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Effect of different types of exercise on quality of life in breast cancer patients and survivors: an umbrella review

Dissertação elaborada com vista à obtenção do Grau de Mestre em

Exercício e Saúde

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Abbreviations

AMSTAR	Assessment of Methodologic Quality of Systematic Reviews
BC	Breast cancer
BRCA1	Breast cancer-associated genes 1
BRCA2	Breast cancer-associated genes 2
CTx	Chemotherapy
EORTC QLQ-BR23	European Organization for Research and Treatment of Cancer breast cancer-specific quality of life questionnaire
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
FACT-B	Functional Assessment of Cancer Therapy-Breast
FACT-G	Functional Assessment of Cancer Therapy-General
GRADE	Grade of Recommendation, Assessment, Development, and Evaluation
HER2	Human epidermal growth factor receptor 2
PA	Physical activity
PR	Progesterone receptor
QoL	Quality of life
RCT	Randomized controlled trial
ROM	Range of motion
RTx	Radiation therapy
SF-36	Short Form Health survey

Abstract

Purpose: To present an umbrella review on previous meta-analysis and systematic reviews addressing the relationship between quality of life (QoL) among breast cancer (BC) patients and survivors and exercise.

Methods: Pubmed, Web of Science, the Cochrane Library, and PEDro databases were searched to identify relevant systematic reviews and meta-analyses. Reviews assessing exercise interventions on QoL as one of the primary outcomes in breast cancer patients and survivors were included. The Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) tool was used to evaluate the quality of evidence. The methodological quality of the included studies were evaluated by the Assessment of Methodologic Quality of Systematic Reviews (AMSTAR) appraisal.

Results: Twenty-five studies met all the inclusion criteria. The AMSTAR score varied from 3 to 11 points with an overall mean of 7.4 points. Out of 25 studies, 23 found beneficial effects of aerobic, resistance, combined, and mind and body exercise in BC patients and survivors, and 2 reported no effects of exercise on QoL. As for GRADE, 7 studies were rated as “high”, 10 as “moderate, 6 as “low”, and 2 as “very low”.

Conclusion: Exercise of any kind can be regarded as beneficial to QoL in BC patients and survivors. Mind and body exercise is emerging as a viable option in the BC field and has shown to have the same benefits as the more conventional forms of exercise. More high-quality studies are needed in BC patients at any stage and BC survivors.

Keywords: breast cancer; breast cancer patients; breast cancer survivors; aerobic exercise; resistance exercise; combined exercise; mind and body; physical activity; quality of life; umbrella review

Resumo

Objetivo: Apresentar uma *umbrella review* de revisões sistemáticas e meta-análises anteriores que abordem a relação entre qualidade de vida em pacientes e sobreviventes de cancro da mama e exercício.

Métodos: As bases de dados da Pubmed, Web of Science, the Cochrane Library, e PEDro *database* foram usadas para identificar revisões sistemáticas e meta-análises relevantes. As revisões que analisavam as intervenções de exercício com a qualidade de vida como um dos *outcomes* principais em pacientes e sobreviventes de cancro da mama foram incluídas. A qualidade de evidência foi avaliada pelo GRADE (*Grade of Recommendation, Assessment, Development, and Evaluation*). A qualidade metodológica dos estudos incluídos foi avaliada pelo AMSTAR (*Assessment of Methodologic Quality of Systematic Reviews*).

Resultados: Vinte e cinco artigos atenderam a todos os critérios de inclusão. A pontuação do AMSTAR variou entre 3 e 11 pontos com uma média geral de 7.4 pontos. Dos 25 estudos, 23 chegaram a resultados positivos sobre o efeito do exercício aeróbio, de força, combinado e exercício *"mind and body"* em pacientes e sobreviventes de cancro da mama, e 2 não reportaram efeitos do exercício na qualidade de vida. Quanto à avaliação feita pelo GRADE, 7 estudos evidenciaram resultados de alta qualidade, 10 de qualidade moderada, 6 baixa e 2 muito baixa.

Conclusão: O exercício de qualquer tipo pode ser considerado benéfico para a qualidade de vida em pacientes e sobreviventes de cancro da mama. Os exercícios "*mind and body*" estão a ganhar cada vez mais destaque no cancro da mama mostrando os mesmos benefícios que as formas mais convencionais de exercício. São necessários mais estudos

de elevada qualidade em pacientes em qualquer estadio e sobreviventes de cancro da mama.

Palavras-chave: cancro da mama; pacientes de cancro da mama; sobreviventes de cancro da mama; exercício aeróbio; exercício de força; exercício combinado; *mind and body*; atividade física; qualidade de vida; *umbrella review*

Chapter 1- Theoretical Framework

Introduction

With an increase in cancer cases over the years, this pathology has become the second major cause of noncommunicable disease related mortality (*Global Report on Noncommunicable Diseases*, 2014). Female breast cancer (BC) has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%) in 2020 (Sung et al., 2021). This pattern is expected to continue to grow over the coming years (Winters et al., 2017), mostly due to changes in demographics such as those of the aging process of the population (Cardoso et al., 2019). Besides non-modifiable risk factors, such as aging and reproductive aspects, environmental factors such as the exogenous estrogen intake, alcohol abuse, excess dietary fat consumption, and physical inactivity are responsible of the increased likelihood of cancer (Sun et al., 2017). To date, worldwide BC prevention strategies have largely focused on educational interventions (such as increasing physical activity (PA) and reducing body mass index and alcohol intake) (Britt et al., 2020). Indeed, reducing all the aforementioned modifiable risk factors is an important component in the primary prevention of the disease and could reduce the social impact of BC (Britt et al., 2020).

Regular PA has been associated with a reduced risk in all-cause mortality for more than 25 non-communicable chronic diseases or conditions (Warburton et al., 2011; Warburton & Bredin, 2016), including that of a BC (Warburton & Bredin, 2017). Evidence shows that physically active women have a 25% lower risk of BC when compared to those who are less active (Lynch et al., 2010). Therefore, PA may be considered a prophylactic and inexpensive tool for primary cancer prevention (Sun et al., 2017). Moreover, exercise has also been described as a strategy to effectively reduce several side effects of treatment in BC patients and survivors (Eyigor & Kanyilmaz,

2014). For instance, BC treatment led to permanent sequalae in approximately 90% of women who experienced an array of physical complications (Beckjord et al., 2014). These may include physical, functional, emotional, and psychosocial changes that can dramatically alter patients' quality of life (QoL) (Beckjord et al., 2014; Dunne & Keenan, 2016). Given the clear beneficial effects of PA in BC patients and survivors, it is important to create conditions so that it can be implemented in a clinical setting and understand what type of exercise has more favorable results.

With this work, we aim to incorporate all information presented in systematic reviews and meta-analyses about the effect of diverse exercise interventions on QoL in BC patients during and after treatment and provide recommendations for future research.

This thesis includes a literature review that targets the worldwide problem of BC. It includes the cancer epidemiology, definitions, and specifies the complexity of the BC disease. Then, it provides a comprehensive relationship between exercise and cancer with an emphasis on exercise effects on QoL in BC patients and survivors. Lastly, it delivers a review of observational, experimental, and systematic reviews and meta-analysis on this topic. Afterward, methodology, results, and a discussion will be presented. Finally, it addresses the strengths and limitations of the present work and main conclusions will be delineated.

Literature Review

1. Cancer

1.1. Epidemiology

According to the World Health Organization, cancer is the second leading cause of noncommunicable disease deaths (8.2 million, or 21.7% of noncommunicable disease deaths) (*Global Report on Noncommunicable Diseases*, 2014). In 2020, there were almost 19.3 million new cases and 10 million cancer deaths worldwide (Sung et al., 2021). In 2040, it is estimated that there will be an increase of 47% in new cancer cases (28.4 million new cancer cases) (Sung et al., 2021). Worldwide, BC is the most diagnosed cancer (11.7% of total cases), followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%). Lung cancer is the leading cause of cancer death (18.0% of the total cancer deaths), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and BC (6.9%) (Sung et al., 2021). In Portugal, the most prevalent cancer is the colorectal (17.4%), followed by the breast (11,6%), prostate (11.2%) and lung cancer (9.0%) (Sung et al., 2021). Considering only females, BC is the most prevalent and represent the first cause of death (Sung et al., 2021).

Similar to every noncommunicable disease, there are both non-modifiable and modifiable risk factors for BC. The non-modifiable risk factors include age, family history of BC, and reproductive factors (early menarche, late menopause, late age at first pregnancy, and low parity) (Sun et al., 2017). Modifiable risk factors include alcohol abuse, obesity, and physical inactivity (Shah et al., 2014). Epidemiologic evidence shows a positive association between PA and survival after BC with preliminary results supporting 40-50% relative risk reduction for mortality (Mctiernan et al., 2018). Some studies have shown that consistent PA reduced the risk of BC, with moderate PA

conferring a 2% decrease in risk and vigorous PA a 5% decrease in risk (Wu et al., 2013). The most common sign/symptom of BC is the presence of a lump in the breast or armpit. A nipple discharge (clear or bloody), pain in the nipple, inverted (retracted) nipple, scaly or pitted skin on the nipple, persistent tenderness of the breast, and unusual breast pain or discomfort can also be presented. As the disease progresses, bone pain (bone metastases), shortness of breath (lung metastases), drop-in appetite (liver metastases), unintentional weight loss (liver metastases), headaches, neurological pain, or weakness become more noticeable (Sharma et al., 2010).

1.2.Cancer definition

The human body is composed of different types of cells in which stem cells stand out. Stem cells are a population of versatile and undifferentiated cells characterized by the ability to extensively proliferate, arise from a single cell, and differentiate into different types of cells and tissue (Kolios & Moodley, 2012), which work together to ensure organismic survival. However, this versatility can represent an important hazard for these cells considering that they may have access to compromised genomic sequences (mutations) losing the ability to assemble and create tissues of normal form and function (Weinberg, 2014). These cells are capable of proliferating in defiance of normal growth regulatory mechanisms and invading and destroying normal tissues (Tysnes & Bjerkvig, 2007).

Cancer initiation and progression is a multi-step process, which is characterized by a progressive genetic alteration that leads to the transformation of normal cells into highly malignant derivates (Tysnes & Bjerkvig, 2007). There are three important classes of genes that play an important role in tumor initiation: proto-oncogenes, tumor suppressor genes, and genes involved in DNA repair mechanisms (Tysnes & Bjerkvig,

2007). Under normal cell functioning, proto-oncogenes promote cell survival or proliferation, tumor suppressor genes inhibit cell survival or proliferation, and the DNA repair genes are responsible to repair or prevent DNA damage (Tysnes & Bjerkvig, 2007). Mutations, amplification, or deletions in these genes as a result of environmental (e.g., lifestyle and radiation exposure) and genetic determinants, as well as mistakes that occur during the DNA replication process (Bajaj et al., 2020), may lead to a de-coupling of biological mechanisms involved in the regulation of normal cell growth and differentiation, and hence lead to development of cancer (Tysnes & Bjerkvig, 2007).

1.3.Breast Cancer

Breast cancer is a heterogeneous disease with distinctive histological and biological characteristics, clinical presentations, and responses to treatment, when compared to other types of cancer (Weigelt et al., 2010). The breast tissue tumors are most commonly derived from the inner lining of milk ducts or the lobules that supply the ducts with milk (Sharma et al., 2010), and arise from ductal hyperproliferation, resulting in either benign tumors or metastatic carcinomas (Sun et al., 2017). Generally, two hypothetical theories were established to explain the initiation and progression of BC. The first is the cancer stem cell theory, which states that all tumor subtypes are derived from the same stem cells or progenitor cells and that genetic and epigenetic mutation in those cells will lead to different tumor phenotypes (Sun et al., 2017). The stochastic theory assumes that each tumor subtype is initiated from a single cell type (stem cell, progenitor, or differentiated cell) and that mutations can gradually accumulate in breast cells, leading to their transformation into tumor cells (Sun et al., 2017).

Half of the BC predisposition syndromes are associated with mutations in two particular tumor suppressor genes that play an important role in cancer initiation and

progression: breast cancer-associated genes 1 and 2 (BRCA1 and BRCA2) (Shah et al., 2014; Sun et al., 2017). A deficiency in BRCA1 leads to the deregulation of cell cycle checkpoint, abnormal centrosome duplication, genetic instability, and eventual apoptosis (Sun et al., 2017). Additionally, genetic changes in the BRCA2 gene, which regulates DNA reparation (Sun et al., 2017), could be associated with errors in the DNA replication process. Women with deleterious mutations in these genes have a significantly higher risk of developing BC (Shah et al., 2014). In total, almost 20% of hereditary BCs and 5-10% of all BCs are caused by these mutations (Balmaña et al., 2011; Paluch-Shimon et al., 2016).

An early BC diagnosis can lead to a good prognosis and a high survival rate (Sun et al., 2017). For better identification of the disease, the tumor, nodes, and metastasis classification are used for classifying the malignancy. This is a system that is based on assessing the tumor size (T0 indicates that no evidence of tumor is present and T1-T4 are used to identify the size and extension of the tumor), regional lymph nodes involvement of the tumor (N0 indicates that no regional nodal spread and N1-N3 indicates some degree of nodal spread), and distant metastasis of the primary tumor (M0 is expressed if no distant metastasis is present and M1 if there is evidence of distant metastasis) (Rosen & Sapra, 2021).

Based on immunohistochemical properties, it is possible to identify 4 intrinsic subtypes of BC tumor biology (Cardoso et al., 2019):

- Luminal A, which is estrogen receptor-positive, human epidermal growth factor receptor 2 (HER2) negative, has low proliferative markers (i.e. low ki67 value) and high progesterone receptor;

- Luminal B, which can be divided into HER2 negative with positive estrogen receptor and either high Ki67 or low progesterone receptor; and HER2 positive with positive estrogen receptor and any level of proliferation or progesterone receptor;
- HER2 (or non-luminal) is absent of estrogen receptor and progesterone receptor;
- Triple-negative BC (or basal-like) is absent of estrogen receptor and progesterone receptor and has negative HER2.

2. Physical activity, exercise and cancer

2.1.Conceptual definitions

Although they are conceptually different, the terms PA and exercise are often used synonymously. However, PA is defined as any bodily movement produced by skeletal muscles that results in energy expenditure (Caspersen et al., 1985), it refers to all movement including during leisure time, for transport to get to and from places, or as part of a person's work (WHO, 2021). The WHO provides recommendations for the amount of physical activity needed for an individual to be healthy depending on their age and specific population groups (pregnancy, chronic conditions, people living with disability) (WHO, 2021). For a healthy adult (aged 18-64 years) it is recommended to perform at least 150-300 minutes of moderate-intensity aerobic physical activity or at least 75-150 minutes of vigorous-intensity aerobic physical activity for week or a combination of both (WHO, 2021). This population should also include muscle-strengthening activities two or more days a week, and also limit the time spent in sedentary behavior (WHO, 2021). Popular ways to increase physical activity level include walking, cycling, sports, active recreation, and play, and can be done at any skill level (WHO, 2021). Regular physical

activity can improve muscular and cardiorespiratory fitness, bone and functional health, reduce the risk of hypertension, coronary heart disease, stroke, diabetes, various types of cancer (including breast cancer and colon cancer), and depression, the risk of falls as well as hip or vertebral fractures, and help maintain a healthy body weight (WHO, 2021). While exercise is a type of PA consisting of planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness (Riebe et al., 2018).

