The effect of training interventions on physical performance, quality of life, and fatigue in patients receiving breast cancer treatment : a systematic review

Title page

Running head:

Training during breast cancer treatment

Title:

The Effect of Training Interventions on Physical Performance, Quality of Life and Fatigue in Patients Receiving Breast Cancer Treatment: a Systematic Review

Nick Gebruers[1,2,4], Melissa Camberlin[1], Fleur Theunissen[1], Wiebren Tjalma[2,3,4], Hanne Verbelen[1], Timia Van Soom[1], Eric van Breda[1],

1. University of Antwerp, department of rehabilitation sciences and physiotherapy REVAKI-MOVANT, Antwerp, Belgium (nick.gebruers@uantwerpen.be, hanne.verbelen@uantwerpen.be, timia.vansoom@uantwerpen.be, eric.vanbreda@uantwerpen.be)
2. Antwerp University Hospital, Multidisciplinary Breast Clinic, Antwerp, Belgium (nick.gebruers@uantwerpen.be, Wiebren.tjalma@uza.be)
3. University of Antwerp, department of medicine, Antwerp, Belgium (Wiebren.tjalma@uantwerpen.be)
4. Antwerp University Hospital, Multidisciplinary Edema Clinic, Antwerp Belgium (nick.gebruers@uantwerpen.be, Wiebren.tjalma@uza.be)

Corresponding author:

Prof. dr. Nick Gebruers

Department of Rehabilitation Sciences and Physiotherapy; MOVANT research group

Faculty of Medicine and Health Sciences

University of Antwerp

Universiteitsplein 1

2610 Antwerp

Belgium

nick.gebruers@uantwerpen.be

Tel: +32 3 265 2876

Fax: +32 3 265 250

This material was not presented anywhere thus far.

Funding was provided by University of Antwerp, no additional funding was requested. Prof. Gebruers has funding by IWT-TBM, grant IWT.150178. No further conflicts of interest to be declared by any of the authors.

The current review was registered on PROSPERO (www.crd.york.ac.uk/PROSPERO); registration CRD42017071940 and used the PRISMA statement for reporting the results.

The Effect of Training Interventions on Physical Performance, Quality of Life and Fatigue in Patients Receiving Breast Cancer Treatment: a Systematic Review

Abbreviations

QoL	**Quality of Life**
6MWT	**6 minute walking test**
12MWT	**12 minute walking test**
CT	**Chemotherapy**
RT	**Radiation therapy**
ADL	**Activities of daily living**
VO_{2peak}	**Peak oxygen uptake**
1RM	**1 repetition maximum**
CV	**Cardiovascular**

Abstract

Objectives: The primary purpose of this systematic review is to structure the available evidence concerning physical exercise programs and their effects on 1) physical performance outcomes, 2) experienced fatigue and 3) quality of life (QoL) in patients during the initial treatment for breast cancer.

Data Sources: A systematic literature search, based upon the PRISMA guideline, up to January 1st, 2018 was performed using four databases. (Web of Science, Cochrane Library for Clinical Trials, PubMed and Medline)

Study selection: Inclusion criteria were: 1) adults >18y; 2) patients with breast cancer undergoing initial treatment; 3) interventions with the aim to influence the patient's physical activity; QoL or fatigue; 4) randomized controlled trials (RCT's) of all ages. The selected studies

were scored for methodological quality and data concerning physical performance, QoL and fatigue were extracted. 28 RCT's were included.

Data extraction: Different treatment modalities during initial treatment were identified (radiation therapy, chemotherapy and combination therapy), as well as different types of physical training interventions (cardiovascular endurance exercise, strengthening programs or combination of both). Therefore, the results were clustered with regard to the above mentioned grouping; extracting every relevant outcome that related to physical performance (6MWT or VO_{2peak}; grip-/ muscle strength), QoL (questionnaires) and fatigue (questionnaires).

Data synthesis: Different training programs (endurance, resistance or a combination of the latter two) were found. These programs were applied during different phases of initial treatment. Some programs were supervised while others were home based. Overall, most training interventions provided an improvement in physical performance and a decrease in perceived fatigue. QoL was the outcome variable least susceptible to improvement.

Conclusion: Different types of exercise programs are available for rehabilitation purposes of breast cancer patients during adjuvant therapy. Overall resistance training or resistance training in combination with CV endurance training provides the best results, especially on physical performance and perceived fatigue.

