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CLINICAL TRIAL

Effects of physical exercise on markers of inflammation in breast cancer patients during adjuvant chemotherapy

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Abstract

Purpose Exercise has been shown to reduce fatigue during cancer treatment. Hypothesized mechanisms include inflammatory pathways. Therefore, we investigated effects of exercise on markers of inflammation in breast cancer patients during adjuvant chemotherapy.

Methods We pooled data from two randomized controlled exercise intervention trials with breast cancer patients during adjuvant chemotherapy ($n = 130$), which had previously shown beneficial effects of exercise on fatigue. Exercise comprised a 12-week resistance training (BEATE study) or an 18-week combined resistance and aerobic training (PACT study). Serum IL-6, IL-1ra, and the IL-6/IL-1ra ratio were quantified at baseline, mid-intervention, post-intervention, and 6–9 months post-baseline.

Results Mixed effect models showed significant increases in IL-6 and IL-6/IL-1ra ratio during chemotherapy and decreases afterwards. Differences between exercise and control group were not significant at any time point. Changes in total cancer-related fatigue were significantly correlated with changes in IL-6/IL-1ra ratio (partial correlation $r = 0.23$) and IL-6 ($r = 0.21$), and changes in physical cancer-related fatigue with changes in IL-6/IL-1ra ratio ($r = 0.21$).

Conclusions Changes in fatigue were slightly correlated with changes in inflammatory markers, and there was a strong inflammatory response to adjuvant chemotherapy. The supervised exercise training did not counteract this increase in inflammation, suggesting that beneficial effects of exercise on fatigue during adjuvant chemotherapy for breast cancer are not essentially mediated by IL-6, IL-1ra, or the IL-6/IL-1ra ratio.

Keywords Exercise · Breast cancer · Fatigue · Chemotherapy · Inflammation · Mechanisms

Introduction

One of the most common and devastating adverse effects from cancer and cancer treatment is fatigue, which can negatively affect quality of life [1, 2]. Cancer-related fatigue is considered a multidimensional construct, consisting of dimensions such as physical fatigue and mental fatigue [2, 3]. Moderate to severe fatigue during adjuvant treatment is reported by over 40% of breast cancer patients [4]. Typically, fatigue is highest during chemotherapy [5]. Breast cancer, the most common cancer type in women worldwide with over 1.67 million new cases annually [6] is often treated with adjuvant chemotherapy to reduce risk of distant recurrence [7]. Consequently, the burden of cancer-related fatigue is high.

The etiology of fatigue is assumed to be multifactorial, with demographic, medical, psychosocial, behavioral, and biological factors having a role [1]. Hypothesized mechanisms include cytokine dysregulation, hypothalamic–pituitary–adrenal (HPA) dysfunction, 5-hydroxy tryptophan (5-HT) neurotransmitter dysregulation, circadian rhythm

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disruption, alterations in adenosine triphosphate (ATP) and muscle metabolism, and vagal afferent activation [8]. Of these, involvement of cytokine dysregulation in the etiology of cancer-related fatigue has gained most attention [1]. In support of this proposed mechanism, reviews indeed show for multiple cancer types significant correlations between fatigue and levels of several inflammatory markers, such as interleukin-6 (IL-6), interleukin-1-receptor antagonist (IL-1ra), interleukin-1β (IL-1β), and neopterin [9, 10]. In breast cancer patients undergoing chemotherapy specifically, changes in levels of interleukin-6 (IL-6) have been found to be significantly correlated with changes in fatigue [11].

Physical exercise has been shown to be an effective intervention to prevent and diminish levels of fatigue in patients during adjuvant cancer treatment [12–15]. Also in breast cancer patients, physical exercise during adjuvant therapy has shown significant beneficial effects on fatigue, with largest effects on the physical fatigue dimension [16–19]. It has been hypothesized that these beneficial effects of exercise on fatigue are mediated by changes in inflammatory state [20, 21]. A recent meta-analysis investigated the effects of exercise on inflammatory markers in breast cancer survivors [22]. Results show significant beneficial exercise effects on IL-6, TNFα, IL-8, and IL-2 when including all exercise programs (i.e., aerobic, combined aerobic/resistance, yoga, and Tai Chi), but did not reach statistical significance when including only aerobic or combined aerobic/resistance exercise programs. However, in all included trials, exercise programs were performed after completion of primary treatment, and effects of exercise programs during adjuvant chemotherapy on inflammatory markers remain unknown. Therefore, we studied the effects of exercise during adjuvant chemotherapy on inflammatory markers in breast cancer patients.