There are several different types of exercise, but to keep the scope of this work focused, we will address those in which the predominant physiological effect targets the cardiorespiratory system (e.g., aerobic exercise), the muscle-skeletal system through strengthening activities (e.g., resistance exercise), and a combination of both (e.g., combined exercise. Aerobic exercise involves large muscle groups in dynamic activities that result in substantial increases in heart rate and energy expenditure. Resistance exercise is specifically designed to increase muscular strength, power, and endurance by varying the resistance, the number of times the resistance is moved in a single group (set) of exercise, the number of sets done, and the rest interval provided between sets (Howley, 2001). Combined exercise is a combination between aerobic and resistance exercise. However, within the exercise oncology field, namely in those with BC, a fourth exercise type is of particular importance, which is mind and body exercises, such as tai chi, qigong, yoga, and pilates. This exercise stimulus comprises low-impact activities, which enhance mind-body coordination, balance and awareness through the practice of a sequence of controlled motions and focused attention (Kwok et al., 2016).

2.2.Exercise effects in cancer patients

Over the past two decades, several studies have provided evidence that PA or exercise reduces the risk of developing a range of different cancer types (such as breast, colorectal, and lung) (Li et al., 2016; Moore et al., 2016). However, only cancer survivors have specific exercise guidelines. The exercise prescription should be individualized according to a cancer survivor's pretreatment aerobic fitness, medical comorbidities, response to treatment, and the immediate or persistent negative effects of treatment that are experienced (Schmitz, Courneya, et al., 2010). According to the most recent guidelines established by the American College of Sports Medicine, the goal of exercise for this population is 150 minutes weekly of moderate-intensity or 75 minutes of vigorous-intensity activity with 3-5 days a week dedicated to aerobic exercise and 2-3 times a week of resistance exercise involving all major muscle groups with at least one set of 8-12 repetitions with low resistance. Flexibility activities are also recommended 2-3 days a week with stretching or range of motion (ROM) exercises for all major muscle groups (Riebe et al., 2018).

This recommendation is geared to counteract the physical deconditioning caused by cancer and its treatment, prevent or delay declines in aerobic fitness and strength, control symptoms, and make everyday activities easier to undertake, thus, helping to maintain independence and improve functional ability and QoL (Dittus et al., 2017; Eyigor & Akdeniz, 2014; Fuller et al., 2018). Indeed, ample evidence has shown that exercise is safe and feasible and associated with significant improvements in select outcomes in patients with early-stage disease receiving conventional cytotoxic adjuvant therapy, with a low incidence of adverse events (Jones & Alfano, 2013; Speck, Courneya, et al., 2010).

Further, some literature published over the last decade suggests that exercise practice following the diagnosis of certain solid tumors might lower the progression of

the disease through direct effects on tumor intrinsic factors (growth rate, metastasis, tumor metabolism, and immunogenicity of the tumor) and reduce cancer-related mortality (Friedenreich et al., 2017; Hojman et al., 2018). The mechanisms whereby this happens are not well understood (Friedenreich et al., 2017), but there are some hypotheses proposed. During exercise performance, many physical (i.e., increase in blood flow, shear stress on the vascular bed, pH regulation, heat production, and sympathetic activation) and endocrine (i.e., stress hormones, myokines, and circulating exosomes) (Hawley et al., 2014) adaptations occur, all of which exert immediate stress on tumor metabolism and homeostasis. Following long-term training, these acute effects lead to intra-tumoral adaptations of improved blood perfusion, enhanced immunogenicity, and metabolism adjustments, which contribute to slower tumor progression (Hojman et al., 2018).

It is important to emphasize that some studies have found differences in the exercise responsiveness of different tumors while using the same exercise protocol, with some tumors (of the same subtype) exhibiting either no change in growth rate or even an increased growth rate with aerobic exercise (Glass et al., 2017; M. Lu et al., 2018). These results reinforce that exercise training is still far from a one-size-fits-all approach and its effects should be interpreted with caution.

2.3.Exercise effects in quality of life

Quality of life is a concept that approaches several generalized levels from the assessment of societal or community wellbeing to the specific evaluation of the situations of individuals or groups (Buss & Dachs, 2020). The most recent definition was established by the World Health Organization, which defines QoL as an individual's perception of their living conditions according to their culture, value systems, goals, expectations, standards, and concerns (Vahedi, 2010).

Considering the inherent subjectivity, the assessment of QoL is still challenging and based mostly on self-reported measures (i.e. questionnaires) that are influenced by beliefs and attitudes and, therefore, prone to bias. However, there are no acceptable alternative means of measurement (Kimberlin & Winterstein, 2008). Within the oncology research field, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-General (FACT-G) are the most common questionnaires (Soni & Cella, 2002). Further, and considering the uniqueness of each cancer, several scales were developed to assess QoL in patients with some specific cancers, such as BC. For this type of cancer, the EORTC QLQ-BR23 (used in conjunction with EORTC-QLQ C30) and the FACT-Breast (FACT-B) are available (Nguyen et al., 2015). The EORTC QLQ-BR23 incorporates five multi-item scales to assess body image, sexual functioning, systemic therapy side effects, breast symptoms, and arm symptoms. The FACT-B provides a more comprehensive analysis of the patient's social well-being, addressing also physical well-being, emotional well-being, and functional well-being, with a focus on concerns specifically relevant to BC patients (Nguyen et al., 2015).

It is well-recognized that a physically active lifestyle promotes feelings of well-being and improves QoL (Felce & Perry, 1995), although the mechanisms by which this relationship works still warrants further investigation (Gillison et al., 2009). QoL is a multidimensional construct under which physical, social, psychological, and spiritual well-being may reside (McAuley et al., 2008). A pathway to QoL through mental and physical health status was suggested by Blane et al., (2008). They proposed that a link between QoL and mental/physical health status exists in which depression and functional limitations mediated the relationships of physical health variables (i.e., blood pressure, body mass index, and lung function) with global QoL (McAuley et al., 2008).

Another perspective on how exercise potentially improves QoL is through a range of psychosocial mechanisms. This hypothesis recognizes that PA provides an opportunity for social interaction (relatedness), mastery in the physical domain (self-efficacy and perceived competence), improvements in self-perceptions of appearance (body image), and independence (autonomy) (Lubans et al., 2016). Decreases in PA across 24 months are associated with decreases in self-efficacy and changes in physical and mental health status, all of which could be directly related to changes in global QoL (McAuley et al., 2008). Some of the physiological and QoL effects of exercise on cancer are illustrated in figure 1.

Figure 1. Physiological and quality of life effects of exercise on cancer

There is strong evidence in humans on the positive effect of exercise on QoL measures. Studies have shown that exercise interventions improved QoL in physical

functioning, physical limitations, general health, mental health, emotional limitations, social functioning, and vitality (Mitchell & Barlow, 2011). Aerobic exercise (particularly walking) was also associated with increased strength, aerobic capacity, and improvement in functional limitations (Mitchell & Barlow, 2011), which demonstrates that this type of exercise could improve independence and, therefore, improve the ability to perform basic activities of daily living. Resistance exercise has also shown to be effective in improving QoL. A 9-month intervention in older adults revealed that resistance exercise performed 2 times weekly was beneficial for the environmental QoL subscale (Kekäläinen et al., 2018). Although these are the most conventional forms of exercise, mind and body exercise has been shown to be a feasible alternative to improve QoL. Compared to an inactive group, older adults who performed yoga improved many aspects of their physical function like strength, flexibility and aerobic fitness, and physical and mental health (Patel et al., 2012; Sivaramakrishnan et al., 2019).

3. Exercise in breast cancer patients and survivors

3.1. Observational studies

Observational data shows that BC patients experience significantly lower QoL as compared to the general population (Kokkonen et al., 2017). Considering the exercise-related literature, some investigations have been conducted to clarify the beneficial effects of exercise on QoL in patients with BC. One observational study found positive changes in self-reported energy, stress, and nausea immediately after both endurance and resistance training sessions in newly diagnosed breast, colorectal, and prostate cancer patients undergoing chemotherapy (CTx) (Johnsson et al., 2019). Furthermore, it was reported that women diagnosed with BC and undergoing treatment who were most active

had better QoL compared with their sedentary counterparts, indicating a positive association between QoL and PA (Canário et al., 2016).

Associations between PA and QoL were also verified in BC survivors. Women that reported any level of PA had subsequently higher physical and mental QoL than sedentary BC survivors (Hart et al., 2018). In addition to PA levels, reducing time in sedentary pursuits also has a substantial impact on BC survivors, since increases in sedentary behavior were associated with lower functional scores, namely physical functioning, role functioning, and cognitive functioning (Nurnazahiah et al., 2020). Moreover, an accelerometer-based study determined that replacing 30 minutes of sedentary activities with active behaviors was associated with higher physical and functional well-being scores and overall QoL in BC survivors (Welch et al., 2019).

3.2.Experimental studies

Beyond the above-mentioned observational evidence, several experimental investigations have been performed to highlight the idea that exercise is paramount for improving the QoL of patients with BC, namely those undergoing anticancer therapy. For instance, significant improvements were found for several QoL domains in BC patients during adjuvant CTx such as social function, global health, physical functioning, pain, and cancer-related symptoms following 12-weeks of resistance exercise intervention performed alone (Schmidt et al., 2015) or in combination with balance and flexibility components (Schmidt et al., 2015; Steindorf et al., 2014). Improvements in QoL in BC patients and survivors were also observed with combined exercise protocols (Landry et al., 2018).

Furthermore, a 2-arm randomized controlled trial (RCT) reported important improvements not only for QoL but also for fatigue and depressive symptoms in

overweight/obese BC survivors following 16-weeks of supervised combined training of moderate-to-vigorous intensity (Dieli-Conwright et al., 2018). In agreement with these results, a 9-month exercise intervention that consisted of resistance training followed by aerobic exercise in BC survivors on aromatase inhibitors therapy found high effect sizes for almost all QoL variables, thus, demonstrating the positive clinical relevance of combined exercise programs for BC survivors using aromatase inhibitors. Moreover, improvements in functioning were reported, which are important for maintaining independence, daily living activities, healthy aging, and reducing the effects of treatment. The effect of exercise on physical functioning may even continue for a long time after treatment (Paulo et al., 2019). A comparison between aerobic, resistance, and aquatic exercise on the self-perceived QoL and physical functionality in BC survivors, reported that the effects of these three distinct exercise protocols were distinct, with the resistance stimulus providing the most noticeable benefits (García-Soidán et al., 2020). Conversely, a 3-arm intervention performed in BC patients who completed adjuvant therapy suggested that a water exercise intervention was more effective for improving emotional well-being and decreasing negative symptoms when compared to pilates and yoga interventions (Odynets et al., 2019). However, the yoga intervention was more effective than the water and pilates exercises in improving social/family well-being (Odynets et al., 2019). Despite being of low to moderate aerobic intensity, Tai Chi Chuan also showed improvements in BC survivors on physical functioning and role limitations due to physical health problems (Sprod et al., 2012).

Altogether, these results reinforce that exercise practice is not only important for BC patients but also for those who already completed the treatment. However, the best exercise type and the dose are still unknown, and more high-quality experimental studies are needed.

3.3.Systematic reviews and meta-analysis

Several systematic reviews were conducted to understand the effects of exercise on QoL in BC patients who were undergoing treatment. Pedometer-based exercise interventions implemented in BC patients receiving CTx were shown to play an important role in improving the QoL in these patients through impacting cognitive functioning, memory, attention, anxiety, fatigue, and depression (Samuel et al., 2020). A recent systematic review conducted by Coughlin et al. (2019), reported that home-based PA interventions improved various cognitive and emotional outcomes in BC patients who were undergoing primary therapy (adjuvant CTx, radiation therapy (RTx)) (Coughlin et al., 2019). Furthermore, a meta-analysis that aimed to investigate the effects of aerobic and resistance exercise, yoga, qigong, tai chi, and pilates during adjuvant RTx on QoL among BC patients suggested that, although non-significant, there was a trend towards QoL improvement in the exercise groups (Lipsett et al., 2017).

A meta-analysis of RCTs and quasi-experimental studies evaluated the effects of several exercise interventions (such as walking, aquatic exercise, strength training, bench press, leg press, seated row, and so on) on QoL in BC survivors taking aromatase inhibitors as their main therapy. The results of this study indicated that exercise was a beneficial strategy that had a favorable effect on QoL in BC survivors (G. Lu & Zheng, 2019). A review to assess the effects of PA interventions after adjuvant therapy for BC women was conducted by Levett-Jones & Jones, (2020) with the modes of PA differing across trials, which included aerobic exercise such as walking, cycling, and water-based exercise; resistance exercise; and yoga, pilates, qigong, or tai chi. Results revealed that PA may have small to moderate beneficial effects on overall QoL, and some QoL domains (such as emotional, perceived physical, and social function) (Levett-Jones & Jones, 2020). Lastly, a systematic review of the literature conducted to describe the role of

exercise training over the past 25 years on major physiological-psychological outcomes measured in BC survivors was performed by Battaglini et al. (2014). Over the years exercise has gained increasing importance in BC patients for the alleviation of decrements of treatment-related side effects (functional capacity, fatigue levels, and depression) (Battaglini et al., 2014). With studies showing promising results in alleviating the decrements caused by anti- cancer treatment, since the years 2000s the medical community show an increase in interest in the use of exercise interventions as a complementary therapy (Battaglini et al., 2014). In recent years, many studies have shown significant improvements in QoL in BC patients who exercised compared to those who did not exercise that showed no difference (Battaglini et al., 2014). These results demonstrate that exercise can be used as a feasible complementary therapy in these patients and has the ability to improve several components of QoL.

Thesis purpose

Although the scientific knowledge in the exercise oncology field has increased in the past decade, increased evidence on the effects of different exercise interventions on QoL in cancer patients is warranted. Given the increase in systematic reviews and meta-analyses in the past two decades, it seems pertinent to synthesize all this information. However, to the best of our knowledge, only one umbrella review has been conducted within the exercise oncology research field, which aimed to understand the effects of exercise on fatigue in cancer patients (Jiang et al., 2020). To date, no umbrella review has been performed to systematize the effects of exercise interventions on QoL in BC patients undergoing any type of anti-cancer therapy and BC survivors. Therefore, we conducted an umbrella review that aimed to examine the effects of different exercise protocols

(aerobic, resistance, combined, and mind and body exercise) on QoL in BC patients during and after treatment.

CHAPTER 2- Umbrella Review

Effect of different types of exercise on quality of life in breast cancer patients and survivors: an umbrella review

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Abstract

Purpose: To systematize the available evidence from published systematic reviews about the effects of different types of exercise interventions on quality of life (QoL) in breast cancer (BC) patients and survivors.