Keywords: Breast cancer, breast neoplasm, physical activity, QoL, fatigue, motor activity, benefit

Introduction

Breast cancer is a devastating disease and is the most frequent diagnosed cancer in women.[1] The lifetime risk of being diagnosed with breast cancer is 1:8.[2] Due to improved screening and awareness programs breast cancer survival rates have doubled during the last 4 decades.[3] In addition, novel and personalized treatment protocols that have also contributed to the increase in overall survival.[4-8] To date, the late five-year relative survival for breast cancer in Europe approximates 83% and is still rising.[9-11]

Although initial therapeutic strategies such as surgery, whether or not preceded by neo-adjuvant chemotherapy (CT), adjuvant CT, radiation therapy (RT), hormone and targeted therapies become more personalized to the patients individual tumor pathology, breast cancer survivors represent a of patients with complex multiple side effects. [12,13],[14] Frequent reported side effects include cardiac toxicity[15], reproductive dysfunction, lymphedema[16] nausea[17,18], vomiting[17,18], pain[17,19], insomnia[17], appetite loss[17], cognitive changes[20,21] and fatigue.[17-19,22,23] Fatigue has been reported as the most frequent occurring side effect (70-100% of the treated patients experience feelings of fatigue on the long term).[3,17,18,22,24-26] Cancer related fatigue often elicits a vicious circle of fatigue induced reductions in physical activity; which exaggerates the feelings of fatigue. Reductions in physical activity have also been shown to reduce muscle mass and muscle strength resulting in decreased ADL empowering feelings of fatigue.[27] In combination with the overall feelings of fatigue diminished levels of physical activity, also have a negative impact on other side effects like health-related quality of life (QoL).[12,17,19,22,23,25,27,28] A growing body of evidence has shown that regular physical activity improves patients with breast cancer ADL and QoL[3,29]. For instance, physical exercise has been shown to be effective for increasing ADL and reductions in the feelings of fatigue.[30] Additionally, there is ample evidence that physical exercise has

beneficial effects on mortality[18,19], perceived fatigue[31,32], ADL[27,33,34], QoL[31,34,35], anxiety and depression.[35,36] Despite growing scientific evidence regarding the beneficial effects of physical exercise many breast cancer patients are reluctant to implement physical exercise in their daily life.[18]

A Cochrane review by Furmaniak et al. showed that there is conclusive evidence regarding the positive effects of exercise training during adjuvant therapy in breast cancer patients.[37] Unfortunately, no distinction between different exercise protocols regarding type of training (resistance training vs endurance vs combined protocols) as well as the type of adjuvant therapy (CT, RT or both) has been made. Therefore, the aim of the present systematic review is to assess the available evidence regarding the effects of physical exercise programs on physical performance, levels of fatigue and QoL in breast cancer patients during the initial treatment period with respect to the different training protocols (endurance, resistance or combined) and the type of adjuvant therapy (CT, RT or both).

Methods

Literature search and selection criteria

The current review was registered on PROSPERO (www.crd.york.ac.uk/PROSPERO); registration number CRD42017071940.

This systematic literature search has been based upon the PRISMA guidelines (http://www.prisma-statement.org) and was performed using four different electronic databases; Web of Science (WoS), Cochrane Library for Clinical Trials, PubMed and Medline. The latest full online search was performed on January 1st 2018 for all databases. Relevant keywords and entry terms were defined using the PICO(S) methodology, which was implemented into a Boolean search to obtain eligible studies. The following keywords were combined; 'breast cancer' (P), 'breast neoplasms' (P), 'Exercise therapy' (I), 'Physical Endurance' (I), 'motor activity' (I), 'physical activity' (O), 'activity level' (O), 'physical fitness' (O), 'quality of life' (O), 'fatigue' (O), 'strength' (O), and 'cardiopulmonary function' (O). No comparison (C) was defined and all studies had to be randomized controlled trials (S); written in English, Dutch or French. The specific search strategies for the four different databases are shown in *Table 1*. In Medline and PubMed, a filter concerning 'document types' was used to define 'randomized controlled trials'. Using WoS the advanced data search method was applied in combination with the filter 'document type: articles' . The selection was conducted by two independent raters (M.C. and F.T.) in two screening phases. In phase one, all citations were screened for eligibility based on title and abstract; for the eligibility criteria used, see table 2. In phase two the full text articles were screened using the same criteria as listed in *Table 2*. In case of disagreement in either of both screening phases, consensus was reached during a consensus meeting moderated by a third researcher (M.C., F.T, N.G).

