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Title:

Effects of physical activity changes induced by behavior change interventions on inflammation and patient-centered outcomes in breast cancer survivors: a systematic review

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ABSTRACT

**Purpose:** Ample evidence supports using behavior change interventions to increase physical activity (PA) in breast cancer survivors (BCSs). This systematic review aims to investigate if behavior change intervention-induced changes in PA can modulate inflammation and improve patient-centered outcomes in this population.

**Methods:** We searched six databases and synthesized evidence from 17 RCTs reporting between-group changes for inflammatory biomarkers, cancer-related fatigue (CRF), aerobic fitness, and/or quality of life (QoL).

**Results:** Two RCTs reported small-to-medium effect size decreases in the ratios of IL6:IL-10 and TNF-a:IL-10 post-intervention. Five RCTs reported significant intervention improvements on aerobic fitness post-intervention; three trials further showed sustained intervention effects at two- and three-month follow-up. Four trials reported beneficial reductions in CRF post-intervention; three trials also showed sustained intervention effects at follow-up. Three trials showed significant improvements in QoL at three and six months; two trials demonstrated sustained intervention effects at two- and three-month follow-up. Further, six trials reported significant improvements in at least one QoL variable.

**Conclusion:** We found limited evidence to support the beneficial effects of PA behavior change interventions on inflammation and patient-centered outcomes in BCSs. Larger RCTs are particularly warranted to explore the causal impact on cytokine balance and possible mediating effects on patient-centered outcomes.

**Keywords:** breast cancer survivors; behavior change interventions; physical activity; inflammation; patient-centered outcomes
INTRODUCTION
Globally, access to early screening modalities and effective treatment options have led to an appreciable decrease in breast cancer mortality (Siegel et al., 2020). For instance, in the United States of America, available data have shown a reduction in breast cancer mortality from 33.2 per 100 000 women to 20.1 per 100 000 women between 1989 and 2018 (i.e., ≈ 40% decline) and an average 5-year relative survival rate of 91% (Siegel et al., 2020). As breast cancer outcomes continue to improve, people with breast cancer now live much longer, sadly, with common consequences of cancer treatment. These treatment-related adverse effects are numerous and include chronic inflammation, cancer-related fatigue (CRF), compromised aerobic fitness, sleep dysfunction, pain, emotional and psychosocial disorders, etcetera (Collado-Hidalgo et al., 2006; Mrozek & Shapiro, 2005). Among breast cancer survivors (BCS), there is a significant reduction in the ability to perform daily activities. With negative impacts on general well-being and quality of life (QoL), these challenges may continue for many years in one out of every three persons, even after treatment (Penttinen et al., 2011; Verhagen & Bleijenberg, 2002).

Previous [exercise efficacy] trials, for example, trials focusing on delivering specific exercise dose to selected samples in a well-controlled research environment, have demonstrated benefits of physical activity/exercise in BCSs (Lahart et al., 2018). Although these interventions have been remarkable given their potential to improve patient-centered outcomes, little progress has only been made in translating their results to a ‘free living’ population of BCSs. Exploring and replicating the gains of exercise efficacy trials in a ‘free living’ population of BCSs may be daunting given the ‘real world’ challenges of achieving specific exercise dose and “sustainable physical activity program” (White et al., 2009). Several factors may determine PA uptake but behavior change, particularly at the individual level, is essential (Kaushal et al., 2018).

PA behavior change interventions, typically involving a set or sets of behavior change strategies often rooted in behavior change theories, are designed to increase PA behavior in a ‘real world’ situation to obtain the benefits of an optimal PA program (Courneya, 2010; Glanz & Bishop, 2010). PA behavior change interventions may involve structured exercise programs, exercise training modalities, or even controlled settings. However, as opposed to achieving specific exercise dose (which is characteristic of exercise efficacy studies), the primary focus of PA behavior change interventions is to create a sustained increase in habitual exercise behavior, among others, by increasing one’s “perceived capability to enact PA and increase the expected positive outcomes of PA through…behavior change techniques” (Courneya, 2010; Kaushal et al., 2018). By providing a unique opportunity to explore and translate the therapeutic benefits of efficacy trials into practice, PA behavior change interventions hold promise for the larger population of BCSs.
Evidence now exists on the ability of behavior change interventions to increase and maintain PA in cancer survivors (Bluethmann et al., 2015; Finne et al., 2018; Grimmett et al., 2019). But the ability of these interventions or the resultant increase in PA to translate to beneficial effects on patient-centered outcomes, i.e., outcomes that are considered relevant from patients’ perspectives, is yet to be established. Therefore, this systematic review aims to investigate if behavior change intervention-induced changes in PA can modulate inflammation and improve patient-centered outcomes in BCSs.

METHODS

The systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42017068138) and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) 2015 guideline (Moher et al., 2009).

Eligibility criteria

**Study design and language:** RCTs of BCSs published in the English language.

**Population:** We defined a BCS according to the National Cancer Institute to include any woman diagnosed with breast cancer, from the time of diagnosis through the balance of her life (Marzorati et al., 2017). We, therefore, included trials that randomized women diagnosed with breast cancer, regardless of age, disease stage, or whether participants had completed active cancer treatment at the time of randomization.

**Intervention:** We included trials that aimed to promote an increase in regular PA participation using identifiable behavior change strategies based on previously established behavior change technique taxonomy or “BCT taxonomy v1” (Michie et al., 2013). We excluded trials combining PA and other components, for instance, weight loss programs or dietary modifications, when we could not rule out synergistic effects.

**Comparator:** We included trials that compared PA behavior change interventions to either an active control including standard therapies other than PA behavior change interventions, usual care, or no treatment/waitlist control.