Methods

We investigated the effects of exercise on inflammatory markers in two comparable, randomized controlled trials (RCTs) in breast cancer patients during adjuvant chemotherapy by pooling individual patient data: the BEATE study ('Bewegung und Entspannung als Therapie gegen Erschöpfung', NCT01106820) [23, 24] and the PACT study ('Physical Activity during Cancer Treatment', ISRCTN43801571, NTR2138) [18, 25]. Study characteristics of both studies are summarized in Table 1. The BEATE study investigated the effects of a 12-week supervised resistance exercise program versus a muscle relaxation control group. Details of the design of the BEATE study [24] and effects on fatigue, quality of life, and depression have been published previously [23]. In short, the BEATE study was conducted at the National Center for Tumor Diseases in Heidelberg, Germany, between 2010 and 2013. The PACT study investigated the effects of an 18-week supervised combined resistance and aerobic exercise program versus usual care. Details of the design of the PACT study [25] and effects on fatigue, quality of life, and physical fitness have been published as well [18]. Briefly, the PACT study was a multicenter RCT which was conducted in seven Dutch hospitals between 2010 and 2013. In parallel with breast cancer patients, also colon cancer patients were invited for the PACT study, of whom the results have been published separately [26]. The BEATE and PACT study were approved by the Medical Ethics Committees of the University of Heidelberg and University Medical Center Utrecht and local Ethical Boards of the participating hospitals, respectively. All patients provided written informed consent.

Participants

In- and exclusion criteria for both studies are summarized in Table 1. Both studies included histologically confirmed, newly diagnosed breast cancer patients, scheduled for adjuvant chemotherapy. Patients with contraindications for physical training/activity were excluded, as well as patients with concurrent malignant diseases (BEATE) or treatment for concurrent malignant diseases in the past 5 years (PACT). The BEATE study excluded patients who already participated in systematic intensive training, whereas the PACT study allowed active patients to participate.

Intervention

Both the BEATE and PACT intervention consisted of twice weekly supervised exercise with progressive intensity. In the BEATE study, the exercise program started in the first or second cycle of chemotherapy, and had a total duration of 12 weeks. Training sessions consisted of progressive resistance exercises, without any specific aerobic exercise. In the PACT study, the exercise program started within 6 weeks from diagnosis (or 10 weeks in case of immediate use of a tissue expander after surgery), and had a total duration of 18 weeks. The training sessions contained both progressive resistance and aerobic exercises. In addition to these supervised sessions, patients were instructed to be physically active for at least 30 min a day, on three other days of the week. Patients randomized to the control group of the BEATE study participated in a 1-h supervised muscle relaxation program twice a week, whereas patients randomized to the control group of the PACT study received usual care without any additional intervention, and were instructed to maintain their habitual physical activity pattern (Table 1).

Table 1 Study characteristics of the BEATE and PACT studies

	BEATE study (2010–2013, $n = 101$)	PACT study (2010–2013, $n = 204$)
Patient characteristics		
Inclusion criteria	Histologically confirmed primary breast cancer after lumpectomy or mastectomy	Histologically confirmed primary breast cancer less than 6 weeks before recruitment (or 10 weeks in case of immediate use of a tissue expander after surgery)
	Scheduled for adjuvant chemotherapy	Scheduled for adjuvant chemotherapy
	Age ≥ 18 years	Age 25–75 years
	Body mass index ≥ 18 kg/m^2	Stage M0
	Ability to understand and follow the study protocol	Ability to read and understand the Dutch language
	Willingness to come to the Heidelberg exercise facilities	Karnofsky performance status ≥ 60 and ability to walk ≥ 100 m
Exclusion criteria	Contraindications for training	Contraindications for physical activity
	Concurrent malignant diseases (except carcinoma in situ of skin or cervix)	Treatment for malignancies in the 5 years preceding recruitment (except basal skin cancer)
	Already participating in systematic intensive resistance or aerobic training (≥ 2 × 1 h/week)	
Intervention characteristics		
Timing	During chemotherapy	During chemotherapy
Duration	12 weeks	18 weeks
Type and intensity	2 × 1 h/week	2 × 1 h/week
	Resistance: Progressive resistance exercises	*Resistance*: Progressive resistance exercises
	3 × 8-12 repetitions 60–80% 1RM	2 × 10 repetitions 65% 1RM, increasing to 1 × 10 repetitions 75% 1RM, and 1 × 20 repetitions 45% 1RM
		Aerobic: 3 × 2 min increasing to 2 × 7 min at VT, and 3 × 4 min increasing to 1 × 7 min below VT
Mode	Supervised	Supervised
Exercise advice	–	In addition to supervised program: PA ≥ 30 min/day, 3 days/week
Control	Supervised relaxation control 12 weeks, 2 × 1 h/week	Usual care
Outcome measures		
Time points	Baseline	Baseline
	Mid-intervention (7 weeks post-baseline)	Post-intervention (18 weeks post-baseline)
	Post-intervention (13 weeks post-baseline)	Long-term (36 weeks post-baseline)
	Long-term (26 weeks post-baseline)	
Inflammatory markers	Interleukin-6	Interleukin-6
	Interleukin-1 receptor antagonist	Interleukin-1 receptor antagonist
		Nicotinamide phosphoribosyltransferase
		Neopterin
		Leptin
		Adiponectin
		Tumor Necrosis Factor-alpha
		C-reactive protein
		Tumor Necrosis Factor-I
		Tumor Necrosis Factor-II
Fatigue	Fatigue assessment questionnaire (FAQ)	Multidimensional fatigue inventory (MFI)

