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Effect of Exercise Interventions on Fatigue for Breast Cancer: A Systematic Review and Meta-Analysis

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EFFECT OF EXERCISE INTERVENTIONS ON FATIGUE FOR BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

by

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ABSTRACT

We conducted a systematic review and meta-analysis on the effect of different exercise interventions on fatigue in patients with breast cancer undergoing active therapy. We found that exercise generally improves fatigue outcomes at 12 weeks after initiation of the exercise intervention. Aerobic exercise intervention improved fatigue, but anaerobic and combination regimens did not show improvement compared to controls. Moreover, no exercise intensity was found to be superior compared to controls. Our findings revealed that there is a need for standardization of exercise regimens in studies in order to identify the most effective exercise regimen.

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Introduction

Breast cancer is one of the most common cancers in the world and in the United States. Its treatment can have significant short and long term impacts on the patient's Health Related Quality of Life (HRQoL), especially fatigue. Fatigue is one of the many domains of HRQoL, and is the most commonly reported side effects of cancer therapy. Physical activity is increasingly incorporated into cancer treatment because of its benefits to HRQoL outcomes such as fatigue. Below is a discussion on the epidemiology of breast cancer, and the effects of treatment on fatigue, followed by an overview of HRQoL, its domains, particularly fatigue, and clinical significance. The introduction will conclude with an exploration of the types of physical activity regimens. The overall aim of this research is to compare the effects of different exercise regimens on fatigue.

Breast Cancer Epidemiology

Breast cancer (BC) is the most common cancer in women [1], with more than 1.7 million new worldwide cases in 2012. This is an increase of 18% from 2008, and is predicted to reach 3.2 million by 2050 [2]. BC is also a leading cause of cancer death in women, with 522,000 worldwide deaths in 2012, second only to lung cancer [2]. The incidence of BC is highest in high income countries, where outcomes have also improved the most [3]. However, the majority of BC deaths occur in low and middle income countries, where the incidence has been increasing by about 5% per year [4, 5].

In the United States, one in eight women will develop BC in their lifetime [6]. The *American Cancer Society* reports that in 2017, there were 315,000 new BC cases, with

40,000 deaths. The probability of recurrence is 20%, with 60% to 80% of recurrences occurring within the first three years [7].

Moreover, there is a disparity in access to care, which remains a barrier to obtaining adequate BC screening and treatment, particularly in developing nations, but also in industrialized nations [8-10]. Inadequate health insurance is one of the major barriers to accessing quality care, even in industrialized nations. Uninsured and underinsured patients with BC have delayed and limited access to cancer treatment, and interventions aimed at improving quality of life [11]. The 2016 *National Health Interview Survey* (NHIS) showed that there are currently 27.6 million uninsured nonelderly individuals in the US, with high cost of premiums cited as the primary reason. The report also reflected poverty as a barrier to being insured, with 80% of uninsured being in families below the 400% Federal Poverty Guidelines level. In addition, the NHIS reported people of color such as Hispanics (16.9%) and Blacks (11.7%) have higher uninsured rates compared to Whites (7.6%). These barriers not only hinder BC screening, but they also hinder adherence to rescreening guidelines [12, 13].

Breast Cancer Treatment and its Impact on Well-Being

The management of BC is becoming increasingly multidisciplinary [14]. This approach requires the involvement of the primary care physician, geneticist, pathologist, oncologist, radiologist, surgeons, and radiation oncology specialists [15, 16]. Breast conserving surgery is the most common treatment for BC, and is accompanied by radiation therapy in 84% of the cases, and chemotherapy in 25% of cases [17]. Treatment can also include adjuvant endocrine therapy, and neoadjuvant or preoperative systemic chemotherapy [16].

However, these approaches can exert a significant burden on the physiology and/or psychology of the BC patient [18], leading to short and/or long term organ system dysfunction, pain, fatigue, edema, musculoskeletal impairment, and psychosocial concerns [17]. These effects of therapy can limit the patient's engagement in activities of daily living, and become a source of prolonged disability [17].

Health Related Quality of Life

Almost all patients with cancer experience physical and/or psychological symptoms related to the cancer itself, or the cancer treatment [19]. Cancer is a difficult event with psychosocial implications, affecting the physical, spiritual, and the emotional well-being of the patient [20]. The diagnosis of cancer alone (and even benign breast disease) can cause high levels of anxiety and distress [21], for not only the patient, but also for family members [22]. Newly diagnosed patients with BC experience negative emotions such as shock, fear, paralysis, confusion, and despair [23].

Additionally, the psychological impact of BC goes beyond the life threatening nature of cancer itself, as patients describe distress due to altered body image, sexual dysfunction, treatment related anxieties, intrusive thoughts with persistent anxiety, marital/partner communication, vulnerability, fear of recurrence, physical symptoms (such as fatigue, pain) and existential concerns regarding mortality [24]. Although most women show good post-treatment psychological adjustment and eventual improvement of Quality of Life (QoL) [25], certain aspects of QoL have been shown to be affected for up to two years after primary surgery for breast cancer, such as body image, cognitive functioning, and insomnia [26]. This is significant given the extended longevity of survivors of BC

due to improved therapy, which indicates that it is no longer sufficient to simply deal with the disease, but that improving QoL is also a priority [18].

The psychological response to breast cancer is an important prognostic factor. There is a significant relationship between psychosocial factors and survival. Depression, denial, and emotional constraints are linked to a significant decrease in chance of survival, while social support, marriage, and acceptance are associated with improved prognosis [27, 28]. Ensuring that patients with cancer have good HRQoL is also important because in situations where treatment options cannot offer cure or disease course modification, they can still result in significant improvement in the patients' QoL [29]. Measurements of HRQoL are reliable and valid, and outcomes have been shown to be responsive to clinical changes [30], further emphasizing the need to include treatment and or adjuvant options that improve HRQoL. Negative psychological symptoms are more severe during the diagnosis and active treatment of BC [24]; and importantly, initial distress around the time of therapy was found to be the most potent predictive factor for long term HRQoL [26], thereby highlighting the urgency to initiate such options at the onset of therapy.

