer diagnosis is an important teachable moment where changes in life style and behaviour could be

achieved, lowering treatment-related side effects and improving survival. Exercise is a global intervention, which improves physical, physiological and psychological aspects of breast cancer patients, and an adequate promotion by oncologist will have to be developed and supported by training counselling by a specialist. As such, hospitals should consider including supervised exercise programs, in order to promote a healthy life style and prevent secondary tumours or comorbidities in breast cancer survival, taking advance of the teachable moment of the cancer diagnosis. As an example, programs to rehabilitate cardiac damage have been established as a treatment in hospitals, and experts in cardiac physiology and exercise train patients in order to rehabilitate cardiac damage and avoid inactivity. Every year, the number of cancer survivor rises, and these present with older age at diagnosis and possible comorbidities. The same scenario could be applied to cancer patients, taking into account the above mentioned. For this reason, exercise intervention should be included as a multifactorial complementary treatment. Appropriate exercise could reduce side effects and further comorbidities that breast cancer patient may present in a long term, increasing the patient's quality of life and survival. This is of capital importance in a world of both growing cancer care costs and global economical restrictions.

Conflict of interest This manuscript is not submitted for publication elsewhere. In addition, the authors declare no conflict of interests.

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