1RM one repetition maximum, *PA* physical activity, *min* minutes, *VT* ventilatory threshold

Outcome assessment

At baseline, mid-intervention for BEATE, post-intervention, and long-term follow-up, patients visited the study centers for outcome assessment (Table 1). In addition to completing questionnaires and performing physical measurements, blood samples were taken at each visit. Blood sampling took place according to a standardized protocol, at least 6 (BEATE) or 7 days (PACT) after a chemotherapy administration. Sampling took place not earlier than 24 h after an

exercise session to measure chronic and not acute effects. Samples were processed within 2 h and stored locally at −80°C until analysis took place. Serum IL-6 and IL-1ra levels were quantified for all samples at the German Cancer Research Center (DKFZ, Heidelberg, Germany), by use of Quantikine Immunoassay kits (R&D Systems, Minneapolis, MN) according to the manufacturer's instruction. Measurements were performed in duplicate at room temperature. The intra-assay coefficients of variation were 4.4 and 3.3% for IL-6 and IL-1ra immunoassays, respectively. Within the PACT study, the following inflammatory markers were also analyzed in serum: neopterin, nicotinamide phosphoribosyltransferase (Nampt) (IRAS, University Utrecht, The Netherlands), leptin, adiponectin, tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), TNF receptor I, and TNF receptor II (SHO Centre for Medical Diagnostics, Velp, The Netherlands). In both studies, IL-6 values below the detection limit were replaced by the detection limit divided by the square root of 2 (16% of IL-6 values). In addition to the individual inflammatory markers, the IL-6/IL-1ra ratio was calculated, which reflects the balance between pro- and anti-inflammatory response.

Fatigue was assessed using the multidimensional Fatigue Assessment Questionnaire (FAQ) in BEATE, and the Multidimensional Fatigue Inventory (MFI) in PACT (Table 1). The FAQ is a validated, 20-item questionnaire, covering the dimensions physical, affective, and cognitive fatigue [27]. The MFI is a validated, 20-item questionnaire, designed to measure the dimensions general fatigue, physical fatigue, mental fatigue, 'reduced activity,' and 'reduced motivation' [3]. For our pooled analyses, we considered the dimensions 'physical fatigue,' 'mental fatigue' (using FAQ cognitive fatigue), and 'total fatigue' (using MFI general fatigue).

Data analysis

Our study population included all patients with an available baseline blood measure and at least one post-intervention measure (Fig. 1). Analyses testing for group effects were performed according to the intention-to-treat principle.