Given the important influence of QoL on clinical decision-making, studies have been increasingly including HRQoL as main end points [31, 32]. HRQoL and QoL are often incorrectly used interchangeably, but they are not indistinguishable [33]. QoL is commonly seen as the way an individual subjectively evaluates one's life through diverse perspectives such as good physical health, happiness, and life satisfaction [34, 35]. Others have described that human needs (psychological, physical, social, marital, structural, etc.) are the basis for QoL, and that the degree of satisfying those needs determine the extent of

QoL [36]. QoL is broader than HRQoL as it includes non-health related features [37], whereas HRQoL concerns the aspects of QoL that are relevant to health [38]; that is, it assesses how the patient's QoL is affected by an illness and/or the treatment [37]. As such, HRQoL is a multidimensional representation of patients' perceptions of the effect that disease and therapy have on their psychological, physical, and social well-being [39] (Table 1).

Table 1. Some Definitions of QoL/HRQoL Commonly Seen in the Literature [40]:

QoL	**HRQoL**
The subjective evaluation of the good and satisfactory character of life as a whole	The functional effect of an illness and its consequent therapy upon the patient as perceived by the patient
The gap between the patient's expectations and achievements. The smaller the gap, the higher the quality of life	The state of well-being that is a composite of two components: the ability to perform everyday activities that reflect physical, psychological, and social well-being; and patient satisfaction with levels of functioning and control of the disease
An individual's overall satisfaction with life and general sense of personal well-being	The extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment [41]
The individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns	The physical, psychological and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations and perceptions [42]

HRQoL covers the subjective perceptions of both the positive and negative characteristics of the patient's symptoms [40]. Assessment and quantification is completed using

patient-reported questionnaires, as opposed to clinician-reported. There is poor correlation between clinician assessment of the severity of the patients' symptoms compared to the patients' self-reporting [40]. HRQoL is multidimensional, consisting of specific domains, each referring to a category of a health related dimension [43]. Each domain focuses on distinct yet interrelated (and in some cases reciprocal) aspects of the patient's health [44].

There is consensus that there are three main domains: the *physical*, the *psychological*, and the *social* features of health [40], although *spirituality* is increasingly being considered as another primary domain [45]. These four domains are known in BC HRQoL literature as Ferrell's QoL domains based on the framework completed by Ferrell and colleagues [45-48]. Other domains, or subdomains thereof, include – but are not limited to – fatigue, role activities, emotional well-being, economics, overall life satisfaction, perceptions of health status [49]; sexuality [50], as well as vitality, pain, and cognitive function [30]. The number of domains and their categorization varies in the literature and in the instruments designed to measure them depending on the degree of generality desired [51].

Health Related Quality of Life Domain - Fatigue

Cancer-related fatigue (CRF) is the most common adverse event reported by patients with cancer [52, 53]. It is defined as feeling of weakness, tiredness, and lack of energy, that is not relieved by rest or sleep [54]. Acute fatigue experienced after physical or emotional exertion is normally perceived. In contrast, CRF is disproportionately higher to the level of exertion, and is more chronic [53]. Up to 90% of patients receiving radiation, and 80% of those receiving chemotherapy experience fatigue.

Psychosocial factors contribute to the development of CRF, as it correlates with depression, anxiety, sleeping disorders, and other psychiatric comorbidities [55]. Additionally, there are somatic factors that contribute to the development of CRF. Although the exact mechanism is not completely understood, contributory somatic factors include deficiencies in vitamins and proteins secondary to malnutrition, build-up of toxic metabolites, infections, overuse of pain and sleep medication, organ dysfunction, and anemia [53, 55].

Patients with cancer have reported that CRF affects their daily living more than pain, and it is often overlooked and undertreated [52]. CRF also contributes to the deterioration of the physical and psychological QoL [53], and limits the patient's ability to return to work [54]. CRF increases during active therapy for cancer, and decreases towards the end [55]; however, CRF can persist for months and even years after completion of therapy [54]. This highlights the importance of addressing CRF during active cancer therapy, and to avoid delays. Likewise, measuring CRF and following its progress throughout therapy is necessary in order to ensure that CRF is being managed appropriately.

HRQoL and Fatigue Measuring Instruments

HRQoL instruments and the domains they measure depend on their classification as either generic, general cancer, cancer site-specific, or even cancer problem-specific instruments [56]. The *European Organization of Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire 30* (EORTC QLQ-C30) is the most widely used instrument for assessing cancer HRQoL [17], and structures its domains as follows: 1) Functional domains (subdomains: physical, role, emotional, cognitive, social,

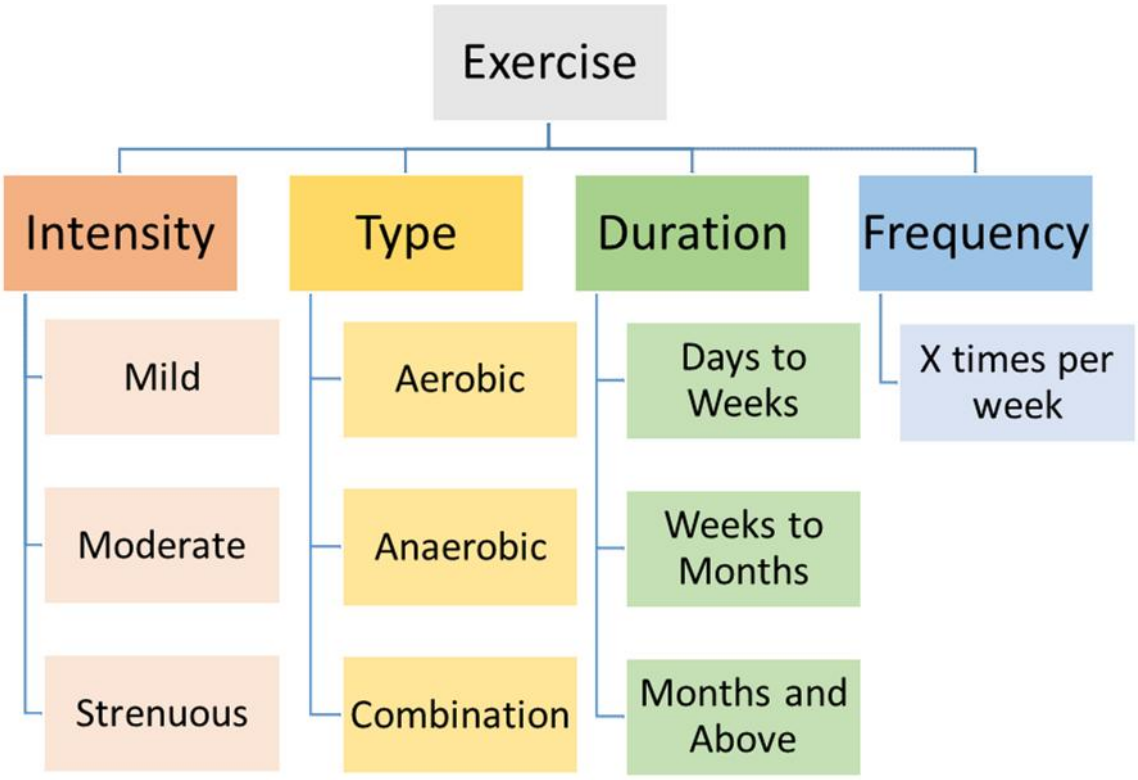
and global QoL); 2) Symptom domains (subdomains: fatigue, nausea/vomiting, and pain); and 3) Single-Item domain (subdomains: dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) [45]. The EORTC QLQ-C30 is an example of a multidimensional instrument that measures fatigue in addition to multiple other domains. Conversely, there are unidimensional instruments that measure only fatigue, such as the Brief Fatigue Inventory (BFI), and the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT) module [55]. Most cancer studies measure CRF using multidimensional instruments [57]. It is possible to aggregate the scores of the domains to obtain a single, convenient score that would represent overall HRQoL [58]. Domain scores can also be reported individually, thereby providing more detailed information about how each aspect is influenced by the disease and treatment [59].

