International Journal of Nursing Studies 99 (2019) 103376

Contents lists available at ScienceDirect

International Journal of Nursing Studies

journal homepage: www.elsevier.com/ijns

The effect of a 12-week home-based walking program on reducing fatigue in women with breast cancer undergoing chemotherapy: A randomized controlled study

Hsiang-Ping Huang[a], Fur-Hsing Wen[b], Tsui-Yun Yang[c], Yung-Chang Lin[d], Jen-Chen Tsai[e], Shiow-Ching Shun[f], Sui-Whi Jane[a,d], Mei-Ling Chen[a,c,d,*]

[a] Department of Nursing, Chang Gung University of Science and Technology, Tao-Yuan, Taiwan
[b] Department of International Business, Soochow University, Taipei, Taiwan
[c] School of Nursing, College of Medicine, Chang Gung University, Tao-Yuan, Taiwan
[d] Division of Medical Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou Branch, Tao-Yuan, Taiwan
[e] School of Nursing, National Yang-Ming University, Taipei, Taiwan
[f] Department of Nursing in College of Medicine, National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 13 March 2019
Received in revised form 19 May 2019
Accepted 16 June 2019

Keywords:
Breast cancer
Chemotherapy
Exercise
Fatigue
Hierarchical linear model
Home-based brisk walking

ABSTRACT

Background: Fatigue is the most common symptom experienced by cancer patients during treatment and can last long after completing treatment. Fatigue in cancer patients who have completed treatment is well known to be reduced by exercise, but the effect of exercise on reducing fatigue in patients under treatment has been inconsistent.
Objectives: The purposes of this study were to examine short-term and long-term effects of an individually tailored, home-based brisk walking program on reducing fatigue in breast cancer patients under chemotherapy.
Design, setting, participants: For this randomized controlled trial, women were recruited from a medical center in northern Taiwan if they were diagnosed with stages I-III breast cancer and experienced insomnia, fatigue, pain, or depressive symptoms after their first cycle of chemotherapy. Consenting participants (N = 159) were randomly assigned to either an exercise (12-week home-based walking program) group (n = 81) or an attention-control group (n = 78).
Methods: The 12-week, home-based brisk walking program started on the first day of the third chemotherapy cycle. Fatigue was measured by the Brief Fatigue Inventory. Covariates, i.e., functional performance, sleep disturbance, anxiety, depression, and exercise-related variables, were also measured. Data were collected at baseline, two times during the exercise intervention, and five times after the exercise intervention (eight times in total). The effects of time-varying and time-invariant predictors on fatigue were analyzed by multilevel modeling.
Results: Fatigue levels increased over time for both groups, even after completing treatment. At the end of the 12-week exercise program, the exercise group had less fatigue than the attention-control group, and this group difference was maintained for the whole study period. At the end of exercise program, women who had spent more time exercising before diagnosis had less fatigue than those who had exercised less often. In addition, patients' fatigue levels at various time points fluctuated along with their functional performance, sleep disturbance, and depression.
Conclusions: Our tailored, home-based brisk walking program effectively reduced fatigue in breast cancer patients under chemotherapy, and this effect lasted after completing treatment.

* Corresponding author at: School of Nursing, College of Medicine, Chang Gung University, No. 259, Wenhua 1st Rd., Guishan Dist., Taoyuan City 33302, Taiwan.
E-mail address: mechenl@mail.cgu.edu.tw (M.-L. Chen).

https://doi.org/10.1016/j.ijnurstu.2019.06.007
0020-7489/

What is already known about the topic?

- Fatigue is a common and distressing symptom experienced by breast cancer patients receiving chemotherapy and may last long after completion of treatment.
- Exercise has been shown to be effective in reducing fatigue for breast cancer survivors after completion of their treatment
- The effects of exercise on reducing breast cancer survivors' fatigue during treatment phase are inconclusive

What this paper adds

- Fatigue levels increased over time for breast cancer survivors undergoing chemotherapy regardless of group membership.
- The effect of home-based brisk walking exercise effectively reduced fatigue for women with breast who were undergoing chemotherapy.
- More habitual exercise time before diagnosis was associated with less fatigue in women with breast cancer after receiving chemotherapy.
- Fatigue levels of women with breast cancer at any given time fluctuated with functional performance, sleep disturbance, and depression at that time.

1. Introduction

Cancer-related fatigue is a common and distressing symptom experienced by breast cancer patients receiving chemotherapy. The cause of cancer-related fatigue is multi-factorial, potentially involving aspects such as tumor-related factors, comorbidities, psychological condition, and could result from cancer treatment or its side effects (Koornstra et al., 2014). Previous study on breast cancer patients showed that, in average, the severity of fatigue in breast cancer patients has been shown to peak on average 4 days after chemotherapy and gradually subside within 14 days after initiation of chemotherapy (Bower, 2014). However, not all patients followed the same fatigue trajectory. Some patients' fatigue did not disappear before the next course of chemotherapy and accumulated over time for months or years after completing chemotherapy (Bower, 2014). Unrelieved fatigue can negatively impact disease recurrence and survival in patients with breast cancer (Bower, 2014; Groenvold et al., 2007).

No "gold standard" is available for treating cancer-related fatigue despite the increasing number of pharmacologic and non-pharmacologic approaches proposed for managing this symptom (NCCN, 2016). One of the most promising non-pharmacologic interventions for cancer-related fatigue is exercise, either aerobic or resistance/strength types of exercise (Meneses-Echavez et al., 2015). Exercise interventions can be delivered in a supervised environment (Meneses-Echavez et al., 2015) or in a home setting (Cornette et al., 2016) depending on feasibility. For breast cancer patients a home-based exercise program may be a good option given that adjuvant treatment is often delivered in outpatient clinics. During the treatment period, cancer patients are suggested to exercise with moderate intensity that can increase heart rate such as brisk walking (NCCN, 2016). The goal is to do aerobic exercise for at least 30 min per day and 5 days per week. If patients cannot continuously exercise for 30 min, they should break it up into three 10-minute sessions during the day (NCCN, 2016).