Quality assessment and data extraction

The methodological quality as well as the data extraction of the selected studies was assessed by two independent researchers (M.C. and F.T.). Methodological quality was evaluated using the checklist for randomized controlled trials (10 items) provided by the Dutch Cochrane Centre (http://Netherlands.cochrane.org). Items could be rated as "?", "0", or "1". An item was rated by "?" if no sufficient information was available in the article. If a criterion was lacking, this item was scored "0". An item was rated "1" if sufficient information was provided and bias was unlikely. If disagreement occurred during the rating, a consensus meeting was held with a third researcher (NG) as moderator. The total quality score, as provided in *table 3*, is the sum of all criteria rated "1". Data extraction was done for every outcome related to physical performance, QoL and perceived fatigue.

Please insert Table 1: Summary of the Boolean search strategies in different databases used.

Please insert Table 2: Summary of inclusion and exclusion criteria used in both screenings.

Results

Selection of studies and study characteristics

The initial search yielded 1512 studies. After removal of duplicates and a first screening, 68 full text articles were retrieved for second screening. Finally, after the second screening, 28 RCT's were included in the current review, see table 3. The selected studies represented a total of 2525 breast cancer patients. The literature search, study selection process and reasons for exclusion are shown in figure 1. All characteristics as well as the methodological quality of the 28 RCT's are presented in *Table 3*.

Please insert Figure 1: flow chart.

Physical exercise programs

Significant heterogeneity in the physical exercise programs was found among the selected studies. Fourteen studies[18,19,23,27,32,35,38-45] used a cardiovascular (CV) endurance training **intervention**. Five[18,32,35,38,39] of these reported on a supervised training program whereas the other nine studies[19,23,27,40-44] [45] were home-based training programs. Ten studies[22,24,25,33,34,36,46-49] used a combined **strength and CV endurance** training intervention. Among these, four[24,34,36,49] used a supervised training, whereas six others[22,25,33,46-48] reported from a home-based program. Three studies[50-52] had a three-arm design. Two used supervised interventions[50,52], where the other study[51] preferred home-based programs. In all three-arm studies a comparison was made between a usual care group, a CV endurance training group and a resistance-training group. Only Wiskemann et al, used a sole progressive resistance protocol.[53]

Details on the interventions, patients and outcome measures used in the included studies are listed in *Table 3*.

Effects of the interventions

CV endurance training for patients receiving CT and RT ; further referred to as 'mixed treatment'.

Four studies[18,19,27,32] investigated physical fitness; of which three studies[18,27,32] showed improvements in aerobic capacity and levels of physical fitness in the exercise groups. Significant improvements for the 12 minute walking test (12 MWT; $p<0.001$[32], $p= 0.02$[27]) and a significant increase in peak oxygen uptake (VO_{2peak})[18] ($p<0.001$) were determined. One

study, of low methodological quality, showed no significant difference between the usual care group and exercise group regarding physical fitness and aerobic capacity in a home-based setting.[19]

Both Mutrie et al.[32] and Ligibel et al.[19] found no significant differences regarding fatigue (FACT-G) between the supervised exercise group and the usual care group. In contrast to the latter findings are the findings of Mock et al.[27] who reported enhanced results (PFS) in the exercising group compared to the less exercising group.

As far as QoL is concerned, no significant differences were reported for the mixed treatment groups after a supervised training program. [32] After a home-based training program a significant positive effect on QoL was reported. [19]

CV endurance training during CT

Both supervised[38,50] and home-based[23,40,42,43,45] CV endurance training programs were employed to improve the physical fitness of breast cancer patients receiving CT.

Hornsby et al.[38] found a significant difference for VO_{2peak}, peak power output and oxygen pulse; all in favor of the aerobic supervised exercise group. Gokal et al.[43] also noted significant better results for physical fitness in the home-based CV endurance training group (p=0,001). Yang et al.[40] showed significant differences over time (p=0.02) regarding physical activity during CT. Vallance et al.[42] showed no significant difference for broad-reach behavior change intervention of low intensity compared to public health guidelines.

Both Schmidt et al.[50] and Chaoul et al.[45] showed that neither interventions nor usual care were able to improve feelings of fatigue symptoms, whereas Headley et al.[23] and Gokal et

al.[43] found less increase in experienced feelings of fatigue in the home-based training group compared to the usual care group (p=0,02). Gokal et al.[43] and Hornsby et al.[38] also showed no difference between a supervised training group and the usual care group concerning the experienced fatigue.