Exercise

There is strong evidence supporting exercise as a non-pharmacological intervention for CRF [60]. The term *Physical Activity* (PA) is defined as any activity that results in any body movement using skeletal muscles leading to an increase in energy expenditure. The term *exercise* is often used interchangeably with PA, but is usually defined as a specific type of PA involving a planned and repetitive body movement aimed at improving fitness, and measured through the parameters of frequency, intensity, and duration [39, 61]. Energy expending exercise is broadly classified as either aerobic, anaerobic or strength/resistance training, or a combination of both, and trials typically report and describe the tools used in the exercise regimen (swimming, cycling, treadmill, weight training, etc.) [39]. For our purposes, we will be addressing exercise as defined above,

and *exercise type* shall refer to whether the regimen was either aerobic, anaerobic (strength/resistance training), or both (Figure 1).

Figure 1. Parameters of Exercise Regimens.



Exercise and Fatigue

Exercise is a non-pharmacological, effective, safe, and low-cost activity [18] that has been shown to positively influence overall HRQoL and fatigue [39, 60, 62]. Moreover, exercise has well documented effects on mental health symptoms highly correlated with CRF, such as reducing depression, social withdrawal, and anxiety; improving sleep and interest in sex; increasing endurance; relieving stress; increasing stamina and energy; and improving cognitive function, mood, and self-esteem [63]. It is thought that exercise ameliorates fatigue in cancer patients by improving cardiovascular fitness, muscle

strength, and increasing physical functioning in daily activities [64]. This counteracts the muscle catabolism and subsequent decrease in functional capacity that occur during cancer treatment [65].

However, the current literature regarding exercise's effect on fatigue in BC is limited by the heterogeneity with regard to the timing of the exercise interventions, as trials commence the intervention either pre-treatment, during treatment (active), or post-treatment [66]. Moreover, there is consistent underreporting of detailed descriptions of the exercise regimens used in studies. Without consistency (which is necessary for reproducibility), an appropriate translation of the findings cannot be made, thereby limiting the ability to determine the dose of exercise received by the participants [61, 67]. As a result, the type of exercise (aerobic vs. anaerobic vs. combination) and/or its intensity (mild vs. moderate vs. strenuous/vigorous) having the largest influence on overall HRQoL or fatigue is yet to be determined [61, 67, 68].

The aims of this systematic review are as follows:

1- Evaluate the effectiveness of exercise interventions on fatigue among women in active treatment for BC at 12 weeks after the start of the exercise intervention.
2- Compare the different intensities of exercise regimens (mild, moderate, or vigorous/strenuous) in ameliorating fatigue in women undergoing active therapy for BC at 12 weeks post-intervention.
3- Determine what exercise type (anaerobic, aerobic, or combination) has the greatest impact on fatigue in women undergoing active therapy for BC at 12 weeks post-intervention.

Methods

Studies Selection

The authors included trials that met the following inclusion criteria: (1) Randomized Controlled Trials (RCTs), or controlled clinical trials (CCTs); (2) Breast cancer as the primary cancer; (3) Adult participants (≥18 years of age); (4) Compared an exercise intervention to a non-exercise control; (5) Exercise intervention was started during active cancer therapy; and (6) Fatigue measured as an outcome. We excluded trials if: (1) Participants were terminally ill; (2) Participants were receiving hospice care; (3) Exercise intervention was started after completion of cancer therapy; or if (4) Exercise intervention was completed before start of cancer therapy.

Exercise was defined as any regimen that lead to an increase in energy expenditure, and followed a planned and repetitive body movement with a specified frequency, intensity, and duration [39, 61]. Exercise intensity was classified as mild, moderate, or vigorous; and exercise type was classified as either aerobic, anaerobic, or both.

The primary outcome was change in CRF, whether it was obtained from a unidimensional instrument, or from a multidimensional instrument. Change in CRF was evaluated as the value at 12 weeks after the start of the exercise intervention compared to prior to the start of the intervention.

Literature Search

This systematic review is part of a project to update a Cochrane Registered Systematic Review by Mishra et al. [39] which examines exercise's effect on HRQoL in patients

with all types of cancers that are undergoing active treatment. We systematically searched the following databases: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Medline, EMBASE, CINAHL, SportDisc, PsycINFO, PEDro, LILACS, SIGLE, and OTSeeker. Additionally, we searched citations using Web of Science and Scopus, and PubMed's related article feature. We also examined the reference list of the articles that fit our eligibility criteria.

Articles published up until the 31st of December 2016 were selected, with no restriction on language or date. An initial search strategy was conducted for Medline, and was adjusted for the other databases. Screening for eligibility was based on titles and abstracts, after which the full-text was examined to confirm eligibility. Two independent reviewers completed the screening, and disagreements were resolved by consensus or by adjudication through a third reviewer.

