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CLINICAL TRIAL

Effect of progressive resistance training on persistent pain after axillary dissection in breast cancer: a randomized controlled trial

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Abstract

Purpose Persistent pain is a known challenge among breast cancer survivors. In secondary analyses of a randomized controlled trial, we examined the effect of progressive resistance training on persistent pain in the post-operative year in women treated for breast cancer with axillary lymph node dissection.

Methods We randomized 158 women after BC surgery with Axillary Lymph Node Dissection (ALND) (1:1) to usual care or a 1-year, supervised and self-administered, progressive resistance training intervention initiated 3 weeks after surgery. A questionnaire at baseline, 20 weeks and 12 months assessed the intensity and frequency of pain, neuropathic pain and influence of pain on aspects of daily life. We analysed the effect using linear mixed models and multinomial logistic regression models for repeated measures.

Results A high percentage of participants experienced baseline pain (85% and 83% in the control and intervention groups respectively) and by the 12 month assessment these numbers were more than halved. A high proportion of participants also experienced neuropathic pain (88% and 89% in control and intervention group respectively), a finding that was stable throughout the study period. The effect on intensity of pain indicators favoured the exercise group, although most estimates did not reach statistical significance, with differences being small.

Conclusion For women who had BC surgery with ALND, our progressive resistance training intervention conferred no benefit over usual care in reducing pain. Importantly, it did not increase the risk of pain both in the short and long term rehabilitative phase.

Keywords Oncology · Breast cancer · Axillary lymph node dissection · Pain · Resistance training

Introduction

Persistent pain after breast cancer (BC) treatment is regarded a major problem in survivorship, with 10–20% of survivors reporting moderate to severe pain up to several years after surgery [1–3]. Risk factors are younger age, patients treated with axillary lymph node dissection (ALND), and pre and postoperative pain [4–8]. Other associated factors are high body mass index (BMI) [9, 10], lymphoedema [7], and psychological factors such as distress, anxiety and depression [11, 12].

In non-cancer populations, exercise has been found to have an effect on pain through a combination of mechanisms such as the endogenous opioid system [13], activation of anti-inflammatory cytokines [14] and descending and ascending pain pathways [15, 16]. Moreover, different exercise modes may affect pain through different mechanisms as they elicit distinct physiological responses [17]. According to a meta-analysis of the analgesic effect of exercise from 2012 [15] resistance exercise rather than aerobic exercise provided pain reduction, but findings were based mainly on animal studies. According to the most recent literature reviews on exercises studies after breast cancer surgery [18–21], only two randomized controlled trials (RCTs) have specifically tested the effect of aerobic/resistance exercise

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on pain postoperatively [22, 23] , and they assessed short exercise programs in small study populations ($N = 37$ and 65) with modest effects on pain suggesting limited importance to the patient.

The use of progressive resistance training (PRT) in the post-operative phase after BC only reaches a weak recommendation based on low quality of the evidence in the most recent national clinical guidelines [24] and has been avoided in the clinic, possibly due to presumed adverse effects such as risk of lymphoedema, provocation of pain and disturbed tissue healing. However, many beneficial effects of PRT have been documented, including examples of superior effects compared to those of other exercise modes. PRT has been positively associated with bone health, dynamic upper quadrant muscular joint stability and in maintaining muscle mass and strength; all areas in which BC survivors can be challenged [25]. For the advantages of PRT to be made available to women after surgery for BC, one of the factors that need to be examined is the effect on pain.

Primary analyses of the current RCT showed that early initiated PRT through the first post-operative year could not prevent lymphoedema in women undergoing ALND for BC. In this report, we present results from analyses on secondary trial outcomes examining the effect on pain.

Methods

Design, participants, randomization and blinding

The current trial, LYCA (ethical approval ID: H-15002714, clinicaltrials.gov: NCT02518477), recruited 158 participants from August 2015 to January 2017 from Copenhagen University Hospitals Herlev and Rigshospitalet and Ringsted Hospital covering East Denmark, with data collection ending by January 2018.

Women were eligible if they were aged 18–75 years, were diagnosed with primary unilateral BC, had surgery including ALND, had no known distant metastases, understood spoken and written Danish and were physically and mentally able to participate in a group exercise regimen. Participants were recruited by staff nurses or physiotherapists on the day of surgery and gave final consent before baseline testing and questionnaire assessment took place 2 weeks post-surgery. A computerised study-database generated the random allocation sequence and allocated participants in a 1:1 ratio to usual care or exercise intervention stratified by BMI (>/< 30) and recruiting hospital in blocks of six. Participants' group status was concealed for assessors, the data manager and the statistician through the use of study identification numbers after baseline testing. Finally, the study coordinator contacted participants with information on allocation assignment.

Breast cancer treatment

All patients were prescribed treatment according to the Danish Breast Cancer Group guidelines [26]. Surgery consisted of breast conserving surgery or mastectomy and all patients included had ALND, either primary or secondary to sentinel lymph node biopsy. Thus according to protocol, all participants had radiotherapy with a radiation field that included the axilla, chest wall or residual breast, as well as parasternal nodes for right sided cancers. Chemotherapy was administered according to risk status, and consisted of cyclophosphamide, anthracycline and taxane. Endocrine therapy was given according to receptor status, and HER-positive patients were offered trazuzumab [27].

Intervention group

The intervention has been described in detail previously [28, 29]. Figure 1 shows a timeline overview of the intervention and measurements. The initiation of the exercise program took place at first opportunity after baseline testing (generally within 1 week) and continued with three times weekly exercise throughout the first post-operative year. In the first 20 weeks, exercise was offered as biweekly physiotherapist-led group-based supervised sessions at set times and self-administered exercise weekly once. In the following 30 weeks all exercise was self-administered, and participants could choose to attend a local exercise facility or exercise at home. The initial exercise load was individually estimated from baseline seven repetition maximum (RM) muscle tests, which measures the maximal weight a person is able to lift seven and only seven times [30].