Methods: Pubmed, Web of Science, the Cochrane Library, and PEDro databases were searched to identify pertinent systematic reviews and meta-analyses. Reviews assessing exercise interventions on QoL as one of the primary outcomes in BC patients and survivors were included. The Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) tool was used to evaluate the quality of evidence. The methodological quality of the included studies was evaluated by the Assessment of Methodologic Quality of Systematic Reviews (AMSTAR) appraisal.

Results: 25 studies met all the inclusion criteria. The AMSTAR score varied from 3 to 11 points with an overall mean of 7.4 points. Out of 25 studies, 23 found beneficial effects of aerobic, resistance, combined, and mind and body exercise in BC patients and survivors. Only 2 systematic reviews reported no effects of exercise on QoL. As for GRADE, 7 studies were rated as “high”, 10 as “moderate, 6 as “low”, and 2 as “very low”.

Conclusion: Exercise can be considered a beneficial strategy to improve QoL in BC patients and survivors. Within the different types of exercise, mind and body exercise is emerging as promising strategy in the BC field and has shown to be as beneficial as other forms of exercise. Given the heterogeneity of exercise interventions, a higher number of high-quality studies are warranted to clarify the underlying effects of different types of exercise on QoL, specially at different stages of BC treatment.

Keywords: breast cancer; physical activity; exercise; quality of life; umbrella review

Graphical Abstract

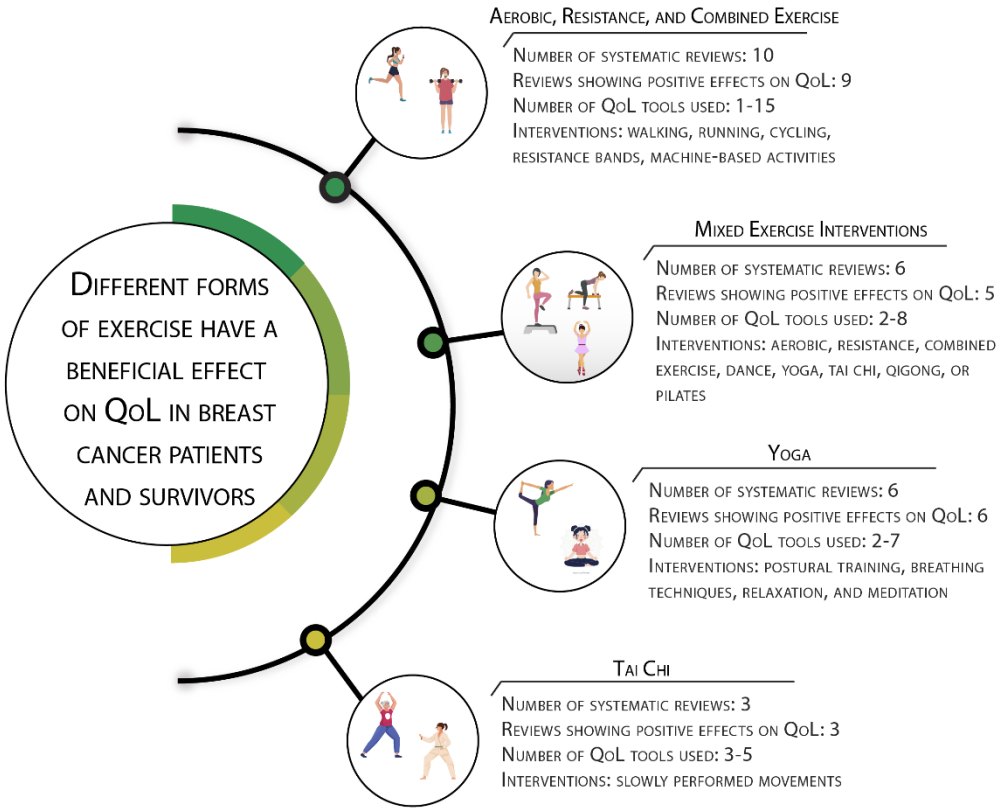

Figure 2. Overview of the umbrella review results

Introduction

According to the International Agency for Research in Cancer, almost 19.3 million new cases of cancer were detected in 2020, with female breast cancer (BC) being the most commonly diagnosed oncological disease with an estimated incidence of 2.3 million new cases (11.7%) (Sung et al., 2021). Despite the scientific and therapeutic breakthroughs in the oncology field that resulted in a noticeable reduction in cancer-related mortality, a 47% and 34% increase in overall cancer and BC incidence, respectively, is expected in 2040 (Sung et al., 2021). This forecast might be explained by demographic changes (e.g., ageing) and the challenges imposed by modern society on the classic risk factors, such as physical inactivity, unhealthy diet, overweight/obesity, and tobacco consumption (*Global Report on Noncommunicable Diseases*, 2014; Stein & Colditz, 2004; Sung et al., 2021).

The World Health Organization defines Quality of life (QoL) as a broad multidimensional concept that represents an individual's perception of their living condition according to their culture, value systems, goals, expectations, standards, and concerns (Vahedi, 2010). Within the cancer setting, patients' QoL has become a major concern, since most of the anticancer therapies might compromise this valuable personal dimension (Beckjord et al., 2014; Dunne & Keenan, 2016) with an important prognostic value (Takada et al., 2019). Indeed, most of the cancer therapeutic approaches have adverse side-effects that might persist for years after treatment completion, such as severe fatigue, sleep disturbance, pain, vomiting, and intestinal and cardiac complications (Fiorentino & Ancoli-Israel, 2007) all of which have a noticeable impact on daily living and survival rate of patients and survivors (Niklasson et al., 2017). Therefore, identifying

efficient clinical management strategies that may attenuate the aforementioned adverse events and, therefore, improve the QoL of cancer patients and survivors is paramount.

Exercise has emerged as a potential, feasible, and cost-effective adjuvant treatment tool for BC with beneficial effects on mortality and QoL (Eyigor & Kanyilmaz, 2014). For instance, an experimental study that compared the effects of different exercise interventions (strength, aqua fitness, and aerobic exercise) in BC survivors suggested that the practice of physical activity (PA) was safe and had beneficial effects on QoL (García-Soidán et al., 2020). In particular, the strength intervention provided the most benefits in physical health parameters as well as in mental health (García-Soidán et al., 2020). In addition, a systematic review assessing the effects of aerobic, resistance, and combined exercise on QoL in BC patients undergoing adjuvant treatment concluded that significant improvements in QoL can be obtained from any type of exercise intervention (i.e. aerobic, resistance, and combined exercise) (Gebruers et al., 2019).

On this topic several systematic reviews/meta-analysis have been performed to synthesize the effects of exercise on QoL in BC patients and survivors. However, the majority of these systematic reviews have included studies with small sample sizes and involved a wide range of exercise interventions, making it difficult to compare the results and establish a general conclusion. Thus, an umbrella review may provide a better understating of the relationship between the effects of exercise and QoL improvements, by synthesizing all of the available information and better inform future interventions.

This study aimed to present an umbrella review of the existing systematic reviews that analyzed exercise interventions geared towards increasing QoL among BC patients and survivors and provide recommendations for future research.

Methods

1. Search strategy

A comprehensive literature search was performed in PubMed, Web of Science, Cochrane Library, and PEDro database until April 16th, 2021. This umbrella review is registered on the PROSPERO international prospective register of systematic reviews (CRD42021252245). The search terms used in this umbrella review were related to BC (breast cancer, carcinoma, patients, survivors) and exercise (exercise, exercise training, physical activity) (Table 1). All obtained articles were stored in a Microsoft Excel document.

Table 1. Databases keywords

Databases	**Keywords**
Pubmed	(breast cancer or breast carcinoma or breast cancer patients or breast cancer survivors) AND (exercise OR physical activity OR exercise training) with systematic review filter
Web of Science	TS=(breast cancer OR breast carcinoma OR breast cancer patients OR breast cancer survivors) AND TS=(exercise OR physical activity OR exercise training) AND TS=(systematic review OR systematic OR meta-analysis OR review)
Cochrane Library	(breast cancer OR breast carcinoma OR breast cancer patients OR breast cancer survivors) AND (exercise OR physical activity OR exercise training)
PEDro	"breast cancer" exercise*

2. Inclusion and exclusion criteria

For the inclusion and exclusion criteria, we followed the PICO structure: **Participants (P)**: adult (>18 years) female patients who were diagnosed with BC with any tumor stage (0 to IV) and BC survivors. Any other type of cancer was excluded; **Intervention (I)**: studies that involved exercise interventions (e.g. aerobic, resistance, combined exercise, yoga, tai chi, qigong, pilates). Studies with exercise training as a part of an intervention with multiple components were excluded; **Comparison (C)**: the intervention group underwent exercise intervention, and the control group did not undergo any exercise intervention; **Outcome (O)**: QoL as one of the primary outcomes; **Other**: publication type was a systematic review and meta-analysis of randomized controlled trials (RCTs) with original full reports. Only studies published in English were included.

3. Study selection and data extraction

The eligible systematic reviews and meta-analysis were assessed independently by two investigators according to inclusion and exclusion criteria by evaluating the titles and abstracts of each paper. If there was not enough information available to evaluate the article, then a full-text version was obtained. Any disagreements were solved by a third investigator. Data were extracted from the eligible studies, which included article identification, purpose, selection criteria, exercise intervention, assessed outcomes, quality assessment, results, conclusions, and observations. All extracted data was stored in a Microsoft Excel file.

4. Quality appraisal

One investigator assessed the methodological quality of the included studies using the "Assessment of Methodologic Quality of Systematic Reviews" (AMSTAR) (Shea et al.,

2009). When doubts arose, a second investigator verified the question. AMSTAR is a reliable and valid 11-item tool to assess the methodological quality of systematic reviews. Items were rated as "0" if there was insufficient information available in the article or a criterion was missing. If there was sufficient information available and the veracity of the item was verified, it was rated as "1". The investigators rated methodological quality as high (score 9-11), moderate (score 5-8), and low (score 0-4).

Additionally, the Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) tool (Norris et al., 2016) was used to rate the quality of evidence for BC patients' and survivors' QoL outcomes. Studies were rated as high, moderate, low, and very low. The GRADE handbook states that five factors reduce the quality of evidence. These are limitations in study design; inconsistency of results; indirectness; imprecision; and publication bias.

Results

1. Study process

A total of 2876 articles were identified, of which 547 were duplicates. After all results from each database were stored in a Microsoft Excel document, a screening through titles and abstracts was performed, which resulted in 121 articles remaining for further evaluation. Finally, we excluded 96 studies for the following reasons: exercise training was part of a multicomponent intervention (n=47); QoL was not one of the primary outcomes evaluated (n=27); systematic reviews that considered investigations other than RCTs (n=9); review articles (n=4); RCT (n=3); umbrella review (n=1); a summary of an existent study (n=1); study protocols (n=2); systematic reviews and meta-analyses involving other types of cancer than BC (n=1); and studies with unspecified findings (n=1). A PRISMA diagram is shown in Figure 3.

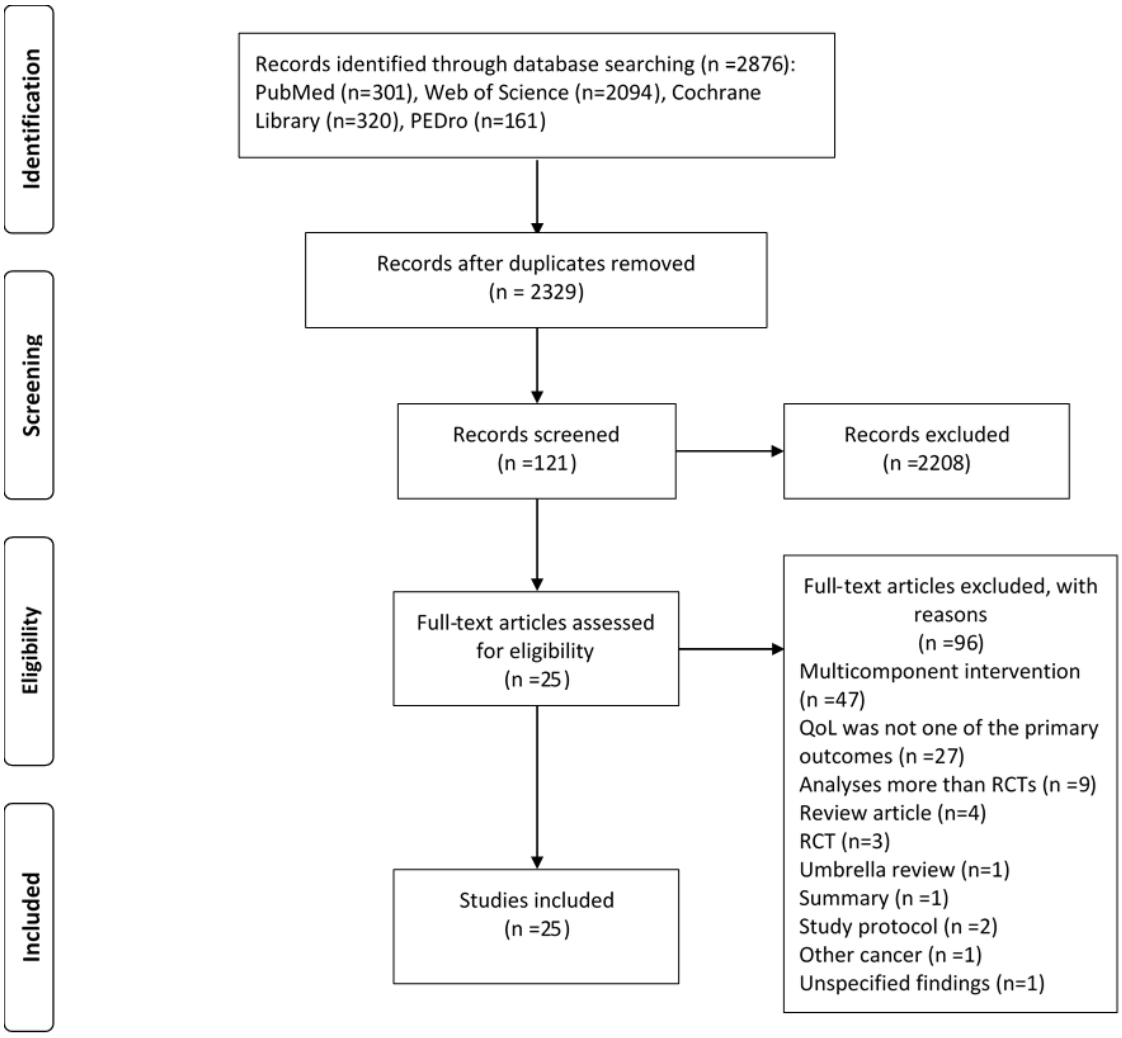

Figure 3. PRISMA flow diagram for search and selection process

2. Characteristics of included studies

The main characteristics of the included studies are described in Table 2, 3 and, 4, with Table 2 including studies performed in BC patients during treatment, and Table 3 and 4 for BC survivors and BC patients during and after treatment, respectively. Of the 25 systematic reviews, 5 included participants during active treatment, 13 included BC patients during and after treatment, and 7 considered patients with complete treatment. Each study included 6 to 36 original trials. The number of tools to assess QoL varied from 1 to 15. The most common tools used were the Functional Assessment of Cancer Therapy-

Breast (FACT-B) (n=22), the European Organization for Research and Treatment of Cancer quality of life core cancer (EORTC QOL-C30) (n=15), the Short-Form Health Survey (SF-36) (n=15), and the Functional Assessment of Cancer Therapy—General (FACT-G) (n=16). The included studies were published between 2006 and 2020.