**Outcomes:** RCTs were only included if a distinct assessment was conducted, and results were provided at baseline and post-intervention and/or ≤ six months follow-up for the following outcomes: Interleukin (IL)-6, Tumor Necrosis Factor (TNF)-α, IL-10, ratios of IL-6 to IL-10 and TNF-α to IL-10, CRF, aerobic fitness, and/or QoL.

Information sources and search strategy

Two authors (EE and UA) searched six databases (CINAHL, the Cochrane Library, ProQuest, AMED, PubMed/ MEDLINE, and Web of Science Core Collection), including trial registers and a directory of open-access repository websites independently up to September 2020. Comprehensive search strings using keywords and controlled vocabularies, including (but not limited to) breast cancer, physical activity, long-term physical activity, sustained physical activity, exercise, exercise
program, supervised exercise, home-based exercise, home-based physical activity, physical activity behavior change, fatigue, cancer-related fatigue, chronic fatigue, long-term fatigue, aerobic function, aerobic fitness, cardiopulmonary fitness, \( \text{VO}_{2\text{max}} \), inflammation, cytokines, inflammatory biomarkers, IL-6, IL-10, TNF-a, and quality of life, in addition to appropriate search syntax and Boolean operators were employed in conducting searches. A search strategy (Additional File 1) was first developed and piloted in the National Library of Medicine database and adapted for searches in other databases. From the reference lists of identified studies and recently published systematic reviews, we further searched for articles relevant to the review.

**Study record, screening, and data management**

We exported the retrieved citations to RefWorks to remove duplicates and further to Microsoft Excel computer software (Microsoft Excel. Redmond, Washington: Microsoft, 2010) to facilitate the screening and selection of articles. Two reviewers (UA and EE) screened the titles and abstracts of all the retrieved articles independently. Eligibility questions and forms were initially developed, piloted, and refined by the review team to drive the screening and selection process. Following the screening of the titles and abstracts of the retrieved studies, UA and EE further read the full texts of eligible studies to determine their suitability for inclusion in the review. Differences in opinions regarding inclusion or exclusion at some points were resolved by discussion and reflection in consultation with EA.

**Risk of bias assessment in individual studies**

Using the Cochrane Collaboration’s Tool for Risk of Bias Assessment, EE and AU assessed each of the eligible RCTs for potential risk of bias (ROB) independently in the key domains of (i) selection bias (random sequence generation, allocation concealment), (ii) performance bias (blinding of personnel and participants), (iii) detection bias (blinding of outcome assessors), (iv) bias due to attrition (incomplete outcome data), (v) reporting bias (selective reporting), and (vi) other bias (other potential sources of bias not captured elsewhere). For each trial, potential ROB was reported as YES (for example, when there is a presence of a source of risk or potential risk of bias), NO (for example, when there is no source of risk or potential risk of bias), and NOT CLEAR (for example, when the presence of a source of risk or potential risk of bias could not be ascertained). Further, studies were rated as high-quality trials or low-quality trials if there were < 3 or ≥3 identifiable sources of bias, respectively. Again, differences in opinions occurring at this stage were resolved by discussion in consultation EA.
Data collection processes

Data items
We extracted data from a range of variables, including participants’ characteristics, sample size, intervention (components, duration, follow-up), control, outcome(s) (names, outcome measures, points of assessment), and results.

Data analysis
Given the variability and methodological heterogeneity across the included studies, data could not be quantitatively analyzed using meta-analysis. However, we analyzed our data using narrative synthesis and present a summary of findings tables (Tables 1 and 3) to enhance readers’ understanding of the findings.

RESULTS

Study inclusion, participants characteristics, and risk of bias assessment
We included 17 RCTs (22 studies) reporting data on 2119 participants in the review (Baruth et al., 2015; Basen-Engquist et al., 2006; Cadmus et al., 2009; Eakin et al., 2012; Cornette et al., 2015; Galiano-Castillo et al., 2016; Hayes et al., 2013; Lahart et al., 2016; Ligibel et al., 2016; Pinto et al., 2005, 2008; Rogers et al., 2013, 2014, 2015, 2016, 2017; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Short et al., 2015; Travier et al., 2015; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007). Details of the studies’ screening and selection processes, including exclusionary reasons, are provided in Figure 1. The number of participants in the included studies ranged from 28 to 377 (Rogers et al., 2013; J. K. H. Vallance et al., 2007). Participants in the included trials were >18 years and sedentary or had exercised < 150 minutes of moderate- to vigorous-intensity PA per week at the time of baseline assessment. Also, most of the participants (>80%) had completed primary cancer treatments (i.e., chemotherapy, radiotherapy, etc.) prior to baseline assessment (Table 1).

The data on the risk of bias for the included RCTs are provided in Table 2. All the trials were particularly rigorous for random sequence generation and selective reporting. Allocation concealment was carried out in nine trials (Cadmus et al., 2009; Galiano-Castillo et al., 2016; Lahart et al., 2016; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Rogers et al., 2014, 2015, 2016, 2017; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Short et al., 2015; Travier et al., 2015; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007). Evidence of participants and personnel blinding lacked in the included trials. Eight trials carried out blinding of outcome assessors and were free of detection bias (Basen-Engquist et al., 2006; Galiano-Castillo et al., 2016; Hayes et al., 2013; Ligibel et al., 2016; Rogers et al., 2013, 2014, 2015, 2016, 2017; Travier et al., 2015). Thirteen trials were free of bias due to attrition (Basen-Engquist et al., 2006; Eakin et al., 2012; Cornette et al., 2015; Galiano-Castillo et
Other potential sources of bias may include loss to follow-up and small sample size (pilot studies) (Basen-Engquist et al., 2006; Cornette et al., 2015; Rogers et al., 2013, 2014; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007). Overall, eight RCTs were adjudged as high-quality trials (Galiano-Castillo et al., 2016; Hayes et al., 2013; Rogers et al., 2014, 2015, 2016, 2017; Travier et al., 2015; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007).

