European Journal of Human Movement, 2018: **41**, 24-48

EXERCISE ONCOLOGY. FROM THEORY TO THE PRACTICE

Soraya Casla-Barrio [1]; Jordi Alfaro-Gamero [2]

1. Unit of Exercise-Oncology Coordinator. Spanish Cancer Associacion, Spain.
2. Medical Oncologist. Hospital of Tarrasa, Spain

ABSTRACT

Exercise-Oncology is an emerging area with a lot of questions for physical activity professionals focused on health. This review collects the general side effects and exercise implication and benefits, such as body composition changes, cardiovascular limitations or functional impairments as lymphedema; exercise relevance in cancer biomarkers related to cancer prognosis; as well as the exercise cautions related to some specific side effects. In addition, exercise recommendations to specialists are explained, including practice suggestions about how to personalize exercise prescription collecting a clinical history in order to control patient's development; how to control exercise intensity with different devices; and, finally, types of exercise and how they should be developed in terms of intensity and volume.

Keywords: exercise-oncology, cancer, physical activity, health

EJERCICIO FÍSICO ONCOLÓGICO. DE LA TEORÍA A LA PRÁCTICA

RESUMEN

El ejercicio físico oncológico es un área muy novedosa en nuestro país que, actualmente, genera muchas dudas a los profesionales del ejercicio físico y la salud. Esta revisión, trata de aportar información general sobre los tipos de efectos secundarios que los pacientes pueden presentar y qué tipo de ejercicio puede ser útil en cada caso. También se introduce la importancia del ejercicio en el cambio de determinados biomarcadores relativos al pronóstico del cáncer, así como algunas cuestiones de seguridad que deben tenerse en cuenta en relación con el ejercicio, si los pacientes presentan determinados efectos secundarios. Por último, se hace un repaso práctico de cómo se debe aplicar las bases de la planificación de un programa de ejercicio a estos pacientes, teniendo en cuenta la importancia de la individualización, el seguimiento de la intensidad o la evolución del programa en los pacientes.

Palabras clave: ejercicio físico oncológico, cáncer, actividad física, salud

Correspondence:
Soraya Casla Barrio
Soraya_casla@aecc.es
Unit of Exercise-Oncology Coordinator. Spanish Cancer Associacion
Avenida Dr. Federico Rubio y Galí, 84. 28040 Madrid, Spain
Submitted: 09/10/2018 *Accepted:* 09/12/2018

INTRODUCTION

Cancer is one of the most common causes of mortality around the world, with around 14.1 million new cases in the world in 2012 (Ferlay et al., 2012), estimating close to 24 million new cases in 2035. It has been estimated that there will be 315,415 new cases of cancer in Spain by 2035, increasing in almost a 50% the total amount of new cases reported in 2012. The Spanish Society of Oncology (SEOM, 2018) has determined that half of the men and one third of the women are expected to be diagnosed with cancer throughout their lives.

However, although the number of cases of cancer continues to increase (SEOM, 2018), there is a gradual decline in the mortality rate (except for lung cancer mortality in women which has shown a 5% increase since 2012). Specifically in colorectal, prostate, breast and uterus cancer, this decline is largely a result of improved screening, which has meant that cancer can be diagnosed in early stages, but it is also due to new and more effective treatment regimens which are focused on target therapies (Cabanes et al., 2010).

The high survival rate of patients with some type of cancers with a high incidence (particularly, prostate, breast, colorectal, bladder and uterus) means they have to live with different side effects produced by anti-cancer treatments. Anti-cancer treatments are associated with several serious side effects which can affect patients for the rest of their lives (Mayer, 2013). For example, more than 66% of breast cancer patients show at least one comorbid condition and more than 33% of them have two or more comorbidities. The most common comorbidities include hypertension, cardiovascular diseases, respiratory diseases, obesity and diabetes and, in post-menopausal women, the incidence of hypothyroidism is increasing dramatically (Kumar et al., 2012). In addition, cancer is the third cause of hospitalization in Spain, due, in part, to the lack of treatment for some of these side effects, such as cancer-related fatigue.

Exercise has shown to be a feasible, safe and effective tool to reduce and prevent some of these side effects, specifically most of those that do not have pharmacological treatment, and, in addition, it may promote the effectiveness of some treatments. For this reason, this review collects the relevance of exercise-oncology programs in cancer patients, providing strategies on how to adapt exercise to patients in order to achieve the personal objectives for all of them.

Importance of a healthy life style in cancer patients. In 2017, the most frequent cancers reported were prostate, lung and colorectal cancer in men; and breast, colorectal, uterus and lung cancer in women (SEOM, 2018). Different studies have established that around 30% of colorectal and breast cancer cases may be prevented following a healthy diet (rich in fruits and vegetables and poor in red meat and processed foods) and avoiding inactivity.

This, joined to tabaco and alcohol consumption and their relationship with different cancers, indicates the importance of a healthy life style to prevent this disease (WHO, 2010).

In 2007, the World Cancer Research Fund and the American Institute for Cancer Research published the international expert report *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective* (2007). The main conclusion of this document is that adult body fatness is related to an increased risk in the main cancers in both sexes. And all the preventive recommendations made to the general population are extensive to cancer survivors to avoid cancer relapse.

For this reason, exercise plays an essential role for cancer patients not only reducing side effects and increasing quality of life, but also improving patients' survival.

General cancer treatment, their main side effects and exercise implication. Cancer is a general term used for many different diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. However, there are many several types of cancer depending on the original tissue that suffers the mutation. In addition, each type of cancer may be divided into different subtypes considering some particularities in protein expression or gene mutations.

The usual treatments in cancer patients are: surgery, chemotherapy, radiotherapy, hormonal therapy, monoclonal antibody therapy and immunotherapy. Treatments are usually decided by a multidisciplinary group of different specialists that take into consideration all the different points of view (Mayer, 2013). It is important to note that every cancer case is unique, and treatment should be as specific as possible depending on the biologic characteristics of the tumour. The most common treatments and their side effects are explained in the next table (table 1).

TABLE 1
Cancer treatments and side effects.

Treatment	Definition	Examples	Type of cancer	Acute side effects	Permanent side effects
Local therapies					
Surgery	It is a local treatment used to remove the cancer from the body. It could remove only the tumour or include a more extensive area (National Cancer Institute). In addition, adjacent lymph nodes could be removed as well if they are infected by tumour cells.	Tumorectomy Mastectomy Colostomy	Solid tumours	Pain Soreness Functional Limitations	Pain Fatigue Endocrine changes Musculoskeletal soft tissue changes Lymphedema
Radiotherapy	The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumours. There are different techniques of radiation, external that comes from a machine outside the body, or internal, which comes from radioactive material placed inside the body near cancer cells. It may be administered after surgery in the place where cancer was or to stop the growth of tumours, as cerebral or bone tumours.	External-beam radiation therapy Brachytherapy	All tumours	Pain Functional limitation Worsen bone health Impaired immune system Gastrointestinal toxicity Skin changes	Cardiovascular change Pulmonary change Cognitive change Reproductive change Musculoskeletal soft tissue changes Lymphedema
Global therapies					
Chemotherapy	It is a cytotoxic or cytostatic drug used to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given orally, by injection or infusion, or on the skin, depending on the type and stage of the cancer being treated. It could by administrated before surgery (neoadjuvant therapy) or after surgery (adjuvant therapy).	Alkylating agents Anti-tumour antibiotics Antimetabolites Topoisomerase Inhibitors Mitotic Inhibitors	All types of cancer	Anaemia Nausea and vomiting General weakness Hair loss Diarrhoea Peripheral and central neuropathy Body weight changes Impaired immune function	Muscle weakness Fatigue Cardiotoxicity Cognitive changes Secondary cancers

TABLE 1 (CONT.)