Data Collection

The data of the selected articles were screened, and when applicable, extracted by two independent reviewers using standardized forms, and verified through consensus. A third reviewer arbitrated when necessary. Data collected from each article included study characteristics, eligibility criteria, number of participants randomized into each arm, description of the control group, demographics, cancer treatment regimen, cancer type and stage, age at diagnosis, and time since diagnosis. Description of the exercise intervention was also extracted, including type, intensity, frequency, duration, number of sessions, exercise format, location, participants, and professionals involved. Adherence, compliance, and contamination rates were also extracted, as well as fatigue outcome

measures, time at which the measurement was made, and side effects. For missing or unclear information/data in a study, we attempted to contact the primary author. Every trial was graded for risk of bias (low, high, or unclear).

The time point for the fatigue outcome was 12 weeks after the start of the exercise intervention. If the 12-week time-point was not reported, we then selected the time point closest to the 12 weeks follow-up up to 4 weeks before or after the 12 week mark. The unit of analysis was the BC patient undergoing active BC therapy randomized to either the exercise intervention group or control group.

The intensity of the activity can be quantified subjectively by assessing rate of perceived exertion of the patient via an interview or self-completed questionnaire; or objectively such as by changes in heart rate and/or recordings of an accelerometer – the most widely used objective measure of exercise [69]. When such measurements are not available, exercise intensity is classified as mild, moderate, or vigorous/strenuous [39]. Mild or light intensity exercise refers to daily activities such as shopping, and working around the house. Moderate intensity exercises expend effort equivalent to a brisk walk, whereas strenuous intensity exercises engage the large muscle groups and cause an evident increase in heart rate [70].

Data Analysis

Data was collected and entered into the software *Review Manager – Version 5 (RevMan 5)*, which was developed and is maintained by Cochrane Reviews for systematic reviews and meta-analyses. A meta-analysis was performed on the change in scores from baseline to the 12 week follow-up. Trials were pooled for random effects meta-analysis for the

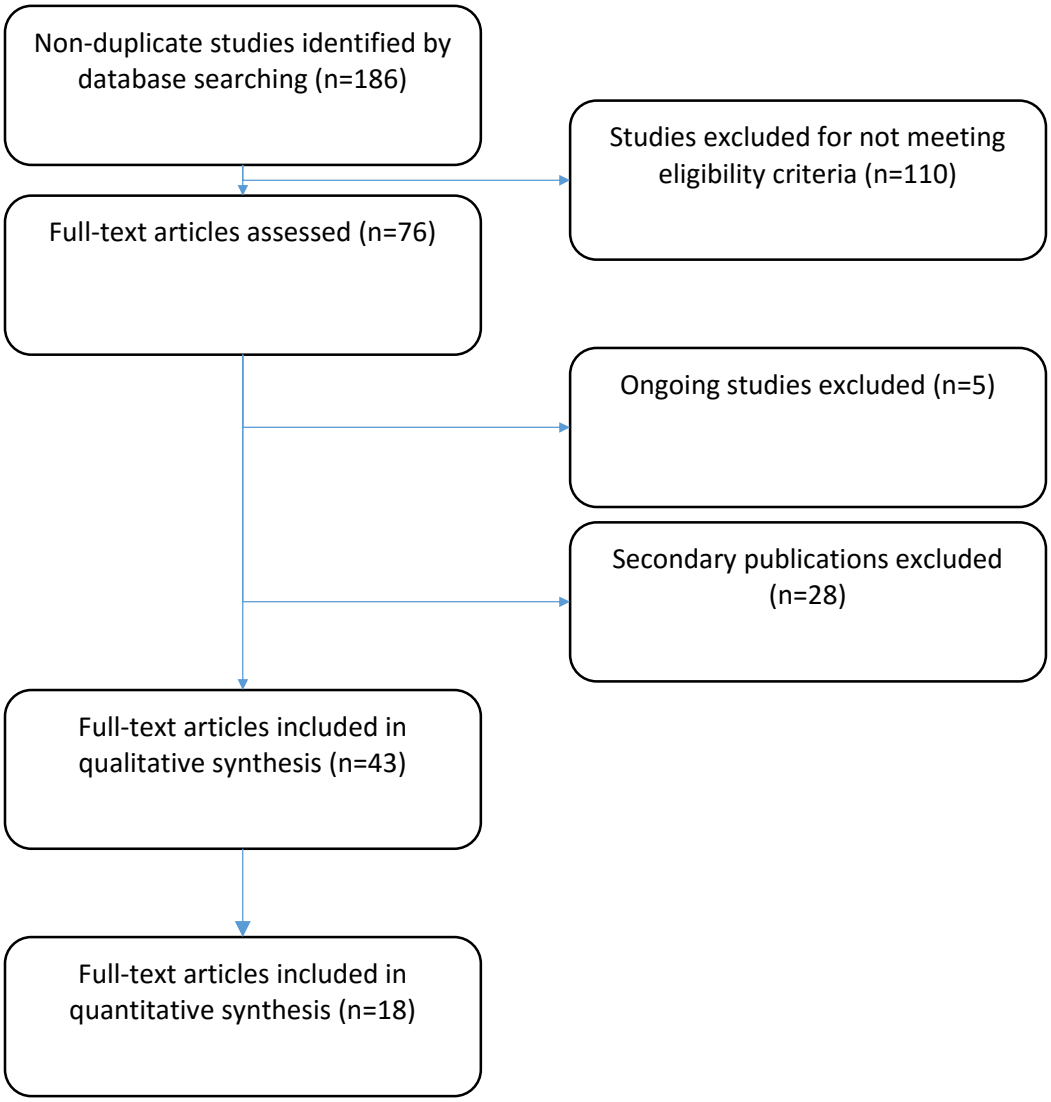
intervention effect estimate (odds ratio and a 95% confidence interval). A weighted mean difference was used for trials using the same instrument for reporting fatigue outcome, and a standardized mean difference was used when the instruments between the trials were different, in which case differences were reported as units of standard deviation [39].

Results

Study Characteristics

Following the systematic literature search, 186 potential non-duplicate articles were retrieved, 76 of which met the eligibility criteria. Of the 76 records meeting the inclusion criteria, 5 were ongoing studies, and an additional 28 were secondary publications, and therefore not included. A total of 43 articles remain on which qualitative synthesis was performed (Figure 2).