Load started at 25RM with 20 repetitions, and was gradually progressed and adapted every month according to 7RM strength tests. From 3 months onwards participants exercised at 10RM with 10–12 repetitions, but were continually progressed to accommodate muscle adaptation. The exercises for the upper limb included biceps curl, shoulder abduction and lawnmower exercise with dumbbells, triceps push-down (machine) and shoulder extension (pulley). Further exercises were aimed at the major muscle groups of lower limb and core.

Control group

The usual care was not standardised in the postoperative or rehabilitation setting, and varied in terms of contact with a physiotherapist, extent and content of physiotherapy offered. However, patients received written information concerning post-operative care as well as mobility exercises. Patients were advised to re-engage in normal physical activity, but to respect pain when lifting or engaging in strenuous physical

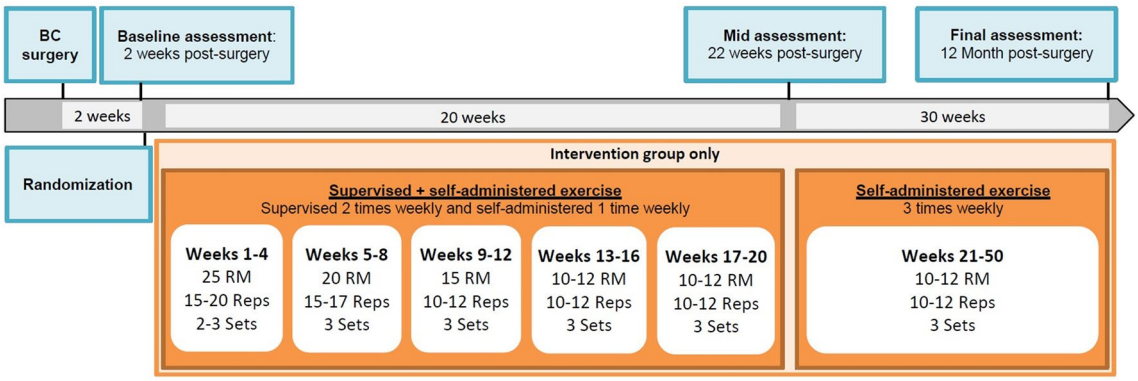

Fig. 1 Timeline overview of the intervention and measurements related to BC surgery, LYCA, East Denmark, 2015–2018. *RM* repetition maximum, *Reps* repetitions

activity involving the upper limb, and that the prolonged strenuous activity of the upper limb should be divided into shorter periods. In all three study hospitals standard procedure included referring patients to physiotherapy in the community setting, which often contained manual therapy and remedial exercise for mobility and restoration of upper limb function for a limited number of weeks. Resistance training was not offered in the early post-operative phase.

Outcome assessment

For information regarding the cancer and cancer-treatment, we linked data from the Danish Breast Cancer Cooperative Group database [27] and patient's medical charts were reviewed for completion of missing data. A paper-format questionnaire distributed by mail or in person containing patient reported outcomes including the pain assessment was collected at baseline, 20 weeks, and at 12-month follow-up, with up to two reminders and new questionnaires were mailed out to non-responding participants.

To assess the different aspects of pain and the influence of pain on daily life in detail, we used a questionnaire comprising multiple pain outcomes. The questionnaire has been content validated in a Danish nationwide breast cancer population, as described by Gärtner et al. [31]. Questions covered the presence of pain with specification to the affected area (breast area, side of the thorax, axilla or arm on the operated side). Intensity of pain was indicated on a numeric rating scale (NRS) from 0 (no pain) to 10 (worst imaginable pain) as well as whether the pain was experienced every day, 1–3 days a week or more rarely for each relevant area. We defined participants as having pain if they indicated for one or more areas that the pain was at least present on a weekly basis, and the highest intensity pain score was used as the intensity measure of their pain.

Secondly, we used a Rasch validated scale specifically designed to measure neuropathic pain in postsurgical patients (NeuPPS), regarding neuropathic pain experienced in the last week [32]. Participants were asked to mark whether or not they had experienced any of the following in the area of surgery: (1) pins and needles, tingling or stabbing sensations, (2) electrical shock or jolt, (3) heat or burning sensation, (4) hypersensitivity to clothes or touch, (5) cold-provoked pain. Each symptom gave one point, adding up to a NeuPPS score ranging from 0 to 5. Using a cut-off of 1, the NeuPPS had a sensitivity of 88% and a specificity of 59% [32].

Finally, single items were included to assess the degree to which pain in the last 24 h had influenced the aspects of their daily life: their general activity, mood, work, relationships with other people, sleep, and enjoyment of life. The scores for each domain were indicated on NRS (score 0–10).

Statistical analyses

Sample size was calculated with the primary aim of detecting a difference in lymphoedema incidence. From results of previous studies, we expected a lymphoedema incidence of 30% in the control group and 10% in the intervention group [33–35]. With $\alpha = 0.05$ and a power of 0.90, allowing 15% loss to follow-up, the estimated sample size was 158 women.

Baseline characteristics were presented separately for each group as numbers with proportions (%) and means with standard deviation (SD).

All statistical analyses were performed on originally assigned groups. First, we examined the effect of the intervention on intensity of pain outcomes using linear mixed models including an interaction between the visit and allocated group at 20 weeks and 12 months allowing for a different intervention effect at the two follow-up assessments.