The effect of exercise on reducing fatigue for breast cancer patients who have completed their treatment has been demonstrated in several meta-analyses (Juvet et al., 2017; McNeely et al., 2006; Meneses-Echavez et al., 2015), but this positive effect of exercise has not been consistently found for patients under treatment (Juvet et al., 2017; Markes et al., 2006; McNeely et al., 2006; van Vulpen et al., 2016; Velthuis et al., 2010). The effects of exercise on ameliorating fatigue during chemotherapy were either not statistically significant (Juvet et al., 2017) or significant with a trivial effect size (Cramp and Byron-Daniel, 2012). Home-based exercise, in particular, was reported to have no effect in reducing fatigue for patients under treatment (Velthuis et al., 2010). The limitations of reviewed studies included considerable degree of clinical heterogeneity, lack of power to demonstrate the beneficial effect of exercise programs due to an insufficient exercise dose, non-tailored exercise, lack of information on exercise intensity (Juvet et al., 2017; Velthuis et al., 2010; Zou et al., 2014), and short follow-up period (Velthuis et al., 2010).

The covariation of fatigue with other symptoms, such as depression, anxiety, sleep difficulty, has been well documented in the literature (Ho et al., 2015). Patients' functional performance is also negatively correlated with fatigue levels (Juvet et al., 2017, Siefert, 2010). To examine the distinct efficacy of exercise on fatigue change, these variables need to be take into consideration.

Based on the literature reviewed and suggestions provided by meta-analysis studies, the primary aim of this study was to examine short- and long-term effects of a tailored home-based brisk walking program on reducing fatigue in a relatively large sample of breast cancer patients under chemotherapy, while controlling for other covariates. The secondary aim was to identify the change patterns of fatigue over time.

2. Methods

2.1. Design

For this randomized controlled trial, consenting participants were randomly assigned to either an exercise group (a 12-week home-based individualized walking program) or an attention-control group. Fatigue and some covariates (such as anxiety, depression, sleep disturbance, and functional status) were collected repeatedly at baseline (O1), two times (O2, and O3) during the exercise intervention (i.e., 4, and 10 weeks after baseline), and five times (O4 to O8) after the exercise intervention (i.e., 1, 6, 10, 24, and 36 weeks after intervention) for a total of eight times. Demographic and prior exercise behaviors were collected at baseline only. Clinical factors were retrieved from medical chart when they were available.

The group assignment sequence was generated randomly by computer based on a 1:1 ratio, and this sequence was kept by an administrative assistant not involved in collecting data or delivering the intervention. Once a patient consented to participate in the study, the data collector transferred this information to the administrative assistant who then decided the group assignment based on the pre-generated sequence. Depending on the group to which the patient was assigned, the administrative assistant then informed the exercise coach or another study nurse to deliver the exercise intervention or attention-control care, respectively. Data collectors were blinded to participants' group membership.

2.2. Sample and setting

Women being treated for breast cancer at Chang Gung Memorial Hospital were recruited by these criteria: (1) diagnosed with stage I-III breast cancer and scheduled for adjuvant chemotherapy, (2) self-reported insomnia, fatigue, pain, or depressive symptoms after the first cycle of chemotherapy, and (3) willing to be randomly assigned to either an exercise (EX) group or attention-control (AC) group. Women were excluded from the study if they had diagnosed sleep or psychiatric disorders, cardiovascular problems, muscle-skeletal

problems, or conditions judged by their treating physicians as unsuitable for exercise. Using the PS-Power and Sample Size Program (version 2.1.31), the sample size was estimated to be 56 (28 for each group) based on an effect size of 1.0, power of 0.8, and significance level of 0.005. Considering a non-adherence rate of 15% (inflation factor R = 2.04) and attrition rate of 25–30%, the required sample size was then adjusted to range from 152 to 163. The target sample size was determined to be 160. The study was approved by the hospital's Institutional Review Board.

2.3. Exercise intervention

This home-based brisk walking program developed in this study was specifically designed for women under chemotherapy based on guidelines of the American College of Sports Medicine (ACSM, 2006). The intensity of exercise was set at moderate and was gradually increased in terms of percentage of heart rate reserved (HRR) from 30% to 70% over the 12-week intervention period. During the same period, exercise frequency (3 times/week to 5 times/week) and duration (15–25 min/session to 35–40 min/session) were also progressively increased. Details of the progressive arrangement have been published (Huang et al., 2015). The exercise program began with a face-to-face instruction provided by an exercise coach with sports education training. To enhance participants' knowledge and motivation for exercise, they were first introduced to the concept and benefits of brisk walking. This introduction also included the proper way to walk briskly in terms of physical gestures and speed, what to wear while walking, potential risk signs to look for, and warm-up and cool-down activities. To individually tailor the exercise and make it effective, the coach also taught each participant the concept of individual target heart rate and how it relates to exercise intensity. Finally, each participant was given a heart rate ring and an exercise log to take home with detailed instructions on how to use them. During the 12-week intervention, the coach made weekly phone calls to participants to reinforce their motivation and adherence to the walking program as well as to solve potential difficulties and discomfort that might have occurred during exercise. To balance the therapist-contact effect, participants in the attention-control group also received weekly phone calls from another master-prepared study nurse specializing in oncology nursing. This nurse talked to patients about managing chemotherapy-related side effects but gave no advice on physical activities.

2.4. Measures

The main outcome variable in this study was fatigue. We also collected data on demographic and clinical characteristics, exercise-related variables (exercise time and intensity), and factors that may have influenced exercise and fatigue (exercise motivation, functional status, anxiety, depression, and sleep disturbance).

2.4.1. Fatigue

Participants' fatigue was assessed using the 9-item Brief Fatigue Inventory (BFI) (Mendoza et al., 1999). The BFI has two components: the first component assesses fatigue severity at its worst, usual, and right now; and the second component assesses fatigue interference with daily activity, mood, walking, work, enjoyment of life, and relations with others. Each item is rated on a 0–10 scale, with higher scores indicating more severe fatigue or more interference to life. Usual fatigue was used as the outcome variable in this study.

2.4.2. Demographic and disease/treatment characteristics

Demographics (age, marital status, education, religion, menopause status, and employment) and disease/treatment characteristics (disease stage, surgery type, chemotherapy regimen, and other adjuvant therapy) were obtained from patients or medical records and collected through a researcher-developed questionnaire. Exercise motivation was also collected in this questionnaire by asking patients to rate the degree (0–10) of their perceived importance of and interest in exercise.