Figure 2. Study Selection PRISMA Flow Diagram.



Of the 43 trials included, 42 were RCTs, and only one was a CCT. Four studies randomized the participants to more than two study arms, the additional arm consisting of an additional variation in the exercise regimen. The remaining 39 studies had two arms: exercise and non-exercise (control) arms.

Participants

A total of 4826 participants were randomized, 2286 of which were randomized to the exercise intervention, and 1985 to the control group. The mean age of participants ranged between 28 and 75 years, with four studies reporting age as a median instead of a mean. Ethnicity was reported in 17 trials, education in 27, employment in 20, previous exercise history in 15 studies, and socio-demographic status in 11. Fourteen trials reported BMI, and mean BMI ranged from 23kg/m^2 to 29kg/m^2 in the intervention group, and 24kg/m^2 to 30kg/m^2in the control group. The treatment regimen was chemotherapy in 17 trials, and radiotherapy in 8 trials.

Exercise Interventions

The exercise regimens varied across studies. Twenty-two trials consisted of an aerobic intervention, two trials consisted of an anaerobic/resistance training regimen, and 19 trials had a combined aerobic and anaerobic intervention. Two studies had two exercise intervention arms, each comprising of either an aerobic or an anaerobic intervention. The duration of the exercise program ranged from 5 weeks to 8 months (modal program duration = 12 weeks in 17 trials). The frequency of the exercise sessions ranged from one time a week to daily (modal frequency = three times a week in 17 trials). Duration of the individual exercise sessions ranged from 10 minutes to 90 minutes (modal session duration = 60 minutes in nine trials).

Exercise intensity was measured by subjective reporting of the participants in two trials, both using the Borg Exertion Scale. Fifteen studies measured intensity objectively: as a percent of maximal heart rate (n=10), maximal oxygen consumption (n=3), and as a

percent of one maximal repetition/power output for resistance/anaerobic training (the maximum resistance of which a person can complete at least one repetition) (n=6). Two trials used multiple objective measurements, and two trials measured intensity both objectively and subjectively. Nine studies had a planned increase in the intensity of the exercise once certain milestones were met.

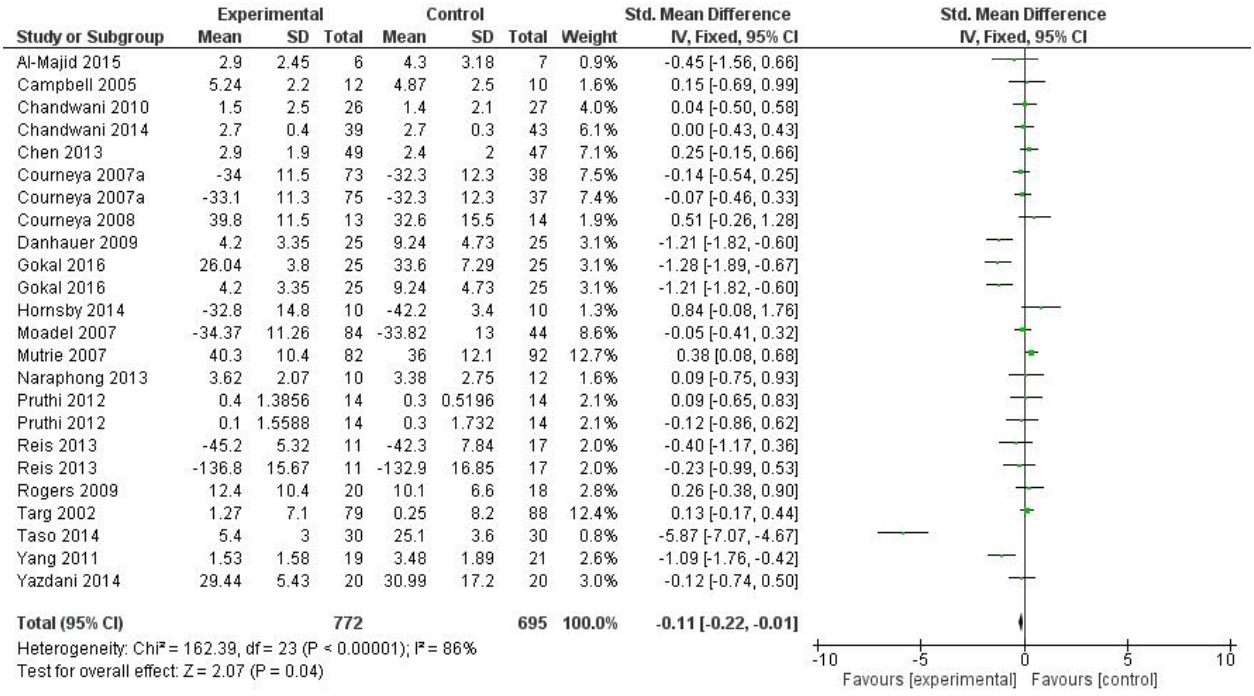
The intensity was categorized in 20 studies; as mild (n=8), moderate (n=5), mild to moderate (n=2), moderate to strenuous (n=4). One study reported that the intensity varied from mild to rigorous depending on the participant, one other reported a scheduled progression in increasing intensity from mild to vigorous, and one study reported intensity as "varied" with no other specifics. Only four studies recorded objective measurements to accompany the category of the description. On the other hand, 14 studies reported objective measurements of the exercise intensity, but did not describe the exercise regimen in the mild/moderate/strenuous categories. In these cases, we used the *American College of Sports Medicine*'s (ACSM) classification system, which categorizes the exercise intensity as mild/moderate/strenuous based on the objective measurements (such as percent of maximal heart rate and rate of exertion). Nine studies did not report exercise intensity either objectively nor subjectively.

Outcomes

Seventeen studies measured fatigue scores using 8 multidimensional instruments, the most common ones were the EORTC QLQ-C30 (n=4) and the Medical Outcomes 36-Item Short Form Health Survey (MOS SF-36) (n=4). Thirty-three trials measured fatigue using unidimensional instruments solely for fatigue (one of which measuring attentional

fatigue), the most common ones were the Piper Fatigue Scale (n=8), the Functional Assessment of Chronic Illness Therapy – FACT-F (n=7), and the Brief Fatigue Inventory (n=7). Fatigue at 12 weeks significantly decreased in the exercise group compared to the control group (Standard Mean Difference (SMD) = -0.11; 95% CI: -0.22 to -0.01) (Figure 3).