**Intervention description**

The included trials varied considerably in the intervention components. However, a combination of different behavior change techniques was evidently used to increase PA (Baruth et al., 2015; Basen-Engquist et al., 2006; Cadmus et al., 2009; Eakin et al., 2012; Cornette et al., 2015; Galiano-Castillo et al., 2016; Hayes et al., 2013; Lahart et al., 2016; Ligibel et al., 2016; Pinto et al., 2005, 2008; Rogers et al., 2013, 2014, 2015, 2016, 2017; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Short et al., 2015; Travier et al., 2015; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007). Strategies such as group sessions, counseling, telephone calls, internet deliveries, weekly tip sheets, leaflets, PA packs, handouts, emails, DVDs, heart rate monitors, pedometers, etc., were generally utilized in all the included trials (Baruth et al., 2015; Basen-Engquist et al., 2006; Cadmus et al., 2009; Eakin et al., 2012; Cornette et al., 2015; Galiano-Castillo et al., 2016; Hayes et al., 2013; Lahart et al., 2016; Ligibel et al., 2016; Pinto et al., 2005, 2008; Rogers et al., 2013, 2014, 2015, 2016, 2017; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Short et al., 2015; Travier et al., 2015; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007). Eight trials were based on the Social Cognitive Theory (Baruth et al., 2015; Eakin et al., 2012; Rogers et al., 2013, 2014, 2015, 2016; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Short et al., 2015; Travier et al., 2015), three trials on the transtheoretical model (Basen-Engquist et al., 2006; Cadmus et al., 2009; Pinto et al., 2005, 2008) and two trials on the theory of planned behavior (Cadmus et al., 2009; Short et al., 2015). Common to most of the included studies was the gradual transitioning (or tapering) of interventions from supervised (specialist-driven) to unsupervised/home-based (patient-driven) programs. Self-efficacy or behavioral control was the most targeted behavior change construct (Baruth et al., 2015; Eakin et al., 2012; Ligibel et al., 2016; Rogers et al., 2013, 2014, 2015, 2016; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Short et al., 2015; Travier et al., 2015). The duration of interventions varied between eight weeks and 27 weeks (Cornette et al., 2015; Galiano-Castillo et al., 2016), with most trials lasting for three or six months. PA behavior change interventions were
delivered and monitored by different personnel, including physiotherapists, exercise physiologists, and clinical psychologists (Tables 1 and 3).

**Between-group differences on review outcomes**

**Inflammation**

Two pilot trials provided data for the effect of PA behavior change intervention on inflammation (Rogers et al., 2013, 2014). Both trials reported small-to-medium effect size decreases in the ratios of IL-6:IL-10 and TNF-α:IL-10 following 12-week intervention programs (Table 3).

**Aerobic fitness**

Eleven articles from 10 trials reported data on aerobic fitness. Five trials reported no significant differences in the changes in oxygen consumption or heart rate immediately post interventions or at follow-up (Cornette et al., 2015; Ligibel et al., 2016; Rogers et al., 2014; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Travier et al., 2015). In contrast, One trial reported an improvement in Submaximal VO₂max after 12 weeks of PA behavior change intervention (3.7 vs. 0.1; p = 0.015) (Rogers et al., 2013). A similar trial reported a significant intervention effect but at three months follow-up (1.8; 95%CI: 0.8 to 2.8; p = 0.001) (Rogers et al., 2015). One trial reported a significant reduction in the time taken to perform a 1-mile test after a 12-week home-based moderate-intensity PA program (−1.11 vs. 0.20; p = 0.001) (Pinto et al., 2005) and at six months follow-up (−0.93 vs. -0.19; p = 0.023) (Pinto et al., 2008). Another study showed beneficial reductions in heart rate for face-to-face (−9.0; 95%CI: -12.9 to -5.2; p <0.05) and telephone-delivered interventions (−6.3; 95%CI: -10.2 to -2.4; p <0.05) 2 months post-intervention (Hayes et al., 2013). Also, one trial reported a significant improvement in the six-minute walk test (measured in feet) (1643 vs. 1546; p = 0.005) after intervention (Basen-Engquist et al. 2006) (Table 3).

**Cancer-related fatigue**

Seventeen articles (14 RCTs) provided data on the changes in the outcome measures of CRF after the intervention and/or at follow-up. CRF was assessed using different tools, including the Functional Assessment for Chronic Illness Therapy – Fatigue Subscale (Baruth et al., 2015; Eakin et al., 2012; Hayes et al., 2013; Ligibel et al., 2016; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009; Short et al., 2015; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007), Linear Analogue Scale (Pinto et al., 2005, 2008), the Fatigue Symptom Inventory (Rogers et al., 2013, 2014, 2017), the Revised Piper Fatigue Scale (Galiano-Castillo et al., 2016), and the Multi-dimensional Fatigue Inventory-20 (Cornette et al., 2015; Travier et al., 2015) (Table 1).
Two trials reported beneficial reductions in CRF immediately post interventions (Galiano-Castillo et al., 2016; Pinto et al., 2005), which was further sustained at three months (Pinto et al., 2008) and six months (Galiano-Castillo et al., 2016) follow-up. On different fatigue composites, Rogers et al. 2017 reported significant decreases in fatigue intensity (-0.6; 95% CI: -0.1 to -0.2; p = 0.004) and interference (-0.8; 95% CI: -1.3 to -0.4; p < 0.001) at 12 weeks and a sustained intervention effect at 3 months follow-up. Further, Travier et al. 2015 reported a significant intervention effect on physical fatigue (−1.3; 95%CI: −2.5 to −0.1; p< 0.05) following an 18-week PA behavior change intervention. Other studies providing data for CRF did not report any significant intervention effects.