Treatment	Definition	Examples	Type of cancer	Acute side effects	Permanent side effects
Hormone therapy	Hormone therapy removes or blocks the action of cancer cells and stops them from growing. Some hormones can cause certain cancers to grow and, if tests show that the cancer cells have hormone receptors, some treatments are used to reduce the production of hormones or block them, as hormone therapy or oophorectomy (removing the ovaries) or orchiectomy (removing the testicles).	Tamoxifen Aromatase Inhibitors LHRH agonist LHRH antagonist Ani-androgens	Breast cancer Prostate cancer Ovarian cancer	Body weight changes Articular pain Fat mass increase Lean mass losses Impaired immune function Gastrointestinal toxicity Second cancer	Fatigue
Immunotherapy	A type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way. Types of immunotherapy include cytokines, vaccines, bacillus Calmette-Guerin (BCG), and some monoclonal antibodies.		Lung cancer Melanoma Breast cancer	Pain Gastrointestinal toxicity	Fatigue Autoimmune disease
Biological therapy	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.		Breast cancer	Cardiovascular damages Impaired immune function	Fatigue

Based on: 1. Institute NC. http://ncim.nci.nih.gov/ncimbrowser/pages/concept_details.jsf.; 2. Society AC. American Government, http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-treating-chemotherapy.; 3 Pinkerton, J. V., & Thomas, S. (2014). Use of SERMs for treatment in postmenopausal women. The Journal of Steroid Biochemistry and Molecular Biology, 142, 142-154. doi:10.1016/j.jsbmb.2013.12.011.; 4. Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., & Schwartz, A. L. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Medicine & Science in Sports & Exercise, 42(7), 1409-1426. doi:10.1249/MSS.0b013e3181e0c112.

Each cancer patient is affected differently by their anti-cancer treatment, first because cancer patients receive different therapies, and secondly because 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, focusing on those that could be reduced or prevented by exercise. Main side effects and their definition are shown in table 2.

TABLE 2
Side effects definition.

Side effect	Definition
Physical Impairments	
Functional Limitations	Functional limitations are defined as reported difficulties to perform everyday tasks and, as such, they contribute to a decline in an individual's functional status (Braithwaite et al., 2010). Functional limitation may be assessed by the joint range of motion or other physical limitations (Melstrom, Melstrom, Ding, & Adrian, 2007) due to the muscle adherence or stiffness produced by surgery or radiotherapy. Examples: articular range reduction in hips, arms, shoulders, mouth.
Lymphedema	A condition in which extra lymph fluid builds up in tissues and causes swelling. It may occur in an arm or leg if the lymph vessels are blocked, damaged, or have been removed by surgery in cancer patients (NCI dictionary).
Sexual Dysfunction	Sexual dysfunction it is a multifactorial problem constructed by several models: a) the mechanistic one, focused almost exclusively on addressing physical sequels and disruptions in organ function produced by some treatments (hormone therapy, surgery and radiotherapy); b) More recently, the complexity of sexuality after cancer has been established and other integrative models have been proposed attending to a more comprehensive understanding of sexuality in the context of cancer (Sanchez Varela, Zhou, & Bober, 2013).
Urinary Incontinence	Urinary incontinence is the leakage of urine when coughing or exercising (stress urinary incontinence) or after a strong uncontrollable urge to urinate (urgency urinary incontinence) (Cody, Jacobs, Richardson, Moehrer, & Hextall, 2012). In women who have gone through the menopause, low estrogen levels may contribute to urinary incontinence.
Physiological Side Effects	
Cardiovascular Fitness Capacity	It refers to the ability to perform large muscle, dynamic, moderate-to-high intensity exercise for prolonged periods. Performance of such exercise depends on the functional state of the respiratory, cardiovascular and skeletal muscle systems (Institute NC dictionary).
Cardiotoxicity	It is the toxicity produced by some cancer drugs or radiation in the left side of the thorax that affects the heart. Clinically, cancer therapeutics-related cardiac dysfunction is defined as a > 10% decrease in left ventricular ejection fraction (LVEF) or a LVEF < 53% confirmed by repeated echocardiography 2-3 weeks apart (Institute NC dictionary) (Xie et al., 2015).

TABLE 2 (CONT.)

Body Composition	
Cachexia and Muscular Alterations	Loss of body weight and muscle mass, and weakness that may occur in patients with cancer. It is characterized by a higher loss of muscle mass than fat mass and by high level of blood inflammation biomarkers (Melstrom et al., 2007).
Weight Gain	It refers to the weight gain after cancer treatments, especially of an increase of fat, which may affect some cancer patients' survivorship. This weigh gain after treatments is more usual in hormone dependent cancers such as breast and prostate (Demark-Wahnefried, Winer, & Rimer, 1993; McTiernan, 2005).
Osteoporosis	A condition that is marked by a decrease in bone mass and density, causing bones to become fragile. In this case, it is produced by treatments, especially in those patients under hormone deprivation (Saylor, Keating, & Smith, 2009; Wiwanitkit & Wiwanitkit, 2013).
Neurological System Effects	
Peripheral Neuropathy	It is a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse over time. Peripheral neuropathy may be caused by cancer or cancer treatment, such as chemotherapy. It may also be caused by physical injury, infection, toxic substances, or conditions such as diabetes, kidney failure, or malnutrition. It is also called neuropathy (Institute NC dictionary).
Chemobrain	It represents a newly described clinical diagnosis associated with cancer therapy. This neuropsychological syndrome induced by pharmacological agents used in oncological therapy is centred on the gradual cognitive decline of the patients which could range from mild inability in performing some tasks to serious attention and memory problems (Gaman, Uzoni, Popa-Wagner, Andrei, & Petcu, 2016).
Global Side Effects	
Fatigue	It is defined as a disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to carry out daily activities. In addition, this kind of fatigue does not disappear after resting, on the contrary it lasts for a long time (Berger, Gerber, & Mayer, 2012; Kilgour et al., 2010).
Sleep Disturbance	Patients describe problems falling asleep (sleep latency), problems staying asleep (awakenings), having restless sleep (quality of perceived sleep), and/or having trouble staying awake during the day (excessive daytime sleepiness). The issues of sleep–wake disturbances are often combined in symptom clusters, especially with cancer-related fatigue and insomnia, which occur pre-treatment, exacerbate during treatment, and continue through survivorship (Dickerson, Connors, Fayad, & Dean, 2014).