As for GRADE, 7 studies were rated with “high” quality, 10 with “moderate” quality, 6 with “low” quality, and 2 with “very low” quality.

Table 2. Characteristics of the included studies in breast cancer patients during treatment.

Autor, year	Studies	Participants	Moment of Treatment	Type of Treatment	Exercise	QoL tools (number)	Effect size (95% CI)	Heterogeneity	Conclusions	GRADE
Aerobic Resistance Combined Exercise										
Gebruers et al., 2019	28	2525	Adjuvant therapy	CTx, RTx, or both	Aerobic Combined	15	NM	NM	Physical exercise improves QoL during anti-cancer treatment in BC patients.	M
Lee & Lee, 2020	29	2989	Adjuvant therapy	ND	Aerobic Resistance Combined	1	d= 0.16 (0.01, 0,33)	I^2= 0%	Exercise interventions had positive effects on QoL in BC patients who undergo adjuvant therapy after surgery.	L
Furmaniak et al., 2016	32	2626	Adjuvant/neoadjuvant therapy	RTx,CTx, or both	Aerobic Resistance Combined	3	SMD= 0.12 (0.00, 0.25)	I^2= 0%	Exercising, while receiving adjuvant treatment for BC, leads to little or no difference in cancer-specific QoL and health-related QoL.	H
Mix										
Shen & Yang, 2020	13	1306	ND	RTx	Resistance Stretching Yoga Qigong	5	SMD= 0.28 (0.14, 0.4)	I^2= 47.7%	Overall, QoL for BC patients was found to improve over time with exercise after RTx.	H
Carayol et al., 2015	36	2723	ND	CTx and/or RTx	Aerobic Resistance Dance Yoga Tai-chi Pilates	4	SMD= 0.16 (0.05, 0.26)	I^2=76%	Exercise-based interventions had a significant beneficial impact on QoL.	M

Abbreviations: BC, breast cancer; CTx, chemotherapy; d, Cohen's d; H, high; L, low; M, moderate; ND, not defined; NM, not measured; QoL, quality of life; RTx, radiation therapy; SMD, standard mean difference

Table 3. Characteristics of the included studies in breast cancer survivors.

Autor, year	Studies	Participants	Moment of Treatment	Exercise	QoL tools (number)	Effect size (95% CI)	Heterogeneity	Conclusions	GRADE
Aerobic Exercise									
Bekhet et al., 2019	12	1120	after treatment	Aerobic	4	NM	NM	Aerobic exercise improved QoL in BC survivors.	M
Liu et al., 2017	9	845	after treatment	Aerobic	2	SMD= 0.49 (0.04, 0.94)	I^2=88.5%	Home-based PA intervention significantly improved the QoL in BC survivors.	M
Resistance Exercise									
Dos Santos et al., 2017	10	1448	after treatment	Resistance	2	NM	NM	Resistance training improved QoL in BC survivors.	H
Aerobic Resistance Combined Exercise									
Dieli-Conwright & Orozco, 2015	26	NS	after treatment	Aerobic Resistance Combined	2	NM	NM	Exercise participation after BC treatments elicits beneficial effects on physical and emotional well-being.	VL
Mix									
Hong et al., 2019	26	1892	after treatment	Aerobic Resistance Combined Yoga Qigong	4	SMD= 0.35 (0.15, 0.54)	I^2= 61%	Exercise intervention (of any type) is beneficial for improving the QoL of BC survivors.	L
Zhu et al., 2016	33	2659	after treatment	Aerobic Resistance Stretching Tai-chi Dance	8	SMD= 0.36 (0.11, 0.62)	I^2= 0%	Exercise improves the QoL in BC survivors.	H
Tai Chi									
Yan et al., 2014	9	426	after treatment	Tai-chi	4	SMD= 0.24 (0.02, 0.45)	I^2= 0%	The Tai Chi group had improved emotional well-being in BC survivors.	M

Abbreviations: BC, breast cancer; H, high; L, low; M, moderate; NS, not specified; NM, not measured; QoL, quality of life; SMD, standard mean difference; VL, very low

Table 4. Characteristics of the included studies in breast cancer patients and survivors.

Autor, year	Studies	Participants	Moment of treatment	Type of treatment	Exercise	QoL tools (number)	Effect size (95% CI)	Heterogeneity	Conclusions	GRADE
Aerobic Resistance Combined Exercise										
Dijck et al., 2016	13	2180	during/after	surgery, CTx and/or RTx	Aerobic Combined	7	NM	NM	Exercise training improves or attenuates the decline in QoL in BC patients undergoing and following anti-cancer treatment.	L
Pastakia & Kumar, 2011	9	NS	during/after	surgery, HT, CTx and/or RTx	Aerobic Resistance Combined	1	NM	NM	Aerobic exercise used with or without resistance training has a positive effect on QoL-related outcomes.	L
Zhang et al., 2018	36	3914	during/after	ND	Aerobic Resistance Combined	14	NM	NM	Different forms of exercise improve QoL.	L
Mix										
Bicego et al., 2009	9	373	during/after	surgery, HT, CTx and/or RTx	Aerobic Resistance Combined Dance Tai-chi Stretching	7	NM	NM	There was a lesser decrease in QoL in the exercise group.	VL
McNeely et al., 2006	14	717	during/after	surgery, HT, CTx and/or RTx	Aerobic Resistance Combined Yoga Tai Chi	2	WMD= 4.58 (0.35, 8.80)	NM	Exercise is an effective intervention to improve QoL in BC patients and survivors.	M

Abbreviations: BC, breast cancer; CTx, chemotherapy; d, Cohen's d; H, high; HT, hormone therapy; L, low; M, moderate; ND, not defined; NS, not specified; NM, not measured; QoL, quality of life; RTx, radiation therapy; SMD, standard mean difference; VL, very low; WMD, weighted mean difference

Table 5. Characteristics of the included studies in breast cancer patients and survivors. (Continued)

Autor, year	Studies	Participants	Moment of treatment	Type of treatment	Exercise	QoL tools (number)	Effect size (95% CI)	Heterogeneity	Conclusions	GRADE
Yoga										
O'Neill et al., 2020	24	1394	during/after	surgery, HT, CTx and/or RTx	Yoga	5	SMD= 0.27 (0.46, 0.07)	I^2= 21%	Yoga is beneficial in improving QoL for women with BC.	H
El-Hashimi & Gorey, 2019	8	545	during/after	ND	Yoga	5	d= 0.14 (0.00, 0.28)	Chi^2= 32.92%	Yoga seems to be as effective as other exercise modalities for improving the QoL of women with BC.	H
Harder et al., 2012	18	760	during/after	surgery, HT, CTx and/or RTx	Yoga	4	NM	NM	Yoga interventions for BC have a neutral or positive effect on a patient's overall QoL.	L
Zhang et al., 2012	6	382	during/after	ND	Yoga	2	SMD= 0.27 (0.02, 0.52)	I^2= 0%	Yoga had a positive effect on QoL.	M
Cramer et al., 2012	12	742	during/after	HT, CTx, RTx	Yoga	5	SMD= 0.62 (0.04, 1.21)	I^2= 0%	Yoga had a moderate, short-term effect on global QoL.	M
Cramer et al., 2017	24	2166	during/after	HT, CTx, RTx	Yoga	7	SMD= 0.22 (0.04, 0.40)	I^2= 19%	Yoga had a positive effect on QoL but was not superior when compared with other exercise forms.	H
Tai Chi										
Luo et al., 2020	15	885	during/after	surgery, HT, CTx and/or RTx	Tai-chi	5	SMD= 0.37 (0.15, 0.59)	I^2= 0%	Tai Chi had positive effects on QoL in BC patients.	M
Liu et al., 2020	16	1268	during/after	surgery, HT, CTx and/or RTx	Tai-chi	3	SMD= 0.32 (0.07, 0.56)	I^2= 67%	Tai Chi as an adjunct to conventional therapy is effective in improving QoL for BC patients.	M

Abbreviations: BC, breast cancer; CTx, chemotherapy; d, Cohen's d; H, high; HT, hormone therapy; L, low; M, moderate; ND, not defined; NS, not specified; NM, not measured; QoL, quality of life; RTx, radiation therapy; SMD, standard mean deviation; VL, very low; WMD, weighted mean difference

3. The methodological quality of included studies

The quality of the included studies assessed by AMSTAR varied from a score of 3 to 11 points with an overall mean of 7.4 points. Only one study achieved the perfect score 11/11, one attained 10/11, four scored 9/11, eight scored 8/11, four studies achieved 7/11, four studies scored 6/11, one study scored 5/11, one study scored 4/11, and just one study achieved 3/11 (Table 5). Hence, six articles were considered with high quality, seventeen with moderate quality, and two with low quality.

Table 5. Individual AMSTAR questions by study.

Autor	AMSTAR questions											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Total**
Gebruers et al.	1	1	1	0	0	1	0	0	0	1	1	6
Lee & Lee	1	1	1	0	0	1	0	0	1	0	1	6
Furmaniak et al.	1	1	1	0	1	1	1	1	1	1	1	10
Shen & Yang	1	1	1	0	0	1	1	0	1	1	1	8
Carayol et al.	1	1	1	1	0	1	0	1	1	1	0	8
Bekhet et al.	1	1	1	0	0	1	0	0	0	1	0	5
Liu et al.	1	1	1	0	0	1	0	0	1	1	1	7
Santos et al.	1	1	1	0	0	1	1	0	0	1	1	7
Dieli-Conwright & Orozco	1	0	0	0	0	1	0	0	0	0	1	3
Hong et al.	1	1	1	0	0	1	1	0	1	1	1	8
Zhu et al.	1	1	1	0	0	1	1	0	1	1	1	8
Yan et al.	1	0	1	1	0	1	1	1	1	1	1	9
Dijck et al.	1	1	1	0	0	1	0	0	0	1	1	6
Pastakia & Kumar	1	1	1	0	0	1	1	1	0	0	0	6
Zhang et al.	1	1	1	0	0	1	1	0	0	1	1	7

Bicego et al.	1	0	1	0	0	1	1	0	0	0	0	4
McNeely et al.	1	0	1	1	0	1	1	1	1	0	1	8
O'Neill et al.	1	1	1	0	0	1	1	0	1	1	1	8
El-Hashimi & Gorey	1	1	1	1	0	1	0	0	1	1	1	8
Harder et al.	1	1	1	0	0	1	1	0	0	1	1	7
J. Zhang et al.	1	1	1	0	0	1	1	1	1	1	1	9
Cramer et al.	1	1	1	0	0	1	1	1	1	1	1	9
Cramer et al.	1	1	1	1	1	1	1	1	1	1	1	11
Luo et al.	1	1	1	0	0	1	1	1	1	1	1	9
Liu et al.	1	1	1	0	0	1	1	0	1	1	1	8

4. Exercise effects in quality of life

Significant improvement in QoL was seen in BC patients during and after treatment. When analyzing the results of each systematic review and looking separately by the time of treatment, we can see that the only group that reported significant improvements in QoL, regardless of exercise, was in BC survivors (Bekhet et al., 2019; Dieli-Conwright & Orozco, 2015; Dos Santos et al., 2017; Hong et al., 2019; X. Liu et al., 2017; Yan et al., 2014; Zhu et al., 2016). In patients undergoing treatment, only one (Furmaniak et al., 2016) of the five included studies showed no significant results of the benefit of exercise on QoL. Likewise, when analyzing the results of reviews that included patients during and after treatment only one (Bicego et al., 2009) of the thirteen studies analyzed showed no significant differences in QoL in the exercise group. In the text below, a division has been made of the effect of each exercise type on QoL in BC patients and survivors.

4.1.Aerobic, Resistance, and Combined Exercise

Reviews addressing the aerobic, resistance, and combined exercise were the most common interventions, encompassing 10 of the 25 included studies (Bekhet et al., 2019; Dieli-Conwright & Orozco, 2015; Dos Santos et al., 2017; Furmaniak et al., 2016; Lee & Lee, 2020; X. Liu et al., 2017; Parker et al., 2009; Pastakia & Kumar, 2011; Van Dijck et al., 2016; X. Zhang et al., 2019). In general, aerobic protocols included activities such as walking, running, cycling, and using cycle ergometers, and resistance training mostly included resistance bands and machine-based activities. With only one study showing no significant effects, the results of our review found a beneficial effect of these interventions in BC patients during and after treatment.

4.2.Mixed Exercise Interventions

Mixed exercise interventions account with 6 of the 25 included reviews (Bicego et al., 2009; Carayol et al., 2015; Hong et al., 2019; McNeely et al., 2006; SHEN & YANG, 2020; Zhu et al., 2016). These interventions comprised activities like aerobic, resistance, combined exercise, dance, yoga, tai chi, qigong, or pilates. Of the 6 studies, only one did not show improvements in QoL in BC patients during and after treatment. These interventions have demonstrated a beneficial effect in QoL on BC patients and survivors.

4.3.Yoga

Yoga interventions counted with 6 of the 25 included reviews (Cramer et al., 2012, 2017; El-Hashimi & Gorey, 2019; Harder et al., 2012; O'Neill et al., 2020; J. Zhang et al., 2012). Yoga consists of an intervention that combines specific physical postures, breathing techniques, relaxation, and meditation (Chong et al., 2011). The results of the

included studies that used yoga reported significant improvements in QoL in BC patients and survivors.

4.4.Tai Chi

Interventions with Tai Chi were observed in 3 of the 25 included studies (L. Liu et al., 2020; Luo et al., 2020; Yan et al., 2014). This intervention revealed significant positive effects in QoL in BC patients during and after treatment.

Discussion

This umbrella review presents an overview assessment of the current evidence of the effects of exercise on QoL in BC patients during and after treatment. Exercise interventions have been implemented in BC patients and survivors, while using a plethora of exercise interventions, such as aerobic, resistance training, a combination of both stimulus, and mind and body exercises, such as stretching, dance, yoga, qigong, tai chi, and Pilate's interventions. Overall, the results indicate a positive effect of different exercise intervention on QoL in BC patients at any stage of their treatment.

It is well recognized that the diagnosis of BC is a stressful experience that can lead to negative feelings such as anxiety, anger, sadness, suffering, guilt, and fear of death (Bower et al., 2015; Brandão et al., 2016; Soo & Sherman, 2015). Alongside the adverse effects of treatment, the changes in body image perception, the sensation of pain caused by surgery, and the limitations in day-to-day functionality significantly impact on the QoL of women with BC (Falk Dahl et al., 2010; Fobair et al., 2006; Jassim et al., 2015; Loaring et al., 2015; Speck, Gross, et al., 2010; White, 2000). Therefore, finding

strategies that increase or mitigate the loss of QoL for these women is of undeniable importance.