Possible correlation between measures from the same person was taken into account using an unstructured covariance matrix. To explore the effect of missing data, we repeated the analyses using multiple imputations. The imputations were carried out using chained equations on the three outcomes per person using normal regression models and including auxiliary variables in the model (age, BMI, surgery type and lymphoedema) for improved imputations. Furthermore, based on analyses on complete data, we estimated the absolute effects for both groups separately and for both follow-ups. The result was graphed as estimated means and 95% confidence intervals (CI).

Second, to examine the effect of the intervention according to clinically meaningful cut-offs, NRS scores were categorised in three levels; "no" (0), "mild" [1–3] and "moderate/severe" [4–10], and NeuPPS in two categories; "no" (0) and "yes" [1–5], and multinomial logistic regression models on complete cases were used for analyses of the effect. To take the repeated measures into account, the variance was adjusted using person as a cluster. Results were presented as conditional odds ratios (COR) with "mild" as reference. The COR represents the odds for experiencing "no" versus "mild", and "moderate/severe" versus "mild" of the outcome, and the odds are conditional on not being in another category than the two categories compared. For neuropathic pain, the COR represents the odds for reporting "yes" versus "no". Based on the results, probabilities of each outcome were estimated and presented graphically with CI. All analyses were carried out using Stata version 14.2.

Results

Participants

No important harms or detrimental effects of the intervention were documented. This has been described in more detail, together with the study population and its characteristics, elsewhere [36]. In brief, 466 patients were eligible and 158 (34%) were enrolled. By randomization, 76 were allocated to control and 82 to intervention. Figure 2 shows the flow of participants through the study. There were no apparent differences in characteristics of the patients at baseline, indicating a balanced randomization (Table 1).

Age at diagnosis ranged from 30 to 74 years (mean = 52, SD = 10). Neoadjuvant chemotherapy was administered to 46 (29%) and 93 (59%) received adjuvant chemotherapy. Hormone treatment was administered to 115 (73%). BMI ranged from 18 to 50, (mean = 26) and approximately 75% of participants had at least college education and were employed fully or part-time at time of diagnosis.

At baseline, pain on a weekly basis was reported by 58 (85%) in the control group and 66 (83%) in the intervention group. This fraction was reduced for both groups at the 20 week and 12 month assessment, with 40% for the control group at both assessments, and 44% and 36% for the intervention group, respectively.

The number of participants experiencing neuropathic pain at baseline was 59 (88%) in the control group and 70 (89%) in the intervention group. The fraction remained stable for

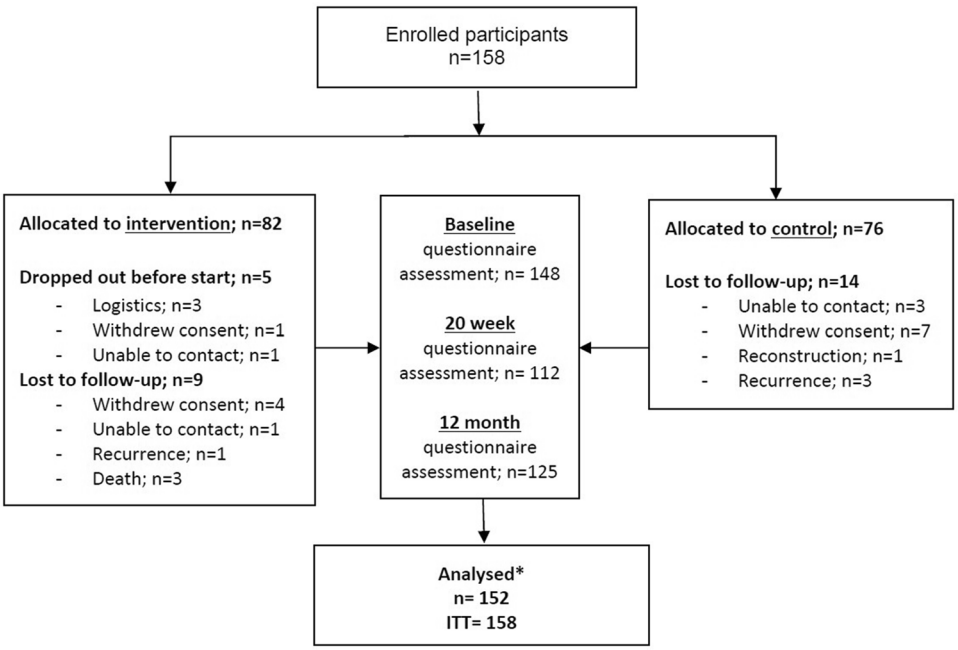

Fig. 2 Recruitment and follow-up with questionnaire assessments of 158 women treated for primary breast cancer with axillary lymph node dissection, LYCA, East Denmark, 2015–2018. *Questionnaire assessments for analysis do not add up, as some participants provided questionnaires at one or two assessment points but all available data was used in mixed model analysis. *ITT* intention to treat analyses, using multiple imputations for missing data

Table 1 Baseline characteristics of 158 women treated for primary breast cancer with axillary lymph node dissection, LYCA, East Denmark, 2015–2018