Quality of life

Fourteen trials (16 studies) reported findings for the effect of PA behavior change interventions on QoL. QoL was measured with Functional Assessment of Cancer Therapy-Breast (FACT-B) (Eakin et al., 2012; Hayes et al., 2013; Lahart et al., 2016; Rogers et al., 2015; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenten, et al., 2009; Short et al., 2015; J. K. Vallance et al., 2008; J. K. H. Vallance et al., 2007), The Medical Outcomes 36-item Short-Form Health Survey (SF-36) (Basen-Engquist et al., 2006; Cadmus et al., 2009; Rogers et al., 2016), The International Breast Cancer Study Group (IBCSG) questionnaire (Baruth et al., 2015), The European Organization of Research and Treatment of Cancer (EORTC) Questionnaire (Cornette et al., 2015; Galiano-Castillo et al., 2016; Ligibel et al., 2016; Travier et al., 2015), and Satisfaction with Life Scale (SWLS) (Rogers et al., 2016) (Table 1).

Three trials reported significant post-intervention effects on QoL (FACT-B) at 12 weeks (Rogers et al., 2015; J. K. H. Vallance et al., 2007) and six months (Lahart et al., 2016). Further, two trials reported a sustained significant intervention effect on QoL at two months (Hayes et al., 2013) and three months follow-ups (Rogers et al., 2015) (Table 3).

Many trials reported significant intervention improvements in different variables of QoL. For instance, three trials reported significant improvements in physical well-being (Rogers et al., 2015), functional well-being (Lahart et al., 2016; Rogers et al., 2015), emotional well-being (Rogers et al., 2015), social well-being (Rogers, Hopkins-Price, Vicari, Pamenten, et al., 2009), trial outcome index (Lahart et al., 2016; Rogers et al., 2015), and breast cancer additional concern (Lahart et al., 2016) measured with FACT-B immediately after the intervention, with continued intervention effects on physical well-being (Rogers et al., 2015) and social well-being (Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009) at three months follow-up. Two trials reported significant intervention effects on the following composites of EORTC QLQ-C30 after intervention: Global health (Galiano-Castillo et al., 2016), physical functioning (Galiano-Castillo et al., 2016), cognitive functioning (Galiano-Castillo et al., 2016), role functioning (Galiano-Castillo et al., 2016), and dyspnea (Ligibel et al., 2016), with significant intervention effects maintained for global health (Galiano-Castillo et al., 2016)
2016), physical functioning (Galiano-Castillo et al., 2016), and cognitive functioning (Galiano-Castillo et al., 2016) at six months follow-up. Further, Rogers et al. 2016 reposted significant intervention improvements for all the SF-36 composites/domains and the SWLS after intervention with sustained intervention effects on vitality and mental health domains of SF-36 at three months follow-up. Similarly, Bansen-Engquist et al. 2006 reported significantly higher scores (indicating better QoL) for SF-36 general health and bodily pain domains after a six-month intervention program. Other studies providing data for QoL or its composites did not report any significant intervention effects after interventions or at follow-up (Table 3).

DISCUSSION

We conducted a review of seventeen RCTs [including 2119 participants] evaluating the effects of behavior change intervention-induced PA on inflammation and patient-centered outcomes in BCSs. We observed that the lack of allocation concealment, participant/personnel, and assessor blinding were the major potential sources of bias in the included studies. Given that findings were generally from a few high-quality trials, the combined evidence is of small-to-moderate quality and should be utilized cautiously in making clinical decisions. Albeit from a limited number of studies, the combined evidence demonstrates the potential to modulate cytokine profile in the direction beneficial for BCSs and improve CRF, aerobic capacity, and QoL in BCSs using PA behavior change interventions.

Inflammation

Two pilot trials reporting findings for the effects of PA behavior change interventions on inflammation did not show any significant between-group effects on the cytokine levels at post interventions (Rogers et al., 2013, 2014). However, the changes reported by both trials are suggestive of potential intervention benefits that could be confirmed in a larger population-based trial. For instance, although IL-6, TNF-α, and IL-10 did not change, small-to-medium decreases in IL-6:IL-10 and TNF-α:IL-10 ratios were consistently reported in both trials (Rogers et al., 2013, 2014). A previous meta-analysis showed that acute exercise might reduce serum concentrations of proinflammatory cytokines, such as IL-6 and TNF-α, in BCSs (Meneses-Echavez et al., 2016). Behavior change interventions do not deliver acute exercise bouts like exercise efficacy trials. Instead, they focus on creating a sustained increase in exercise behavior. Acute bouts of exercise may only produce a transient effect on serum inflammatory mediators (Meneses-Echavez et al., 2016). And given the chronic and low-grade nature of inflammation in BCSs, the short-lived effect of acute exercise bouts is unlikely to create long-term (adaptive) changes in the cytokine levels (Meneses-Echavez et al., 2016). BCSs may not achieve a rapid change in serum inflammatory biomarkers after receiving a PA behavior change intervention. However, the combined evidence from the two pilot trials suggests that PA behavior change interventions may modulate the cytokine system to create a
balance in the ratios of pro:anti-inflammatory biomarkers to cause an overall reduction in chronic inflammation (Rogers et al., 2013, 2014). This hypothesis warrants further investigations using sufficiently powered and more prolonged duration trials.