Four studies[23,35,38,50] discussed the effects on QoL of breast cancer patients receiving CT. Schmidt et al.[50] showed a significant decrease in physical function during treatment (p=0.001). Three other studies[23,35,38] compared the exercising and usual care group and demonstrated no significant differences concerning QoL (p>0.05). No differences in QoL (FACIT-F, FACT-G, EORTC-QLQ-C30) outcome could be detected for supervised[23,50] and home-based training programs[35,38].

CV endurance training during RT

Milecki et al.[39] showed that supervised CV endurance training significantly increased the result of the 6 MWT (p=0.00). These findings were confirmed by Drouin et al.[44] who reported a significantly increased VO_{2peak} (p>0,001) and improvement in physical fitness during a home-based CV endurance training.

Regarding experienced feelings of fatigue, Reis et al.[41] showed that a home-based Nia training (Nia is a cardiovascular and whole-body conditioning program based upon martial arts, dance arts and healing arts) three times a week for twelve weeks had no significant effect (p>0.05) over usual care.

Combined CV endurance and resistance training during mixed treatment

Concerning the outcome physical fitness five[33,36,47-49] studies have been retrieved. In response to home-based interventions, two studies found no significant differences in physical fitness (Active Australian Survey, 6MWT, Grip Strength, Leg Press).[33,47] One study reported greater improvements in the 3min step test for the intervention group compared to usual care, whereas no differences in strength were observed.[48] In line with previous mentioned studies; Campbell et al.[36] and Travier et al.[49] showed improved physical fitness in the supervised training group compared to usual care group for the 12 MWT(p=0.001)[36], the VO_{2peak} and for power at ventilatory threshold (95%CI, 0.0 to 0.2, ES=0.31)[49].

Five studies[22,33,36,47,49] have studied feelings of experienced fatigue following a combination training program. Haines et al.[33] showed a trend of lower fatigue in the home-based training group, whereas Travier et al.[49] showed lower physical fatigue in a supervised training group. Three other studies [22,33,36] showed no significant differences in experienced fatigue between a home-based[22,33] or supervised[36] training group and usual care.

For QoL,Haines et al.[33] and Campbell et al.[36] showed significant improvement of QoL compared to control groups. However, one study[47], of low methodological quality, using a home-based intervention found no significant difference on QoL.

Combined CV endurance and resistance training during CT

Three studies[25,34,52] showed no significant differences between training groups and control groups on physical fitness, whereas two studies[46,51] that were of less methodological quality showed significant improved results for physical fitness after a home-based training program.

We found only, one study[51] that investigated the effect of home-based strength training. Enhanced results for 1 repetition maximum (1RM) of the following exercises were found: seated row and leg press in the training group.

Courneya et al.[34] and Husebo et al.[25] demonstrated no differences of feelings of fatigue between supervised[34] and/or home-based[25] training programs. However, Husebo et al.[25] showed an increase in experienced fatigue during CT in both groups.

Cornette et al.[46] demonstrated no changes in QoL following a CV endurance and resistance training during CT.

Combined CV endurance and resistance training during RT

Only one study[24] investigated feelings of experienced fatigue and QoL in patients receiving RT. For both outcomes, significant changes were found between control and exercise groups, all in favor of the supervised training group.

Resistance training during RT

Only one study was found that investigated a progressive resistance training protocol during RT[53]. It was found that patients receiving the intervention training improved significantly on peak torque and isometric contractions of large muscle groups. No effect on perceived fatigue was found between patients receiving resistance training and patients in the relaxation group (control group).

Please insert Table 3: data-extraction.

Discussion

Selection of the studies and study characteristics

The present review assessed the available evidence regarding the effects of physical exercise and/or rehabilitation programs on physical performance, experienced feelings of fatigue and QoL in patients with breast cancer during their initial treatment (defined as: surgery, CT and/or RT). The results of this systematic review demonstrate that:

1) Different types of exercise programs (CV endurance training, resistance training or a mix of the latter two, supervised or home-based) are available for rehabilitation purposes of breast cancer patients.
2) Many of the included studies found positive effects on physical performance.[18,24,27,32,36,38-40,44,46,48,49,51,53], but only few studies found significant results regarding the outcome measures for experienced fatigue and QoL.
3) Resistance training or resistance training in combination CV endurance seems to provide the best results, especially regarding physical performance outcomes and feelings of experienced fatigue.