2.4.3. Exercise time and intensity

Actual exercise frequency, duration, and heart rate during exercise were recorded by participants in the exercise group using a researcher-developed weekly exercise log. The target heart rate for a specific time period was written down by each patient on their log. Participants monitored their heart rate using a U.S. Federal Communications Commission- and European Committee for Electrotechnical Standardization-approved sport-pulse ring that detected heart rates of 30–250 beats/min with an error <3%. Participants were also asked to document their uncomfortable signs/symptoms, if any, during exercise in this log. Participants in the control group were asked to record their spontaneous exercise behaviors in terms of mode and duration.

2.4.4. Functional status

Function status was assessed using the Karnofsky Performance Status scale (KPS) (Schag et al., 1984) and 6-minute walk test (6MWT) (Kervio et al., 2003). The KPS assesses functional performance status using an 11-point scale ranging from 0 (dead) to 100 (normal). The 6MWT measures the distance (in feet or meters) that a participant can walk in 6 min. Both measurements have been widely used in cancer patients with satisfactory reliability and validity (de Kock et al., 2013; Schmidt et al., 2013)

2.4.5. Anxiety and depression

Anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS comprises two subscales assessing anxiety (7 items) and depression (7 items). Each item is scored from 0 to 3 and the subscale total scores range between 0 and 21, with higher scores indicating more anxiety or depressive symptoms. The HADS is a commonly used measure of anxiety and depression for people with physical disease (Vodermaier and Millman, 2011) and the Chinese version demonstrated good validity and reliability in cancer patients (Chen et al., 2000).

2.4.6. Sleep disturbance

Patients' sleep disturbance was measured by the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-rated questionnaire that differentiates poor from good sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The score for each domain ranges from 0 to 3, and the total score ranges from 0 to 21, where higher scores indicate poorer sleep quality. The Chinese-version PSQI had satisfactory reliability and validity in patients with lung cancer (Chen et al., 2008).

2.5. Procedure

Participants' baseline data were collected by the research assistant on the first day of the second chemotherapy cycle. On the first day of the third chemotherapy cycle, the exercise coach delivered individual instruction in the home-based walking program and taught participants how to use the pulse ring and exercise log. To enhance adherence to the prescribed exercise, the coach made weekly phone calls to each participant in the EX group. To counterbalance the effect of therapist contact, the first author made weekly phone calls, where no exercise information was

mentioned, to each participant in the AC group. Participants returned their weekly exercise logs at O3 (the first 6-week logs) and O4 (the second 6-week logs). Participants completed follow-up questionnaires when they were waiting for a chemotherapy appointment at the outpatient clinic. If the participant was not scheduled to return to the hospital at data collection time point, a telephone interview was made by the research assistant.

2.6. Statistical analysis

We used multilevel model to answer the primary and secondary research questions. Individual differences in change of fatigue was modeled in level I and the intervention effect (group membership) on fatigue level (intercept) and change time slop) was modeled at level II. To examine the short-term effect of exercise, the intercept of fatigue was centered at time 4 (i.e., the 16th week during the study period), immediately after the 12-week exercise program. Long-term effect of exercise was examined by checking the group difference across time after the end of exercise intervention. To compare the group effect, we adopted an intention-to-treat strategy to include all participants' data regardless of their adherence. Information regarding exercise adherence in this study has been published (Huang et al., 2015). To check whether missing data were missing at random, participants with and without missing data on fatigue at each time were compared on their fatigue data at the previous time.

The detailed process of multi-level analysis can be divided into three steps: The first step was to determine the best unconditional change pattern of fatigue (i.e., to be linear or quadratic) using maximum likelihood estimation where; the second step involved a series of univariate analyses to explore potential level-I and level-II covariates based on the selected change pattern; the final step was to test a multivariate two-level model where significant level-I and level-II covariates and group membership were entered into the model. Potential level-I time-varying covariates were functional status (6MWT and KPS scores), sleep disturbance, anxiety, and depression. Level-II time-invariant covariates included demographic and disease/treatment characteristics, exercise time before diagnosis, and group membership. Information regarding exercise adherence in this study has been published (Huang et al., 2015). To check whether missing data were missing at random, participants with and without missing data on fatigue at each time were compared on their fatigue data at the previous time.

3. Results

3.1. Subject recruitment and follow-up

Among 492 patients assessed for eligibility, 271 patients were qualified. Of the 271 qualified patients, 159 agreed to participate in this study and were randomly assigned to the exercise group ($n = 81$) or the control group ($n = 78$) (Fig. 1). The proportion of patients who completed measurements varied across the 7 follow-up times, from 65.6% to 93.4% for the exercise group and 77.6% to 93.1% for the control group. The reasons for missing data included dropped out of the study, missed appointment, time constrained during clinic visit, or too ill physically. The between-group dropout rate was not significantly different. Missing data on fatigue at each time was not correlated with fatigue level at the previous time, indicating that data were missing at random.

3.2. Sample characteristics

Participants had a mean (SD) age of 48.31 years ($SD = 8.26$), and most were married (83.6%). The majority was diagnosed with stage II breast cancer (58.4%), with 57.2% and 40.9% receiving breast

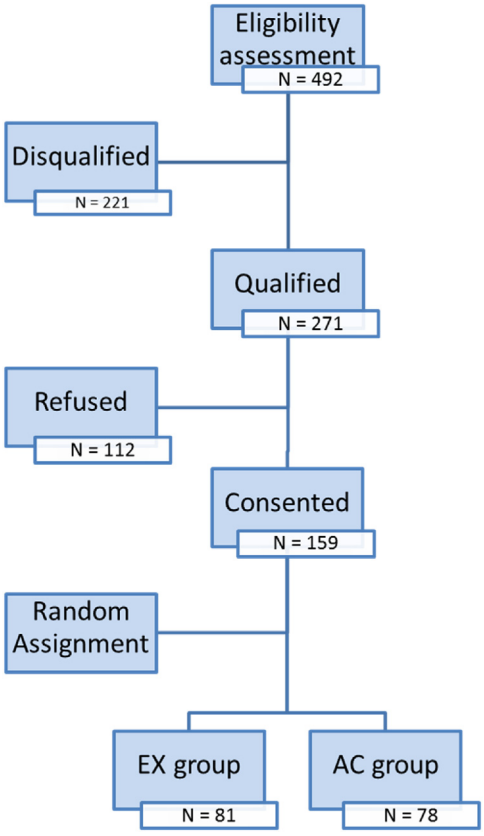

Fig. 1. Flowchart of Subject Recruitment.

conserving surgery (BCS) and mastectomy, respectively. For adjuvant chemotherapy, the majority received CEF (Cyclophosphamide, Epirubicin, and 5-fluoroutacil) combined with Taxane (40.3%) or CEF (33.3%). The percentages of other adjuvant therapies received were 48.4% for radiotherapy, 62.9% for hormonal therapy and 17.0% for targeted therapy. The EX and AC groups did not differ significantly in demographic and clinical variables (Table 1).