**Patient-centered outcomes**

The broader evidence from the included trials supports PA behavior change interventions to improve aerobic capacity in breast cancer survivors. Three trials that were particularly rigorous in random sequence generation, allocation concealment, assessor blinding, and outcome reporting recorded beneficial improvements in oxygen consumption or heart rate after interventions (Rogers et al., 2013, 2015) and at follow-up (Hayes et al., 2013; Rogers et al., 2015). Two other trials showed significant intervention effects on six-minute and one-mile walk tests following PA behavior change interventions and at follow-up (Basen-Engquist et al., 2006; Pinto et al., 2005, 2008). Studies reporting nonsignificant intervention effects were generally low quality or pilot studies (Cornette et al., 2015; Ligibel et al., 2016; Rogers et al., 2014; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009).

Fourteen trials provided data for CRF. We found that only two trials recorded beneficial overall fatigue reductions after 8 to 12-week PA behavior change interventions (Galiano-Castillo et al., 2016; Pinto et al., 2005) and six months follow-up (Galiano-Castillo et al., 2016; Pinto et al., 2008). In two high-quality trials, PA behavior change interventions further decreased physical fatigue (Travier et al., 2015) and fatigue intensity/interference with daily activities (Rogers et al., 2017) after the interventions and at three months follow-up (Rogers et al., 2017). PA behavior change interventions also improved QoL in BCSs, with intervention benefits sustained at least two months (Hayes et al., 2013; Lahart et al., 2016; Rogers et al., 2015; J. K. H. Vallance et al., 2007). Further, we found that many trials reported significant improvements in different variables and composites of QoL in BCSs even at follow-up (Basen-Engquist et al., 2006; Galiano-Castillo et al., 2016; Lahart et al., 2016; Ligibel et al., 2016; Rogers et al., 2015, 2016; Rogers, Hopkins-Price, Vicari, Markwell, et al., 2009; Rogers, Hopkins-Price, Vicari, Pamenter, et al., 2009). Additionally, PA behavior change intervention resulted in satisfaction with life in BCSs (Rogers et al., 2016).

By focusing only on PA behavior change interventions and patient-centered outcomes in BCSs, our review appears to be the first of its kind, making it challenging to compare these findings with previous works adequately. However, compared to previous studies, particularly a recent Cochrane review, our review lends credibility to future investigations on the potential role of behavior change intervention-induced PA for improving patient-centered outcomes in BCSs (Battaglini et al., 2014; Lahart et al., 2018). Our recent findings, although not conclusive, are supported by the recent review by Lahart et al. 2018. In their meta-analysis, they showed small-to-moderate effect size benefits for CRF, aerobic fitness, and QoL in BCSs after receiving PA interventions (Lahart et al., 2018). PA
behavior change interventions may significantly improve treatment-related outcomes in BCSs, but there is a need to confirm this hypothesis further in future trials. Remarkably, our recent findings on the potential of PA behavior change interventions to modulate the cytokine pool and possibly create a pro:anti-inflammatory cytokine balance to favor an overall reduction in chronic inflammation is most worthy of further investigations. Evidence exists to show that chronic inflammation partly mediates treatment-related adverse effects in BCSs (Meneses-Echavez et al., 2016). The ability of [a sustained increase in] regular PA programs to effectively mitigate these negative effects, particularly CRF, may also be mediated by a reduction in chronic inflammation (Meneses-Echavez et al., 2016). Although the current evidence is limited, we recommend integrating PA behavior change interventions in routine management and cancer survivorship plans for BCSs, given that previous studies have demonstrated the safety of PA in BCSs (Battaglini et al., 2014).

We could not calculate an overall effect size for each outcome given the limited number of trials reporting on these outcomes or their composites, besides the marked variation and methodological heterogeneity in the included trials. We consider this a major limitation for the current review. However, our review’s strength is evident in the comprehensiveness of the databases searched and the robustness of the search and the data extraction processes.

CONCLUSIONS
Our review has revealed the potential of PA behavior change interventions to modulate inflammation and improve CRF, aerobic fitness, and QoL in BCSs. The positive findings reported in our review are generally from a few high-quality trials and must be interpreted with caution in making clinical decisions. Further investigations are warranted to confirm the abilities of PA behavior change interventions to improve patient-centered outcomes in BCSs effectively. Focus should be given to chronic inflammation as a potential mediator of intervention effects. Future trials should aim to achieve well-powered/relatively homogenous samples and longer intervention durations. We also recommend the integration of PA behavior change interventions in routine breast cancer management and survivorship plans.

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Data Availability
There is no data available.

Competing interest
The authors declare that they have no competing interests.
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REFERENCES