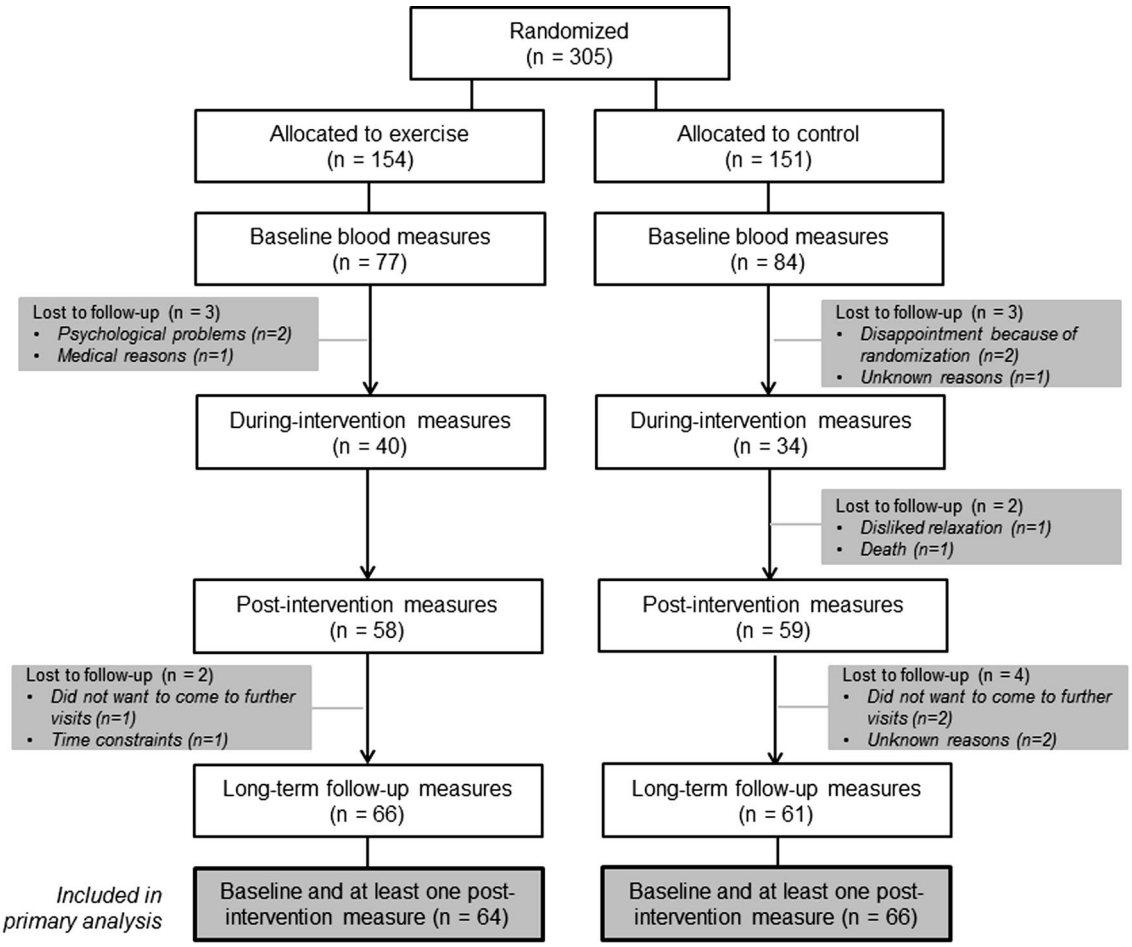

Fig. 1 Flow chart of patients participating in the BEATE study and PACT study

Descriptive statistics were used to summarize the characteristics of the study population.

Because of skewed distributions of the inflammatory markers, all values were transformed to a natural logarithmic scale. To determine between-group differences in inflammatory markers, mixed effect models were used with mid-intervention, post-intervention, and long-term follow-up values of inflammatory markers as dependent variables, the randomization group as independent variable, and the baseline inflammatory marker value (continuous) as covariate. For within-group differences, the baseline inflammatory markers were considered also as dependent variables instead of as covariate. Models were adjusted for study (BEATE or PACT), menopausal status (premenopausal or postmenopausal), radiotherapy status (no, current or previous treatment with radiotherapy), hormone receptor status (triple negative, Her2Neu+ and ER/PR+, Her2Neu+ and ER&PR−, Her2Neu− and ER/PR+), baseline body mass index (continuous), and age (continuous). Depending on Akaike's Information Criterion, we used either a compound symmetry correlation matrix (IL-6, Nampt, leptin, TNF-α, and TNF receptor I) or an unstructured covariance matrix (IL-1ra, IL-6/IL-1ra ratio, neopterin, adiponectin, CRP, TNF receptor II). As mid-intervention values had been collected only in BEATE, a sensitivity analysis excluding this values was performed, as well as a sensitivity analysis replacing the IL-6 values below detection limit by maximum likelihood estimation [28]. Because changes in body weight have been shown to be an important mediator in the association between exercise and inflammatory markers and adipokines [29], we initially adjusted only for baseline BMI. Because average weight gain turned out to be largest in the exercise group, we additionally performed a sensitivity analysis in which we also adjusted for changes in body mass index.

As a consequence of using a natural logarithmic scale, the geometric mean is presented at baseline. For the between-group differences, the exponent (anti-logarithm) of the estimated outcome is presented, which represents the treatment effect ratio (TER). A TER of > 1 indicates an on average higher level of the investigated inflammatory maker, whereas a TER of < 1 indicates a lower level, as compared with the reference.