Means and standard deviations for exercise-related characteristics before diagnosis, fatigue, functional status (KPS and 6MWT), sleep disturbance, anxiety, and depression at baseline are in Table 2. Nearly half the participants engaged in regular exercise before diagnosis (47.8%). Of these participants, the majority exercised more than 5 days per week (64.5%). The mean perceived importance of exercise, on a 0–10 scale, was 8.77, while the mean score for being keen on exercise was only 5.65. The mean initial fatigue level at baseline was 1.01 (SD = 1.87). The mean 6MWT distance was 441.25 (SD = 87.37) meters, which was within the normal adult range (Enright, 2003). Participants' overall functional status was good, with a mean KPS of 89.91 (SD = 5.16). The overall quality of sleep was not good, with a mean PSQI score of 7.52 (SD = 4.00), which was greater than the suggested cut-off score of 5 for poor sleep quality. For psychological variables, the mean HADS scores for anxiety and depression were 5.76 (SD = 3.42) and 4.96 (SD = 3.14), respectively. Both HADS scores were lower than the

Table 1
Demographic and disease/treatment characteristics ($N = 159$).

Variable	Total ($N = 159$) Mean (SD)/n (%)	EX group ($n = 81$) Mean (SD)/n (%)	AC group($n = 78$) Mean (SD)/n (%)	t/χ^2	P
Age (years)	48.31 (8.26)	48.32 (7.90)	48.31 (8.65)	−0.010	0.992
Height (cm)	156.01 (4.78)	155.73 (4.70)	156.28 (4.87)	0.690	0.491
Weight (kg)	57.24 (9.76)	57.85 (11.35)	56.62 (7.79)	−0.799	0.425
Marital status				0.928	0.336
Never married	14 (8.8)	9 (11.1)	5 (6.4)		
Married/partnered	133 (83.6)	70 (86.4)	63 (80.8)		
Divorced	6 (3.8)	2 (2.5)	4 (5.1)		
Widowed	6 (3.8)	0 (0.0)	6 (7.7)		
Menopause				1.263	0.261
Yes	60 (37.7)	34 (42.0)	26 (33.3)		
No	99 (62.3)	47 (58.0)	52 (66.7)		
Religion				0.106	0.745
None	45 (28.3)	22 (27.2)	23 (29.5)		
Buddhism	75 (47.2)	40 (49.4)	35 (44.9)		
Christianity/Catholicism	8 (5.0)	3 (3.7)	5 (6.4)		
Taoism	31 (19.5)	16 (19.7)	15 (19.2)		
Employment				0.106	0.745
None	45 (28.3)	22 (27.2)	23 (29.5)		
Full time	110 (69.2)	56 (69.1)	54 (69.2)		
Part time	4 (2.5)	3 (3.7)	1 (1.3)		
Education level				2.119	0.908
< Elementary school	32 (20.1)	19 (23.5)	13 (16.7)		
Junior high school	26 (16.4)	12 (14.8)	14 (17.9)		
Senior high school	67 (42.1)	34 (42.0)	33 (42.3)		
> College	34 (21.4)	16 (19.7)	18 (23.1)		
AJCC disease stage				5.216	0.516
I	59 (37.1)	33(40.7)	26 (33.4)		
IIa	60 (37.7)	28 (34.6)	32 (41.0)		
IIb	17 (10.7)	9 (11.1)	8 (10.3)		
IIIa	11 (6.9)	5 (6.2)	6 (7.6)		
IIIb	2 (1.3)	0	2 (2.6)		
IIIc	10 (6.3)	6 (7.4)	4 (5.1)		
Surgery type				1.057	0.589
MRM	66(41.5)	33 (40.7)	33 (42.3)		
BCS	92 (57.9)	47 (58.0)	45 (57.7)		
MRM + BCS (Bilateral)	1 (0.6)	1 (1.2)	0		
Lymph node dissection				0.066	0.797
Yes	86 (54.1)	43 (53.1)	43 (55.1)		
No	73 (45.9)	38 (46.9)	35 (44.9)		
Chemotherapy regimen				2.446	0.654
CMF	38 (23.9)	21 (25.9)	17 (21.8)		
CEF	55 (34.6)	28 (34.6)	27 (34.6)		
CEF + Taxane	64 (40.3)	31 (38.4)	33 (42.3)		
Taxane only	1 (0.6)	1 (1.2)	0		
CLF	1 (0.6)	0	1 (1.3)		
Radiotherapy				0.521	0.471
Yes	77 (48.4)	37 (45.6)	40 (51.2)		
No	78 (49.1)	42 (51.9)	36 (46.2)		
Missing	4 (2.5)	2 (2.5)	2 (2.6)		
Hormone therapy				0.193	0.661
Yes	100 (62.9)	50 (61.7)	50 (64.1)		
No	54 (34.0)	29 (35.8)	25 (32.1)		
Missing	5 (3.1)	2 (2.5)	3 (3.8)		
Target therapy				0.103	0.748
Yes	27 (17.0)	13 (16.1)	14 (17.9)		
No	132 (83.0)	68 (83.9)	64 (82.1)		

Abbreviations: AJCC, American Joint Committee on Cancer; MRM, modified radical mastectomy; BCS, breast conservation surgery; CMF, Cyclophosphamide, Methotrexate, 5-fluorouracil; CEF, Cyclophosphamide, Epirubicin, 5-fluorouracil; CLF, Cyclophosphamide, Lipo-Dox, 5-fluorouracil.

Table 2
Descriptive statistics of study variables at baseline (N = 159).