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<td>Cytokines: IL-6, IL-10, and TNF-a (12 hr fast; MILLIPLEX MAP human sensitive high cytokine assay) Detection limits were 0.64pg.mL⁻¹ for IL-6, IL-10, and TNF-alpha</td>
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<td>BCSs (n=28; stage I, II, IIIA), off treatment</td>
<td>Social Cognitive Theory (6 discussion sessions + face-to-face update counseling)</td>
<td>G1: 3-month exercise intervention (150 min/wk supervised → HB moderate-intensity aerobic walking, twice-weekly resistance training with resistance bands)</td>
<td>Cytokines: IL-6, IL-10 and TNF-a (12 hr fast; high sensitive high cytokine assay) with a detection limits of 0.1pg.mL⁻¹ for IL-6, 0.15pg.mL⁻¹ for IL-10, and 0.05pg.mL⁻¹ for TNF-a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Go: Written material on healthy eating and being active; no specific recommendation on exercise behavior</td>
<td>Fatigue intensity/interference: FSI Aerobic fitness: Submaximal VO₂max.</td>
</tr>
<tr>
<td>Rogers et al. 2015, 2016, 2017</td>
<td>Post-primary treatment BCS (n=222; a history of ductus carcinoma in situ or stage I-III A)</td>
<td>Social Cognitive Theory (6 discussion sessions + face-to-face update counseling)</td>
<td>G1: 3-month tapered exercise intervention (supervised → HB) to attain ≥150 min/wk moderate-intensity physical activity at week 7</td>
<td>Aerobic fitness: Submaximal VO₂max Fatigue intensity/interference: FSI QoL: FACT-B, SF-6, SWLS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Go: Written material on healthy eating and being active; no specific recommendation on exercise behavior</td>
<td></td>
</tr>
<tr>
<td>Hayes et al. 2013</td>
<td>Women diagnosed with invasive breast cancer (n=194; stage: 0-III).</td>
<td>To provide for behavior change, the intervention was initially specialist-driven but continued as patient-driven over time, allowing participants to develop knowledge, exercise skills, and confidence</td>
<td>G1: 8-month intervention program of both aerobic and strength-based exercises (≥180 min of exercise per week)</td>
<td>Fatigue: FACIT-Fatigue Fitness: 3mins step test (Lower heart rate indicated higher fitness) QoL: FACT-B+4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Go: Received written or verbal encouragement for PA participation during and after breast cancer</td>
<td></td>
</tr>
<tr>
<td>Rogers et al. 2009a, 2009b</td>
<td>Sedentary BCS under hormonal therapy (n=41; stage: I-III A.)</td>
<td>Social Cognitive Theory (6 discussion sessions + 3 face-to-face update counseling)</td>
<td>G1: 3-month supervised → HB exercise intervention targeting 150 min of moderate-intensity exercise per week</td>
<td>Aerobic fitness. Submaximal VO₂max. Fatigue: FACT-Fatigue QoL: FACT-B</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Exercise Prescription</td>
<td>Outcome Measures</td>
<td>Study Type</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>--------------</td>
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</tr>
<tr>
<td>Baruth et al. 2015</td>
<td>Early BCSs post treatment (n= 32; stage: I-III).</td>
<td>Social Cognitive Theory (Initial one-on-one counseling session + short telephone counseling calls)</td>
<td>G1: 12-week home-based walking program</td>
<td>Fatigue: FACT-Fatigue QoL: SF-36; IBCSG QoL Core Questionnaire</td>
</tr>
<tr>
<td>Pinto et al. 2005, 2008</td>
<td>BCSs post-treatment (n=86; stage: 0-II).</td>
<td>Transtheoretical Model (weekly PA counseling via phone calls + mailed weekly tip sheets on PA and cancer survivorship)</td>
<td>G1: In-person instruction on exercising at moderate-intensity HB exercise level</td>
<td>Aerobic fitness: Rockport 1-mile walk test Fatigue: Linear analog scale</td>
</tr>
<tr>
<td>Galiano-Castillo et al. 2016</td>
<td>BCSs post-adjuvant therapy (n=81; stage: I-III).</td>
<td>Tailored exercise program + telephone calls to improve adherence</td>
<td>G1: 8-week individualized internet-based aerobic + resistance exercise intervention</td>
<td>Fatigue: R-PFS (revised) QoL: EORTC QLQ-C30</td>
</tr>
</tbody>
</table>

Participants were advised to continue with exercise prescription at the end of the exercise program

G0: Written material on healthy eating and being active; no specific recommendation on exercise behavior
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Cornette et al. 2015 | Breast cancer patients under chemotherapy (n=44; stage: I-IIIB) | Weekly telephone calls for motivation, encouragement, and monitoring | G1: 27 weeks of supervised HB adapted PA (endurance and strength training)  
G0: Conventional management; maintained current PA level |
G2: Step pedometer + 12-week step calendar  
G3: Print material + Step pedometer The COM group  
G0: Standard PA recommendation |
| Basen-Engquist et al. 2006 | BCS post treatment (n = 60; stage: 0-4) | Transtheoretical model (group meetings + pedometer) | G1: 21 sessions of 90 min group meetings + booklets about increasing PA matched to participants' stage of readiness  
G0: Written materials on breast cancer-related topics; no group meeting |
| Ligibel et al. 2016 | Individuals with metastatic breast cancer (n=101; stage: I-IIIA) | Series of in-person and telephone contacts for building self-efficacy | G1: 16-week supervised + HB moderate-intensity aerobic exercise program  
G0: 16 weeks of routine care |
| Lahart et al. 2016 | BCS diagnosed with invasive breast cancer (n = 80; Stage: I-III) | Face-to-face counseling + telephone calls + mailed PA reminder leaflets + PA packs and DVDs | G1: Unsupervised home-based PA (exercise goal of 30mins of moderate-intensity physical activity 3-5days/week at month 1-3 and 5-7days/week at month 3-6 of intervention)  
G0: Standard information on PA; maintained current lifestyle |
| Cadmus et al. 2009 | Newly diagnosed BCS (n = 50; stage 0-IIa) | Theory of Planned Behavior and The Transtheoretical Model (Telephone meetings + Polar heart rate monitor + weekly information handouts) | G1: 6 month-home based PA (exercise goal of 30mins moderate-vigorous intensity exercise)  
G0: Participants did not receive the study's PA program although they could exercise on their own |
| Travier et al. 2005 | Breast cancer patients (n = 204) | Social Cognitive Theory (36 Group sessions) | G1: 18-week individualized supervised aerobic + resistance exercise program (60 minute/session, 2 times per week)  
Fatigue: MFI  
Aerobic fitness: Peak VO2  
QoL: EORTC Questionnaire |
Participants maintained their habitual physical activity pattern.