Since physical training has become a corner stone in breast cancer rehabilitation the above mentioned findings show the importance of the current systematic review. A Cochrane review by Furmaniak et al.[37] concluded that exercise is beneficial for improving physical fitness, QoL and perceived fatigue. As shown in their respective forest plots; all types of intervention (CV endurance, resistance training or combination of both) during all types of adjuvant therapy

were analyzed jointly; resulting in favor of exercise in comparison to standard care. The current systematic review ennoble the findings of Furmaniak et al. by clearly demonstrating that not all types of intervention are able to produce the same significant results during the different adjuvant regimes. Our results warrant carefulness in interpreting the meta-analyses performed by Furmaniak et al.[37] For that reason, we will focus on the outcome measures with regard to the different exercise programs the in the following sections of the discussion:

Physical Performance

Physical performance in this review is regarded as the assessment of the level of physiological fitness or exercise capacity. From that perspective, VO_{2peak}, the 6 and 12 MWT were most often used in the literature reviewed. Grip strength and strength testing of large muscle groups were also commonly used for assessing physical performance. Studies using a supervised training program showed better results on physical performance outcomes than home-based approaches. This is especially true for studies during CT and RT [18,19,32,36,49,53]. Although not substantiated by evidence, the majority studies during CT alone used home-based approaches with conflicting results i.e. no differences between the intervention and control group[25,42,45,52] or significant improvements in the intervention group[40,46,51]. The only study that used a supervised protocol showed a significant improvement in VO_{2peak} for the intervention group[31].

As far as RT is concerned, only 4 studies were available. The best, from a methodological point of view,study [44] reported a significant improvement in physical performance for the intervention group over the control group during a home-based approach. A study[41] with a lower methodological score reported no differences in physical performance between the

intervention and control group. Two studies[53] used a supervised program and demonstrated a significant improvement in favor of the intervention over the control group[39] during a supervised program.

Perceived Fatigue.

Perceived fatigued is extremely subjective and difficult to assess. Two studies that investigated physical activity interventions during RT, showed an improvement in perceived fatigue.[24,41] A striking finding, however, is that both studies, supervised or home-based, used strength training as intervention strategy. Similar observations were reported for interventions in patients receiving a mixed treatment of RT and CT. The two studies that used strength exercises during a supervised program found a significant improvement for perceived fatigue over the control group[36,49]. Interestingly, the only study that used strength exercises in a home-based program did not show any differences between the intervention and control group. During CT, only one study[43] showed improvements in perceived feelings of fatigue for the intervention group. The intervention as used by Gokal et al. was a self-managed high intensity walking program without any strength exercises[43]. All other studies were not able to find any differences between the intervention and control group [23,25,34,46,50]. Overall we can conclude that incorporating resistance exercises in both the supervised as well as home based programs are able to reduce the perceived fatigue.

QoL

Only one study investigated QoL in a group of patients receiving RT only showed a significant increase in QoL for the intervention group receiving a supervised CV endurance and resistance exercises program.[24] None of the studies that studied the Qol in patients receiving CT were able to demonstrate improvements for any of the chosen interventions [23,35,38,50]. Interestingly 3 out of 5 studies in patients receiving both CT and RT found significantly improved QoL score in the intervention groups [19,33,49]. Although a reason for this differences is not easy to provide, the high level of heterogeneity in selected QoL questionnaires makes comparison between studies difficult and the selection of questionnaires could have an important effect on the final result. For instance, Travier et al. used both the EORTC-QLQ-C30 and SF-36, disease specific and generic questionnaires and reported significant improvements for the intervention group using the SF-36 but not for the EORTC-QLQ-C30. [49]

Breast cancer is a complex disease, and more and more patients receive, based on the characteristics of their tumor (TNM-classification) an individual tailored treatment plan. Regarding the fact that different treatment protocols cause different side effects,[17-19,22,23] it is reasonable to assume that a variety in outcome measures and an overall range in daily activities makes it difficult to compare results between the selected studies.

Limitations of the incorporated studies and current review

A major drawback we observed in the selected studies is the wide range in the duration of the training intervention i.e. from 5 weeks till 6 months and from 9 weeks till 8 months for supervised and home-based programs, respectively (see table 3). Due to the heterogeneity in the duration of the different training interventions, it is impossible to make an unambiguous

statement which training intervention, short or long, is advantageous in breast cancer rehabilitation. A second drawback is the wide range of different exercise workouts that have been used in the resistance training programs which makes comparison at least challenging. Based on the included studies, conclusions can only be drawn based on the methodological quality of all individual studies. A third limitation is the information concerning the medical treatment (type of surgery, chemotherapy scheme, radiation scheme) making it impossible to link medical treatment, adherence to exercise therapy and beneficial effects of training. Fourth, a broad range of eligibility criteria was found among the selected RCT's, hampering comparison and conclusion forming. Finally, physical fitness itself is a very broad concept and we can only reflect on the outcome measures reported in the selected studies.