This umbrella review, by reviewing previous systematic reviews/meta-analysis, reinforces the notion that several forms of exercise have a noticeable impact on BC patients' QoL. Indeed, there are some potential mechanisms that could explain this relationship. Although the side effects of anticancer therapies are more noticeable during the treatment phase, these consequences may persist for many years after the end of treatment (Fiorentino & Ancoli-Israel, 2007). One of the most common features of anticancer therapies is the impact on body composition since an increase in fat mass followed by a reduction of muscle mass and a substantial reduction in bone mineral density are frequently observed (Iwase et al., 2021) and may lead to some clinical manifestations such as fatigue, pain, and muscle weakness (Tarpey et al., 2019). Besides those direct effects on body composition, BC patients undergoing treatment tend to have lower levels of PA and more time spent in sedentary pursuits, which also elicits unfavorable long-term changes in the physical fitness component (Iwase et al., 2021). Altogether, these alterations are consistent with the development of a chronic inflammatory state and thus a more favorable environment for the development and progression of the tumor mass, as well as, increased resistance to therapy and the appearance of eventual metastases (Iwase et al., 2021).

Within this scope, aerobic exercise is an effective strategy to ameliorate body composition (Pérez-Martin et al., 2001) not only by counteracting the above-mentioned harmful effects induced by the treatment but also by promoting a better body image perception (Courneya et al., 2015). In addition, aerobic exercise also increases functional capacity, reduces fatigue, sleep disturbances, feelings of nausea, while improving mood (Kirshbaum, 2007) with valuable implications on QoL (Ohira et al., 2006). These positive

effects of aerobic exercise are in line with the results found in the included studies. Out of all 14 studies that include aerobic exercise as an exercise intervention, 12 reported that aerobic exercise can decrease the consequences caused by anticancer treatment, thus improving QoL in BC patients during and after treatment.

As already mentioned, increases in fat mass are often accompanied by decreases in muscle mass (Iwase et al., 2021) initiating the development of sarcopenia which heightens the likelihood of adverse events including falls, fractures, physical disability, and death (Cruz-Jentoft et al., 2019). Furthermore, the non-preservation of muscle mass also plays a predominant role in the increment of the treatment-related toxicity that is experienced by BC patients (Iwase et al., 2021). In a previous clinical investigation, it was found that BC patients with sarcopenia are 50% more likely to experience treatment toxicity when compared to those who do not lose muscle mass (20% of probability) (Prado et al., 2009). Resistance training has shown a significant effect in improving lean body mass and muscle strength in BC patients thus reversing sarcopenia with an enhancement in mobility and physical function that lead to an improved QoL (Courneya et al., 2015; Fragala et al., 2019). This type of exercise is also known to improve symptoms of lymphedema (Schmitz, 2010) which is one of the major side effects of cancer-treatment experienced by about 20% of all BC patients (DiSipio et al., 2013). Lymphedema is a chronic and progressive problem characterized by a regional swelling of the arm (in the case of BC) (Cheville et al., 2003; Nelson, 2016) that can lead to severe tension in the arm (tightness), pain (Gautam et al., 2011), restricted movements and reduced joint motion (de Godoy & Godoy, 2013), it also affects the ability to perform activities of daily living and has a negative impact on QoL (Kilbreath et al., 2012). The potential mechanisms of exercise in adapting the lymphatic system are very limitedly known (Schmitz, Ahmed, et al., 2010), however exercise is known to provide a basic

pump mechanism in venous drainage stimulated by skeletal muscle contraction (Witte & Witte, 1987). These beneficial effects of resistance exercise can be seen in the positive results of the included studies in this review where 10 of the 12 reviews that comprises resistance exercise as an intervention recognizes that resistance exercise has a positive impact on the QoL in this population.

Of the 25 included studies, 6 evaluated exclusively the effect of yoga in BC patients and survivors (Cramer et al., 2012, 2017; El-Hashimi & Gorey, 2019; Harder et al., 2012; O'Neill et al., 2020; J. Zhang et al., 2012). In our review, all the yoga studies demonstrated a beneficial effect on QoL. In recent years, yoga interventions have been widely investigated as a feasible strategy to prevent or treat medical conditions such as stress, insomnia, obesity, anxiety, diabetes, hypertension, oxidative stress, glucose tolerance, dyslipidemia, neurodegenerative disease, and coronary heart disease (Khalsa, 2004; Penman et al., 2012; Taneja, 2014). Moreover, yoga has also been used as a complementary therapy for BC-related impairments to help patients to cope with the disease (Fouladbakhsh & Stommel, 2010). Results from existing research suggest that yoga improves treatment-related changes in mental health, fatigue, sleep quality, and other aspects of QoL (Danhauer et al., 2017). Therefore, and considering the BC scenario, yoga can be an alternative to conventional exercise interventions and might be considered a more tolerable activity since it is a low-impact stimulus.

Out of all included studies, only 2 did not show significant differences in QoL. A study performed by Furmaniak et al. (2016) aiming to systematize the effects of aerobic, resistance, and combined exercise in BC patients during chemotherapy (CTx) and/or radiation therapy (RTx) suggested that there was little to no difference in QoL resulting from exercise regardless of the type. Likewise, the systematic review conducted by Bicego et al. (2009) reported no noticeable effects of exercise training in QoL in BC

patients during and after treatment. These lack of changes in QoL following exercise interventions may be a reflection of the included studies in these systematic reviews. For instance, the Bicego et al. (2009) review included women with metastatic BC (stage IV). The benefits of exercise may be less pronounced when applied to Stage IV BC patients, whose QoL is more adversely affected due to having more deleterious cancer side effects like bone pain, shortness of breath, drop-in appetite, unintentional weight loss, headaches, neurological pain, and/or weakness (Sharma et al., 2010).

Regarding the methodological quality assessment, 68% of the studies were classified as being moderate quality according to AMSTAR scores. Considering the analyzed studies, two items of the AMSTAR scale stood out. The first one was item #5 "Was a list of studies (included and excluded) provided?". This information was provided by only two Cochrane reviews. Then, item #4 "Was the status of publication (i.e., grey literature) used as an inclusion criterion?", only five authors indicated whether they excluded or not any reports (from the systematic review) based on their publication status (i.e. language, etc.). Furthermore, and according to the GRADE scale classification, the most prevalent factor that lowered the quality level was the publication bias, which can lead to systematic under or over-estimation of the underlying beneficial/harmful effects of exercise due to the selective publication of studies (Schünemann et al., 2013). The other critical point that downgrades the quality of evidence in the included studies was the inconsistency and unexplained heterogeneity of results (Schünemann et al., 2013). Indeed, this can lead to differences in the underlying treatment effect due to the widely differing estimates of the treatment effect (i.e., heterogeneity or variability in results) across studies (Schünemann et al., 2013).

Although the included studies in this systematic review show similar results, there are some methodological issues that make it difficult to generalize the findings. First,

there were only few high-quality review studies identified. Thus, future work is needed in this research field to clarify the actual effect of exercise in QoL and to present reliable recommendations for this population. Second, different questionnaires were used to assess QoL. This is a subjective measure based mostly on self-reported measures. Currently, there is a lack of commonly acknowledged gold-standard questionnaires, making it impossible for the authors to use the same one, which could lead to a bias in the results. The most common questionnaire used in about 85% of the included studies was FACT-B. This questionnaire not only presents items about physical, social/family, emotional, and functional well-being, but also BC-specific items addressing questions like body image, sexual functioning, arm symptoms, and cancer-treatment side effects. This is not a time-consuming questionnaire and can be performed in about 10-15 minutes. The more specified questions and the time used to complete the questionnaire may be the reasons by which it is one of the more commonly used questionnaires by investigators in the research setting. Lastly, there were several studies addressing the various types of intervention at different treatment periods. However, none specify which type of exercise was best for each anticancer treatment phase that could bring to a generalization of results. More studies specifying the type of intervention in the different phases of treatment are needed to understand which type of exercise is actually effective in improving the QoL of these patients and in which phase it will present the more noticeable benefits.

To the best of our knowledge, this is the first umbrella review to evaluate the effects of exercise on QoL in BC patients and survivors. A major strength of our review was the inclusion of only systematic reviews/meta-analysis of RCTs. RCTs are the best study design for controlling variables in order to observe a true treatment effect. We also included any BC stage or exercise intervention, allowing our review to encompass a wide range of studies and be more comprehensive. Moreover, beyond focusing on the

conventional forms of exercise (aerobic, resistance, or combined exercise), this review also assessed the effect of mind and body exercise, which is an important type of exercise commonly used and implemented in BC patients. Despite its strengths, this umbrella review had some limitations that are important to highlight. First, only English studies were included, thus, limiting the inclusion of other potential articles. Also, to analyze exclusively the exercise effect in this population, interventions that did not comprise only exercise (e.g., exercise plus diet) were excluded. Therefore, we could be missing valuable data and information by not including these interventions. Finally, this review only includes the findings presented in previous systematic reviews/meta-analysis, so the exclusion of negative results is a possibility.

Based on our findings, it is possible to make some recommendations for future research. First, it is necessary to reach a consensus on the best questionnaire to access QoL in this population so that future studies can use a gold standard questionnaire, which is the best and most up to date, in order to avoid such diversity as exists today and, by using the same questionnaire in different studies, to be able to draw more precise conclusions and recommendations on this subject. Second, more studies are needed to access the effect of each type of exercise in the different BC stages, since each stage has different adverse effects on QoL of these patients and thus making more specific recommendations. Third, is also needed more studies approaching the effect of different types of exercise interventions at different stages of treatment to be able to link the beneficial effects of exercise to anti-cancer treatment and see if exercise has a positive effect at any stage of treatment and at what stage it will or will not be most beneficial. Lastly, there needs to be a greater number of high-quality studies performed.

Conclusion

Based on the results of the included studies, we conclude that aerobic, resistance combined, and mind and body exercise have a beneficial effect on QoL in BC patients and survivors. It is also possible to verify a positive effect of exercise in BC patients during treatment, but due to the small number of reviews on the effects of exercise in each treatment phase, it is not possible to draw specific conclusions. Additionally, all reviews that addressed only BC survivors found a significant improvement in their QoL, and thus it can be concluded that exercise is beneficial on BC survivors. Future research is required with a focus on high-quality trials addressing the optimal dose of the different exercise interventions in different stages of disease and treatment for more specific recommendations to be made and implemented.

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Reference list

Bajaj, J., Diaz, E., & Reya, T. (2020). Stem cells in cancer initiation and progression. *Journal of Cell Biology*, *219*(1), 1–12. https://doi.org/10.1083/jcb.201911053

Balmaña, J., Díez, O., Rubio, I. T., & Cardoso, F. (2011). BRCA in breast cancer: ESMO clinical practice guidelines. *Annals of Oncology*, *22*(SUPPL. 6), 31–34. https://doi.org/10.1093/annonc/mdr373

Battaglini, C. L., Mills, R. C., Phillips, B. L., Lee, J. T., Story, C. E., Nascimento, M. G. B., & Hackney, A. C. (2014). Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature. *World Journal of Clinical Oncology*, *5*(2), 177–190. https://doi.org/10.5306/wjco.v5.i2.177

Beckjord, E. B., Reynolds, K. A., Van Londen, G. J., Burns, R., Singh, R., Arvey, S. R., Nutt, S. A., & Rechis, R. (2014). Population-level trends in posttreatment cancer survivors concerns and associated receipt of care: Results from the 2006 and 2010 LIVESTRONG Surveys. *Journal of Psychosocial Oncology*, *32*(2), 125–151. https://doi.org/10.1080/07347332.2013.874004

Bekhet, A. H., Abdalla, A. R., Ismail, H. M., Genena, D. M., Osman, N. A., El Khatib, A., & Abbas, R. L. (2019). Benefits of aerobic exercise for breast cancer survivors: A systematic review of randomized controlled trials. *Asian Pacific Journal of Cancer Prevention*, *20*(11), 3197–3209. https://doi.org/10.31557/APJCP.2019.20.11.3197

Bicego, D., Brown, K., Ruddick, M., Storey, D., Wong, C., & Harris, S. R. (2009). Effects of exercise on quality of life in women living with breast cancer: a

systematic review. *The Breast Journal*, *15*(1), 45–51. https://doi.org/10.1111/j.1524-4741.2008.00670.x

Blane, D., Netuveli, G., & Montgomery, S. M. (2008). Quality of life, health and physiological status and change at older ages. *Social Science and Medicine*, *66*(7), 1579–1587. https://doi.org/10.1016/j.socscimed.2007.12.021

Bower, J. E., Crosswell, A. D., Stanton, A. L., Crespi, C. M., Winston, D., Arevalo, J., Ma, J., Cole, S. W., & Ganz, P. A. (2015). Mindfulness meditation for younger breast cancer survivors: a randomized controlled trial. *Cancer*, *121*(8), 1231–1240. https://doi.org/10.1002/cncr.29194

Brandão, T., Tavares, R., Schulz, M. S., & Matos, P. M. (2016). Measuring emotion regulation and emotional expression in breast cancer patients: A systematic review. *Clinical Psychology Review*, *43*, 114–127. https://doi.org/10.1016/j.cpr.2015.10.002

Britt, K. L., Cuzick, J., & Phillips, K. A. (2020). Key steps for effective breast cancer prevention. *Nature Reviews Cancer*, *20*(8), 417–436. https://doi.org/10.1038/s41568-020-0266-x

Buss, L. A., & Dachs, G. U. (2020). Effects of Exercise on the Tumour Microenvironment. *Advances in Experimental Medicine and Biology*, *1225*, 31–51. https://doi.org/10.1007/978-3-030-35727-6_3

Canário, A. C. G., Cabral, P. U. L., De Paiva, L. C., Florencio, G. L. D., Spyrides, M. H., & Da Silveira Gonçalves, A. K. (2016). Physical activity, fatigue and quality of life in breast cancer patients. *Revista Da Associacao Medica Brasileira*, *62*(1), 38–44. https://doi.org/10.1590/1806-9282.62.01.38

Carayol, M., Delpierre, C., Bernard, P., & Ninot, G. (2015). Population-, intervention- and methodology-related characteristics of clinical trials impact exercise efficacy during adjuvant therapy for breast cancer: A meta-regression analysis. *Psycho-Oncology*, *24*(7), 737–747. https://doi.org/10.1002/pon.3727

Cardoso, F., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rubio, I. T., Zackrisson, S., & Senkus, E. (2019). Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *30*(8), 1194–1220. https://doi.org/10.1093/annonc/mdz173

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports (Washington, D.C. : 1974)*, *100*(2), 126–131.

