

JOURNAL-BASED CME ARTICLE

The Effectiveness of a Deep Water Aquatic Exercise Program in Cancer-Related Fatigue in Breast Cancer Survivors: A Randomized Controlled Trial

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Statement of Need

Cancer-related fatigue (CRF) is mainly characterized by tiredness to exhaustion, which is not precipitated by activity. It can also occur after activity if it is out of proportion to the level of exertion and is not relieved by or in fact may be worsened with rest. Between 56% to 95% of breast cancer survivors experience CRF after treatment. Nearly 20% of breast cancer survivors can suffer from CRF several years after completing treatment. A moderate to high level of CRF is associated with reduced quality of life and perceived as a barrier to exercise, thus justifying the need to seek different methods of treatment for these patients.

Previous research has investigated the effects of exercise as a nonpharmacologic treatment for CRF with clinical impact ranging from small to moderate effect sizes on CRF; these studies have mainly focused on land-based exercise programs, although many benefits can be obtained in an aquatic environment. Different properties of water could increase potential benefits of exercise, such as buoyancy, which significantly decreases stress on weight-bearing joints, bones, and muscles, thereby reducing pain.

Exercise can reduce depression, anxiety, and improve mood state in breast cancer survivors. Aquatic group exercise interventions have also been shown to improve psychological state in several conditions.

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To support the attainment of knowledge, competence, and performance, the learner should be able to achieve the following objectives:

1. Identify the components of deep water aquatic exercise for cancer-related fatigue and how they can be applied in practice.
2. List the outcomes of deep water aquatic exercise for cancer-related fatigue.
3. Compare deep water aquatic exercise for cancer-related fatigue to other modalities.
4. Evaluate the limitations of deep water aquatic exercise for cancer-related fatigue.

Planning Committee

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Estimated time to complete this activity – 2.0 hours

Abstract

Objective: To investigate the effectiveness of an 8-week aquatic program on cancer-related fatigue, as well as physical and psychological outcomes in breast cancer survivors.

Design: A randomized controlled trial.

Setting: Outpatient clinic, urban, academic medical center, and a sport university swimming pool.

Participants: Breast cancer survivors (N=68) were randomly assigned to either an experimental (aquatic exercise group in deep water pool) group or a control (usual care) group.

Interventions: The intervention group attended aquatic exercise sessions 3 times per week for 8 weeks in a heated deep swimming pool. Sessions lasted 60 minutes in duration: 10 minutes of warm-up, 40 minutes of aerobic and endurance exercises, and 10 minutes of cool-down exercises. Patients allocated to the usual care group followed the oncologist's recommendations in relation to a healthy lifestyle.

Main Outcome Measures: Values for fatigue (Piper Fatigue Scale), mood state (Profile of Mood States), and abdominal (trunk curl static endurance test) and leg (multiple sit-to-stand test) strength were collected at baseline, after the last treatment session, and at a 6-month follow-up.

Results: Immediately after discharge, the aquatic exercise group showed a large effect size in total fatigue score ($d=.87$; 95% confidence interval, .48–1.26), trunk curl endurance ($d=.92$; 95% confidence interval, 1.97–3.83), and leg strength ($d=1.10$; .55–2.76), but negligible effects in vigor, confusion, and disturbance of mood ($d<.25$). At the 6-month follow-up period, the aquatic exercise group maintained large to small effect sizes in fatigue scores, multiple sit-to-stand test, and trunk curl static endurance ($.25>d>.90$) and negligible effects for the fatigue-severity dimension and different scales of the Profile of Mood States ($d<.25$).

Conclusion: An aquatic exercise program conducted in deep water was effective for improving cancer-related fatigue and strength in breast cancer survivors.

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Cancer-related fatigue (CRF) is mainly characterized by tiredness to exhaustion that is not precipitated by activity. It can also occur after activity if it is out of proportion to the level of exertion and is not relieved by or in fact may be worsened with rest.¹ Between 56% and 95% of breast cancer survivors experience CRF after treatment.² Close to 20% of breast cancer survivors can suffer CRF several years after finishing their curative treatment.^{3,4} A moderate to high level of CRF is associated with reduced quality of life in these patients^{1,5-7} and is perceived as a barrier to include exercise in their lifestyle,⁸ justifying the need to seek different methods of treatment for these patients.

Previous research has investigated the effects of exercise as nonpharmacologic treatment for CRF,⁹⁻¹¹ with clinical impact ranging from small to moderate effect sizes on CRF.¹⁰⁻¹² There continues to exist limited research examining the effects of exercise for patients with cancer who experience CRF.^{7,12,13} New studies are necessary to identify optimal treatment options for individuals with CRF to improve their quality of life.