Characteristic	Control ($n=76$)		Intervention ($n=82$)	
	Mean, *n*	SD, %	Mean, *n*	SD, %
Sociodemographic and physical profile				
Age (years)	52	10	53	10
Education				
Short or medium	10	13	13	15
Long	47	62	49	60
Other	11	14	17	21
Data missing	8	11	3	4
Employment				
Full or part-time at diagnosis,	53	70	63	77
Not employed, pensioned, sick leave, other	15	20	17	21
Data missing	8	10	2	2
Body mass index (kg/m^2)	26.6	5	26.5	6
≤ 25	33	43	39	48
> 25 – ≤ 30	26	34	22	27
> 30	17	22	21	26
Medical and surgical profile				
Histologic stage of malignancy				
1	16	21	12	15
2	35	46	48	59
3	18	24	15	18
Data missing	7	9	7	9
Surgical protocol				
Lumpectomy	41	54	43	52
Mastectomy	35	46	39	48
Number of lymph nodes resected	20	7	19	9
Number of positive lymph nodes	3.0	3	2.9	4
Tumour diameter (mm)	23	12	22	12
Data missing	27	36	22	27
Chemotherapy[a]				
Adjuvant	45	59	48	59
Neoadjuvant	21	28	25	30
Hormone treatment	51	67	64	78
Data missing	2	3	0	
Self-reported swelling at baseline*	1.2	1.6	0.7	1.4
Health behaviour				
Physical activity before diagnosis				
Inactive	4	6	0	
< 30 min daily	22	32	30	38
Active ≥ 30 min daily	22	32	32	40
Active > 30 min daily + high intensity more than twice weekly	20	29	18	23
Smoking				
Current smoker	5	9	4	5
Ex-smoker	34	52	34	42
Never smoked	26	39	43	53
Alcohol consumption				
No. of units per week	3.6	4.1	5.1	5.7
None	22	29	22	27
Data missing	11	14	9	11

SD standard deviation

*Self-reported swelling of the arm on the affected side, measured on Numeric Rating Scale from 0 (min) to 10 (max)

[a]During the study period (January 2017), national guidelines regarding the taxane regimen were changed from docetaxel to paclitaxel. Participants were evenly distributed between the groups before and after this change. Ten and nine participants in the control and intervention groups, respectively, were not prescribed chemotherapy

Table 2 Effect of intervention as change from baseline to 20-week and 12-month assessment: Results of analyses using complete data for continuous outcomes (pain, neuropathic pain, and aspects of daily life influenced by pain) of 158 women treated for primary breast cancer with axillary lymph node dissection, LYCA, East Denmark, 2015–2018

	Effect	95% CI	Overall *p*
Pain		*N* = 152, obs. = 384	0.227
20 weeks exercise	−0.39	−1.04; 0.26	
20 weeks control	0	Reference	
12 months exercise	−0.59	−1.27; 0.09	
12 months control	0	Reference	
Neuropathic pain		*N* = 147, obs. = 363	0.049
20 weeks exercise	−0.41	−0.75; −0.08	
20 weeks control	0	Reference	
12 months exercise	−0.11	−0.55; 0.33	
12 months control	0	Reference	
Pain influence on: general activity		*N* = 152, obs. = 383	0.074
20 weeks exercise	−0.61	−1.25; 0.04	
20 weeks control	0	Reference	
12 months exercise	−0.58	−1.16; −0.01	
12 months control	0	Reference	
Mood		*N* = 152, obs. = 384	0.205
20 weeks exercise	−0.53	−1.12; 0.06	
20 weeks control	0	Reference	
12 months exercise	−0.31	−0.86; 0.24	
12 months control	0	Reference	
Work		*N* = 152, obs. = 380	0.094
20 weeks exercise	−0.71	−1.41; −0.00	
20 weeks control	0	Reference	
12 months exercise	−0.60	−1.28; 0.08	
12 months control	0	Reference	
Relationships		*N* = 152, obs. = 384	0.013
20 weeks exercise	−0.54	−1.00; −0.08	
20 weeks control	0	Reference	
12 months exercise	−0.71	−1.21; −0.22	
12 months control	0	Reference	
Sleep		*N* = 152, obs. = 385	0.112
20 weeks exercise	−0.57	−1.27; 0.13	
20 weeks control	0	Reference	
12 months exercise	−0.69	−1.42; 0.03	
12 months control	0	Reference	
Life enjoyment		*N* = 152, obs. = 384	0.107
20 weeks exercise	−0.57	−1.20; 0.05	
20 weeks control	0	Reference	
12 months exercise	−0.53	−1.12; 0.07	
12 months control	0	Reference	

Exercise intervention group, *Control* control group, *95% CI* 95% confidence interval, *p*—*p* value, *p* expresses the level of significance for that assessment point, and overall *p* expresses the overall level of significance for the repeated measures for that outcome, *N* number of participants, *Obs.* observations

both groups at the 20 week and 12 month assessments. There was no significant difference between groups regarding the frequency of participants experiencing pain or neuropathic pain (data not shown).

Although results favoured the intervention group for all continuous outcomes (pain, neuropathic pain, and the influence of pain on six aspects of daily life), most differences were not statistically significant (Table 2).

The estimates for overall effect across time points were significant for two outcomes; influence of pain on relationships with other people and neuropathic pain intensity. However, in both cases the difference did not exceed 1 point on NRS and 0.5 points on NeuPPS, and must therefore be considered clinically unimportant differences.

In analyses using multiple imputed data (Supplementary Table A), the estimates for all pain outcomes were similar and did not give rise to any new interpretation of the results. The absolute estimates and CI of all pain outcomes per group and visit based on complete data from Table 2 are presented graphically in Fig. 3, illustrating the tendency of lower follow-up pain scores for the intervention group.

In analyses of categorical outcomes, estimates favoured the intervention group but did not reach overall statistical significance (supplementary Table B), with COR ranging from 0.05 to 0.72. A panel of plots for the probability of scoring in the three categories for each outcome is presented in Fig. 4.