To pool fatigue outcomes, we recoded individual scores into standardized z-scores by subtracting the individual score from the mean score at baseline and dividing the result by the mean standard deviation at baseline. Exercise effects on fatigue were modeled using a similar mixed effects model as described above, resulting in a between-group difference in z-scores, which corresponds to a Cohen's d effect size. Effect sizes < 0.2 indicate "no difference," effect sizes of 0.2–0.5 indicate "small differences," effect sizes of 0.5–0.8 indicate "medium differences," and effect sizes ≥ 0.8 indicate "large differences" [30]. To investigate the association between changes in inflammatory markers with changes in fatigue levels, partial correlation coefficients were calculated, with adjustment for study, menopausal status, radiotherapy status, hormone receptor status, baseline body mass index, and age. Data were analyzed using IBM SPSS Statistics 20.0. Statistical significance was set at a probability of $p < 0.05$ for all analyses.

Results

Of the 154 patients who were randomized to the exercise intervention of the BEATE ($n = 52$) or PACT study ($n = 102$), baseline blood samples were obtained from 77 patients (BEATE $n = 42$ (81%), PACT $n = 35$ (34%)). Of the 151 patients allocated to the control group (BEATE $n = 49$, PACT $n = 102$), baseline blood samples were taken from 84 patients (BEATE $n = 42$ (86%), PACT $n = 42$ (41%)). Because blood sampling was added as an amendment to the already ongoing PACT study, blood samples are not available for all patients. However, after the amendment blood was collected systematically, the groups remained balanced. Thirty-one patients without any follow-up measurement were excluded, leaving a total of 130 patients (exercise intervention $n = 64$, control n = 66) for primary analysis (Fig. 1).

Baseline patient characteristics

Patients in the exercise and control groups were comparable with respect to baseline characteristics (p values > 0.05) (Table 2). All patients were female and were, on average, overweight. The majority of patients were not (yet) treated with radiotherapy at baseline (81.3% in the exercise group and 75.8% in the control group). In the BEATE study, all patients initiated chemotherapy prior to randomization. In the PACT study, 6 out of 52 patients (11.5%) already started chemotherapy at baseline.

Courses of IL-6, IL-1ra, and IL-6/IL-1ra ratio and effects of exercise

Levels of IL-1ra generally increased during chemotherapy for both groups (Table 3). Largest within-group changes were obtained from baseline to mid-intervention (significant TER in the control group: 1.44 [95% confidence interval (95% CI): 1.11; 1.86]). At long-term follow-up, IL-1ra levels recovered to baseline values in both groups. No significant between-group differences were observed for IL-1ra at any time point.

For IL-6 levels, a significant increase was observed from baseline to post-intervention for both the exercise group and the control group (TER 2.11 [95% CI 1.26; 3.52] and 1.69 [95% CI 1.04; 2.74], respectively). From baseline to

Table 2 Baseline characteristics of the pooled patient population

	Control ($n = 66$)	Intervention ($n = 64$)
Age in years (mean ± SD)	52.3 ± 9.3	50.8 ± 9.1
BMI in kg m^{-2} (mean ± SD)	26.6 ± 4.8	26.1 ± 4.8
Study [*n* (%)]		
BEATE	38 (57.6)	40 (62.5)
PACT	28 (42.4)	24 (37.5)
Tumor stage [*n* (%)]		
I	18 (27.3)	23 (35.9)
II	38 (57.6)	32 (50.0)
III	10 (15.2)	7 (10.9)
Unknown	–	2 (3.1)
Menopausal status [*n* (%)]		
Premenopausal	34 (51.5)	32 (50.0)
Postmenopausal	31 (47.0)	26 (40.6)
Unknown	1 (1.5)	6 (9.4)
Receptor status [*n* (%)]		
Triple negative	9 (13.6)	6 (9.4)
Her2+ and ER/PR+	12 (18.2)	15 (23.4)
Her2+ and ER&PR−	4 (6.1)	4 (6.3)
Her2− and ER/PR+	41 (62.1)	39 (60.9)
Radiotherapy [*n* (%)]		
Yes	16 (24.2)	12 (18.8)
No	50 (75.8)	52 (81.3)
VO2 peak at baseline in L min^{-1} (mean ± SD)	1.6 ± 0.4	1.6 ± 0.5

long-term follow-up, levels of IL-6 showed a decrease, which was significant in the exercise group (TER 0.40 [95% CI 0.21; 0.74]). No significant between-group differences were observed. A sensitivity analysis using maximum likelihood estimation for the IL-6 values below detection limit yielded similar results.

IL-6/IL-1ra ratio levels showed rather similar baseline to post-intervention and baseline to long-term follow-up differences as IL-6 levels. Again, no between-group differences were observed. A sensitivity analysis excluding the mid-intervention values did not change the results, nor did a sensitivity analysis with adjustment for changes in BMI.