Limitations of the current review are: 1) no meta-analysis was performed based upon the heterogeneity among the selected RCT's; 2) only information is provided on patients able to engage in exercise programs; 3) although personalization in exercise programs is probably warranted, we did not find any information concerning this item.

Recommendations for further research are multiple and need to be addressed with care i.e. 1) for patients undergoing RT more high quality studies are required. In addition, more differentiation of the different effects of the training interventions are necessary.

2) Further research is also indicated to determine which exercises/training are beneficial to use in clinical practice and to achieve the best effects on physical performance outcomes. Also the use of studies with a high methodological quality are mandatory to distinguish between the effects of different exercise drills and programs during the initial treatment period.

3) It is recommendable that studies on the topic addressed in this review should include more details including information on treatment plans (e.g. neo-adjuvant vs adjuvant CT or RT), type

of surgery (important for possible limb use or disuse effects) and description of the exact physical activity plans.

4) Finally, responder analysis was lacking in most of the included studies. Such analysis could shed more light on the deficiencies of training modalities and give way to therapists to provide optimal and personalized training programs for their patients. .

It can carefully be stated that the addition of a physical exercise program containing both CV endurance training and resistance exercises is beneficial in improving physical performance, reducing experienced fatigue and affecting QoL positively for patients undergoing breast cancer treatment. The optimal (personalized) program has yet to be developed.

Conclusion

We conclude that based on the heterogeneity of the selected study's conclusions regarding the type and supervision of physical rehabilitation programs need to be formulated with caution.

To date, ambiguous evidence is present regarding the enhancement of the QoL by different training programs. This needs further attention since QoL is one of the most often used outcome measures in cancer research.

Overall, we must conclude that there is evidence that exercise programs during the initial treatment period provide hopeful results, but there is a need for high quality studies.

Conflicts of interest

The authors did not receive any funding for any of the steps taken to write this systematic review.

None of the authors have any conflict of interest to declare.

The data table created for this systematic review is under the control of prof. dr. Nick Gebruers; and available on request.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Kootstra JJ, Hoekstra-Weebers JE, Rietman JS, de Vries J, Baas PC, Geertzen JH, et al. A longitudinal comparison of arm morbidity in stage I-II breast cancer patients treated with sentinel lymph node biopsy, sentinel lymph node biopsy followed by completion lymph node dissection, or axillary lymph node dissection. Ann Surg Oncol 2010;17:2384-94.
3. Juvet LK, Thune I, Elvsaas IKO, Fors EA, Lundgren S, Bertheussen G, et al. The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: A meta-analysis. Breast 2017;33:166-77.
4. Christiansen P, Carstensen SL, Ejlertsen B, Kroman N, Offersen B, Bodilsen A, et al. Breast conserving surgery versus mastectomy: overall and relative survival-a population based study by the Danish Breast Cancer Cooperative Group (DBCG). Acta Oncol 2018;57:19-25.
5. Eggemann H, Altmann U, Costa SD, Ignatov A. Survival benefit of tamoxifen and aromatase inhibitor in male and female breast cancer. J Cancer Res Clin Oncol 2018;144:337-41.
6. Kast K, Schoffer O, Link T, Forberger A, Petzold A, Niedostatek A, et al. Trastuzumab and survival of patients with metastatic breast cancer. Arch Gynecol Obstet 2017;296:303-12.
7. Roberts MC, Miller DP, Shak S, Petkov VI. Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. Breast Cancer Res Treat 2017;163:303-10.
8. Yoon TI, Hwang UK, Kim ET, Lee S, Sohn G, Ko BS, et al. Survival improvement in hormone-responsive young breast cancer patients with endocrine therapy. Breast Cancer Res Treat; 2017;165:311-20.
9. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015; 385:977-1010.
10. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol 2014;15:23-34.
11. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374-403.
12. Dean A. Primary breast cancer: risk factors, diagnosis and management. Nursing Standard 2008;22:9.
13. Van de Wiel M, Dockx Y, Van den Wyngaert T, Stroobants S, Tjalma WAA, Huizing MT. Neoadjuvant systemic therapy in breast cancer: Challenges and uncertainties. Eur J Obstet Gynecol Reprod Biol 2017;210:144-56.
14. Diaby V, Tawk R, Sanogo V, Xiao H, Montero AJ. A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. Breast Cancer Res Treat 2015;151:27-40.
15. Bengala C, Zamagni C, Pedrazzoli P, Matteucci P, Ballestrero A, Da Prada G, et al. Cardiac toxicity of trastuzumab in metastatic breast cancer patients previously treated with high-dose chemotherapy: a retrospective study. Br J Cancer 2006;94:1016-20.
16. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;14:500-15.
17. Adamsen L, Quist M, Andersen C, Møller T, Herrstedt J, Kronborg D, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ (clinical research ed)2009:b3410.