Side effect limitations and exercise implication. Although during treatments there are different side effects that could be related to the different drugs used in each cancer, there is a group of permanent-reversible treatments that are common among cancer patients. These side effects may result in comorbidities if they are not reduced or restored and they may be related with other side effects that occur later.

We could summarize side effects in five groups:

- PHYSICAL IMPAIRMENTS: they are all those side effects that are related with a functional limitation or dysfunction. They are usually related to local treatments as surgery or, in some cases, with radiotherapy, such as lymphedema. Sometimes they may be consequence of systemic treatments, such as arthralgia produced by aromatase-inhibitors. In all of these side effects, exercise-oncology is really useful to restore the global function and, specifically in these cases, integrative work between exercise physiologists (i.e. exercise science professionals specialist in exercise-oncology) and physiotherapists is essential for patients.
- PHYSIOLOGICAL SIDE EFFECTS: they are related to those side effects that affect some organs or systems implicated in maintaining an adequate fitness capacity level, as these are important in the patients' global health and in the cardiac impairment prevention. Exercise-oncology objectives should be focused on bringing back the organs and system´s functionality. If patients are diagnosed with any problem related to cardio toxicity, they must be supervised by a cardiologist.
- BODY COMPOSITION ALTERATIONS: these side effects are usually produced by tumour cells and cancer treatments. These changes in body composition may not only alter the metabolic function, but they are also related with specific-cancer mortality in patients. Exercise-oncology is essential to achieve a body composition balance, increasing muscle mass in patients and controlling or reducing fat mass if it is needed. To achieve the best exercise adaptation, a nutritionist intervention could be essential.
- NEUROLOGICAL SYSTEM: in this group we include the side effects related to peripheral and cognitive alteration because there is evidence of alteration in the brain structure. In this group, exercise effect is unknown, and the potential restoration is theoretical. Especially in chemobrain therapy, the potential effect may be linked to a cognitive or psychological program, focused on this problem.
- PSYCHOLOGICAL IMPAIRMENTS: some patients present different psychological distress, such as depression, anxiety, fatigue related-cancer or sleep disturbance, although active patients have shown an improvement in all of them. These benefits are multiplied when exercise-oncology programs are developed in-group. Of course, if patients present a diagnosed psychological problem, they may be treated by a professional psycho-oncologist.

These side effect impacts on patients' daily lives and the exercise implications are explained in table 3, including the type of exercise and exercise mechanism and adding in each part if another professional should be implicated in the process.

TABLE 3
Side effect, implication and the effective exercise intervention supervised by an exercise-oncology specialist.

Side effect	Implication	Exercise intervention	Exercise mechanisms
Physical Side Effects			
Other professional implicated: physiotherapist			
Physical Limitation	Limitation in daily activities and pain.	Soft articular movements. Stretching. Progressive muscle strength training in both, arms and legs.	Enhances tissue extensibility and promotes normal range of mobility avoiding muscle contractures and alterations in the mechanics of the affected joints. Resistance exercise increases muscular strength, improves range of motion, and reduces weight, body fat and systemic inflammation levels.
Lymphedema	Limitation in daily activities and pain.	Stretching to reduce pain. Resistance exercise.	Stretching improves tissue extensibility. Subfascial lymphedema system is improved by resistance exercise and muscle strength.
Sexual Disfunction	Sexual relationship reduction and psychological and social problems.	Pelvic floor exercise routine.	Increases vaginal lubrication and sensations.
Urinary Disfunction	Social impairments and limitations.	Pelvic floor exercise routine.	Urinary incontinence control by training pelvic floor muscles.
Physiological Side Effect			
Other professional implicated: cardiologist if it was needed, especially in cardiotoxicity problems			
Fitness Capacity	Metabolic and cardiac illness precursor.	Aerobic exercise with intensity changes. Resistance exercise.	Intensity changes in aerobic exercise and resistance training improve muscle cell adaptation in both senses, molecular and physiological, as well as the cardiovascular adaptation to increase peripheral blood flow.
Cardiotoxicity	Cardiac illness precursor.	Aerobic exercise with intensity changes.	Reduction of global inflammation. Cardiac capacity and strength of the cardiac muscle increased with a combined training program. Increase of peripheral blood vessels.

TABLE 3 (CONT.)

Side effect	Implication	Exercise intervention	Exercise mechanisms
Body Composition Side Effects			
Other professional implicated: nutritionist			
Cachexia	Metabolic illness, global inflammation and death. As well as sarcopenic obesity precursor.	Aerobic exercise with intensity changes. Resistance exercise.	Reduces inflammation. Improves mitochondrial and muscle restoration. Restores energy balance production.
Weight Gain	Survival reduction and second cancer risk increase.	Aerobic exercise with intensity changes. Resistance exercise.	Calorie waste and metabolism increase. Muscle mass increase, preventing sarcopenia obesity.
Bone loss	Bone fracture, daily activities limitation and pain.	Upper-body resistance exercise to recover spine bone mass. Impact aerobic exercise to recover hip-bone mass.	Resistance and impact exercise promote bone regeneration decreasing osteoporosis levels.
Neurological System Effects			
Other professional implicated: psychologist in cognitive impairments			
Peripheral Neuropathy	Daily activities limitation, balance loss and pain.	Aerobic exercise. Resistance exercise.	Exercise improves muscle movement and restores nerve connections.
Cognitive Impairments	Work activities limitation and depression precursor.	Aerobic exercise.	Improving cerebral plasticity.
Psychological Impairments			
Other professional implicated: psychologist			
Sleep Disturbance	Biological restauration implications and fatigue	Aerobic exercise	Reduces global inflammation and increases acute fatigue which in turn improves rest necessities.
Cancer Related Fatigue	Daily and work activities limitation and depression precursor.	Combining exercise: aerobic and strength.	Moderate to high intensity exercise presented the best results reducing cancer-related fatigue, due to improvement in muscle mass, reduction of global inflammation and increase of cardiovascular capacity.
Psychological Problems	Daily and work activities limitation.	Group and guided exercise.	Training with people in the same situation may reduce these side effects.