Discussion

Results of the present study show no effect of PRT on post-operative pain throughout the first year with adjuvant therapy after ALND. Although estimates tended to favour the intervention group, statistical significance was not reached for most outcomes, however, consistently pointing towards an interpretation that the exercise intervention did not lead to increased pain when compared with usual care. Previous research has repeatedly documented the impaired shoulder function and reduced muscle strength on the affected side in women undergoing surgery for breast cancer [37–39]. In post-operative regimes after other types of surgery and cancer treatment, resistance training is necessary for gaining full recovery, suggesting that PRT could potentially have this effect also after breast cancer surgery and treatment. However, standard clinical practice today does not involve PRT in the post-operative rehabilitation, likely due to caution with regards to lymphoedema risk, provoked pain levels and disturbed tissue healing. With this study we have demonstrated that if supervised by a physiotherapist, PRT can be carried out safely while respecting pain, thereby not contradicting the possibility that PRT can have a beneficial role in the early post-operative setting and beyond.

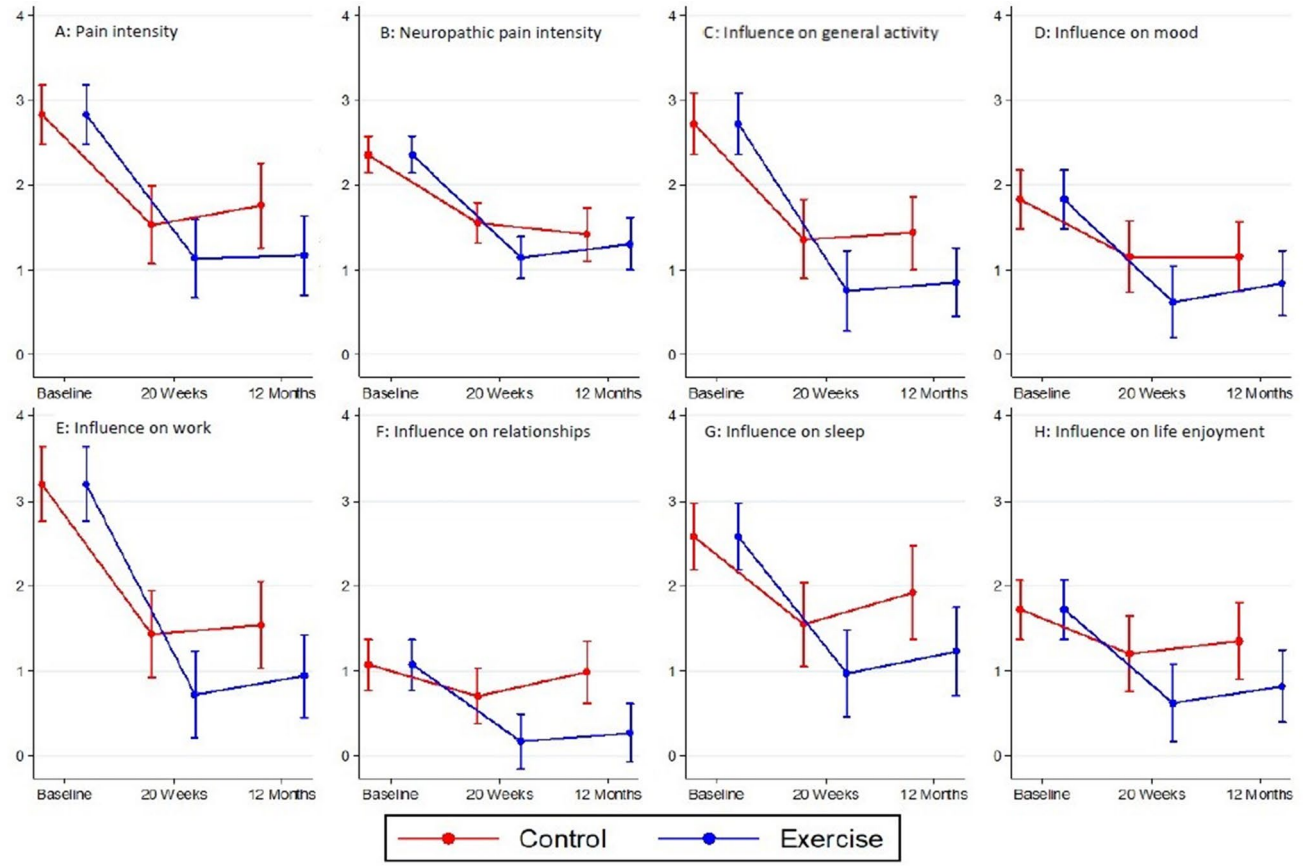

Fig. 3 Estimated levels for pain, neuropathic pain, and the influence of pain on the aspects of daily life of 158 women treated for primary breast cancer with axillary lymph node dissection, LYCA, East Denmark, 2015–2018. **a** estimated pain intensity (0–10). **b** Estimated neuropathic pain intensity (0–5). **c** Estimate for the impact of pain on general activity (0–10). **d** Estimate for the impact of pain on mood (0–10). **e** Estimate for the impact of pain on work (0–10). **f** Estimate for the impact of pain on relationships (0–10). **g** Estimate for the impact of pain on sleep (0–10). **h** Estimate for the impact of pain on life enjoyment (0–10)

The 20-week assessment is likely to represent the time when most patients experience an accumulation of treatment side effects from chemotherapy and radiotherapy, also affecting pain negatively. Encouragingly, in this study, we did not find evidence that this was the case. Furthermore, at this timepoint, we found that a person in the intervention group had a 76% lower risk than a person in the control group of experiencing moderate/severe pain compared to mild pain. The comparison of the "moderate/severe" category versus the "mild" category corresponds to the cut-off point for pain level of clinical relevance used in other studies [1, 40], and to the patient, this might be the difference between a truly bothersome pain and an acceptable pain.