18. Kim CJ, Kang DH, Smith BA, Landers KA. Cardiopulmonary responses and adherence to exercise in women newly diagnosed with breast cancer undergoing adjuvant therapy. Cancer Nurs 2006;29:156-65.
19. Ligibel JA, Giobbie-Hurder A, Shockro L, Campbell N, Partridge AH, Tolaney SM, et al. Randomized trial of a physical activity intervention in women with metastatic breast cancer. Cancer 2016;122:1169-77.
20. Henneghan A. Modifiable factors and cognitive dysfunction in breast cancer survivors: a mixed-method systematic review. Support Care Cancer 2016;24:481-97.
21. Morean DF, O'Dwyer L, Cherney LR. Therapies for Cognitive Deficits Associated With Chemotherapy for Breast Cancer: A Systematic Review of Objective Outcomes. Arch Phys Med Rehabil 2015;96:1880-97.
22. Heim ME, v d Malsburg ML, Niklas A. Randomized controlled trial of a structured training program in breast cancer patients with tumor-related chronic fatigue. Onkologie 2007;30:429-34.
23. Headley JA, Ownby KK, John LD. The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer. Oncology Nursing Forum 2004;31:977-83.
24. Hwang JH, Chang HJ, Shim YH, Park WH, Park W, Huh SJ, et al. Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. Yonsei Medical Journal 2008;49:443-50.
25. Husebo AM, Dyrstad SM, Mjaaland I, Soreide JA, Bru E. Effects of scheduled exercise on cancer-related fatigue in women with early breast cancer. ScientificWorldJournal 2014;2014:271828.
26. Lipsett A, Barrett S, Haruna F, Mustian K, O'Donovan A. The impact of exercise during adjuvant radiotherapy for breast cancer on fatigue and quality of life: A systematic review and meta-analysis. Breast 2017;32:144-55.
27. Mock V, Frangakis C, Davidson NE, Ropka ME, Pickett M, Poniatowski B, et al. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. Psycho-Oncology 2005;14:464-77.
28. Mock V, Burke M, Sheehan P, Creaton E, Winningham M, McKenney-Tedder S, et al. A nursing rehabilitation program for women with breast cancer receiving adjuvant chemotherapy. Oncology nursing forum1994:899-907; discussion 8.
29. Zeng Y, Huang M, Cheng AS, Zhou Y, So WK. Meta-analysis of the effects of exercise intervention on quality of life in breast cancer survivors. Breast Cancer 2014; 21:262-74.
30. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity for women with breast cancer after adjuvant therapy. Cochrane Database Syst Rev 2018;1:CD011292.
31. Battaglini C, Mihalik J, Bottaro M, Dennehy C, Petschauer M, Hairston L, et al. Effect of exercise on the caloric intake of breast cancer patients undergoing treatment. Brazilian journal of medical and biological research = revista brasileira de pesquisas medicas e biologicas2008:709-15.
32. Mutrie N, Campbell AM, Whyte F, McConnachie A, Emslie C, Lee L, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. Bmj 2007;334:517.
33. Haines TP, Sinnamon P, Wetzig NG, Lehman M, Walpole E, Pratt T, et al. Multimodal exercise improves quality of life of women being treated for breast cancer, but at what cost? Randomized trial with economic evaluation. Breast Cancer Res Treat 2010;124:163-75.
34. Courneya KS, Segal RJ, Gelmon K, Reid RD, Mackey JR, Friedenreich CM, et al. Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy. Cancer Epidemiology, Biomarkers & Prevention 2007;16:2572-8.
35. Backman M, Wengstrom Y, Johansson B, Skoldengen I, Borjesson S, Tarnbro S, et al. A randomized pilot study with daily walking during adjuvant chemotherapy for patients with breast and colorectal cancer. Acta Oncol 2014;53:510-20.
36. Campbell A, Mutrie N, White F, McGuire F, Kearney N. A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. European Journal of Oncology Nursing 2005;9:56-63.

37. Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev 2016;9:CD005001.
38. Hornsby WE, Douglas PS, West MJ, Kenjale AA, Lane AR, Schwitzer ER, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. Acta Oncologica 2014;53:65-74.
39. Milecki P, Hojan K, Ozga-Majchrzak O, Molinska-Glura M. Exercise tolerance in breast cancer patients during radiotherapy after aerobic training. Wspolczesna Onkologia-Contemporary Oncology 2013;17:205-9.
40. Yang CY, Tsai JC, Huang YC, Lin CC. Effects of a home-based walking program on perceived symptom and mood status in postoperative breast cancer women receiving adjuvant chemotherapy. J Adv Nurs 2011;67:158-68.
41. Reis D, Walsh ME, Young-McCaughan S, Jones T. Effects of Nia exercise in women receiving radiation therapy for breast cancer. Oncology Nursing Forum 2013;40:E374-81.
42. Vallance J, Friedenreich C, Lavallee C, Culos-Reed N, Mackey J, Walley B, et al. Exploring the Feasibility of a Broad-Reach Physical Activity Behavior Change Intervention for Women Receiving Chemotherapy for Breast Cancer: a Randomized Trial. Cancer epidemiology, biomarkers & prevention2017:391-8.
43. Gokal K, Wallis D, Ahmed S, Boiangiu I, Kancherla K, Munir F. Effects of a self-managed home-based walking intervention on psychosocial health outcomes for breast cancer patients receiving chemotherapy: a randomised controlled trial. Supportive care in cancer2017:1139-66.
44. Drouin J, Armstrong H, Krause S, Orr J, Birk T, Hryniuk W. Effects of aerobic exercise training on peak aerobic capacity, fatigue, and psychological factors during radiation for breast cancer. Rehabilitation oncology2005:11-7.
45. Chaoul A, Milbury K, Spelman A, Basen-Engquist K, Hall MH, Wei Q, et al. Randomized trial of Tibetan yoga in patients with breast cancer undergoing chemotherapy. 2018;124:36-45.
46. Cornette T, Vincent F, Mandigout S, Antonini MT, Leobon S, Labrunie A, et al. Effects of home-based exercise training on VO2 in breast cancer patients under adjuvant or neoadjuvant chemotherapy (SAPA): a randomized controlled trial. European Journal of Physical and Rehabilitation Medicine 2016;52:223-32.
47. Eakin EG, Lawler SP, Winkler EA, Hayes SC. A randomized trial of a telephone-delivered exercise intervention for non-urban dwelling women newly diagnosed with breast cancer: exercise for health. Ann Behav Med 2012;43:229-38.
48. Hayes SC, Rye S, Disipio T, Yates P, Bashford J, Pyke C, et al. Exercise for health: a randomized, controlled trial evaluating the impact of a pragmatic, translational exercise intervention on the quality of life, function and treatment-related side effects following breast cancer. Breast Cancer Research & Treatment 2013;137:175-86.
49. Travier N, Velthuis MJ, Bisschop CNS, van den Buijs B, Monninkhof EM, Backx F, et al. Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial. Bmc Medicine 2015;13.
50. Schmidt T, Weisser B, Durkop J, Jonat W, Van Mackelenbergh M, Rocken C, et al. Comparing Endurance and Resistance Training with Standard Care during Chemotherapy for Patients with Primary Breast Cancer. Anticancer Res 2015;35:5623-9.
51. Schwartz AL, Winters-Stone K, Gallucci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. Oncology Nursing Forum 2007;34:627-33.
52. Dolan LB, Gelmon K, Courneya KS, Mackey JR, Segal RJ, Lane K, et al. Hemoglobin and aerobic fitness changes with supervised exercise training in breast cancer patients receiving chemotherapy. Cancer Epidemiology, Biomarkers & Prevention 2010;19:2826-32.
53. Wiskemann J, Schmidt ME, Klassen O, Debus J, Ulrich CM, Potthoff K, et al. Effects of 12-week resistance training during radiotherapy in breast cancer patients. Scand J Med Sci Sports 2017;27:1500-10.

Figure

Figure 1: Flow chart of the systematic search and selection process