Side effects and exercise cautions. Although exercise might be really effective in an integrative way, preventing or reducing different side effects with the same intervention, some of these side effects may reduce exercise adaptation, increase injury risk or produce exercise limitation. All these aspects should be taken into account in order to preserve patients' health and safety. Based on different studies and reviews, the following are exercise adaptation suggestions:

- In first place, a period of rest is recommended after surgery, with a duration adapted to each specific situation before starting the exercise training. In any case, the surgeon authorization is mandatory (Schmitz et al., 2010).
- Patients with peripheral neuropathy or dizziness produced by treatments or illnesses have a high risk of falling, and it would be better to perform exercise indoors (Denlinger et al., 2014).
- Other patients suffer osteoporosis or bone metastasis, and, in this case, the knowledge of where the metastases are and doing exercise in a safe environment should be essential for patients (Sasso et al., 2015).
- Muscular or articular pain suggests that exercise intensity may be reviewed, or activity may be adapted. This situation is usually present in patients undergoing hormone treatment, after surgery or after mammary reconstruction. Stretching and gentle movements are suggested as an effective intervention (Guru, Manoor, & Supe, 2012).
- Sex hormone deprivation is related to poor muscle regeneration activity, which increases the risk of injury. In this case, more time of rest between activities and adapting the exercise intensity to patients' necessities will be the best option (Wiwanitkit & Wiwanitkit, 2013).
- Some patients present breathing capacity reduction due to both, illness and treatments. In this case, exercise adaptation to patients' physical level and necessities are really important. In addition, a clinical history of cardiomyopathy or other cardiac events should be studied before exercise initiation and the patient should carry out a Cardiopulmonary Effort Test under medical supervision (Schmitz et al., 2010).

Cancer biomarkers and exercise effects. Cancer microenvironment is a complex cell state in which different molecules are related with the growth or inhibition of cancer cells. These molecules are called cancer biomarkers, defined as different type of molecules related to cancer diagnosis, prognosis and survival. Some of these biomarkers have shown sensitivity to exercise programs, which promote the global effect of exercise, especially insulin levels (Fairey et al., 2003), inflammation levels (Fairey et al., 2005; Friedenreich et al., 2012; Han et al., 2011; Heikkila, Ebrahim, & Lawlor, 2007), immune function

(Fairey, Courneya, Field, Bell, Jones, & Mackey, 2005) and sex hormone levels (Friedenreich et al., 2010; Kumar, Riccardi, Cantor, Dalton, & Allen, 2005). All of them may be modified by the adequate exercise program, having an impact on cancer patient's survival (table 4).

TABLE 4
Exercise evidence in cancer biomarkers.

Cancer biomarkers	Exercise evidence
Insulin	Aerobic exercise with intensity changes produces better metabolic adaptation in muscle cells and decreases IGF-1 levels and increases IGFBP-3 levels. Combined exercise (strength and aerobic) decreases serum insulin levels. Resistance exercise improves lean body mass and reduces body fat mass.
Immune cell function	Aerobic exercise increases immune cell function by increasing NK cell cytotoxicity.
Inflammatory cytokines	Aerobic exercise decreases C-reactive protein.
Sex hormones	Aerobic exercise decreases plasma estradiol and increases sex hormone-binding globulin (SHBG) levels.

Exercise-oncology: general considerations

Exercise-Oncology: an approach to exercise physiologist role.

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 will promote bone regeneration in order to prevent osteoporosis (Coleman, Body, Gralow, & Lipton, 2008). Thus, if patients like cycling or swimming, it will be better that they combine these activities with brisk walking, jogging, dancing or any activity in which the weight is supported by the legs (Palombaro, Black, Buchbinder, & Jette, 2013; Rietman et al., 2003). Another example stresses the need to start with light movements to increase body muscle tone before including kettlebells or extra weight. Such can be obtained with articular/analytic movements, 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 exercise physiologists at a point during the cancer trajectory could be a good option for promoting the beneficial effects of training (Jones & Courneya, 2002). As some technical aspects have to be demonstrated, a combined informative and practice exercise session would be an ideal option in

order to obtain a behavioural change in patients after treatments (Short, James, Stacey, & Plotnikoff, 2013).

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 continue training and manage psychological implications (Jones & Courneya, 2002) 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 (Mishra et al., 2012).

Along the lines of group-based training, the physical setting of the training also plays an important role. A supervised training intervention performed in a hospital setting has proven most efficient in mediating physiological and psychological improvements. Yet, these studies are costly and resource consuming. Training sessions in gyms under the supervision of an exercise specialist may be equally efficient. At the other end of the spectrum, home-based training studies have showed that this training setting also improves physical condition, but that it is harder to keep the motivation going in this setting.

How much exercise is need. The time aspect might be a significant barrier for some patients. The general recommendation of physical activity is 150 min of exercise in 3 to 5 days of moderate-intensity or 70 min of high-intensity exercise combining 2 days of resistance exercise and 3 days of aerobic exercise (Schmitz et al., 2010). But this can vary; 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 (DiSipio, Rye, Newman, & Hayes, 2013). The beginning has to be progressive in order to achieve an adequate progression and adaptation to exercise.

Although it is the general recommendation for cancer survivors, it may be interesting to note that they are the same recommendations issued to healthy people, and it is important to take into account that cancer survivors do not have the same physiological condition as people who have not been under cancer treatments. In the first place, cancer survivors present a lower VO2peak compared to sedentary people (Gil-Rey, Quevedo-Jerez, Maldonado-Martin, & Herrero-Roman, 2014). In addition, some treatments as hormone therapy could reduce metabolic activity which added to some specific side effects could produce lower exercise tolerance and adaptation (Herrero, San Juan, Fleck, Foster, & Lucia, 2007; Newton & Galvao, 2008).

However, in contrast to this, other studies focused on patients' survival include the reference time of 9 METS that correspond to 180 min of exercise walking at 5 km/h (Chen et al., 2011; Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005; Irwin et al., 2011), which suggests that the same exercise

indication to patients and healthy people may not be correct. However, little is known about this respect and further research should be developed at this point.

Exercise program adaptation to patients' necessities. To design an exercise intervention for cancer patients, our first objective is to know the patients' necessities, their type of cancer, their cancer treatments, if the patient is under treatment or if the treatment has been finished and, finally the patient´s fitness level in order to personalize intensity intervention. Figure 1 shows this process.

1. CLINICAL HISTORY: an exercise-oncology specialist should collect type of cancer and patient cancer treatments, as well as other comorbidities that may affect the exercise prescription. In this sense, the knowledge of the treatment side effects is essential for an individual prescription.
2. PHYSICAL IMPAIRMENTS: objective limitations, as range of motion limitation, or limitation referred by the patient will be collected to individualize the exercise program and to know which program adaptation should be considered.
3. BODY COMPOSITION: this test will be very important in order to know if the patient is suffering cachexia, sarcopenia or other disbalance in body composition. Obesity should be studied considering fat percentage better than body mass index.
4. EXERCISE INTENSITY: exercise programs should be adapted to the patients' basal level. In this sense, patient information should be collected to personalize exercise. In addition, intensity control by specific devices will be useful not only for intensity control, but also to allow patients to increase their knowledge about themselves.

Patients' fitness level and other comorbidities are relevant in order to personalize exercise programs. Specially if the patients show any cardiac damage, in which case cardiologists are responsible of exercise evaluation (Schmitz et al., 2010).