Variable	Total (N = 159) Mean (SD)/n (%)	EX group (n = 81) Mean (SD)/n (%)	AC group(n = 78) Mean (SD)/n (%)	t/χ^2	P
Regular exercise before diagnosis	76 (47.8)	36 (44.4)	40 (51.3)	0.745	0.388
Exercise frequency before diagnosis, (days/week) (n = 76)				6.411	0.379
< 2	3 (3.9)	2 (5.6)	1 (2.5)		
3 – 4	24 (31.6)	10 (27.8)	14 (35.0)		
> 5	49 (64.5)	24 (66.7)	25 (62.5)		
Exercise amount before diagnosis, (min/week) (n = 76)	111.60 (129.02)	104.92 (128.22)	118.62 (130.61)	0.577	0.565
Interest in exercise	5.65 (2.71)	5.80 (2.61)	5.48 (2.81)	−0.734	0.464
Perceived importance of exercise	8.77 (1.67)	8.91 (1.69)	8.63 (1.64)	−1.081	0.281
BFI	1.01 (1.87)	1.07 (2.02)	0.96 (1.75)	−0.181	0.857
6MWT (m)	441.25 (87.37)	436.58 (78.23)	447.33 (98.48)	0.997	0.332
KPS	89.91 (5.16)	90.37 (5.82)	89.46 (4.44)	−0.978	0.331
PSQI	7.52 (4.00)	7.69 (4.24)	7.32 (3.74)	−0.118	0.906
HADS-A	5.76 (3.42)	5.58 (3.06)	5.95 (3.74)	−0.547	0.585
HADS-D	4.96 (3.14)	4.58 (3.19)	5.34 (3.07)	0.848	0.398

Abbreviations: BFI, Brief Fatigue Inventory; 6MWT, Six-Minute Walking Test; KPS, Karnofsky Performance Scale; PSQI, Pittsburgh Sleep Quality Index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

suggested cut-off for doubtful cases (>7). These characteristics did not differ significantly by group. No EX-group participants reported any severe negative effect of exercise.

3.3. Adherence in the exercise and control groups

Good adherence ($\geq$ 80%) for participants in the EX group were 56.8% and 58.0% for time and intensity adherence, respectively, and 59.3% for either one. Detailed weekly means and SDs for exercise time, exercise intensity, and associated adherence rates for the EX group have been published (Huang et al., 2015) (Table 3). For the AC group, exercise duration less than 45 min per week (including no exercise) was defined as good adherence. The good adherence rate for the AC control group was 41.0%; in other words, 59% of the AC group participants spontaneous exercised to a certain degree.

3.4. Unconditional change pattern of fatigue

To determine the overall trajectory of fatigue, we compared the model deviance of linear and quadratic growth models. We found that the quadratic model did not significantly improve the model fit over that of the linear model, with a deviance difference of 1.671 (df = 4) (Table S1). For reasons of parsimony, the linear change pattern was adopted as the base model for further analyses. *3.5. The short-terms and long-term effects of home-based walking on fatigue*

Univariate analysis identified that fatigue levels at each time were associated with the following time-varying covariates: functional status (both KPS and 6MWT), anxiety, depression, and sleep disturbance. In addition, fatigue levels at the post exercise intervention were associated with two time-invariant covariates: education and exercise time before diagnosis. All these variables were entered into a multivariate model, except for the 6MWT score, which was highly correlated with KPS score. The group effect was examined by entering "group" as a Level-II predictor for the fatigue intercept and time coefficient. Patients in the EX group had a significantly lower fatigue level than the AC group immediately after the intervention (coefficient = −0.276, P = 0.006) (Table 4), and this group difference on fatigue was maintained until the end of data collection (Fig. 2).

3.5. The adjusted change pattern of fatigue between groups

After controlling for co-variables mentioned above, overall fatigue levels increased significantly over time (coefficient = 0.017, P = 0.027), but this increase was more obvious in the AC group than in the EX group (Fig. 2) although the attenuating effect of exercise on the time-slope coefficient did not reach significance (P = 0.157).

Table 3
Means and standard deviations of exercise time, intensity, and corresponding adherence rate at each week for exercise group.

Exercise Time												
Week (n)	1 (48)	2 (52)	3 (53)	4 (46)	5 (55)	6 (56)	7 (49)	8 (50)	9 (53)	10 (51)	11 (49)	12 (52)
Exercise time[a]	149.83 (105.82)	188.02 (116.08)	184.92 (105.07)	149.85 (118.62)	206.58 (164.86)	190.54 (134.59)	184.08 (115.11)	182.28 (126.88)	207.21 (158.3)	199.24 (136.16)	185.02 (139.72)	203.37 (122.80)
Adherence rate (%)	97.82 (9.90)	97.01 (11.67)	99.37 (4.58)	92.08 (18.61)	91.42 (21.87)	96.07 (11.75)	82.68 (27.35)	81.94 (25.52)	75.68 (30.67)	76.57 (28.46)	74.02 (30.55)	80.00 (26.41)
Exercise Intensity												
Week (n)	1 (47)	2 (51)	3 (52)	4 (46)	5 (54)	6 (50)	7 (47)	8 (49)	9 (48)	10 (47)	11 (45)	12 (48)
Highest HR[b]	126.73 (18.63)	127.42 (15.93)	129.22 (15.83)	124.75 (15.43)	126.40 (14.66)	128.37 (14.55)	127.98 (12.27)	127.90 (12.70)	131.79 (12.68)	131.45 (11.36)	131.83 (10.10)	131.83 (12.38)
Adherence rate (%)	98.53 (4.52)	98.89 (3.68)	98.90 (4.08)	98.81 (3.63)	97.67 (5.27)	98.72 (4.15)	99.18 (1.94)	97.16 (4.13)	95.14 (6.25)	95.79 (4.78)	96.44 (4.29)	95.86 (5.54)

[a] Exercise time = total exercise minutes per week.
[b] Highest HR = highest mean heart rate during exercise.

Table 4
Models of exercise effect on fatigue: intent-to-treat analysis (N = 159).