Most RCTs examining the effect of exercise on pain after BC tested the effect of aerobic or combined aerobic and resistance training. Evidence from these trials is modest and inconsistent, with merely 50% of studies showing small effects of limited if any clinical importance [18, 19]. Only one trial tested the effect of PRT alone. Lymphoedema was the primary outcome variable, and the intervention was an early initiated 6-month program of PRT after BC in a population similar to the present study ($n = 204$) [41]. However, they used activity restriction and not usual care as comparison and their pain assessment was less extensive, consisting of one single-item assessing pain during activity. They found higher levels of pain in the intervention group at 6 months but no difference between groups in the long term, which is somewhat conflicting our findings. We observed mostly non-significant declines in pain scores from baseline to 20 weeks, and maintained levels at 12 months. Our findings are otherwise in keeping with previous studies where a tendency towards a positive effect of exercise in general is seen, although the magnitude of the effects does not reach levels of clinical relevance [18, 19].

There might be various explanations to why our intervention did not consistently show significant pain-reductions. First, there might be an unidentified subgroup in which resistance training is more effective. A previous trial examined a sedentary subgroup of BC survivors ($n = 28$) and the effect of a 12-week combined exercise program [42].

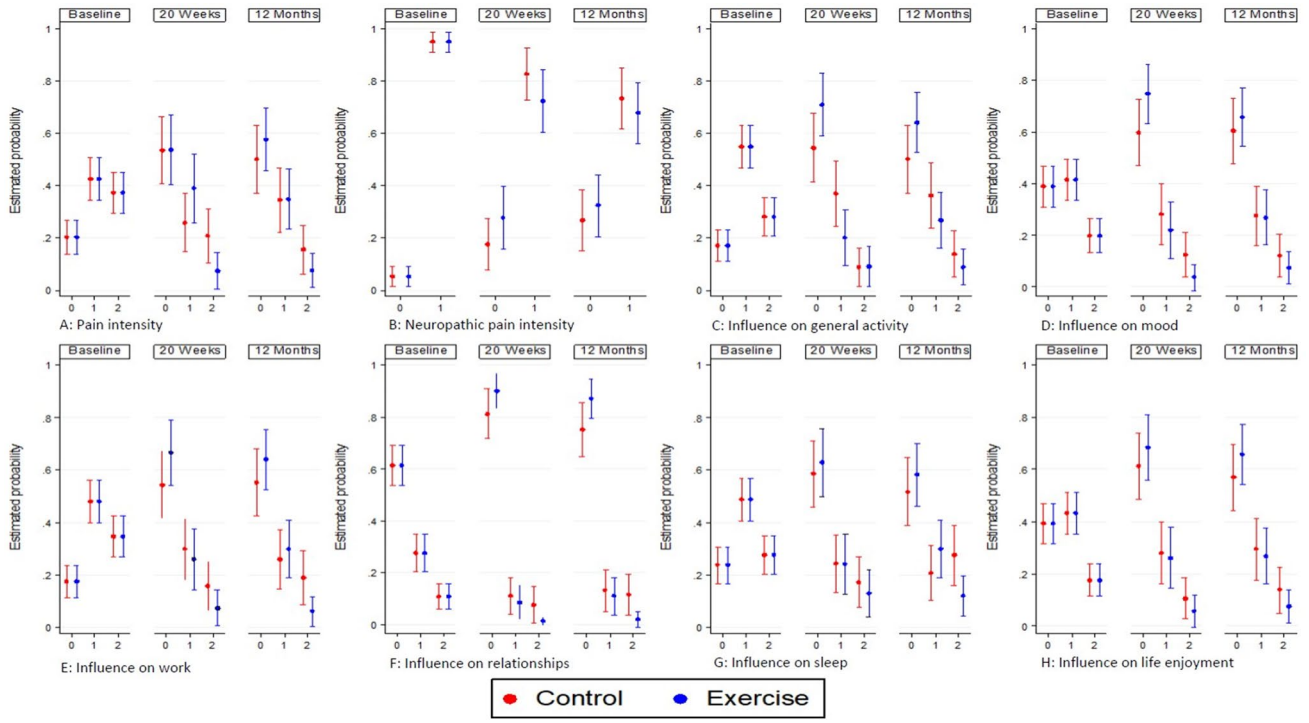

Fig. 4 Panel of plots for probability of pain and aspects of daily life influenced by pain at each assessment point, of 158 women treated for primary breast cancer with axillary lymph node dissection, LYCA, East Denmark, 2015–2018. Categories are 0 = none; 1 = mild; 2 = moderate/severe. Neuropathic pain in two categories; 0 = no, 1 = yes. **a** estimated probability pain. **b** Estimated probability of neuropathic pain. **c** Estimated probability for the influence of pain on general activity. **d** Estimated probability for the influence of pain on mood. **e** Estimated probability for the influence of pain on work. **f** Estimated probability for the influence of pain on relationships. **g** Estimated probability for the influence of pain on sleep. **h** Estimated probability for the influence of pain on life enjoyment

Results indicated a significant pain reduction in the intervention group, but no change in the control group. Another larger trial examined a subgroup of women over the age of 60 years with mixed cancer diagnoses ($n = 109$) and the effect of a 6-week homebased combined walking and resistance exercise program during chemotherapy. Results showed that exercise prevented an otherwise increase in neuropathic pain intensity [43]. In both subgroups addressed above, the control group did not experience a pain reduction over time, contrary to what could be expected and was also found for the control group in the present study. Subsequently it can be speculated that in a group with a worse pain prognosis, e.g. sedentary women with reports of post-operative pain, the potential for an effect of intervention could be larger.

Second, explanations might be found in the limitations of this study. The lack of a substantial difference between intervention and usual care is a potential issue, as usual care was heterogeneous across municipalities in Eastern Denmark and many participants attended rehabilitation including some element of exercise. Knowledge at present does not specify which resistance or combined exercise protocol is the most efficient in reducing low-grade inflammation [44] or releasing endogenous opioids [13]. However, there is likely to be a dose–response relationship involved [15], and it is most likely that the intervention group exercised at a higher intensity and volume, and for a longer period than in usual care.