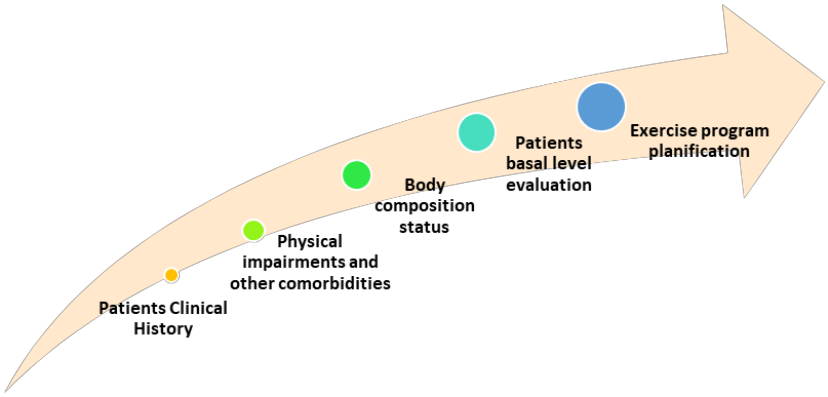

FIGURE 1: Exercise-oncology process.

Exercise intensity adaptation. Exercise intensity monitoring should be adapted depending on the type of exercise: cardiopulmonary exercise or strength exercise. In addition, it also depends on the test used to evaluate fitness level.

A *cardiopulmonary exercise test* is the gold standard to adapt resistance exercise level to each patient. However, it is not always possible to perform, in which case the Karvonen equation allows the prescription of exercise intensity by heart rate reserve percentage and, at same time, the patient can control their heart rate (Hansen, Stevens, Eijnde, & Dendale, 2012).

In case of resistance training with elastic bands, repetitions of the exercise are the way to control the intensity. Once we start with strength machines, *1 Repetition Maximum* (1RM) test could be performed to adapt the intensity related to their maximum (Schmitz et al., 2010), always between 40 to 75% of their 1RM (Travier et al., 2015).

In addition, subjective perception of effort might be useful for the intensity control, completing the other objective methods: i.e., Borg scale is a very easy to use tool to control the intensity based on the patient's perception of effort (Balady et al., 2000).

Exercise tests and devices used to control intensity are collected in table 5.

TABLE 5
Tests and devices to the exercise intensity control.

Type of exercise	Test	Device to control
Cardiovascular Exercise	CPET (Cardiopulmonary Exercise Test)	% of VO2max: Heart Rate Monitor
	SubMaximal Test	% VO2max estimated: Heart Rate Monitor
	Heart Rate Reserve Method	%HRR: Heart Rate Monitor
	Speed	Podometer
		Mobile Phone Apps that use GPS and assess speed
Strength Exercise	Subjective Perception	Borg Scale
	Estimated 1RM	% kg lifted in estimated 1RM Weight moved in the machine
	1RM*	% kg lifted in 1RM. Weight moved in the machine
	Endurance Strength	Elastic bands
		Autoweight exercise

**Repetition maximum.*

Type of exercise

Exercise intervention may have different parts and types of exercise, always combining endurance and strength exercises, starting with a warm-up and always stretching at the end of the session. Different types of exercises are described below:

Cardiopulmonary exercise. Aerobic training involves training of the cardio-vascular system under aerobic conditions. The benefits of aerobic exercise are related to improvements in the cardiac function (Kim, Kang, Smith, & Landers, 2006), with an increase of physical capacity (Courneya et al., 2003), a reduction of weight gain (Demark-Wahnefried et al., 2008) and a good management of fatigue and depression (Humpel & Iverson, 2007; McNeely et al., 2006) in cancer patients. Training at a moderate-intensity facilitates such improvements in cancer survivors (Irwin, 2009). Patients may start at between 41-64% of VO2max in order to achieve health improvements, but taking into account that cancer patients present lower fitness capacity than healthy population (Balady

et al., 2000; Galanti, Stefani, & Gensini, 2013). Intensity should be increased gradually to keep obtaining physical improvements. The best option is to perform an interval training with periods of high intensity (e.g. 85% of heart rate), followed by low intensity intervals.

It will improve strength, physical capacity and reduce insulin resistance of muscles, being an effective way to avoid diabetes and to increase the metabolic waste of patients. In addition, this kind of training has been demonstrated to be a safe way to train in patients with cardiac damage or cancer patients, obtaining better results than normal training (Arena, Myers, Forman, Lavie, & Guazzi, 2012; Gibala, Little, Macdonald, & Hawley, 2012; Jones et al., 2009; Kessler, Sisson, & Short, 2012; Wisloff, Ellingsen, & Kemi, 2009).

Strength exercise. Strength training is essential to rebuild muscle mass and reduce functional limitations, especially in those patients that present cachexia (Hayes et al., 2012; Sagen, Karesen, & Risberg, 2009), although all cancer patients present reductions in muscle mass levels that should be reverted through this type of training.

Primary exercise intervention should be prescribed by the rehabilitation department attending to patients' necessities. After the specialist recommendations, the first objective should be to recovery muscle sensation and muscle nerve activity, as well as to improve the range of movement and activate the tissues that have been damaged by radiation and surgery. After two to four weeks of this kind of training, training with elastic bands could be initiated, always being careful with the body positions. Following international recommendations, it could be ideal to exercise a global routine of strength training carried out a couple of days per week. Between 10 to 15 repetition of each exercise in 2 sets is enough in order to maintain muscle tone with this method (Balady et al., 2000). The best way is to start with more repetitions and less resistance and, gradually, increase the resistance while the repetitions are reduced. With this exercise, 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. The next step in strength training will be the use of strength machines. If these kinds of machines are used, 40 to 75% of 1 RM is the ratio recommended to work, at least at the beginning (Travier et al., 2015).

However, some patients, especially those with risk of lymphedema, may not be sure to perform this type of exercise. Yet, several studies show that strength training does not induce lymphedema if training starts progressively, using, at least, the first month of the exercise program to develop upper-limb and leg mobility (Hayes et al., 2012; Schmitz, Ahmed, & Yee, 2002; Schmitz et al., 2010). In addition, it has been observed that strength training does not worsen lymphedema symptoms, if they exist (Cormie et al., 2013).

Not enough evidence about strength intervention routine has been found in the survivors' guidelines, so it is important to note that this type of intervention should be adapted as much as possible to the patients' necessities. It is important that a specialist controls the main aspects of these interventions: the posture, to start with low loads or, if it possible, to make a test to know the initial level of strength to prescribe a personal strength training. It is important to remind them that exercise never has to produce pain.

Stretching. At the end of a training, introduce a whole body stretching routine, in order to relax muscle and mind, and improve muscle flexibility and the joint range of motion (Balady et al., 2000). The most efficient relaxation of muscle mass is by maintaining each stretch between 20 to 30 s in a passive way.

Stretching should be focused on the surgery area, in order to achieve improvements in joint and body mobility and to reduce muscle adherences. This stretching is really important in breast cancer patients due to the surgery area. Arm-shoulder stretching has been proved to be an effective intervention to recover physical functioning and mobility (Pfeiler et al., 2013).