Fixed effect	Coefficient	SE	df	P
Fatigue intercept ($\pi 0$)				
Intercept ($\beta 00$)	1.277	0.097	148	<0.001
Group ($\beta 01$)	−0.276	0.097	148	0.006
Education ($\beta 02$)	0.030	0.028	148	0.293
Exercise time before diagnosis (min/wk) ($\beta 03$)	−0.002	0.001	148	0.001
KPS (slope) ($\pi 1$)				
Intercept ($\beta 10$)	−0.070	0.016	810	<0.001
PSQI (slope) (π_2)				
Intercept (β_{20})	0.155	0.034	810	<0.001
HADS-A (slope) (π_3)				
Intercept (β_{30})	0.289	0.218	810	0.185
HADS-D (slope) (π_4)				
Intercept (β_{40})	0.451	0.227	810	0.046
Time (slope) (π_5)				
Intercept (β_{50})	0.017	0.007	150	0.027
Group(β_{51})	−0.007	0.005	150	0.157

Note: Equations for multivariate prediction models.
Level-1 Model
Fatigue = $\pi_0 + \pi_1 \times$ KPS + $\pi_2 \times$ PSQI + $\pi_3 \times$ HADS-A + $\pi_4 \times$ HADS-D + $\pi_5 \times$ Time + ε.
Level-2 Model
$\pi_0 = \beta_{00} + \beta_{01} \times$ Group + $\beta_{02} \times$ Education + $\beta_{03} \times$ Exercise time before diagnosis + u_0.
$\pi_1 = \beta_{10}$.
$\pi_2 = \beta_{20}$.
$\pi_3 = \beta_{30}$.
$\pi_4 = \beta_{40}$.
$\pi_5 = \beta_{50} + \beta_{51} \times$ Group + u_5.

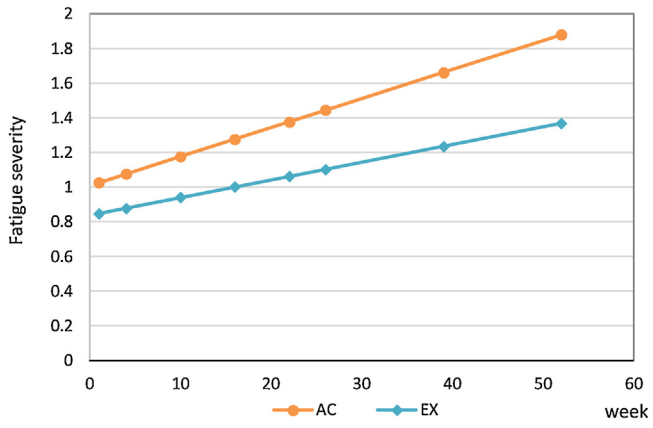

Fig. 2. Comparison of Fatigue Levels by Group.

4. Discussion

In this randomized controlled study, we found that compared to the attention-control group, the exercise group who participated in our 12-week home-based exercise program reported less fatigued at the end of exercise program and this group difference was maintained for the whole study period. However, we also found that fatigue levels increasing over time for both the exercise and attention-control groups even after completing treatment. Participants who had spent more time in exercise before diagnosis were also less fatigued. In addition, better functional performance, lower sleep disturbance, and depression at a given time was associated with less fatigue at that time. The effect of exercise on reducing fatigue after treatment has been well documented in previous meta-analysis studies (Juvet et al., 2017; McNeely et al., 2006; Meneses-Echavez et al., 2015). However, whether this effect can be extrapolated to patients under treatment is inconclusive (Juvet et al., 2017; Markes et al., 2006; McNeely et al., 2006; Velthuis et al., 2010). Our study demonstrated the positive effect of our home-based brisk walking program on reducing fatigue during chemotherapy, even with low exercise adherence rates. This finding suggests that exercise interventions are possible during treatment and may be initiated early, as suggested by (May et al., 2018), to help breast cancer survivors establish long-term healthy behaviors. Exercise is a cost-effective intervention in relieving fatigue and was shown to be more effective than pharmacological management (Mustian et al., 2017). Furthermore, the home-based brisk walking program evaluated in this study is particularly appealing compared to institution-based exercise programs due to its low cost and less time restriction.

Our finding that fatigue did not diminish with the completion of treatment is consistent with previous reports (Bower et al., 2006; Goedendorp et al., 2012; Ho et al., 2015); however other studies reported that fatigue only increases during chemotherapy but improves after completion of chemotherapy (Schmidt et al., 2015a, b, Spichiger et al., 2011). The finding that the home-based walking exercise failed to stop the increasing trend of fatigue is similar to the result of an early study (Headley et al., 2004) and this phenomenon may be related to the relatively low dose of exercise received given that the adherence rate was not high (less than 60%) in this study. Poor weekly adherence was found to be associated with higher fatigue in that week (Huang et al., 2015). Prolonged fatigue may negatively affect breast cancer survivors' quality of life by reducing their functioning in various aspects and working ability (Abrahams et al., 2018; Chan and Molassiotis, 2014). Determinants associated with long-term fatigue in breast cancer survivors was reported in one population-based study (Schmidt et al., 2015a,b). More studies are needed to explore the factors contributing to unresolved fatigue.

Our finding that longer pre-diagnosis exercise times were associated with less fatigue during cancer treatment is consistent with previous research (Meneses-Echavez et al., 2015; Schwartz et al., 2001). Patients who spend more time on exercise before the onset of disease are more likely to keep a habit of regular exercise during treatment and therefore more likely to receive the benefit of exercise on reducing fatigue. The strength of muscle power resulting from regular exercise may reduce fatigue caused by cancer treatment. Sedentary habits induce muscle catabolism,

which makes cancer fatigue a self-perpetuating condition(Lucia et al., 2003; Meneses-Echavez et al., 2015). We found that participants' fatigue levels at each time fluctuated with their functional performance, an association that has been reported in many studies (Huang et al., 2014; Milne et al., 2008; Schneider et al., 2007; Wolvers et al., 2018). These covariates may help developing to tailor future exercise interventions, for example, by adopting motivation strategies or adjusting exercise dosage for those without an exercise habit before diagnosis or those with poorer functional performance.

Another two time-varying factors found to be associated with worse fatigue were depression and sleep disturbance. These associations are not surprising because fatigue has often been found in behavioral studies in the same symptom cluster that contains depression and sleep disturbance (Ho et al., 2015; Nho et al., 2018). From a theoretical perspective, fatigue is often considered an indicator of depression and has been reported as a non-somatic symptom of depression (Ho et al., 2015). From a physiological viewpoint, hypothalamic-pituitary-adrenal axis dysfunction caused by cancer treatment may result in a flattened diurnal cortical cycle and disrupted circadian rhythm. The former has been associated with fatigue (Bower et al., 2005), and the latter can interfere with sleep (LaVoy et al., 2016). Lastly, a pro-inflammatory cytokine-based mechanism was proposed to explain the symptom clusters (i.e., pain, fatigue, depression, cognitive impairment, and sleep disturbance) observed in cancer patients (Lee et al., 2004), and this hypothesis has been supported by accumulated empirical evidence (Bower et al., 2018; Doong et al., 2015; Illi et al., 2012).