Cheville, A. L., McGarvey, C. L., Petrek, J. A., Russo, S. A., Thiadens, S. R. J., & Taylor, M. E. (2003). The grading of lymphedema in oncology clinical trials. *Seminars in Radiation Oncology*, *13*(3), 214–225. https://doi.org/10.1016/S1053-4296(03)00038-9

Chong, C. S. M., Tsunaka, M., Tsang, H. W. H., Chan, E. P., & Cheung, W. M. (2011). Effects of yoga on stress management in healthy adults: A systematic review. *Alternative Therapies in Health and Medicine*, *17*(1), 32—38. http://europepmc.org/abstract/MED/21614942

Coughlin, S. S., Caplan, L. S., & Williams, V. (2019). Home-based physical activity interventions for breast cancer patients receiving primary therapy: a systematic review. *Breast Cancer Research and Treatment*, *178*(3), 513–522. https://doi.org/10.1007/s10549-019-05424-4

Courneya, K. S., Crawford, J. J., & Adams, S. C. (2015). Physical Activity and Exercise

Interventions in Cancer Survivors. *Psycho-Oncology*, *February 2015*, 515–520. https://doi.org/10.1093/med/9780199363315.003.0067

Cramer, H., Lange, S., Klose, P., Paul, A., & Dobos, G. (2012). Yoga for breast cancer patients and survivors: A systematic review and meta-analysis. *BMC Cancer*, *12*. https://doi.org/10.1186/1471-2407-12-412

Cramer, H., Lauche, R., Klose, P., Lange, S., Langhorst, J., & Dobos, G. J. (2017). Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. *Cochrane Database of Systematic Reviews*, *2017*(1). https://doi.org/10.1002/14651858.CD010802.pub2

Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., Cooper, C., Landi, F., Rolland, Y., Sayer, A. A., Schneider, S. M., Sieber, C. C., Topinkova, E., Vandewoude, M., Visser, M., & Zamboni, M. (2019). Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing*, *48*(1), 16–31. https://doi.org/10.1093/ageing/afy169

Danhauer, S. C., Addington, E. L., Sohl, S. J., Chaoul, A., & Cohen, L. (2017). Review of yoga therapy during cancer treatment. *Supportive Care in Cancer*, *25*(4), 1357–1372. https://doi.org/10.1007/s00520-016-3556-9

de Godoy, J. M. P., & Godoy, M. de F. G. (2013). Evaluation of a new approach to the treatment of lymphedema resulting from breast cancer therapy. *European Journal of Internal Medicine*, *24*(1), 59–62. https://doi.org/10.1016/j.ejim.2012.08.008

Dieli-Conwright, C. M., Courneya, K. S., Demark-Wahnefried, W., Sami, N., Lee, K., Sweeney, F. C., Stewart, C., Buchanan, T. A., Spicer, D., Tripathy, D., Bernstein, L., & Mortimer, J. E. (2018). Aerobic and resistance exercise improves physical fitness, bone health, and quality of life in overweight and obese breast cancer

survivors: A randomized controlled trial 11 Medical and Health Sciences 1117 Public Health and Health Services. *Breast Cancer Research*, *20*(1), 1–10. https://doi.org/10.1186/s13058-018-1051-6

Dieli-Conwright, C. M., & Orozco, B. Z. (2015). Exercise after breast cancer treatment: Current perspectives. *Breast Cancer: Targets and Therapy*, *7*, 353–362. https://doi.org/10.2147/BCTT.S82039

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. https://doi.org/10.1016/S1470-2045(13)70076-7

Dittus, K. L., Gramling, R. E., & Ades, P. A. (2017). Exercise interventions for individuals with advanced cancer: A systematic review. *Preventive Medicine*, *104*, 124–132. https://doi.org/10.1016/j.ypmed.2017.07.015

Dos Santos, W. D. N., Gentil, P., de Moraes, R. F., Ferreira Júnior, J. B., Campos, M. H., de Lira, C. A. B., Freitas Júnior, R., Bottaro, M., & Vieira, C. A. (2017). Chronic Effects of Resistance Training in Breast Cancer Survivors. *BioMed Research International*, *2017*, 8367803. https://doi.org/10.1155/2017/8367803

Dunne, M., & Keenan, K. (2016). CE: Late and long-term sequelae of breast cancer treatment. *American Journal of Nursing*, *116*(6), 36–45. https://doi.org/10.1097/01.NAJ.0000484223.07306.45

El-Hashimi, D., & Gorey, K. M. (2019). Yoga-Specific Enhancement of Quality of Life Among Women With Breast Cancer: Systematic Review and Exploratory Meta-Analysis of Randomized Controlled Trials. *Journal of Evidence-Based Integrative Medicine*, *24*, 1–9. https://doi.org/10.1177/2515690X19828325

Eyigor, S., & Akdeniz, S. (2014). Is exercise ignored in palliative cancer patients? *World Journal of Clinical Oncology*, *5*(3), 554–559. https://doi.org/10.5306/wjco.v5.i3.554

Eyigor, S., & Kanyilmaz, S. (2014). Exercise in patients coping with breast cancer: An overview. *World Journal of Clinical Oncology*, *5*(3), 406–411. https://doi.org/10.5306/wjco.v5.i3.406

Falk Dahl, C. A., Reinertsen, K. V, Nesvold, I.-L., Fosså, S. D., & Dahl, A. A. (2010). A study of body image in long-term breast cancer survivors. *Cancer*, *116*(15), 3549–3557. https://doi.org/10.1002/cncr.25251

Felce, D., & Perry, J. (1995). Quality of life: Its definition and measurement. *Research in Developmental Disabilities*, *16*(1), 51–74. https://doi.org/10.1016/0891-4222(94)00028-8

Fiorentino, L., & Ancoli-Israel, S. (2007). Sleep dysfunction in patients with cancer. *Current Treatment Options in Neurology*, *9*(5), 337–346. https://doi.org/10.1007/s11940-007-0019-0

Fobair, P., Stewart, S. L., Chang, S., D'Onofrio, C., Banks, P. J., & Bloom, J. R. (2006). Body image and sexual problems in young women with breast cancer. *Psycho-Oncology*, *15*(7), 579–594. https://doi.org/10.1002/pon.991

Fouladbakhsh, J. M., & Stommel, M. (2010, January). Gender, symptom experience, and use of complementary and alternative medicine practices among cancer survivors in the US cancer population. In *Oncology Nursing Forum* (Vol. 37, No. 1). https://doi.org/10.1188/10.ONF.E7-E15

Fragala, M. S., Cadore, E. L., Dorgo, S., Izquierdo, M., Kraemer, W. J., Peterson, M.

D., & Ryan, E. D. (2019). Resistance training for older adults: position statement from the national strength and conditioning association. *The Journal of Strength & Conditioning Research*, *33*(8). https://doi.org/10.1519/JSC.0000000000003230

Friedenreich, C. M., Shaw, E., Neilson, H. K., & Brenner, D. R. (2017). Epidemiology and biology of physical activity and cancer recurrence. *Journal of Molecular Medicine*, *95*(10), 1029–1041. https://doi.org/10.1007/s00109-017-1558-9

Fuller, J. T., Hartland, M. C., Maloney, L. T., & Davison, K. (2018). Therapeutic effects of aerobic and resistance exercises for cancer survivors: a systematic review of meta-analyses of clinical trials. *British journal of sports medicine*, *52*(20), 1311-1311. https://doi.org/10.1136/bjsports-2017-098285

Furmaniak, A. C., Menig, M., & Markes, M. H. (2016). Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database of Systematic Reviews*, *2016*(9). https://doi.org/10.1002/14651858.CD005001.pub3

García-Soidán, J. L., Pérez-Ribao, I., Leirós-Rodríguez, R., & Soto-Rodríguez, A. (2020). Long-term influence of the practice of physical activity on the self-perceived quality of life of women with breast cancer: A randomized controlled trial. *International Journal of Environmental Research and Public Health*, *17*(14), 1–12. https://doi.org/10.3390/ijerph17144986

Gautam, A. P., Maiya, A. G., & Vidyasagar, M. S. (2011). Effect of home-based exercise program on lymphedema and quality of life in female postmastectomy patients: pre-post intervention study. *Journal of Rehabilitation Research and Development*, *48*(10), 1261–1268. https://doi.org/10.1682/jrrd.2010.05.0089

Gebruers, N., Camberlin, M., Theunissen, F., Tjalma, W., Verbelen, H., Van Soom, T., & van Breda, E. (2019). The effect of training interventions on physical

performance, quality of life, and fatigue in patients receiving breast cancer treatment: a systematic review. *Supportive Care in Cancer*, *27*(1), 109–122. https://doi.org/10.1007/s00520-018-4490-9

Gillison, F. B., Skevington, S. M., Sato, A., Standage, M., & Evangelidou, S. (2009). The effects of exercise interventions on quality of life in clinical and healthy populations; a meta-analysis. *Social Science and Medicine*, *68*(9), 1700–1710. https://doi.org/10.1016/j.socscimed.2009.02.028

Glass, O. K., Bowie, M., Fuller, J., Darr, D., Usary, J., Boss, K., Choudhury, K. R., Liu, X., Zhang, Z., Locasale, J. W., Williams, C., Dewhirst, M. W., Jones, L. W., & Seewaldt, V. (2017). Differential response to exercise in claudin-low breast cancer. *Oncotarget*, *8*(60), 100989–101004. https://doi.org/10.18632/oncotarget.21054

World Health Organization. (2014). *Global status report on noncommunicable diseases 2014* (No. WHO/NMH/NVI/15.1). World Health Organization.

Harder, H., Parlour, L., & Jenkins, V. (2012). Randomised controlled trials of yoga interventions for women with breast cancer: A systematic literature review. *Supportive Care in Cancer*, *20*(12), 3055–3064. https://doi.org/10.1007/s00520-012-1611-8

Hart, V., Trentham-Dietz, A., Berkman, A., Fujii, M., Veal, C., Hampton, J., ... & Sprague, B. L. (2018). The association between post-diagnosis health behaviors and long-term quality of life in survivors of ductal carcinoma in situ: a population-based longitudinal cohort study. *Quality of Life Research*, *27*(5), 1237-1247. https://doi.org/10.1007/s11136-018-1807-6

Hawley, J. A., Hargreaves, M., Joyner, M. J., & Zierath, J. R. (2014). Integrative biology of exercise. *Cell*, *159*(4), 738–749.

https://doi.org/10.1016/j.cell.2014.10.029

Hojman, P., Gehl, J., Christensen, J. F., & Pedersen, B. K. (2018). Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. *Cell Metabolism*, *27*(1), 10–21. https://doi.org/10.1016/j.cmet.2017.09.015

Hong, F., Ye, W., Kuo, C. H., Zhang, Y., Qian, Y., & Korivi, M. (2019). Exercise intervention improves clinical outcomes, but the "time of session" is crucial for better quality of life in breast cancer survivors: A systematic review and meta-analysis. *Cancers*, *11*(5), 1–19. https://doi.org/10.3390/cancers11050706

Howley, E. T. (2001). Type of activity: Resistance, aerobic and leisure versus occupational physical activity. *Medicine and Science in Sports and Exercise*, *33*(6 SUPPL.). https://doi.org/10.1097/00005768-200106001-00005

Iwase, T., Wang, X., Shrimanker, T. V., Kolonin, M. G., & Ueno, N. T. (2021). Body composition and breast cancer risk and treatment: mechanisms and impact. *Breast Cancer Research and Treatment*, *186*(2), 273–283. https://doi.org/10.1007/s10549-020-06092-5

Jassim, G. A., Whitford, D. L., Hickey, A., & Carter, B. (2015). Psychological interventions for women with non-metastatic breast cancer. *The Cochrane Database of Systematic Reviews*, *5*, CD008729. https://doi.org/10.1002/14651858.CD008729.pub2

Jiang, M., Ma, Y., Yun, B., Wang, Q., Huang, C., & Han, L. (2020). Exercise for fatigue in breast cancer patients: An umbrella review of systematic reviews. *International Journal of Nursing Sciences*, *7*(2), 248–254. https://doi.org/10.1016/j.ijnss.2020.03.001

Johnsson, A., Demmelmaier, I., Sjövall, K., Wagner, P., Olsson, H., & Tornberg, Å. B. (2019). A single exercise session improves side-effects of chemotherapy in women with breast cancer: an observational study. *BMC Cancer*, *19*(1), 1–9. https://doi.org/10.1186/s12885-019-6310-0

Jones, L. W., & Alfano, C. M. (2013). Exercise-oncology research: Past, present, and future. *Acta Oncologica*, *52*(2), 195–215. https://doi.org/10.3109/0284186X.2012.742564

Kekäläinen, T., Kokko, K., Sipilä, S., & Walker, S. (2018). Effects of a 9-month resistance training intervention on quality of life, sense of coherence, and depressive symptoms in older adults: randomized controlled trial. *Quality of Life Research*, *27*(2), 455–465. https://doi.org/10.1007/s11136-017-1733-z

Khalsa, S. B. S. (2004). Yoga as a therapeutic intervention: a bibliometric analysis of published research studies. *Indian Journal of Physiology and Pharmacology*, *48*(3), 269–285.

Kilbreath, S. L., Refshauge, K. M., Beith, J. M., Ward, L. C., Lee, M., Simpson, J. M., & Hansen, R. (2012). Upper limb progressive resistance training and stretching exercises following surgery for early breast cancer: a randomized controlled trial. *Breast Cancer Research and Treatment*, *133*(2), 667–676. https://doi.org/10.1007/s10549-012-1964-1

Kimberlin, C. L., & Winterstein, A. G. (2008). Validity and reliability of measurement instruments used in research. *American Journal of Health-System Pharmacy*, *65*(23), 2276–2284. https://doi.org/10.2146/ajhp070364

Kirshbaum, M. N. (2007). A review of the benefits of whole body exercise during and after treatment for breast cancer. *Journal of Clinical Nursing*, *16*(1), 104–121.

https://doi.org/10.1111/j.1365-2702.2006.01638.x

Kokkonen, K., Saarto, T., Mäkinen, T., Pohjola, L., Kautio, H., Järvenpää, S., & Puustjärvi-Sunabacka, K. (2017). The functional capacity and quality of life of women with advanced breast cancer. *Breast Cancer*, *24*(1), 128–136. https://doi.org/10.1007/s12282-016-0687-2

Kolios, G., & Moodley, Y. (2012). Introduction to stem cells and regenerative medicine. *Respiration*, *85*(1), 3–10. https://doi.org/10.1159/000345615

Kwok, J. J. Y. Y., Choi, K. C., & Chan, H. Y. L. (2016). Effects of mind–body exercises on the physiological and psychosocial well-being of individuals with Parkinson's disease: A systematic review and meta-analysis. *Complementary Therapies in Medicine*, *29*, 121–131. https://doi.org/10.1016/j.ctim.2016.09.016

Landry, S., Chasles, G., Pointreau, Y., Bourgeois, H., & Boyas, S. (2018). Influence of an Adapted Physical Activity Program on Self-Esteem and Quality of Life of Breast Cancer Patients after Mastectomy. *Oncology (Switzerland)*, *95*(3), 188–191. https://doi.org/10.1159/000489265

Lee, J., & Lee, M. G. (2020). Effects of exercise interventions on breast cancer patients during adjuvant therapy: A systematic review and meta-analysis of randomized controlled trials. *Cancer Nursing*, *43*(2), 115–125. https://doi.org/10.1097/NCC.0000000000000682

Levett-Jones, T., & Jones, M. (2020). Physical activity for women diagnosed with breast cancer after adjuvant therapy: A Cochrane review summary. *International Journal of Nursing Studies*, *103*(1). https://doi.org/10.1016/j.ijnurstu.2018.12.002

Li, T., Wei, S., Shi, Y., Pang, S., Qin, Q., Yin, J., Deng, Y., Chen, Q., Wei, S., Nie, S.,

& Liu, L. (2016). The dose-response effect of physical activity on cancer mortality: Findings from 71 prospective cohort studies. *British Journal of Sports Medicine*, *50*(6), 339–345. https://doi.org/10.1136/bjsports-2015-094927

Lipsett, A., Barrett, S., Haruna, F., Mustian, K., & O'Donovan, A. (2017). The impact of exercise during adjuvant radiotherapy for breast cancer on fatigue and quality of life: A systematic review and meta-analysis. *Breast*, *32*, 144–155. https://doi.org/10.1016/j.breast.2017.02.002

Liu, L., Tan, H., Yu, S., Yin, H., & Baxter, G. D. (2020). The effectiveness of tai chi in breast cancer patients: A systematic review and meta-analysis. *Complementary Therapies in Clinical Practice*, *38*, 101078. https://doi.org/10.1016/j.ctcp.2019.101078

Liu, X., Li, H., Guo, C., & Cui, S. (2017). Effects of home-based physical activitieson the health outcomes in early-stage breast cancer survivors: A meta-analysis. *International Journal of Clinical and Experimental Medicine*, *10*(11), 15129–15139.