In any case, stretching should be focused on the main muscles used during the session, but, in cancer survivors, it is equally important to also stretch the muscles that are affected by the surgery, the upper or lower limbs close to the affected area in order to prevent joint dysfunctions (Kim do, Sim, Jeong, & Kim, 2010).

For all patients stretching will relax the body and improve movement, reducing damaged tissue stiffness.

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

1. Insist that patients go as soon as possible to a specialist if they note warm, sore muscles, redness or pain in their limbs.
2. The patients should receive exercises to do at home. The effect will be greater if they repeat the exercise every day.
3. To start, gentle range of motion exercises to warm up the area are indicated, including, at least, waist, shoulder, elbow, wrist and neck in upper-limb lymphedema; and ankle, knee and waist if the lymphedema is in the lower-limb. It is better to include whole joints in order to get a global feeling of relaxation.
4. It is recommended to stretch the whole body every day, including specific stretching of muscles and limbs affected by the surgery, especially at the end of the exercise session.

The patients have to be invited to ask their care provider for the specific strength exercise to improve their posture, reduce lymphedema and recover

nerve function (Cormie et al., 2013), and not to forget to highlight to use a compression garment, following the specialist suggestions.

CONCLUSIONS

Exercise-oncology is a growing area, not only because of the scientific evidence of its effectiveness in preventing or reducing different side effects, but also because of the patient's interest in increasing their quality of life. In this sense, to achieve a correct establishment of this area, and to ensure patients' safety and the efficacy of exercise programs, some aspects should be taken into consideration:

- The exercise physiologist that will plan the exercise programs and exercises with the patients requires specific qualification.
- Provide exercise-oncology knowledge to the oncologist and other specialist clinicians in two different senses: a) to understand the physiological mechanisms underlying the exercise planning and b) to provide effective exercise suggestions to the patients.
- Work together and in consonance between the different professionals implicated in the patient progress, including: physiotherapists, exercise physiologists, nutritionists, oncologists, cardiologists and other care providers.
- Continue researching and publishing new data related to exercise-oncology.
- Look for new areas of research to improve the knowledge in different points not covered yet.

At this moment, a new window of opportunity to physical activity specialists or exercise physiologists is opening, which will be a great challenge, in order to adapt the usual care to new cancer patients' necessities. This must include a new kind of professionals to improve cancer patients' treatments, survival and quality of life.

REFERENCES

Arena, R., Myers, J., Forman, D. E., Lavie, C. J., & Guazzi, M. (2013). Should high-intensity-aerobic interval training become the clinical standard in heart failure?. *Heart Failure Reviews, 18*(1), 95-105. doi:10.1007/s10741-012-9333-z.

Balady, G. J., Berra, K. A., Golding, L. A., Gordon, N. F., Mahler, D. A., Myers, J. N., & Sheldahl, L. M. (2000). *ACSM's Guidelines for exercise testing and prescription.* Sixth Edition (E. P. Johnson Ed.). Baltimore: Lippincott Williams & Wilkins.

Berger, A. M., Gerber, L. H., & Mayer, D. K. (2012). Cancer-related fatigue: implications for breast cancer survivors. *Cancer, 118*(8 Suppl), 2261-2269. doi:10.1002/cncr.27475.

Braithwaite, D., Satariano, W. A., Sternfeld, B., Hiatt, R. A., Ganz, P. A., Kerlikowske, K., & Caan, B. J. (2010). Long-term prognostic role of functional limitations among women with breast cancer. *Journal of the National Cancer Institute, 102*(19), 1468-1477. doi:10.1093/jnci/djq344.

Cabanes, A., Vidal, E., Aragones, N., Perez-Gomez, B., Pollan, M., Lope, V., & Lopez-Abente, G. (2010). Cancer mortality trends in Spain: 1980-2007. *Annals of oncology, 21*(Suppl 3), 14-20. doi:10.1093/annonc/mdq089.

Chen, X., Lu, W., Zheng, W., Gu, K., Matthews, C. E., Chen, Z., & Shu, X. O. (2011). Exercise after diagnosis of breast cancer in association with survival. *Cancer Prevention Research, 4*(9), 1409-1418. doi:10.1158/1940-6207.CAPR-10-0355.

Cody, J. D., Jacobs, M. L., Richardson, K., Moehrer, B., & Hextall, A. (2012). Oestrogen therapy for urinary incontinence in post-menopausal women. *Cochrane Database Systematic Review, 10*, CD001405. doi:10.1002/14651858.CD001405.pub3.

Coleman, R. E., Body, J. J., Gralow, J. R., & Lipton, A. (2008). Bone loss in patients with breast cancer receiving aromatase inhibitors and associated treatment strategies. *Cancer Treatment Reviews, 34, 31-42.* doi:10.1016/j.ctrv.2008.03.005.

Cormie, P., Pumpa, K., Galvao, D. A., Turner, E., Spry, N., Saunders, C., & Newton, R. U. (2013). Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: a randomised controlled trial. *Journal of Cancer Survivorship, 7*(3), 413-424. doi:10.1007/s11764-013-0284-8.

Courneya, K. S., Mackey, J. R., Bell, G. J., Jones, L. W., Field, C. J., & Fairey, A. S. (2003). Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *Journal of Clinical Oncology, 21*(9), 1660-1668. doi:10.1200/JCO.2003.04.093.

Demark-Wahnefried, W., Case, L. D., Blackwell, K., Marcom, P. K., Kraus, W., Aziz, N., & Shaw, E. (2008). Results of a diet/exercise feasibility trial to prevent adverse body composition change in breast cancer patients on adjuvant chemotherapy. *Clinical Breast Cancer, 8*(1), 70-79. doi:10.3816/CBC.2008.n.005.

Demark-Wahnefried, W., Winer, E. P., & Rimer, B. K. (1993). Why women gain weight with adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology, 11*(7), 1418-1429. doi:10.1200/JCO.1993.11.7.1418.

Denlinger, C. S., Ligibel, J. A., Are, M., Baker, K. S., Demark-Wahnefried, W., Dizon, D., & National comprehensive cancer (2014). Survivorship: healthy lifestyles, version 2.2014. *Journal of the National Comprehensive Cancer Network, 12*(9), 1222-1237.

Dickerson, S. S., Connors, L. M., Fayad, A., & Dean, G. E. (2014). Sleep-wake disturbances in cancer patients: narrative review of literature focusing on improving quality of life outcomes. *Nature and Science of Sleep, 6*, 85-100. doi:10.2147/NSS.S34846.

DiSipio, T., Rye, S., Newman, B., & Hayes, S. (2013). Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *The Lancet Oncology, 14*(6), 500-515. doi:10.1016/S1470-2045(13)70076-7.