Associations with fatigue

We found significant beneficial effects of exercise on fatigue in both RCTs, and comparable effects in the subgroup with available blood samples. In the PACT study, effects on post-intervention fatigue were small with effect sizes (ES) of −0.23 (general fatigue) and −0.30 (physical fatigue) [18]. The BEATE study showed comparable effects on post-intervention total fatigue (ES = -0.29) and physical fatigue (ES = −0.34) [23]. Pooled analyses of our subgroup with available blood measures also showed positive exercise effects on post-intervention total fatigue (ES = −0.40 [95% CI −0.72; −0.09]) and physical cancer-related fatigue (ES = −0.35 [95% CI −0.66; −0.04]).

Baseline to post-intervention changes in levels of IL-6 were positively correlated with changes in physical cancer-related fatigue (partial correlation coefficient (*r*):0.21) and changes in levels of IL6/IL1ra-ratio were positively correlated with changes in total fatigue and physical cancer-related fatigue (*r* 0.23 and 0.21, respectively) (Table 4).

Exercise effects on additional inflammatory markers (PACT study)

Exercise effects on neopterin, Nampt, leptin, adiponectin, TNF-α, CRP, TNF receptor I, and TNF receptor II are summarized in Online Resource 1. In general, levels of the pro-inflammatory markers showed a pattern of increase from baseline to post-intervention, and recovered to baseline values at long-term follow-up. An exception is Nampt, which was still significantly increased at long-term follow-up compared to baseline in both the exercise and control group (TER: 1.66 [95% CI 1.05; 2.61] and 1.58 [95% CI 1.08; 2.32], respectively). For CRP, significantly lower levels were observed at long-term follow-up compared to baseline in the exercise group (TER: 0.54 [95% CI 0.30; 0.96]). The levels of the anti-inflammatory marker adiponectin showed an opposite pattern compared to the pro-inflammatory markers, with decreases from baseline to post-intervention, and recovery at long-term follow-up. For all markers, no significant between-group differences were observed, except for leptin post-intervention (TER: 1.40 [95% CI 1.01; 1.93]). After adjustment for changes in BMI, this between-group difference attenuated and lost significance (TER: 1.19 [95% CI 0.88; 1.62]). Adjustment for BMI changes did not affect the exercise effects on other biomarkers. Changes in levels of Nampt and leptin were negatively associated with changes in total fatigue (r −0.47, $p = 0.01$ and r −0.49, $p = 0.01$) and physical cancer-related fatigue (r −0.45, $p = 0.02$ and r −0.40, $p = 0.03$). No significant correlations were found for the other inflammatory markers with total fatigue, physical fatigue, or mental fatigue (results not shown).

Discussion

In our study with pooled individual patient data of two randomized controlled trials in breast cancer patients, we observed that levels of IL-6 and IL-6/IL-1ra ratio increased during chemotherapy, and recovered after chemotherapy. Changes in levels of inflammatory markers were significantly associated with changes in levels of total fatigue (IL-6 and IL-6/IL1-ra ratio) and physical cancer-related fatigue

Table 3 Exercise effects on IL-6, IL-1ra, and IL-6/IL-1ra ratio

Outcome	Group	Baseline geometric mean	Baseline to mid-intervention		Baseline to post-intervention		Baseline to long-term follow-up	
			Within-group difference: TER (95% CI)	Between-group difference: TER (95% CI)	Within-group difference: TER (95% CI)	Between-group difference: TER (95% CI)	Within-group difference: TER (95% CI)	Between-group difference: TER (95% CI)
IL-1ra	Exercise	301.2	1.27 (0.99; 1.62)	0.89 (0.63; 1.25)	1.14 (0.95; 1.38)	0.99 (0.77; 1.26)	0.99 (0.82; 1.20)	1.09 (0.93; 1.27)
	Control	296.9	1.44 (1.11; 1.86)**	Reference	1.18 (0.99; 1.41)	Reference	0.93 (0.78; 1.11)	Reference
IL-6	Exercise	0.94	1.55 (0.89; 2.72)	1.40 (0.70; 2.78)	2.11 (1.26; 3.52)**	1.32 (0.76; 2.30)	0.40 (0.21; 0.74)**	0.67 (0.38; 1.18)
	Control	0.82	1.16 (0.65; 2.08)	Reference	1.69 (1.04; 2.74)*	Reference	0.65 (0.37; 1.17)	Reference
IL-6/IL-1ra	Exercise	0.0031	1.19 (0.66; 2.16)	1.69 (0.79; 3.62)	1.83 (1.09; 3.07)*	1.34 (0.76; 2.34)	0.39 (0.21; 0.72)**	0.62 (0.35; 1.09)
	Control	0.0028	0.76 (0.41; 1.41)	Reference	1.42 (0.87; 2.33)	Reference	0.70 (0.40; 1.22)	Reference