Figure 3. Effect of Exercise on Fatigue.



When analyzed according to exercise regimen intensity, regimens categorized as mild did not have a significant effect on fatigue scores at 12 weeks compared to controls (SMD = 0.21; 95% CI: 0.02 to 0.39) (Figure 4). The moderate intensity studies showed no significant difference when compared to controls (SMD = -0.03; 95% CI: -0.22 to 0.15). Of the four studies categorized as strenuous, two had eligible data, and the analysis showed no significant difference between the exercise intervention and the control group (SMD = 0.18; 95% CI: -0.34 to 0.69). Due to the low number of strenuous regimen

studies, we combined them with the moderate intensity studies. Our analysis showed that this group's results favor the exercise intervention in improving fatigue outcomes over the control group, although it was not statistically significant (SMD = -0.10; 95% CI: -0.25 to 0.06) (Figure 5).

Figure 4. Effect of Mild Intensity Exercise on Fatigue Outcomes.

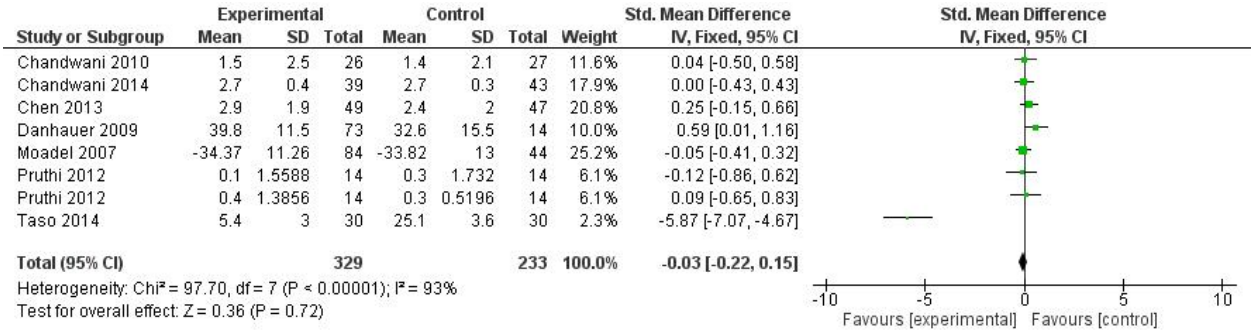
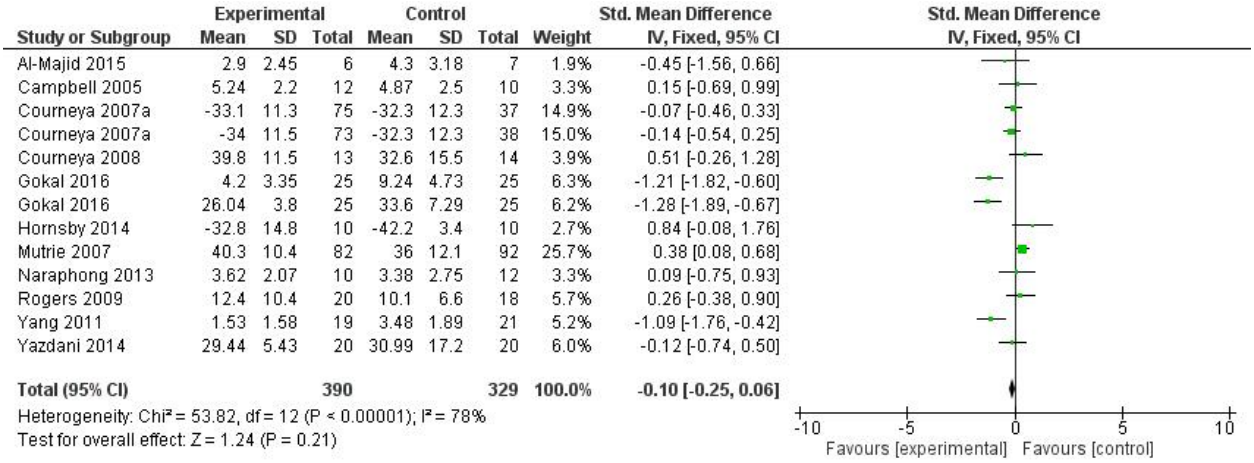


Figure 5. Effect of Moderate and Strenuous Intensity Exercise on Fatigue Outcomes.



According to exercise type, the aerobic intervention showed a significant improvement in fatigue scores at 12 weeks compared to baseline (SMD = -0.19; 95% CI: -0.37 to -0.01) (Figure 6). Of the four studies with exercise regimens consisting of anaerobic regimens only, one of them had eligible data, and showed non-significant effect on fatigue scores (SMD = -0.14; 95% CI: -0.54 to 0.25). The combination regimens equally showed no

effect on fatigue scores compared to controls (SMD = 0.04; 95% CI: -0.14 to 0.21) (Figure 7).

Figure 6. Effect of Aerobic Exercise on Fatigue.