Despite the above positive effects of exercise on fatigue, this study has several limitations. First, the exercise program might have been initiated too late in terms of the treatment course. To recruit participants who experienced fatigue due to chemotherapy, we scheduled the exercise program to start at the third cycle of chemotherapy. For those who already experienced fatigue, their motivation to exercise may have been decreased and consequently their adherence to the prescribed exercise was decreased. Second, the low adherence rates for both the EX and AC groups may have underestimated the efficacy of exercise. Third, participants recruited from a single hospital may have limited the generalizability of our findings.

Declaration of Competing Interest

None.

Acknowledgement

This study was supported by a research grant from the National Science Council of Taiwan (Grant number: NSC 97-2314-B-182-035-MY3).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijnurstu.2019.06.007.

References

Abrahams, H.J.G., Gielissen, M.F.M., Verhagen, C.A., Knoop, H., 2018. The relationship of fatigue in breast cancer survivors with quality of life and factors to address in psychological interventions: a systematic review. Clin. Psychol. Rev. 63, 1–11.
ACSM, 2006. ACSM's Guidelines for Exercise Testing and Prescription. Lippincott William & Wilkins, Philadelphia.
Bower, J.E., 2014. Cancer-related fatigue – mechanisms, risk factors, and treatments. Nat. Rev. Clin. Oncol. 11 (10), 597–609.
Bower, J.E., Ganz, P.A., Desmond, K.A., Bernaards, C., Rowland, J.H., Meyerowitz, B.E., Belin, T.R., 2006. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer 106 (4), 751–758.
Bower, J.E., Ganz, P.A., Dickerson, S.S., Petersen, L., Aziz, N., Fahey, J.L., 2005. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology 30 (1), 92–100.
Bower, J.E., Wiley, J., Petersen, L., Irwin, M.R., Cole, S.W., Ganz, P.A., 2018. Fatigue after breast cancer treatment: biobehavioral predictors of fatigue trajectories. Health Psychol. 37 (11), 1025–1034.
Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 28 (2), 193–213.
Chan, C.W.H., Molassiotis, A., 2014. The impact of fatigue on Chinese cancer patients in Hong Kong. Support. Care Cancer 9 (1), 18–24.
Chen, M.L., Chang, H.K., Yeh, C.H., 2000. Anxiety and depression in Taiwanese cancer patients with and without pain. J. Adv. Nurs. 32 (4), 944–951.
Chen, M.L., Yu, C.T., Yang, C.H., 2008. Sleep disturbances and quality of life in lung cancer patients undergoing chemotherapy. Lung Cancer 62 (3), 391–400.
Cornette, T., Vincent, F., Mandigout, S., Antonini, M.T., Leobon, S., Labrunie, A., Venat, L., Lavau-Denes, S., Tubiana-Mathieu, N., 2016. Effects of home-based exercise training on VO2 in breast cancer patients under adjuvant or neoadjuvant chemotherapy (SAPA): a randomized controlled trial. Eur. J. Phys. Rehabil. Med. 52 (2), 223–232.
Cramp, F., Byron-Daniel, J., 2012. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst. Rev. 11, CD006145.
de Kock, I., Mirhosseini, M., Lau, F., Thai, V., Downing, M., Quan, H., Lesperance, M., Yang, J., 2013. Conversion of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG) to Palliative Performance Scale (PPS), and the interchangeability of PPS and KPS in prognostic tools. J. Palliat. Care 29 (3), 163–169.
Doong, S.H., Dhruva, A., Dunn, L.B., West, C., Paul, S.M., Cooper, B.A., Elboim, C., Abrams, G., Merriman, J.D., Langford, D.J., Leutwyler, H., Baggott, C., Kober, K., Aouizerat, B.E., Miaskowski, C., 2015. Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. Biol. Res. Nurs. 17 (3), 237–247.
Enright, P.L., 2003. The six-minute walk test. Respir. Care 48 (8), 783–785.
Goedendorp, M.M., Andrykowski, M.A., Donovan, K.A., Jim, H.S., Phillips, K.M., Small, B.J., Laronga, C., Jacobsen, P.B., 2012. Prolonged impact of chemotherapy on fatigue in breast cancer survivors: a longitudinal comparison with radiotherapy-treated breast cancer survivors and noncancer controls. Cancer 118 (15), 3833–3841.
Groenvold, M., Petersen, M.A., Idler, E., Bjorner, J.B., Fayers, P.M., Mouridsen, H.T., 2007. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. Breast Cancer Res. Treat. 105 (2), 209–219.
Headley, J.A., Ownby, K.K., John, L.D., 2004. The effect of seated exercise on fatigue and quality of life in women with advanced breast cancer. Oncol. Nurs. Forum 31 (5), 977–983.
Ho, S.-Y., Rohan, K.J., Parent, J., Tager, F.A., McKinley, P.S., 2015. A longitudinal study of depression, fatigue, and sleep disturbances as a symptom cluster in women with breast cancer. J. Pain Symptom Manage. 49 (4), 707–715.
Huang, H.P., Chen, M.L., Liang, J., Miaskowski, C., 2014. Changes in and predictors of severity of fatigue in women with breast cancer: a longitudinal study. Int. J. Nurs. Stud. 51 (4), 582–592.
Huang, H.P., Wen, F.H., Tsai, J.C., Lin, Y.C., Shun, S.C., Chang, H.K., Wang, J.S., Jane, S.W., Chen, M.C., Chen, M.L., 2015. Adherence to prescribed exercise time and intensity declines as the exercise program proceeds: findings from women under treatment for breast cancer. Support. Care Cancer 23 (7), 2061–2071.
Illi, J., Miaskowski, C., Cooper, B., Levine, J.D., Dunn, L., West, C., Dodd, M., Dhruva, A., Paul, S.M., Baggott, C., Cataldo, J., Langford, D., Schmidt, B., Aouizerat, B.E., 2012. Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. Cytokine 58 (3), 437–447.
Juvet, L.K., Thune, I., Elvsaas, I.K.O., Fors, E.A., Lundgren, S., Bertheussen, G., Leivseth, G., Oldervoll, L.M., 2017. 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 33, 166–177.
Kervio, G., Carre, F., Ville, N.S., 2003. Reliability and intensity of the six-minute walk test in healthy elderly subjects. Med. Sci. Sports Exerc. 35 (1), 169–174.
Koornstra, R.H., Peters, M., Donofrio, S., van den Borne, B., de Jong, F.A., 2014. Management of fatigue in patients with cancer – a practical overview. Cancer Treat. Rev. 40 (6), 791–799.
LaVoy, E.C., Fagundes, C.P., Dantzer, R., 2016. Exercise, inflammation, and fatigue in cancer survivors. Exerc. Immunol. Rev. 22, 82–93.
Lee, B.N., Dantzer, R., Langley, K.E., Bennett, G.J., Dougherty, P.M., Dunn, A.J., Meyers, C.A., Miller, A.H., Payne, R., Reuben, J.M., Wang, X.S., Cleeland, C.S., 2004. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. Neuroimmunomodulation 11 (5), 279–292.
Lucia, A., Earnest, C., Perez, M., 2003. Cancer-related fatigue: can exercise physiology assist oncologists? Lancet Oncol. 4 (10), 616–625.
Markes, M., Brockow, T., Resch, K.L., 2006. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst. Rev. (Online) 4, CD005001.
May, A.M., Hiensch, A.E., Witlox, L., Velthuis, M., Wall, E.V.D., Peeters, P.H.M., group, P.s, 2018. Four-year effects of physical exercise during adjuvant treatment on fatigue and physical activity in breast and colon cancer patients. J. Clin. Oncol. 36 (7_suppl), 99.