Fairey, A. S., Courneya, K. S., Field, C. J., Bell, G. J., Jones, L. W., & Mackey, J. R. (2003). Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. *Cancer Epidemiology and Prevention Biomarkers, 12*(8), 721-727.

Fairey, A. S., Courneya, K. S., Field, C. J., Bell, G. J., Jones, L. W., & Mackey, J. R. (2005). Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. *Journal of Applied Physiology, 98*(4), 1534-1540. doi:10.1152/japplphysiol.00566.2004.

Fairey, A. S., Courneya, K. S., Field, C. J., Bell, G. J., Jones, L. W., Martin, B. S., & Mackey, J. R. (2005). Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. *Brain, Behavior, and Immunity, 19*(5), 381-388. doi:10.1016/j.bbi.2005.04.001.

Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., & Bray, F. (2012). *GLOBOCAN*. From Lyon, France: International Agency for Research on Cancer.

Friedenreich, C. M., Neilson, H. K., Woolcott, C. G., Wang, Q., Stanczyk, F. Z., McTiernan, A., & Courneya, K. S. (2012). Inflammatory marker changes in a yearlong randomized exercise intervention trial among postmenopausal women. *Cancer Prevention Research, 5*(1), 98-108. doi:10.1158/1940-6207.CAPR-11-0369.

Friedenreich, C. M., Woolcott, C. G., McTiernan, A., Ballard-Barbash, R., Brant, R. F., Stanczyk, F. Z., & Courneya, K. S. (2010). Alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among postmenopausal women. *Journal of Clinical Oncology, 28*(9), 1458-1466. doi:10.1200/JCO.2009.24.9557.

Galanti, G., Stefani, L., & Gensini, G. (2013). Exercise as a prescription therapy for breast and colon cancer survivors. *International Journal of General Medicine,, 6*, 245-251. doi:10.2147/IJGM.S42720

Gaman, A. M., Uzoni, A., Popa-Wagner, A., Andrei, A., & Petcu, E. B. (2016). The Role of Oxidative Stress in Etiopathogenesis of Chemotherapy Induced Cognitive Impairment (CICI)-"Chemobrain". *Aging and Disease, 7*(3), 307-317. doi:10.14336/AD.2015.1022.

Gibala, M. J., Little, J. P., Macdonald, M. J., & Hawley, J. A. (2012). Physiological adaptations to low-volume, high-intensity interval training in health and disease. *The Journal of Physiology, 590*(5), 1077-1084. doi:10.1113/jphysiol.2011.224725.

Gil-Rey, E., Quevedo-Jerez, K., Maldonado-Martin, S., & Herrero-Roman, F. (2014). Exercise Intensity Guidelines for Cancer Survivors: a Comparison with Reference Values. *International Journal of Sports Medicine, 35*(14), e1-e9. doi:10.1055/s-0034-1389972.

Guru, K., Manoor, U. K., & Supe, S. S. (2012). A comprehensive review of head and neck cancer rehabilitation: physical therapy perspectives. *Indian Journal of Palliative Care, 18*(2), 87-97. doi:10.4103/0973-1075.100820.

Han, Y., Mao, F., Wu, Y., Fu, X., Zhu, X., Zhou, S., & Zhao, Y. (2011). Prognostic role of C-reactive protein in breast cancer: a systematic review and meta-analysis. *The International Journal of Biological Markers, 26*(4), 209-215. doi:10.5301/JBM.2011.8872.

Hansen, D., Stevens, A., Eijnde, B. O., & Dendale, P. (2012). Endurance exercise intensity determination in the rehabilitation of coronary artery disease patients: a critical re-appraisal of current evidence. *Sports Medicine, 42*(1), 11-30. doi:10.2165/11595460-000000000-00000.

Hayes, S. C., Johansson, K., Stout, N. L., Prosnitz, R., Armer, J. M., Gabram, S., & Schmitz, K. H. (2012). Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. *Cancer, 118*(8 Suppl), 2237-2249. doi:10.1002/cncr.27467.

Heikkila, K., Ebrahim, S., & Lawlor, D. A. (2007). A systematic review of the association between circulating concentrations of C reactive protein and cancer. *Journal of Epidemiology & Community Health, 61*(9), 824-833. doi:10.1136/jech.2006.051292.

Herrero, F., San Juan, A. F., Fleck, S. J., Foster, C., & Lucia, A. (2007). Effects of detraining on the functional capacity of previously trained breast cancer survivors. *International Journal of Sports Medicine, 28*(3), 257-264. doi:10.1055/s-2006-924348.

Holmes, M. D., Chen, W. Y., Feskanich, D., Kroenke, C. H., & Colditz, G. A. (2005). Physical activity and survival after breast cancer diagnosis. *JAMA, 293*(20), 2479-2486. doi:10.1001/jama.293.20.2479.

Humpel, N., & Iverson, D. C. (2007). Depression and quality of life in cancer survivors: is there a relationship with physical activity? *International Journal of Behavioral Nutrition and Physical Activity, 4*, 65. doi:10.1186/1479-5868-4-65.

Institute, N. C. http://ncim.nci.nih.gov/ncimbrowser/pages/concept_details.jsf.

Irwin, M. L. (2009). Physical activity interventions for cancer survivors. *British Journal of Sports Medicine, 43*(1), 32-38. doi:10.1136/bjsm.2008.053843.

Irwin, M. L., McTiernan, A., Manson, J. E., Thomson, C. A., Sternfeld, B., Stefanick, M. L., & Chlebowski, R. (2011). Physical activity and survival in postmenopausal women with breast cancer: results from the women's health initiative. *Cancer Prevention Research, 4*(4), 522-529. doi:10.1158/1940-6207.CAPR-10-0295.

Jones, L. W., & Courneya, K. S. (2002). Exercise counseling and programming preferences of cancer survivors. *Cancer Practice, 10*(4), 208-215.

Jones, L. W., Eves, N. D., Peddle, C. J., Courneya, K. S., Haykowsky, M., Kumar, V., & Reiman, T. (2009). Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. *Applied Physiology, Nutrition, and Metabolism, 34*(2), 197-202. doi:10.1139/H08-104.

Kessler, H. S., Sisson, S. B., & Short, K. R. (2012). The potential for high-intensity interval training to reduce cardiometabolic disease risk. *Sports Medicine, 42*(6), 489-509. doi:10.2165/11630910-000000000-00000.

Kilgour, R. D., Vigano, A., Trutschnigg, B., Hornby, L., Lucar, E., Bacon, S. L., & Morais, J. A. (2010). Cancer-related fatigue: the impact of skeletal muscle mass and strength in patients with advanced cancer. *Journal Cachexia Sarcopenia Muscle, 1*(2), 177-185. doi:10.1007/s13539-010-0016-0.

Kim, C. J., Kang, D. H., Smith, B. A., & Landers, K. A. (2006). Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. *Cancer Nursing, 29*(2), 156-165.

Kim do, S., Sim, Y. J., Jeong, H. J., & Kim, G. C. (2010). Effect of active resistive exercise on breast cancer-related lymphedema: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation, 91*(12), 1844-1848. doi:10.1016/j.apmr.2010.09.008.