Mixed effects models on pooled data of the BEATE study and PACT study were calculated with mid-intervention, post-intervention, and long-term follow-up values as dependent variables, adjusted for study, menopausal status, hormone receptor status, radiotherapy status, baseline body mass index, and age as well as the baseline value of the inflammatory marker (only for between-group differences). Mid-intervention values were measured in the BEATE study (7 weeks post-baseline), post-intervention values were measured in the BEATE study (13 weeks post-baseline) and PACT study (18 weeks post-baseline), and long-term follow-up values were measured in the BEATE study (26 weeks post-baseline) and PACT study (36 weeks post-baseline)

TER treatment effect ratio, *CI* confidence interval, *IL-1ra* interleukin-1 receptor antagonist, *IL-6* interleukin-6

* Significant at level $p < 0.05$

** Significant at level $p < 0.01$

Table 4 Partial correlations of baseline to post-intervention changes in inflammatory marker levels with changes in fatigue

Parameter	IL-1ra		IL-6		IL-6/IL-1ra ratio	
	r	*p* value	*r*	*p* value	*r*	*p* value
Total fatigue	− 0.09	0.40	**0.21**	**0.04**	**0.23**	**0.02**
Physical fatigue	− 0.10	0.32	0.18	0.07	**0.21**	**0.03**
Cognitive fatigue	− 0.08	0.41	0.13	0.21	0.15	0.13

Bold coefficients indicate statistical significance at level $p < 0.05$

(IL-6/IL-1ra ratio). We did not observe effects of exercise on inflammatory markers IL-6, IL-1ra, and IL-6/IL-1ra ratio.

Our results on the course of inflammatory markers during and after chemotherapy expand current knowledge from previous studies that had observed increased serum IL-6 in breast cancer patients during chemotherapy [31, 32], and decrease after end of chemotherapy [31]. Paclitaxel every 3 weeks had been observed to increase IL-6 in a study with 90 breast cancer patients, yet this increase was not observed for weekly, lower dosed paclitaxel regimens [33]. In contrast, IL-6 levels during anthracycline-based chemotherapies appeared to be not increased in other studies [34, 35]. Due to a wide variety of chemotherapy schemata that however mostly included some taxan-based treatments, we were not able to investigate effects of specific cytostatics. Of interest is the substantial increase in IL-6 levels we observed during chemotherapy, as demonstrated by within-group post-intervention TERs of 1.69 and 2.11, indicating an approximate increase of IL-6 levels of 69 and 110% in the control and exercise group, respectively. In addition, we observed that IL-6 and the IL-6/IL-1ra ratio decreased again after chemotherapy, reaching levels similar to baseline approximately three to 4 months after chemotherapy in both groups. As in the BEATE study baseline measurements were taken during the 1st or 2nd chemotherapy cycle, the follow-up levels were lower than the baseline levels. The large increase of IL-6 levels during chemotherapy, followed by a recovery after the end of therapy, suggests that IL-6 is strongly responsive to treatment with chemotherapy. Clinically, this is of importance as it indicates that in general patients recover from chemotherapy in terms of inflammation on the long-term. Nevertheless, during chemotherapy, inflammatory processes might contribute to severe side-effects

such as fatigue. Effective treatments to reduce chemotherapy-induced inflammation still need to be defined.

While most of the other measured pro-inflammatory markers also showed a recovery to baseline levels or decrease below baseline levels (CRP in the exercise group) at long-term follow-up, the long-term course of Nampt deviated by showing a prolonged elevation in both the control and exercise group. Nampt, also known as visfatin or pre-B cell colony-enhancing factor 1 (PBEF1), is hypothesized to facilitate inflammation and angiogenesis and to have a multifunctional role in carcinogenesis, with influence on aspects as apoptosis and cancer cell metastasis [36]. With suggested potential roles for Nampt as biomarker for cancer diagnosis and prognosis [37], information on the natural course of Nampt is essential and this observed prolonged increase needs further investigation.