Loaring, J. M., Larkin, M., Shaw, R., & Flowers, P. (2015). Renegotiating sexual intimacy in the context of altered embodiment: the experiences of women with breast cancer and their male partners following mastectomy and reconstruction. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *34*(4), 426–436. https://doi.org/10.1037/hea0000195

Lu, G., Zheng, J., & Zhang, L. (2020). The effect of exercise on aromatase inhibitor-induced musculoskeletal symptoms in breast cancer survivors: a systematic review and meta-analysis. *Supportive Care in Cancer*, *28*(4), 1587-1596.

https://doi.org/10.1007/s00520-019-05186-1

Lu, M., Sanderson, S. M., Zessin, A., Ashcraft, K. A., Jones, L. W., Dewhirst, M. W., Locasale, J. W., & Hsu, D. S. (2018). Exercise inhibits tumor growth and central carbon metabolism in patient-derived xenograft models of colorectal cancer. *Cancer & Metabolism*, *6*(1), 1–11. https://doi.org/10.1186/s40170-018-0190-7

Lubans, D., Richards, J., Hillman, C., Faulkner, G., Beauchamp, M., Nilsson, M., Kelly, P., Smith, J., Raine, L., & Biddle, S. (2016). Physical activity for cognitive and mental health in youth: A systematic review of mechanisms. *Pediatrics*, *138*(3). https://doi.org/10.1542/peds.2016-1642

Luo, X. C., Liu, J., Fu, J., Yin, H. Y., Shen, L., Liu, M. L., Lan, L., Ying, J., Qiao, X. L., Tang, C. Z., & Tang, Y. (2020). Effect of Tai Chi Chuan in breast cancer patients: A systematic review and meta-analysis. *Frontiers in Oncology*, *10*(April). https://doi.org/10.3389/fonc.2020.00607

Lynch, B. M., Neilson, H. K., & Friedenreich, C. M. (2010). Physical activity and breast cancer prevention. *Physical activity and cancer*, 13-42. https://doi.org/10.1007/978-3-642-04231-7_2

McAuley, E., Doerksen, S. E., Morris, K. S., Motl, R. W., Hu, L., Wójcicki, T. R., White, S. M., & Rosengren, K. R. (2008). Pathways from physical activity to quality of life in older women. *Annals of Behavioral Medicine*, *36*(1), 13–20. https://doi.org/10.1007/s12160-008-9036-9

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. https://doi.org/10.1503/cmaj.051073

Mctiernan, A., Friedenreich, C. M., Katzmarzyk, P. T., Powell, K. E., Macko, R., Buchner, D., Pescatello, L. S., Bloodgood, B., Tennant, B., Vaux-bjerke, A., George, S. M., & Troiano, R. P. (2018). *Physical Activity in Cancer Prevention and Survival: A Systematic Review*. 1252–1261. https://doi.org/10.1249/MSS.0000000000001937

Medicine, A. C. of S. (2017). *ACSM's exercise testing and prescription*. Lippincott williams & wilkins.

Mitchell, T., & Barlow, C. E. (2011). Review of the role of exercise in improving quality of life in healthy individuals and in those with chronic diseases. *Current Sports Medicine Reports*, *10*(4), 211–216. https://doi.org/10.1249/JSR.0b013e318223cc9e

Moore, S. C., Lee, I. M., Weiderpass, E., Campbell, P. T., Sampson, J. N., Kitahara, C. M., Keadle, S. K., Arem, H., De Gonzalez, A. B., Hartge, P., Adami, H. O., Blair, C. K., Borch, K. B., Boyd, E., Check, D. P., Fournier, A., Freedman, N. D., Gunter, M., Johannson, M., … Patel, A. V. (2016). Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. *JAMA Internal Medicine*, *176*(6), 816–825. https://doi.org/10.1001/jamainternmed.2016.1548

Nelson, N. L. (2016). Breast cancer-related lymphedema and resistance exercise: A systematic review. *Journal of Strength and Conditioning Research*, *30*(9), 2656–2665. https://doi.org/10.1519/JSC.0000000000001355

Nguyen, J., Popovic, M., Chow, E., Cella, D., Beaumont, J. L., Chu, D., Digiovanni, J., Lam, H., Pulenzas, N., & Bottomley, A. (2015). EORTC QLQ-BR23 and FACT-B for the assessment of quality of life in patients with breast cancer: A literature

review. *Journal of Comparative Effectiveness Research*, *4*(2), 157–166. https://doi.org/10.2217/cer.14.76

Niklasson, A., Paty, J., & Rydén, A. (2017). Talking about breast cancer: which symptoms and treatment side effects are important to patients with advanced disease?. *The Patient-Patient-Centered Outcomes Research, 10*(6), 719-727. https://doi.org/10.1007/s40271-017-0242-z

Norris, S. L., Meerpohl, J. J., Akl, E. A., Schünemann, H. J., Gartlehner, G., Chen, Y., & Whittington, C. (2016). The skills and experience of GRADE methodologists can be assessed with a simple tool. *Journal of Clinical Epidemiology*, *79*, 150-158.e1. https://doi.org/10.1016/j.jclinepi.2016.07.001

Nurnazahiah, A., Shahril, M. R., Syamimi, Z. N., Ahmad, A., Sulaiman, S., & Lua, P. L. (2020). Relationship of objectively measured physical activity and sedentary behaviour with health-related quality of life among breast cancer survivors. *Health and quality of life outcomes*, *18*(1), 1-10. https://doi.org/10.1186/s12955-020-01513-x

O'Neill, M., Samaroo, D., Lopez, C., Tomlinson, G., Santa Mina, D., Sabiston, C., Culos-Reed, N., & Alibhai, S. M. H. (2020). The Effect of Yoga Interventions on Cancer-Related Fatigue and Quality of Life for Women with Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Integrative Cancer Therapies*, *19*. https://doi.org/10.1177/1534735420959882

Odynets, T., Briskin, Y., & Todorova, V. (2019). Effects of Different Exercise Interventions on Quality of Life in Breast Cancer Patients: A Randomized Controlled Trial. *Integrative Cancer Therapies*, *18*. https://doi.org/10.1177/1534735419880598

Ohira, T., Schmitz, K. H., Ahmed, R. L., & Yee, D. (2006). Effects of weight training on quality of life in recent breast cancer survivors: the Weight Training for Breast Cancer Survivors (WTBS) study. *Cancer*, *106*(9), 2076–2083. https://doi.org/10.1002/cncr.21829

Paluch-Shimon, S., Cardoso, F., Sessa, C., Balmana, J., Cardoso, M. J., Gilbert, F., Senkus, E., & on behalf of the ESMO Guidelines Committee. (2016). Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO clinical practice guidelines for cancer prevention and screening. *Annals of Oncology*, *27*(Supplement 5), v103–v110. https://doi.org/10.1093/annonc/mdw327

Parker, J. S., Mullins, M., Cheang, M. C. U., Leung, S., Voduc, D., Vickery, T., Davies, S., Fauron, C., He, X., Hu, Z., Quackenbush, J. F., Stijleman, I. J., Perou, C. M., & Bernard, P. S. (2009). *Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes*. *27*(8). https://doi.org/10.1200/JCO.2008.18.1370

Pastakia, K., & Kumar, S. (2011). Exercise parameters in the management of breast cancer: A systematic review of randomized controlled trials. *Physiotherapy Research International*, *16*(4), 237–244. https://doi.org/10.1002/pri.505

Patel, N. K., Newstead, A. H., & Ferrer, R. L. (2012). The effects of yoga on physical functioning and health related quality of life in older adults: A systematic review and meta-analysis. *Journal of Alternative and Complementary Medicine*, *18*(10), 902–917. https://doi.org/10.1089/acm.2011.0473

Paulo, T. R. S., Rossi, F. E., Viezel, J., Tosello, G. T., Seidinger, S. C., Simões, R. R., De Freitas, R., & Freitas, I. F. (2019). The impact of an exercise program on quality of life in older breast cancer survivors undergoing aromatase inhibitor

therapy: A randomized controlled trial. *Health and Quality of Life Outcomes*, *17*(1), 1–12. https://doi.org/10.1186/s12955-019-1090-4

Penman, S., Cohen, M., Stevens, P., & Jackson, S. (2012). Yoga in Australia: Results of a national survey. *International Journal of Yoga*, *5*(2), 92–101. https://doi.org/10.4103/0973-6131.98217

Pérez-Martin, A., Raynaud, E., & Mercier, J. (2001). Insulin resistance and associated metabolic abnormalities in muscle: effects of exercise. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity*, *2*(1), 47–59. https://doi.org/10.1046/j.1467-789x.2001.00024.x

Prado, C. M. M., Baracos, V. E., McCargar, L. J., Reiman, T., Mourtzakis, M., Tonkin, K., Mackey, J. R., Koski, S., Pituskin, E., & Sawyer, M. B. (2009). Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, *15*(8), 2920–2926. https://doi.org/10.1158/1078-0432.CCR-08-2242

Riebe, D., Ehrman, J. K., Liguori, G., & Magal, M. (2018). *ACSM's Guidelines for Exercise Testing and Prescription. 10th ed. Philidelphia, PA: Wolters Kluwer*, 226-267.

Rosen, R. D., & Sapra, A. (2020). TNM classification. *StatPearls [Internet]*.

Samuel, S. R., Gandhi, A. R., Vijaya Kumar, K., & Prakash Saxena, P. U. (2020). Pedometer-based exercise interventions for patients with breast cancer receiving chemotherapy - A systematic review. *Indian Journal of Palliative Care*, *26*(1), 105–109. https://doi.org/10.4103/IJPC.IJPC_175_19

Schmidt, M. E., Wiskemann, J., Armbrust, P., Schneeweiss, A., Ulrich, C. M., & Steindorf, K. (2015). Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: A randomized controlled trial. *International Journal of Cancer*, *137*(2), 471–480. https://doi.org/10.1002/ijc.29383

Schmitz, K. H. (2010). Balancing lymphedema risk: exercise versus deconditioning for breast cancer survivors. *Exercise and Sport Sciences Reviews*, *38*(1), 17–24. https://doi.org/10.1097/JES.0b013e3181c5cd5a

Schmitz, K. H., Ahmed, R. L., Troxel, A. B., Cheville, A., Lewis-Grant, L., Smith, R., Bryan, C. J., Williams-Smith, C. T., & Chittams, J. (2010). Weight lifting for women at risk for breast cancer-related lymphedema: a randomized trial. *JAMA*, *304*(24), 2699–2705. https://doi.org/10.1001/jama.2010.1837

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvão, D. A., Pinto, B. M., Irwin, M. L., Wolin, K. Y., Segal, R. J., Lucia, A., Schneider, C. M., Von Gruenigen, V. E., & Schwartz, A. L. (2010). American college of sports medicine roundtable on exercise guidelines for cancer survivors. *Medicine and Science in Sports and Exercise*, *42*(7), 1409–1426. https://doi.org/10.1249/MSS.0b013e3181e0c112

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. *Updated October*, *2013*.

Shah, R., Rosso, K., & David Nathanson, S. (2014). Pathogenesis, prevention, diagnosis and treatment of breast cancer. *World Journal of Clinical Oncology*, *5*(3), 283–298. https://doi.org/10.5306/wjco.v5.i3.283

Sharma, G. N., Dave, R., Sanadya, J., Sharma, P., & Sharma, K. K. (2010). Various types and management of breast cancer: an overview. *Journal of Advanced Pharmaceutical Technology & Research*, *1*(2), 109–126.

Shea, B. J., Hamel, C., Wells, G. A., Bouter, L. M., Kristjansson, E., Grimshaw, J., Henry, D. A., & Boers, M. (2009). AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *Journal of Clinical Epidemiology*, *62*(10), 1013–1020. https://doi.org/10.1016/j.jclinepi.2008.10.009

SHEN, Q., & YANG, H. (2020). The impact of post-radiotherapy exercise on women with breast cancer: A meta-analysis of randomized controlled trials. *Journal of Rehabilitation Medicine*, *52*(10). https://doi.org/10.2340/16501977-2740

Sivaramakrishnan, D., Fitzsimons, C., Kelly, P., Ludwig, K., Mutrie, N., Saunders, D. H., & Baker, G. (2019). The effects of yoga compared to active and inactive controls on physical function and health related quality of life in older adults-systematic review and meta-analysis of randomised controlled trials. *International Journal of Behavioral Nutrition and Physical Activity*, *16*(1), 1–22. https://doi.org/10.1186/s12966-019-0789-2

Soni, M. K., & Cella, D. (2002). Quality of life and symptom measures in oncology: an overview. *The American journal of managed care*, *8*(18 Suppl), S560-73.