Adding to this is the risk of selection into the study, in that more women who were already likely to exercise anyway might have signed up for our study, and as we do not restrict activity in the control group it might have diluted the effect of the intervention. Furthermore, missing data, especially at the 20 week assessment, might have introduced wider confidence intervals or skewed the effect estimates in either direction. However, we additionally analysed data including multiple imputation to assess this factor and it did not change estimates notably. Finally, it is likely that the power to detect a difference in pain outcomes was insufficient, as pain was not a primary end-point in this trial, and the relatively high number of statistical tests performed in this study introduces a risk of type 1 error, where a statistically significant finding might be due to chance.

This study has novelty in several aspects. First, in a research field where evidence mostly stem from observational studies, we tested a unimodal resistance training intervention which is useful if we wish to distinguish between the effects of different exercise modes. Second, the intervention

duration and the length of follow-up were longer than what has previously been reported in studies of pain after BC. Third, this study adds substance to the research within the field by including a study population at high risk for experiencing persistent pain and initiating the intervention in the early post-operative phase and extending through the adjuvant therapy period and beyond. This particular period carries challenges with mounting side effects making it difficult to maintain or achieve sufficient and sustainable exercise habits. All the above are aspects that need attention for evidence based recommendations to be formed for the group of women with BC. Finally, this study holds a strength in the detailed assessment tool developed to assess pain and neuropathic pain after BC and validated in the background population.

Conclusion

In a BC population at high risk for experiencing persistent pain, there is no consistent evidence of an effect of PRT on intensity of pain, neuropathic pain and the influence of pain on aspects of daily life. However, restrictive and cautious behaviour in relation to PRT in BC rehabilitation could be reconsidered, as we found no evidence of negative effects on pain in this setting. In order to provide evidence based recommendations for managing persistent pain after BC, further studies should examine PRT at different intensities and volumes. Moreover, it should be established whether effects are different for subgroups in order to allow a more personalised approach.

Author contributions GA participated in designing and executing the experiment, and in writing the manuscript. KGA was involved in designing the measurement tools, planning the analyses and in the writing of the manuscript. PEB was involved in planning the analyses and in the writing of the manuscript. CJ, NK, BZ, OH and SOD participated in designing the experiment and in writing the manuscript. CL participated in planning and execution of the study and in writing the manuscript. EWA was involved in planning and performing the statistical analyses and in writing the manuscript.

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Availability of data and Materials Data supporting the results reported in this paper is stored at the Danish Cancer Society Research Center according to the EU General Data Protection Regulation.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study was approved by the ethical committee in the ethical approval (H-15002714), and all procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All participants gave informed consent to participate before any study related activities were performed.

References

1. Mejdahl MK, Andersen KG, Gartner R, Kroman N, Kehlet H (2013) Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. BMJ 346:f1865
2. Meretoja TJ, Leidenius MHK, Tasmuth T, Sipila R, Kalso E (2014) Pain at 12 months after surgery for breast cancer. JAMA 311(1):90–92
3. Andersen KG, Duriaud HM, Jensen HE, Kroman N, Kehlet H (2015) Predictive factors for the development of persistent pain after breast cancer surgery. Pain 156(12):2413–2422
4. Meretoja TJ, Andersen KG, Bruce J, Haasio L, Sipila R, Scott NW et al (2017) Clinical prediction model and tool for assessing risk of persistent pain after breast cancer surgery. J Clin Oncol 35(15):1660–1667
5. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ et al (1993) The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85(5):365–376
6. Andersen KG, Jensen MB, Tvedskov TF, Kehlet H, Gartner R, Kroman N (2013) Persistent pain, sensory disturbances and functional impairment after immediate or delayed axillary lymph node dissection. Eur J Surg Oncol 39(1):31–35
7. Leysen L, Beckwee D, Nijs J, Pas R, Bilterys T, Vermeir S et al (2017) Risk factors of pain in breast cancer survivors: a systematic review and meta-analysis. Support Care Cancer 25(12):3607–3643
8. Andersen KG, Kehlet H (2011) Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. J Pain 12(7):725–746
9. Miaskowski C, Cooper B, Paul SM, West C, Langford D, Levine JD et al (2012) Identification of patient subgroups and risk factors for persistent breast pain following breast cancer surgery. J Pain 13(12):1172–1187
10. Miaskowski C, Paul SM, Cooper B, West C, Levine JD, Elboim C et al (2014) Identification of patient subgroups and risk factors for persistent arm/shoulder pain following breast cancer surgery. Eur J Oncol Nurs 18(3):242–253
11. Bruce J, Thornton AJ, Powell R, Johnston M, Wells M, Heys SD et al (2014) Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. Pain 155(2):232–243
12. Mejdahl MK, Mertz BG, Bidstrup PE, Andersen KG (2015) Preoperative distress predicts persistent pain after breast cancer treatment: a prospective cohort study. J Natl Compr Cancer Netw 13(8):995–1003 **(quiz)**
13. Goldfarb A (2013) Exercise and endogenous opiates. Endocrinology of physical activity and sport, 2nd edn. Humana Press, Totowa, pp 21–36
14. Kami K, Tajima F, Senba E (2017) Exercise-induced hypoalgesia: potential mechanisms in animal models of neuropathic pain. Anat Sci Int 92(1):79–90