Elevated levels of pro-inflammatory markers have previously been associated with fatigue [9] and other side-effects of breast cancer and its treatment, e.g., cognitive function [31, 38] and accelerated aging [39]. We differentiated fatigue by its dimensions, because a recent meta-analysis has shown that physical cancer-related fatigue is the dimension most sensitive to exercise during adjuvant breast cancer treatment [16]. We observed a small, positive correlation of changes in total fatigue with changes in the pro-/anti-inflammatory ratio and IL-6, and small, negative correlations with changes in leptin and Nampt. The pro/anti-inflammatory ratio, leptin and Nampt were also correlated with physical cancer-related fatigue. No correlations were seen for the other inflammatory markers. Findings of a previous quantitative review revealed small, positive correlations of IL-6 and IL-1ra with (unidimensional) cancer-related fatigue ($r = 0.12$, p value $= 0.004$ and $r = 0.24$, p value < 0.001). IL-6/IL-1ra ratio, Nampt, and leptin were not assessed [9]. Although our findings on IL-6 are in line with that review, it is important to note that the longitudinal design of our study allowed for calculation of correlations between changes in inflammatory markers and changes in fatigue. The aforementioned review also included cross-sectional correlations, which only provides information on a specific point in time. A further strength of our analysis and difference to that review is that we could assess correlations with the different dimensions of fatigue separately, and found that levels of the aforementioned biomarkers were associated with total and physical cancer-related fatigue, but not with mental fatigue.

With regard to exercise, we did not discover significant intervention effects on IL-6, IL-1ra, and the IL-6/IL-1ra ratio. Our findings are in line with those of a recent meta-analysis, in which no statistically significant effects of aerobic or combined aerobic/resistance exercise programs on inflammatory markers in breast cancer survivors were found [22]. The exercise programs included in that review were, however, implemented after the completion of primary breast cancer treatment, in contrast to our exercise programs that were performed during adjuvant therapy. Our current study is the first to evaluate exercise effects on inflammatory markers during adjuvant chemotherapy for breast cancer. Importantly, additional markers may be involved in the inflammatory pathway and thus, our results should be considered as a first exploration of mechanisms for exercise effects during chemotherapy among patients with breast cancer. In a previous study, we evaluated effects of exercise during adjuvant radiotherapy [40]. In that study, we found that the increase of IL-6 and the IL-6/IL-1ra ratio during radiotherapy was counteracted by physical exercise. Possibly, exercise indeed has the ability to prevent or diminish increases in IL-6 levels in breast cancer patients, but the effect of chemotherapy is just too strong to be effectively counteracted by exercise during active treatment.

Regarding the biomarkers investigated in our study, we only observed a significant exercise intervention effect on leptin post-intervention, unexpectedly in favor of the control group. Leptin is a central adipokine and, thus, changes in leptin levels have been reported to be strongly associated with changes in total body fat [29]. As expected, after adjusting for changes in body mass index, which were larger in the exercise group, the between-group difference for leptin diminished and lost statistical significance.

This study has several strengths and limitations. Both, the PACT study and BEATE study had a good intervention adherence and extensive data collection. IL-6 and IL-1ra were quantified in the same way and in the same laboratory for both studies. This offered a unique and excellent opportunity to combine the data to investigate our research question. Limitations are, that, although both RCTs evaluated a supervised exercise program during chemotherapy, there were also differences between the two studies in terms of duration of the intervention and intensity and mode of exercise, i.e., resistance or combined resistance and aerobic exercise, which may have limited our ability to observe effects in the pooled analysis. Baseline blood samples for the two studies were taken at different time points and only a subset of patients provided blood samples; however, this did not limit validity of our intervention results since baseline characteristics were distributed equally between our intervention and control group. Furthermore, in the PACT study no blood was collected at mid-intervention. Our sensitivity analysis excluding the mid-intervention values did however not yield different results. A further limitation is that the inflammatory markers neopterin, Nampt, leptin, adiponectin, TNF-α, CRP, TNF receptor I, and TNF receptor II were only collected in one RCT, limiting the power for analyses on these markers. Last, it is important to note that besides the inflammatory markers that were assessed in the current study, also other markers might be of interest when evaluating exercise effects, e.g., IL-8 and IL-2 [22]. Hence,

no definite conclusions can be drawn and future studies are needed to confirm our findings and further explore exercise effects on systemic inflammation during chemotherapy by investigating other potential markers of interest.

In conclusion, our study showed pronounced increases of IL-6 and IL-6/IL-1ra ratio in breast cancer patients during chemotherapy and recovery after completion of chemotherapy, indicating strong inflammatory responses to chemotherapy. Changes in IL-6 and the IL-6/IL-1ra ratio showed a significant, slight correlation with changes in fatigue. Yet, the supervised exercise training did not significantly counteract the effects of chemotherapy on IL-1ra, IL-6, and the IL-6/IL-1ra ratio and no significant group differences were observed. Thus, our results suggest that our previously observed beneficial effects of exercise on fatigue during adjuvant chemotherapy are not necessarily mediated by the investigated inflammatory markers.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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