Soo, H., & Sherman, K. A. (2015). Rumination, psychological distress and post-traumatic growth in women diagnosed with breast cancer. *Psycho-Oncology*, *24*(1), 70–79. https://doi.org/10.1002/pon.3596

Speck, R. M., Courneya, K. S., Mâsse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *Journal of Cancer Survivorship*, *4*(2), 87–100.

https://doi.org/10.1007/s11764-009-0110-5

Speck, R. M., Gross, C. R., Hormes, J. M., Ahmed, R. L., Lytle, L. A., Hwang, W.-T., & Schmitz, K. H. (2010). Changes in the Body Image and Relationship Scale following a one-year strength training trial for breast cancer survivors with or at risk for lymphedema. *Breast Cancer Research and Treatment, 121*(2), 421–430. https://doi.org/10.1007/s10549-009-0550-7

Sprod, L. K., Janelsins, M. C., Palesh, O. G., Carroll, J. K., Heckler, C. E., Peppone, L. J., ... & Mustian, K. M. (2012). Health-related quality of life and biomarkers in breast cancer survivors participating in tai chi chuan. *Journal of Cancer Survivorship*, *6*(2), 146-154. https://doi.org/10.1007/s11764-011-0205-7

Stein, C. J., & Colditz, G. A. (2004). Modifiable risk factors for cancer. *British journal of cancer*, *90*(2), 299-303. https://doi.org/10.1038/sj.bjc.6601509

Steindorf, K., Schmidt, M. E., Klassen, O., Ulrich, C. M., Oelmann, J., Habermann, N., Beckhove, P., Owen, R., Debus, J., Wiskemann, J., & Potthoff, K. (2014). Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: Results on cancer-related fatigue and quality of life. *Annals of Oncology*, *25*(11), 2237–2243. https://doi.org/10.1093/annonc/mdu374

Sun, Y. S., Zhao, Z., Yang, Z. N., Xu, F., Lu, H. J., Zhu, Z. Y., Shi, W., Jiang, J., Yao, P. P., & Zhu, H. P. (2017). Risk factors and preventions of breast cancer. *International Journal of Biological Sciences*, *13*(11), 1387–1397. https://doi.org/10.7150/ijbs.21635

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). *Global Cancer Statistics 2020 : GLOBOCAN Estimates of*

Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Takada, K., Asano, Y., Goto, W., Takahashi, K., Shibutani, M., Amano, R., Takashima, T., Tomita, S., Hirakawa, K., Ohira, M., & Kashiwagi, S. (2019). Prognostic value of quality of life in endocrine therapy for elderly patients with breast cancer: A retrospective study. *Anticancer Research*, *39*(6), 2941–2950. https://doi.org/10.21873/anticanres.13424

Taneja, D. K. (2014). Yoga and health. *Indian Journal of Community Medicine*, *39*(2), 68–72. https://doi.org/10.4103/0970-0218.132716

Tarpey, M. D., Amorese, A. J., Balestrieri, N. P., Fisher-Wellman, K. H., & Spangenburg, E. E. (2019). Doxorubicin causes lesions in the electron transport system of skeletal muscle mitochondria that are associated with a loss of contractile function. *The Journal of Biological Chemistry*, *294*(51), 19709–19722. https://doi.org/10.1074/jbc.RA119.008426

Tysnes, B. B., & Bjerkvig, R. (2007). Cancer initiation and progression: Involvement of stem cells and the microenvironment. *Biochimica et Biophysica Acta - Reviews on Cancer*, *1775*(2), 283–297. https://doi.org/10.1016/j.bbcan.2007.01.001

Van Dijck, S., Nelissen, P., Verbelen, H., Tjalma, W., & Gebruers, N. (2016). The effects of physical self-management on quality of life in breast cancer patients: A systematic review. *Breast*, *28*, 20–28. https://doi.org/10.1016/j.breast.2016.04.010

Warburton, D. E. R., & Bredin, S. S. D. (2016). Reflections on Physical Activity and Health: What Should We Recommend? *Canadian Journal of Cardiology*, *32*(4), 495–504. https://doi.org/10.1016/j.cjca.2016.01.024

Warburton, D. E. R., & Bredin, S. S. D. (2017). Health benefits of physical activity: A systematic review of current systematic reviews. *Current Opinion in Cardiology*, *32*(5), 541–556. https://doi.org/10.1097/HCO.0000000000000437

Warburton, D. E. R., Gledhill, N., Jamnik, V. K., Bredin, S. S. D., McKenzie, D. C., Stone, J., Charlesworth, S., & Shephard, R. J. (2011). Evidence-based risk assessment and recommendations for physical activity clearance: Consensus Document 2011. *Applied Physiology, Nutrition and Metabolism*, *36*(SUPPL.1), 266–298. https://doi.org/10.1139/H11-062

Weigelt, B., Geyer, F. C., & Reis-Filho, J. S. (2010). Histological types of breast cancer: How special are they? *Molecular Oncology*, *4*(3), 192–208. https://doi.org/10.1016/j.molonc.2010.04.004

Weinberg, R.A., The Biology of Cancer. 2th ed. 2014, New York: Garland Science, Taylor & Francis Group.

Welch, W. A., Cottrell, A., Ehlers, D., Gavin, K. L., Aguinaga, S., Nielsen, A., Solk, P., Mcauley, E., & Phillips, S. M. (2019). *Effects of reallocating sedentary time with physical activity on quality of life indicators in breast cancer survivors*. *April*, 1430–1437. https://doi.org/10.1002/pon.5091

White, C. A. (2000). Body image dimensions and cancer: a heuristic cognitive behavioural model. *Psycho-Oncology*, *9*(3), 183–192. https://doi.org/10.1002/1099-1611(200005/06)9:3<183::aid-pon446>3.0.co;2-l

Winters, S., Martin, C., Murphy, D., & Shokar, N. K. (2017). Breast cancer epidemiology, prevention, and screening. *Progress in molecular biology and translational science*, *151*, 1-32. https://doi.org/10.1016/bs.pmbts.2017.07.002

Witte, C. L., & Witte, M. H. (1987). Contrasting patterns of lymphatic and blood circulatory disorders. *Lymphology*, *20*(4), 171–178.

World Health Organization. (2021). *Physical activity fact sheet* (No. WHO/HEP/HPR/RUN/2021.2). World Health Organization.

Wu, Y., Zhang, D., & Kang, S. (2013). Physical activity and risk of breast cancer: A meta-analysis of prospective studies. *Breast Cancer Research and Treatment*, *137*(3), 869–882. https://doi.org/10.1007/s10549-012-2396-7

Yan, J. H., Pan, L., Zhang, X. M., Sun, C. X., & Cui, G. H. (2014). Lack of efficacy of tai chi in improving quality of life in breast cancer survivors: A systematic review and meta-analysis. *Asian Pacific Journal of Cancer Prevention*, *15*(8), 3715–3720. https://doi.org/10.7314/APJCP.2014.15.8.3715

Zhang, J., Yang, K. H., Tian, J. H., & Wang, C. M. (2012). Effects of yoga on psychologic function and quality of life in women with breast cancer: A meta-analysis of randomized controlled trials. *Journal of Alternative and Complementary Medicine*, *18*(11), 994–1002. https://doi.org/10.1089/acm.2011.0514

Zhang, X., Li, Y., & Liu, D. (2019). Effects of exercise on the quality of life in breast cancer patients: a systematic review of randomized controlled trials. *Supportive Care in Cancer*, *27*(1), 9–21. https://doi.org/10.1007/s00520-018-4363-2

Zhu, G., Zhang, X., Wang, Y., Xiong, H., Zhao, Y., & Sun, F. (2016). Effects of exercise intervention in breast cancer survivors: A meta-analysis of 33 randomized controlled trails. *OncoTargets and Therapy*, *9*, 2153–2168. https://doi.org/10.2147/OTT.S97864

Appendix A- GRADE table for breast cancer patients during treatment

Question: Exercise compared to no exercise for breast cancer patients undergoing treatment

Autor	Certainty assessment							Nº of patients		Effect	Certainty
	Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	exercise	No exercise	Absolute (95%CI)	
Gebruers et al., 2018	28	randomised trials	not serious	serious [a]	not serious	not serious	none	1422	1061	see comment d **0.16**	⊕⊕⊕◯ MODERATE
Lee & Lee, 2020	29	randomised trials	serious [b]	not serious	not serious	not serious	publication bias strongly suspected [c]	1790	1199	**Cohen higher** (0 to 0.33 higher)	⊕⊕◯◯ LOW
Furmaniak et al., 2016	32	randomised trials	not serious	not serious	not serious	not serious	none	1890	1346	SMD **0.12 SD higher** (0 to 0.25 higher)	⊕⊕⊕⊕ HIGH
Shen & Yang, 2020	13	randomised trials	not serious	not serious	not serious	not serious	none	655	641	SMD **0.28 SD higher** (0.14 higher to 0.4 higher)	⊕⊕⊕⊕ HIGH
Corayol et al., 2015	36	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [d]	1479	1244	SMD **0.16 SD higher** (0.05 higher to 0.26 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. High unexplained heterogeneity

b. Risk of bias was not assessed

c. Publication bias was not measured

d. publication bias persisted for QoL suggesting that analyses may be biased in the sense of an overestimation of exercise effect on QoL

Appendix B- GRADE table for breast cancer patients after treatment

Question: Exercise compared to no exercise for breast cancer survivors

Autor	Certainty assessment							Nº of patients		Effect	Certainty
	Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	exercise	No exercise	Absolute (95%CI)	
Bekhet et al., 2019	12	randomised trials	not serious	serious [a]	not serious	not serious	none	1021	648	see comment	⊕⊕⊕◯ MODERATE
Liu et al., 2017	9	randomised trials	not serious	serious [b]	not serious	not serious	none	423	422	SMD **0.49 SD higher** (0.037 higher to 0.942 higher)	⊕⊕⊕◯ MODERATE
Santos et al., 2017	10	randomised trials	not serious	not serious	not serious	not serious	none	-	-	see comment	⊕⊕⊕⊕ HIGH
Dieli-Conwright & Orozco, 2015	26	randomised trials	serious [c]	serious [d]	serious [e]	not serious	publication bias strongly suspected [f]	-	-	see comment	⊕◯◯◯ VERY LOW
Hong et al., 2019	26	randomised trials	not serious	serious [g]	not serious	not serious	publication bias strongly suspected [h]	929	923	SMD **0.35 SD higher** (0.15 higher to 0.54 higher)	⊕⊕◯◯ LOW
Zhu et al., 2016	33	randomised trials	not serious	not serious	not serious	not serious	none	994	918	SMD **0.36 SD higher** (0.11 higher to 0.62 higher)	⊕⊕⊕⊕ HIGH
Yan et al., 2014	9	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [i]	211	207	SMD **0.24 SD higher** (0.02 higher to	⊕⊕⊕◯ MODERATE

							0.45 higher)

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. Heterogeneity was not assessed

b. High heterogeneity

c. Risk of bias was not assessed

d. Heterogeneity was not assessed

e. Did not follow the PICO stategy

f. Publication bias was not measured

g. High heterogeneity

h. Publication bias was not assessed

i. Publication bias was not assessed because of the limited number (below 10) of studies included in each analysis

Appendix C- GRADE table for breast cancer patients during and after treatment

Question: Exercise compared to no exercise for breast cancer patients during and after treatment

Autor	Certainty assessment							Nº of patients		Effect	Certainty
	Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	exercise	No exercise	Absolute (95%CI)	
Djick et al., 2016	13	randomised trials	not serious	serious [a]	not serious	not serious	publication bias strongly suspected [b]	1324	856	see comment	⊕⊕◯◯ LOW
Pastaskia & Kumar, 2011	9	randomised trials	not serious	serious [c]	not serious	not serious	publication bias strongly suspected [d]	-	-	see comment	⊕⊕◯◯ LOW
Zhang et al., 2018	36	randomised trials	not serious	serious [e]	not serious	not serious	publication bias strongly suspected [f]	2376	1794	see comment	⊕⊕◯◯ LOW
Bicego et al., 2009	9	randomised trials	serious [j]	serious [k]	not serious	not serious	publication bias strongly suspected [l]	-	-	see comment	⊕◯◯◯ VERY LOW
McNeely et al., 2006	14	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [m]	-	-	WMD **4.58 higher** (0.35 higher to 8.8 higher)	⊕⊕⊕◯ MODERATE
O'Neill et al., 2020	24	randomised trials	not serious	not serious	not serious	not serious	none	674	829	SMD **0.27 SD higher** (0.46 higher to 0.07 higher)	⊕⊕⊕⊕ HIGH
El-Hashimi & Gorey, 2019	8	randomised trials	not serious	not serious	not serious	not serious	none	272	273	d **0.14 Cohen higher** (0 to 0.28 higher)	⊕⊕⊕⊕ HIGH

Harder et al., 2012	18	randomised trials	not serious	serious [n]	not serious	not serious	publication bias strongly suspected [o]	463	424	see comment	⊕⊕◯◯ LOW
Zhang et al., 2012	6	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [p]	217	165	SMD **0.27 SD higher** (0.02 higher to 0.52 higher)	⊕⊕⊕◯ MODERATE
Cramer et al., 2012	12	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [q]	-	-	SMD **0.62 SD higher** (0.04 higher to 1.21 higher)	⊕⊕⊕◯ MODERATE
Cramer et al., 2017	24	randomised trials	not serious	not serious	not serious	not serious	none	-	-	SMD **0.22 SD higher** (0.04 higher to 0.4 higher)	⊕⊕⊕⊕ HIGH
Luo et al., 2020	15	randomised trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [r]	485	487	SMD **0.37 SD higher** (0.15 higher to 0.59 higher)	⊕⊕⊕◯ MODERATE
Liu et al., 2020	16	randomised trials	not serious	serious [s]	not serious	not serious	none	610	513	SMD **0.32 SD higher** (0.07 higher to 0.56 higher)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **SMD:** Standardised mean difference

Explanations

a. Heterogeneity was not assessed

b. In some studies, the control group became more active, therefore the difference between both groups could be less

c. Heterogeneity between participant selection criteria, type of exercise prescription and primary outcome measures and time points

d. Publication bias was not assessed

e. Heterogeneity on type of intervention, frequency and duration of exercise sessions, program duration, and QoL measurements

f. Publication bias was not assessed

g. Risk of bias was not assessed

h. Heterogeneity was not assessed

i. Publication bias was not assessed

j. Risk of bias was not assessed

k. Heterogeneity was not assessed

l. Publication bias was not assessed

m. Publication bias was not assessed

n. Heterogeneity was not assessed

o. Publication bias was not assessed

p. Funnel plots to assess publication bias were not created according to recommendations because of the small number of eligible studies

q. Funnel plots to assess publication bias were not created due to the small number of eligible studies

r. Publication bias was not analyzed because the number of eligible studies in each meta-analysis was <10

s. Heterogeneity due to different populations, including phase of breast cancer survivorship (breast cancer survivors, or breast cancer patients undergoing adjunct cancer treatment), breast cancer treatment received, and participants' baseline physical activity level

Appendix D- AMSTAR questionnaire

1. Was an ‘‘a priori’’ design provided?
   The research question and inclusion criteria should be established before the conduct of the review.
   ☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable

2. Was there duplicate study selection and data extraction?
   There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
   ☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable

3. Was a comprehensive literature search performed?
   At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.
   ☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable

4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?
   The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.
   ☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable

5. Was a list of studies (included and excluded) provided?
   A list of included and excluded studies should be provided.
   ☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable

6. Were the characteristics of the included studies provided?
   In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.
   ☐ Yes ☐ No ☐ Can’t answer ☐ Not applicable

7. Was the scientific quality of the included studies assessed and documented?
   ‘‘A priori’’ methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-

controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.

☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
   The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
   ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
   For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).
   ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

10. Was the likelihood of publication bias assessed?
    An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).
    ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

11. Was the conflict of interest included?
    Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.
    ☐ Yes ☐ No ☐ Can't answer ☐ Not applicable