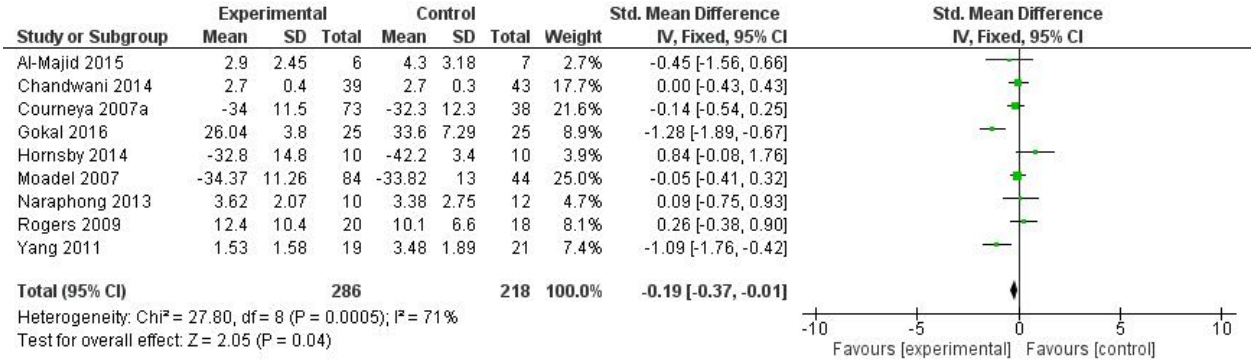
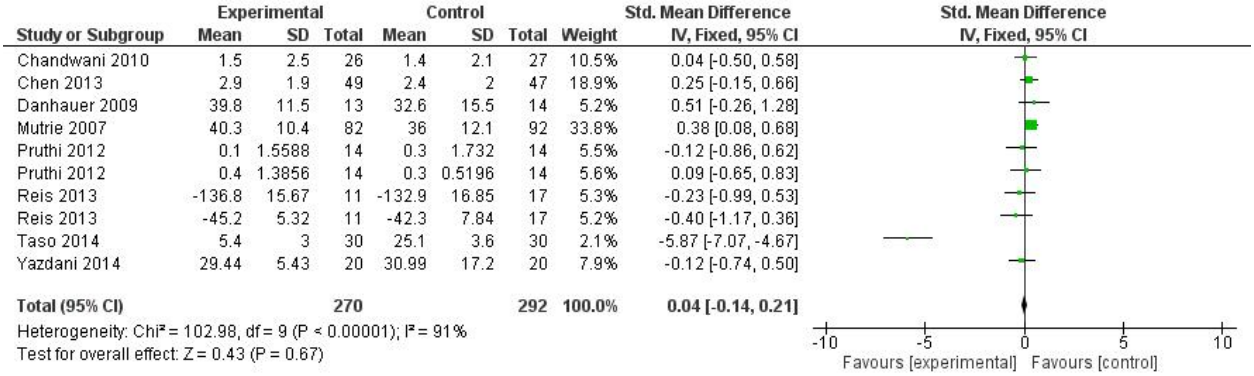


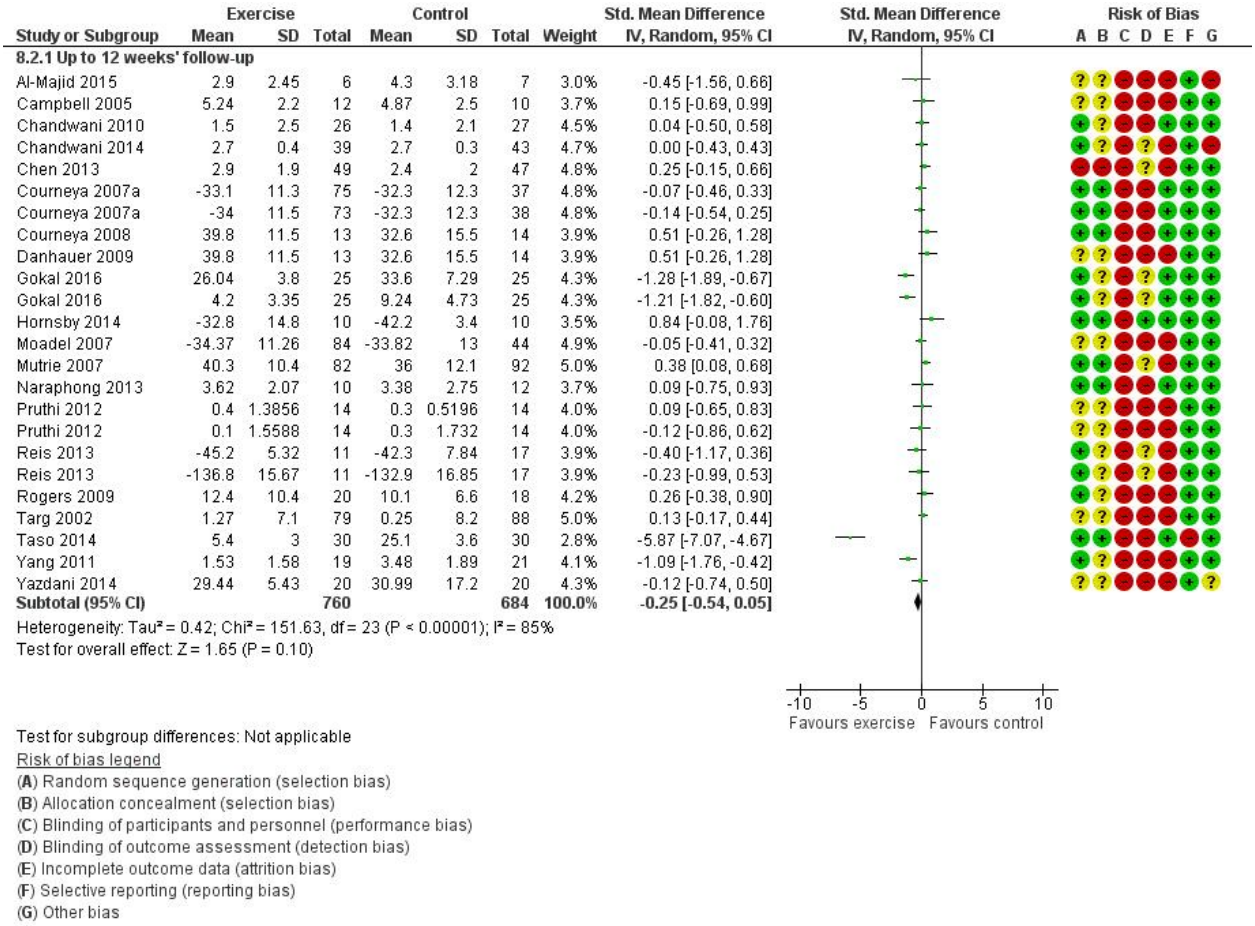
Figure 7. Effect of Combination Exercise on Fatigue.



Risk of Bias

The risk of bias was moderate to high in all studies selected. Performance bias was high in all trials as a result of the knowledge of the intervention by the participants. Selection bias was low in most studies due to use of appropriate randomization sequences, whereas detection and attrition biases were high (Figure 8).

Figure 8. Risk of Bias



Discussion

Our study showed that exercise during BC therapy significantly improves fatigue outcomes in patients with BC at 12 weeks. Our analysis also showed that no exercise intensity is superior to another. We also showed that aerobic regimens significantly improved fatigue outcomes in patients with BC at 12 weeks, but that neither anaerobic nor combination regimens showed such statistical effect.