McNeely, M.L., Campbell, K.L., Rowe, B.H., Klassen, T.P., Mackey, J.R., Courneya, K.S., 2006. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. Can. Med. Assoc. J. 175 (1), 34–41.
Mendoza, T.R., Wang, X.S., Cleeland, C.S., Morrissey, M., Johnson, B.A., Wendt, J.K., Huber, S.L., 1999. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer 85 (5), 1186–1196.
Meneses-Echavez, J.F., Gonzalez-Jimenez, E., Ramirez-Velez, R., 2015. Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis. BMC Cancer 15, 77.
Milne, H.M., Wallman, K.E., Gordon, S., Courneya, K.S., 2008. Effects of a combined aerobic and resistance exercise program in breast cancer survivors: a randomized controlled trial. Breast Cancer Res. Treat. 108 (2), 279–288.
Mustian, K.M., Alfano, C.M., Heckler, C., Kleckner, A.S., Kleckner, I.R., Leach, C.R., Mohr, D., Palesh, O.G., Peppone, L.J., Piper, B.F., Scarpato, J., Smith, T., Sprod, L.K., Miller, S. M., 2017. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. JAMA Oncol. 3 (7), 961–968.
NCCN, 2016. Exercising during cancer treatment. Patient and Caregiver Resources. National Comprehensive Cancer Network, Fort Washington, PA.
Nho, J.H., Kim, S.R., Park, M.H., Kweon, S.S., 2018. Symptom clusters and quality of life in breast cancer survivors after cancer treatment in a tertiary hospital in Korea. Eur. J. Cancer Care e12919.
Schag, C.C., Heinrich, R.L., Ganz, P.A., 1984. Karnofsky performance status revisited: reliability, validity, and guidelines. J. Clin. Oncol. 2 (3), 187–193.
Schmidt, K., Vogt, L., Thiel, C., Jager, E., Banzer, W., 2013. Validity of the six-minute walk test in cancer patients. Int. J. Sports Med. 34 (7), 631–636.
Schmidt, M.E., Chang-Claude, J., Seibold, P., Vrieling, A., Heinz, J., Flesch-Janys, D., Steindorf, K., 2015a. Determinants of long-term fatigue in breast cancer survivors: results of a prospective patient cohort study. Psychooncology 24 (1), 40–46.
Schmidt, M.E., Wiskemann, J., Armbrust, P., Schneeweiss, A., Ulrich, C.M., Steindorf, K., 2015b. Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: a randomized controlled trial. Int. J. Cancer 137 (2), 471–480.
Schneider, C.M., Hsieh, C.C., Sprod, L.K., Carter, S.D., Hayward, R., 2007. Exercise training manages cardiopulmonary function and fatigue during and following cancer treatment in male cancer survivors. Integr. Cancer Ther. 6 (3), 235–241.
Schwartz, A.L., Mori, M., Gao, R., Nail, L.M., King, M.E., 2001. Exercise reduces daily fatigue in women with breast cancer receiving chemotherapy. Med. Sci. Sports Exerc. 33 (5), 718–723.
Siefert, M.L., 2010. Fatigue, pain, and functional status during outpatient chemotherapy. Oncol. Nurs. Forum 37 (2), E114–E123.
Spichiger, E., Muller-Frohlich, C., Denhaerynck, K., Stoll, H., Hantikainen, V., Dodd, M., 2011. Prevalence of symptoms, with a focus on fatigue, and changes of symptoms over three months in outpatients receiving cancer chemotherapy. Swiss Med. Wkly. 141, w13303.
van Vulpen, J.K., Peeters, P.H.M., Velthuis, M.J., van der Wall, E., May, A.M., 2016. Effects of physical exercise during adjuvant breast cancer treatment on physical and psychosocial dimensions of cancer-related fatigue: a meta-analysis. Maturitas 85, 104–111.
Velthuis, M.J., Agasi-Idenburg, S.C., Aufdemkampe, G., Wittink, H.M., 2010. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. Clin. Oncol. (R. Coll. Radiol.) 22 (3), 208–221.
Vodermaier, A., Millman, R.D., 2011. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Support. Care Cancer 19 (12), 1899–1908.
Wolvers, M.D.J., Leensen, M.C.J., Groeneveld, I.F., Frings-Dresen, M.H.W., De Boer, A., 2018. Longitudinal associations between fatigue and perceived work ability in cancer survivors. J. Occup. Rehabil..
Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67 (6), 361–370.
Zou, L.-Y., Yang, L., He, X.-L., Sun, M., Xu, J.-J., 2014. Effects of aerobic exercise on cancer-related fatigue in breast cancer patients receiving chemotherapy: a meta-analysis. Tumour Biol. 35 (6), 5659–5667.