**Key:**
- BCSs = Breast cancer survivors;
- PA = Physical activity;
- HB = Home based;
- G1/G2/G3 = Intervention groups;
- G0 = Control group;
- FSI = Fatigue Symptom Inventory;
- PROMIS = Patient-Reported Outcomes Measurement Information System;
- FACT-F = Functional Assessment of Cancer Therapy-Fatigue;
- FACIT = Functional Assessment of Chronic Illness Therapy-Fatigue Scale;
- R-PFS = The Piper Fatigue Scale-revised;
- MFI-20 = Multidimensional fatigue inventory;
- QoL = Quality of life;
- FACT-B = Functional Assessment of Cancer Therapy-Breast questionnaire;
- SF-36 = The Medical Outcomes 36-item Short-Form Health Survey;
- EORTC QLQ-C30 = European Organization of Research and Treatment of Cancer; IBCSG QoL = The International Breast Cancer Study Group QoL Core Questionnaire;
- SWLS = Satisfaction with Life Scale.
Table 2: Risk of bias in individual studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Sources/Potential sources of bias</th>
<th>Selection bias</th>
<th>Performance bias</th>
<th>Detection bias</th>
<th>Bias due to attrition</th>
<th>Reporting bias</th>
<th>Other bias</th>
<th>Quality Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Random sequence generation</td>
<td>Allocation concealment</td>
<td>Participants and personnel blinding</td>
<td>Blinding of outcome assessors</td>
<td>Incomplete data</td>
<td>Selective reporting</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Rogers et al. 2014</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Rogers et al. 2013</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Rogers et al. 2015, 2016, 2017</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Hayes et al. 2013</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Rogers et al. 2009a, 2009b</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Baruth et al. 2015</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Eakin et al. 2012</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>Short et al. 2012</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Pinto et al. 2005, 2008</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Galvano-Castillo et al. 2016</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<td>No</td>
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</tr>
<tr>
<td>Cornette et al. 2015</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Loss to follow-up</td>
</tr>
<tr>
<td>J. K. Vallance et al. 2008, 2009</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Loss to follow-up</td>
</tr>
<tr>
<td>Basen-Engquist et al. 2006</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Ligibel et al. 2016</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Lahart et al. 2016</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Cadmus et al. 2009</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Travier et al. 2005</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>-</td>
</tr>
</tbody>
</table>

Summary of potential sources of risk of bias in the included studies utilizing the Cochrane's Collaboration Tool for Risk of Bias Assessment: ‘Yes’ indicates the potential presence of bias.

*Studies were rated as high-quality trials or low-quality trials if there were < 3 or ≥3 identifiable sources of bias, respectively.
## Table 3: Summary of results in included trials

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Inflammatory biomarkers</th>
<th>Cancer-related fatigue</th>
<th>Aerobic fitness</th>
<th>Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rogers et al. 2014</td>
<td>At 3 months: Small/moderate increases in IL-6 (0.8 ± 4.7; d = 0.16; p &gt;0.05) and TNF-α (1.3 ± 2.5; d = 0.5; p &gt;0.05) Small decrease in IL-10 (-0.7 ±4.0; d = -0.18; p &gt;0.05), IL-6:IL-10 ratio (-0.6 ±4.3; d = -0.13; p &gt;0.05) and TNF-α:IL-10 ratio: -3.8 ± 16.6; d =-0.23; p &gt;0.05)</td>
<td>At 3 months: Changes in fatigue intensity, interference and general fatigue (p &gt;0.05)</td>
<td>At 3 months: Changes in aerobic capacity (p &gt;0.05)</td>
<td>-</td>
</tr>
<tr>
<td>Rogers et al. 2013</td>
<td>At 3 months: large increase in IL-6 (3.9 vs. -2.0; d = 0.7; p &gt;0.05) Small decreases in IL-10 (-0.26 vs. 3.0; d = -0.3; p = NS) and TNF-α (-2.26 vs -1.9; d = -0.2; p &gt;0.05) Small to moderate decreases in the ratios of IL-6:IL-10 (-0.7 vs 0.18; d = -0.4; p &gt;0.05) and IL-6:TNF-α ratios (-0.01 vs. 0.43; d = -0.4; p &gt;0.05)</td>
<td>At 3 months: Changes in fatigue intensity and interference (p &gt;0.05)</td>
<td>At 3 months: Beneficial improvement in aerobic capacity (3.7 vs. 0.1; p = 0.015)</td>
<td>-</td>
</tr>
<tr>
<td>Rogers et al. 2015, 2016, 2017</td>
<td>-</td>
<td>Beneficial reduction in fatigue intensity (-0.6; 95% CI: -0.1 to -0.2; p = 0.004) and interference (-0.8; 95% CI: -1.3 to -0.4; p &lt; 0.001) at 3 months</td>
<td>At 3 months: Increase in aerobic fitness (1.0; 95%CI: 0.0 to 2.0; p &gt;0.05)</td>
<td>At 3 months: Significant improvement in quality of life (6.4; 95%CI: 3.1 to 9.7; p &lt; 0.001) and quality of life variables including physical well-being (1.5; 95%CI: 0.5 to 2.4; p = 0.002), functional well-being (2.3; 95%CI: 1.3 to 3.3; p &lt; 0.001), emotional wellbeing (0.9; 95%CI: 0.3 to 1.5; p = 0.003), and trial outcome index (4.6; 2.3 95%CI: 6.9; p &lt;0.001) of FACT-B, beneficial improvements in the physical health (2.1; 95%CI: 0.3 to 3.9; p = 0.023) and mental health (5.2; 95%CI: 2.8 to 7.6; p &lt;0.001) composites of SF-36; beneficial improvements in the physical functioning (6.4; 95%CI: 1.9 to 11.0; p = 0.006), role-functioning (8.6; 95%CI: 3.0 to 14.2; p = 0.002), bodily pain (6.2;</td>
</tr>
<tr>
<td>Study</td>
<td>Follow-up</td>
<td>Findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hayes et al. 2013</td>
<td>At 2 months follow up</td>
<td>Beneficial changes in fatigue for telephone-delivered intervention (6.8; 95%CI: 3.9 to 9.8; p &gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rogers et al. 2009a, 2009b</td>
<td>At 3 months</td>
<td>Changes in cancer-related fatigue (p &gt; 0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baruth et al. 2015</td>
<td>At 3 months</td>
<td>Change in cancer-related fatigue (p &gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eakin et al. 2012</td>
<td>At 2 months follow up</td>
<td>Change in cancer-related fatigue (p &gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short et al. 2012</td>
<td>At ~1 months follow up</td>
<td>Change in cancer-related fatigue (p &gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pinto et al. 2005, 2008</td>
<td>At 3 months</td>
<td>Significant reduction in fatigue level (-15.39 vs. 0.62; p = 0.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 95%CI: 1.4 to 11.0; p = 0.012, general health (5.8; 95%CI: 2.2 to 9.4; p 0.002), vitality (12.5; 95%CI: 8.0 to 17.0; p <0.001), social functioning (9.8; 95%CI: 4.1 to 15.4; p = 0.001), role emotional (9.8; 95%CI:4.7 to 16.0; p <0.001), and mental health (7.; 95%CI: 3.1 to 11.2; p = 0.001) domains of SF-36; beneficial improvements in satisfaction with life (2.4; 95%CI: 0.9 to 3.9; p = 0.001) 