Kumar, M., Nagpal, R., Hemalatha, R., Verma, V., Kumar, A., Singh, S., & Yadav, H. (2012). Targeted cancer therapies: the future of cancer treatment. *Acta Bio Medica Atenei Parmensis, 83*(3), 220-233.

Kumar, N. B., Riccardi, D., Cantor, A., Dalton, K., & Allen, K. (2005). A case-control study evaluating the association of purposeful physical activity, body fat distribution, and steroid hormones on premenopausal breast cancer risk. *The Breast Journal, 11*(4), 266-272. doi:10.1111/j.1075-122x.2005.21693.x.

Mayer, E. L. (2013). Early and late long-term effects of adjuvant chemotherapy. A*merican Society of Clinical Oncology - Educational Book*, *9*, 9-14.

McNeely, M. L., Campbell, K. L., Rowe, B. H., Klassen, T. P., Mackey, J. R., & Courneya, K. S. (2006). Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ, 175*(1), 34-41. doi:10.1503/cmaj.051073.

McTiernan, A. (2005). Obesity and cancer: the risks, science, and potential management strategies. *Oncology (Williston Park), 19*(7), 871-881.

Melstrom, L. G., Melstrom, K. A., Jr., Ding, X. Z., & Adrian, T. E. (2007). Mechanisms of skeletal muscle degradation and its therapy in cancer cachexia. *Histology and Histopathology, 22*(7), 805-814. doi:10.14670/HH-22.805.

Mishra, S. I., Scherer, R. W., Geigle, P. M., Berlanstein, D. R., Topaloglu, O., Gotay, C. C., & Snyder, C. (2012). Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Systematic Review, 8*, CD007566. doi:10.1002/14651858.CD007566.pub2.

Newton, R. U., & Galvao, D. A. (2008). Exercise in prevention and management of cancer. *Current Treatment Options in Oncology, 9*(2-3), 135-146. doi:10.1007/s11864-008-0065-1.Palombaro, K. M., Black, J. D., Buchbinder, R., & Jette, D. U. (2013). Effectiveness of exercise for managing osteoporosis in women postmenopause. *Physical Therapy, 93*(8), 1021-1025. doi:10.2522/ptj.20110476.

Pfeiler, G., Konigsberg, R., Hadji, P., Fitzal, F., Maroske, M., Dressel-Ban, G., & Dubsky, P. (2013). Impact of body mass index on estradiol depletion by aromatase inhibitors in postmenopausal women with early breast cancer. *British Journal of Cancer*, *109*, 1522–1527. doi:10.1038/bjc.2013.499.

Pinkerton, J. V., & Thomas, S. (2014). Use of SERMs for treatment in postmenopausal women. *The Journal of Steroid Biochemistry and Molecular Biology*, *142*, 142-154. doi:10.1016/j.jsbmb.2013.12.011.

Rietman, J. S., Dijkstra, P. U., Hoekstra, H. J., Eisma, W. H., Szabo, B. G., Groothoff, J. W., & Geertzen, J. H. (2003). Late morbidity after treatment of breast cancer in relation to daily activities and quality of life: a systematic review. *European Journal of Surgical Oncology, 29*(3), 229-238.

Sagen, A., Karesen, R., & Risberg, M. A. (2009). Physical activity for the affected limb and arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with two years follow-up. *Acta Oncologica, 48*(8), 1102-1110. doi:10.3109/02841860903061683.

Sanchez Varela, V., Zhou, E. S., & Bober, S. L. (2013). Management of sexual problems in cancer patients and survivors. *Current Problems in Cancer, 37*(6), 319-352. doi:10.1016/j.currproblcancer.2013.10.009.

Sasso, J. P., Eves, N. D., Christensen, J. F., Koelwyn, G. J., Scott, J., & Jones, L. W. (2015). A framework for prescription in exercise-oncology research. *Journal of Cachexia, Sarcopenia and Muscle, 6*(2), 115-124. doi:10.1002/jcsm.12042.

Saylor, P. J., Keating, N. L., & Smith, M. R. (2009). Prostate cancer survivorship: prevention and treatment of the adverse effects of androgen deprivation therapy. *Journal of General Internal Medicine, 24* (Suppl 2), S389-394. doi:10.1007/s11606-009-0968-y.

Schmitz, K. H., Ahmed, R. L., & Yee, D. (2002). Effects of a 9-month strength training intervention on insulin, insulin-like growth factor (IGF)-I, IGF-binding protein (IGFBP)-1, and IGFBP-3 in 30-50-year-old women. *Cancer Epidemiology and Prevention Biomarkers, 11*(12), 1597-1604.

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., & Schwartz, A. L. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine & Science in Sports & Exercise, 42*(7), 1409-1426. doi:10.1249/MSS.0b013e3181e0c112.

SEOM. (2018). *Las cifras del cáncer en España 2018*.Obtenido de: https://www.seom.org/seomcms/images/stories/recursos/Las_Cifras_del_cancer_en_Espana2018.pdf: Spanish Society of Medical Oncology.

Short, C. E., James, E. L., Stacey, F., & Plotnikoff, R. C. (2013). A qualitative synthesis of trials promoting physical activity behaviour change among post-treatment breast cancer survivors. *Journal of Cancer Survivorship*, *7*(4), 570–581. doi:10.1007/s11764-013-0296-4.

Travier, N., Velthuis, M. J., Steins Bisschop, C. N., van den Buijs, B., Monninkhof, E. M., Backx, F., & May, A. M. (2015). Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial. *BMC Medicine, 13*, 121. doi:10.1186/s12916-015-0362-z.

Society AC. American Government. Retrieved from: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-treating-chemotherapy

World Cancer Research Fund, & American Institute for Cancer Research (2007). *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, *1.* American Institute for Cancer Research. Retrieved from: http://www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf.

WHO. (2010). *Recomendaciones mundiales sobre actividad física para la salud*. Suiza: World Health Organization.

Wisloff, U., Ellingsen, O., & Kemi, O. J. (2009). High-intensity interval training to maximize cardiac benefits of exercise training? *Exercise and Sport Sciences Reviews, 37*(3), 139-146. doi:10.1097/JES.0b013e3181aa65fc.

Wiwanitkit, S., & Wiwanitkit, V. (2013). Postmenopausal osteoporosis, breast cancer, and aromatase inhibitor. *Revista da Associação Médica Brasileira, 59*(3), 217. doi:10.1016/j.ramb.2012.12.008.

Xie, Y., Collins, W. J., Audeh, M. W., Shiao, S. L., Gottlieb, R. A., Goodman, M. T., & Mehta, P. K. (2015). Breast Cancer Survivorship and Cardiovascular Disease: Emerging Approaches in Cardio-Oncology. *Current Treatment Options in Cardiovascular Medicine, 17*(12), 60. doi:10.1007/s11936-015-0421-y.