15. Naugle KM, Fillingim RB, Riley JL 3rd (2012) A meta-analytic review of the hypoalgesic effects of exercise. J Pain 13(12):1139–1150
16. Kroll HR (2015) Exercise therapy for chronic pain. Phys Med Rehabil Clin N Am 26(2):263–281
17. Haff G, Triplett N (2015) Essentials of strength training and conditioning, 6th–7th edn. Human Kinetics, Champaign, pp 115–135
18. Furmaniak AC, Menig M, Markes MH (2016) Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev 9:Cd005001
19. Lahart IM, Metsios GS, Nevill AM, Carmichael AR (2018) Physical activity for women with breast cancer after adjuvant therapy. Cochrane Database Syst Rev 1:Cd011292
20. McNeely ML, Campbell K, Ospina M, Rowe BH, Dabbs K, Klassen TP et al (2010) Exercise interventions for upper-limb dysfunction due to breast cancer treatment. Cochrane Database Syst Rev 6:Cd005211
21. Cheema BS, Kilbreath SL, Fahey PP, Delaney GP, Atlantis E (2014) Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 148(2):249–268
22. Hwang JH, Chang HJ, Shim YH, Park WH, Park W, Huh SJ et al (2008) Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. Yonsei Med J 49(3):443–450
23. Cormie P, Pumpa K, Galvao DA, Turner E, Spry N, Saunders C et al (2013) Is it safe and efficacious for women with lymphedema secondary to breast cancer to lift heavy weights during exercise: a randomised controlled trial. J Cancer Surviv 7(3):413–424
24. Sundheddstyrelsen. National Clinical Guidelines concerning complications following surgery for early breast cancer- prevention, treatment and rehabilitation of impairments in shoulder and arm and arm lymphedema in adults who have undergone surgery for early breast cancer Copenhagen: Sundhedsstyrelsen; 2016
25. Kirkham AA, Bland KA, Sayyari S, Campbell KL, Davis MK (2016) Clinically relevant physical benefits of exercise interventions in breast cancer survivors. Curr Oncol Rep 18(2):12
26. Danish Breast Cancer Cooperative Group [internet]. Copenhagen: Danish Breast Cancer Cooperative Group; [Nationwide clincial database]. http://www.dbcg.dk/
27. Jensen MB, Laenkholm AV, Offersen BV, Christiansen P, Kroman N, Mouridsen HT et al (2018) The clinical database and implementation of treatment guidelines by the Danish Breast Cancer Cooperative Group in 2007–2016. Acta Oncol 57(1):13–18
28. Ammitzboll G, Johansen C, Lanng C, Andersen EW, Kroman N, Zerahn B et al (2019) Progressive resistance training to prevent arm lymphedema in the first year after breast cancer surgery: results of a randomized controlled trial. Cancer 125(10):1683–1692
29. Ammitzbøll G, Lanng C, Kroman N, Zerahn B, Hyldegaard O, Kaae Andersen K et al (2017) Progressive strength training to prevent LYmphoedema in the first year after breast CAncer—the LYCA feasibility study. Acta Oncol 56(2):360–366
30. Heyward V, Gibson A (2014) Assessing muscular fitness. In: Huls S (ed) Advanced fitness assessment and exercise prescription, 7th edn. Human Kinetics, Champaign, pp 153–180
31. Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H (2009) Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 302(18):1985–1992
32. Mejdahl MK, Christensen KB, Andersen KG (2019) Development and validation of a screening tool for surgery-specific neuropathic pain scale for postsurgical patients. Pain Phys 22:81–90
33. Torres Lacomba M, Yuste Sanchez MJ, Zapico Goni A, Prieto Merino D, Mayoral del Moral O, Cerezo Tellez E et al (2010) Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. BMJ 340:b5396
34. Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM (2002) Physiotherapy after breast cancer surgery: results of a randomised controlled study to minimise lymphoedema. Breast Cancer Res Treat 75(1):51–64
35. Johansson K, Branje E (2010) Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis. Acta Oncol 49(2):166–173
36. Ammitzboll G, Johansen C, Lanng C, Andersen EW, Kroman N, Zerahn B et al (2019) Progressive resistance training to prevent arm lymphedema in the first year after breast cancer surgery: results of a randomized controlled trial. Cancer 125:1683–1692
37. Kootstra JJ, Dijkstra PU, Rietman H, de Vries J, Baas P, Geertzen JH et al (2013) A longitudinal study of shoulder and arm morbidity in breast cancer survivors 7 years after sentinel lymph node biopsy or axillary lymph node dissection. Breast Cancer Res Treat 139(1):125–134
38. Akoochakian M, Davari HA, Alizadeh MH, Rahnama N (2017) Evaluation of shoulder girdle strength more than 12 month after modified radical mastectomy and axillary nodes dissection. J Res Med Sci 22:81
39. Hidding JT, Beurskens CH, van der Wees PJ, van Laarhoven HW, Nijhuis-van der Sanden MW (2014) Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review. PLoS ONE 9(5):e96748
40. Gerbershagen HJ, Rothaug J, Kalkman CJ, Meissner W (2011) Determination of moderate-to-severe postoperative pain on the numeric rating scale: a cut-off point analysis applying four different methods. Br J Anaesth 107(4):619–626
41. Sagen A, Karesen R, Risberg MA (2009) Physical activity for the affected limb and arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with two years follow-up. Acta Oncol 48(8):1102–1110
42. Reis AD, Pereira P, Diniz RR, de Castro Filha JGL, Dos Santos AM, Ramallo BT et al (2018) Effect of exercise on pain and functional capacity in breast cancer patients. Health Qual Life Outcomes 16(1):58
43. Kleckner IR, Kamen C, Gewandter JS, Mohile NA, Heckler CE, Culakova E et al (2018) Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. Support Care Cancer 26(4):1019–1028
44. de Jesus Leite MAF, Puga GM, Arantes FJ, Oliveira CJF, Cunha LM, Bortolini MJS et al (2018) Effects of combined and resistance training on the inflammatory profile in breast cancer survivors: a systematic review. Complement Ther Med 36:73–81

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