Upon reviewing the literature, we found that most research includes exercise regimens initiated after therapy completion. A systematic review by Fairman et al. in 2016

examined exercise regimens only during active BC therapy in 17 studies [71]. Their results were reported based on the cancer therapy received: chemotherapy (CX), radiation (RT), chemotherapy and radiation (CXRT). They found that fatigue improved in patients on CX receiving resistance training (although the effect was negligible), and that fatigue worsened for those on combination exercise regimens, but that included only one trial. For patients receiving CXRT, large improvement in fatigue was seen in both aerobic, and anaerobic exercise regimens, but there were no studies with combination exercise regimens. The possible explanations for the differences with our results could be attributed to study selection (different inclusion criteria), their use of different time points at which outcomes were measured, and their use of Cohen's *d* effect size for calculating the results.

Our results are in agreement with the literature that exercise generally improves HRQoL and fatigue outcomes among patients who have completed cancer therapy [39, 72, 73]. However, another review found that the effect of aerobic exercise was non-significant, but that combination and anaerobic-only regimens had a significant effect on fatigue [73]. A review by Zeng et al. found that exercise significantly improves QoL in patients with cancer, and sub-group analysis revealed that aerobic exercise showed significant results, but that combination regimens did not (anaerobic-only analysis was not done) [72].

A potential explanation for the differences in findings is the high level of heterogeneity among studies. Studies vary by eligibility criteria, timing of treatment, exercise regimens, and instruments used for measuring outcomes. Inter-study variability is a potential barrier to accurate estimation of the differences in exercise regimens. Furthermore, bias was

moderate to high in all studies. Masking of participants and personnel was evidently high as it is not possible to blind either to the intervention. Reporting, detection, and attrition biases were also high. On the other hand, most studies had low selection bias as random sequences were most often adequately generated.

In our review, there was significant heterogeneity in the intensity of the exercise regimens, in the reporting of the intensity, and in the categorization of the intensity. Of the 20 studies that reported intensity as a category, only four complemented the intensity description with objective measurements. Nine studies did not report intensity either by objective measurement or by categorization. We were able to use the ACSM classification system for aerobic type exercise by converting objective measurements (such as percent of maximal HR) to intensity category, but such conversion system is not available for anaerobic exercise regimens.

Variability was also evident in outcome reporting. Fifteen instruments were used to report outcomes, 8 of which were multidimensional instruments, and 7 were unidimensional and unique for fatigue. Although we used the data from the more commonly used instruments, and used SMD analysis in order to compile the results together, this did not account for clinically significant effects detectable within each instrument. The multitude of measuring instruments prompted us to recommend psychometric analysis for the construct validity of the scales used, and between the different scales. This allowed better comparisons across the different scales used, and better interpretation of the results and their implication in clinical practice. This issue may be resolved with the consistent and

uniform use of the Patient Reported Outcomes Measurement Information System (PROMIS) [74].

In order for future studies to provide clearer understanding of what exercise regimens are effective in improving fatigue (and other HRQoL outcomes), the description of the exercise regimens needs to be more detailed. Ideally, all studies should report exercise intensity by objective measures that can be reproduced in other trials, and that can be compared to other studies without the need for conversion systems. This will allow the determination of what exercise regimens are effective in clinical practice.

Surprisingly, the reporting of the demographic information of the study participants was poor across studies. Only 40% of studies reported ethnicity, 26% socio-economic status, and 33% BMI. The poor reporting of demographics across studies limits generalizability and can also potentially account for the results obtained. Previous exercise history was reported only in 35% of the trials, and this parameter also needs to be reported better in order to account for potential contamination, and to better understand the effect of an exercise history on treatment effects on cancer. Future studies should collect and present these parameters more consistently.

Most studies compared an exercise regimen to a non-exercise control. Only two studies had two exercise regimens in addition to the control. This indicates that there is a need to conduct studies comparing different exercise regimens to each other (such as comparing an aerobic regimen to an anaerobic regimen), in order to better estimate which ones are more effective, and consequently help guide in the clinical management of patients with BC.

For cancer prevention, the American Cancer Society (ACS) recommends a minimum of 150 minutes of moderate-to-strenuous exercise a week; to consume a minimum of 5 servings of vegetables and fruits a day; and to not smoke [75]. Studies have shown that cancer patients who adhere to the exercise portion set by the ACS had better HRQoL outcomes than those who did not [62, 76]. Although all three lifestyle modifications recommendations of the ACS improved HRQoL independently, exercise showed the strongest association [77].

The ACS recommends exercise during cancer therapy, and maintaining activity as much as possible [75]. The ACSM concluded that exercise is safe and efficacious in improving fatigue during cancer treatment. It suggests that the exercise regimen should be individualized according to the cancer type, the individual preferences, and to the therapy, [78]. This highlights the importance of implementing an exercise regimen during cancer therapy.

While there are specific recommendations for exercise regimens for the prevention of cancer, and for cancer survivors, there are no specific recommendations for regimens during active therapy. Although individualized regimens are recommended, there are currently no standardized guidelines that can help guide either the patient or the clinicians in prescribing an individualized exercise regimen in active treatment. Moreover, there is a lack of awareness by healthcare providers regarding appropriate exercise recommendations [79]. Given the benefits of exercise regimens, and the importance of starting as early as early as possible, we agree with the literature that more research is needed to determine the optimal exercise parameters in the categories of intensity,

regimen duration, type, frequency, and session duration [39, 72]. This will allow specific instructions to be provided, and for the patients and clinicians to have a reference during active cancer therapy.

Conclusion

Our review demonstrated that exercise, specifically aerobic type, is effective in improving fatigue outcomes at 12 weeks in patients with BC undergoing active therapy. However, the heterogeneity of regimens and in outcomes reporting in the literature are substantial. This is a potential reason that can explain why other regimens were not found to be effective. We also found that there is a lack of guidelines for exercise regimens during active cancer treatment. The variability in exercise regimens allows for many choices to select from, but it is not known which ones are clinically effective. This highlights the necessity to conduct more robust studies that can help in establishing specific regimens and recommendations to guide the patients and the clinicians. Exercise is a safe and efficacious intervention that can provide significant short and long-term benefits to fatigue and HRQoL to patients with BC. Establishing guidelines is urgently needed, and can be an important step in improving outcomes.

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