At 3 months follow up: Sustained increase in quality of life (3.8; 95%CI: 0.5 to 7.2; p = 0.025) and physical well-being (1.0; 95%CI: 0.1 to 2.0; p = 0.030) components of FACT-B; sustained benefits on the mental health composite of SF-36 (3.0; 95%CI: 0.5 to 5.4; p = 0.017); and vitality (7.8; 95%CI: 3.3 to 12.4; p = 0.001) and mental health (4.3; 95%CI: 0.2 to 8.5; p = 0.038) domains of SF-36
<table>
<thead>
<tr>
<th>Study</th>
<th>At 8 weeks: Beneficial reduction cancer-related fatigue $d = -0.89$; 95% CI: -1.3 to -0.48; $p &lt; 0.001$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornette et al. 2015</td>
<td>At 27 weeks: Changes in cancer-related fatigue ($p &gt; 0.05$)</td>
</tr>
<tr>
<td>J. K. Vallance et al. 2008, 2009</td>
<td>At 6 months follow up: Sustained improvements in quality of life variables including functional well-being $d = 1.90$; 95% CI: 0.24 to 3.55; $p = 0.025$</td>
</tr>
<tr>
<td>Ligibel et al. 2016</td>
<td>At 16 weeks: Changes in cancer-related fatigue ($p &gt; 0.05$)</td>
</tr>
<tr>
<td>Lahart et al. 2016</td>
<td>At 6 months: Beneficial improvements in quality of life ($5.05$; 95% CI: 10.69 to 9.40; $p = 0.024$) and quality of life variables including functional well-being (1.90; 95% CI: 0.24 to 3.55; $p = 0.025$), trial outcome index (5.64; 95% CI: 2.33 to 8.45; $p = 0.001$), and breast cancer additional concerns (2.84; 95% CI: 0.79 to 4.89; $p = 0.007$)</td>
</tr>
<tr>
<td>Cadmus et al. (2009)</td>
<td>At 6 months: Changes in quality of life variables ($p &gt; 0.05$)</td>
</tr>
</tbody>
</table>
### Key
MFI = Multidimensional Fatigue Inventory; EORTC = European Organization of Research and Treatment of Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention Effect</th>
<th>Exercise Effect</th>
<th>Quality of Life Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travier et al. 2005</td>
<td>At 18 weeks: Beneficial intervention effect on physical fatigue of MFI ($-1.3; 95% CI: -2.5 to -0.1; p &lt; 0.05$). Changes in other MFI variables ($p &gt; 0.05$). Changes in fatigue quality list ($p &gt; 0.05$).</td>
<td>At 18 weeks: Aerobic fitness ($p &gt; 0.05$)</td>
<td>At 18 weeks: Change in quality of life ($p &gt; 0.05$)</td>
</tr>
</tbody>
</table>
Figure 1. PA behavior change intervention (BCI) review PRISMA flow diagram
### Additional file 1

**Initial search strategy_PubMed**

<table>
<thead>
<tr>
<th>Patient /population</th>
<th>#1</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>#2</td>
<td>exercise OR exercise intervention OR physical exercise OR aerobic exercise OR aerobic training OR aerobic activities OR resistance training OR activity bout OR high intensity OR moderate intensity OR vigorous intensity OR strength training&quot; OR activity bout OR walking OR physical activity) AND (pedometer OR accelerometer OR step counts OR daily steps OR daily walking OR home based OR community based OR group based OR unsupervised OR lifestyle OR lifestyle change OR lifestyle modification OR lifestyle behavior&quot; OR behavior change OR cognitive behavior OR health promotion OR patient education OR lifestyle education OR structured patient education</td>
</tr>
<tr>
<td>Outcomes</td>
<td>#3</td>
<td>Inflammation OR cytokines OR inflammatory biomarkers OR IL-6 OR IL-10 OR TNF-a OR HRQOL OR quality of life OR wellbeing OR fatigue OR cancer related fatigue OR cardiopulmonary fitness OR fitness OR aerobic fitness OR aerobic capacity OR cardiovascular endurance OR VO2 OR walk test</td>
</tr>
<tr>
<td>P+I+O</td>
<td>#4</td>
<td>#1 AND #2 AND #3</td>
</tr>
<tr>
<td>P+I+O+ Intervention studies</td>
<td>#5</td>
<td>#4 AND “randomized controlled trial”</td>
</tr>
</tbody>
</table>