A potential contributor to CRF may be abnormalities of energy balance,¹⁴ which are associated with diminution of muscle

biosynthesis.¹⁵ These deficits are sensitive to neuromuscular measures of skeletal muscle endurance.¹⁶ In fact, deficits in muscular performance are associated with a reduction in the quality of life and increase in symptoms related to cancer in breast cancer survivors.^{17,18}

Previous research has mainly focused on land-based exercise programs, but many benefits can be obtained with the aquatic environment. Different properties of water such as buoyancy, which significantly decreases the stress on weight-bearing joints, bones, and muscles, thereby reducing pain, can increase the potential benefits of exercise.¹⁹ Water immersion decreases axial loading, allowing patients to perform exercises that they are otherwise unable to do on land.²⁰ Different resources can be used in aquatic therapy. A chest-high pool is used to reduce pain and stiffness during weight-bearing exercise. A recent report²¹ found that water exercise in a chest-high pool had no effect on CRF in breast cancer survivors suffering from hormone therapy-associated arthralgia pain. Exercises such as running in deep water produce a lower heart rate, which may relate to hydrostatic pressure and water depth and the subsequent increase in venous return and stroke volume.²² These physiological responses result in lower perceived exertion than would be experienced with the same exercise intensity conducted on land.²³ It is not known whether an aquatic exercise program could result in reductions in CRF.

Exercise has shown the ability to reduce depression²⁴ and anxiety²⁵ and improve mood²⁶ state in breast cancer survivors.

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Table 1 Exercises of water-based program

Type of Exercise	Duration	Frequency
Warm-up exercises (10min)		
Aerobic activities		
Mobility		
Stretching exercises		
Training program (40min)		
1–4wk		
Cardiovascular exercises: Different horizontal movements: forward and backward jogging with arms moving, pulling, and pressing, leaps, leg crossovers, and hopping movements focusing on movement in multiple directions	5–10min	
Endurance exercise: (no equipment used)		Week 1: learning exercises and familiarization with the aquatic environment
1. Bicycling in different body positions		Week 2: 10–12 repetitions×2 sets
2. Flexion/extension of elbow/wrist with a neutral shoulder position		Week 3: 12–15 repetitions×2 sets
3. Maintain hip and trunk vertical with legs movements		Week 4: 10–12 repetitions×3 sets
4. Hip rotation, adduction-abduction standing		
5. Flexion/extension of the shoulder		
6. Hip extension with control of low back position		
5–8wk		
Aerobic exercises: Different horizontal movements: forward and backward jogging with arms moving, pulling, and pressing, leaps, leg crossovers, and hopping movements focusing on movement in multiple directions	10–15min	
Cardiovascular exercise: (use pool noodles, pull buoy, swimming board)		Week 1: learning exercises and familiarization with the aquatic environment
1. Bicycling in different body positions		Week 2: 10–12 repetitions×2 sets
2. Flexion/extension of elbow/wrist with neutral shoulder position		Week 3: 12–15 repetitions×2 sets
3. Maintain hip and trunk vertical with legs movements		Week 4: 10–12 repetitions×3 sets
4. Hip rotation, adduction-abduction standing		
5. Flexion/extension of the shoulder		
6. Hip extension with low back in neutral position		
Cool-down exercises (10min)		
Walking slowly with breathing exercises		
Stretching exercise of main muscles used during the sessions		

Aquatic group exercise interventions have also been shown to improve the psychological state in several conditions.^{27,28} To the best of our knowledge, there are no studies reporting psychological effects of aquatic exercise in breast cancer survivors. We hypothesized that an exercise program in deep water could improve the physical and psychological states in fatigued breast cancer survivors.

Thus, the purpose of the present clinical trial was to analyze the effects of an 8-week aquatic exercise program in a deep water pool and 6 months after finishing the program on fatigue, psychological outcomes, muscular strength, and endurance in breast cancer survivors.

Methods

Design

Our study was a randomized controlled clinical trial. Eligible participants were randomly assigned to either an aquatic exercise group or a control group. Computer-generated numbers produced a sequence that was entered into opaque envelopes. These envelopes were opened by a blinded researcher after the first outcome measurement.

List of abbreviations:

ANOVA	analysis of variance
CI	confidence interval
CRF	cancer-related fatigue
PFS	Piper Fatigue Scale

Participants

Participants were recruited from the Breast Oncology Unit of the Hospital Virgen de las Nieves, Granada, Spain. Patients were approached and enrolled by oncologists and nurses from the radiotherapy and the breast oncology units. A researcher contacted individuals by phone to determine eligibility and schedule an initial clinical interview. To be eligible for the study, participants had to be between 25 and 65 years old, had a diagnosis of breast cancer (stages I–IIIa), finished oncology treatment except hormone therapy in the previous 18 months, and exhibit a clinically significant fatigue (>3 in total score of the Piper Fatigue Scale [PFS]). Patients were excluded if they were receiving oncology treatment at the time of the study or they had physical limitations associated with orthopedic conditions. The research protocol was reviewed and approved by the Ethics Committee of the Virgen de las Nieves Hospital (Granada, Spain). The study was carried out between March 2009 and June 2010, following the ethical guidelines of the Declaration of Helsinki, last modified in 2000.

Outcome measures

After patients provided informed consent, baseline measurements were obtained. Reassessment occurred at postintervention at 8 weeks and 6 months after discharge. All outcomes were conducted by the same trained assessors across all data collection points. Assessors were blinded to treatment allocation. Data collection took place in a university clinical laboratory of Faculty of Health Sciences of the University of Granada.

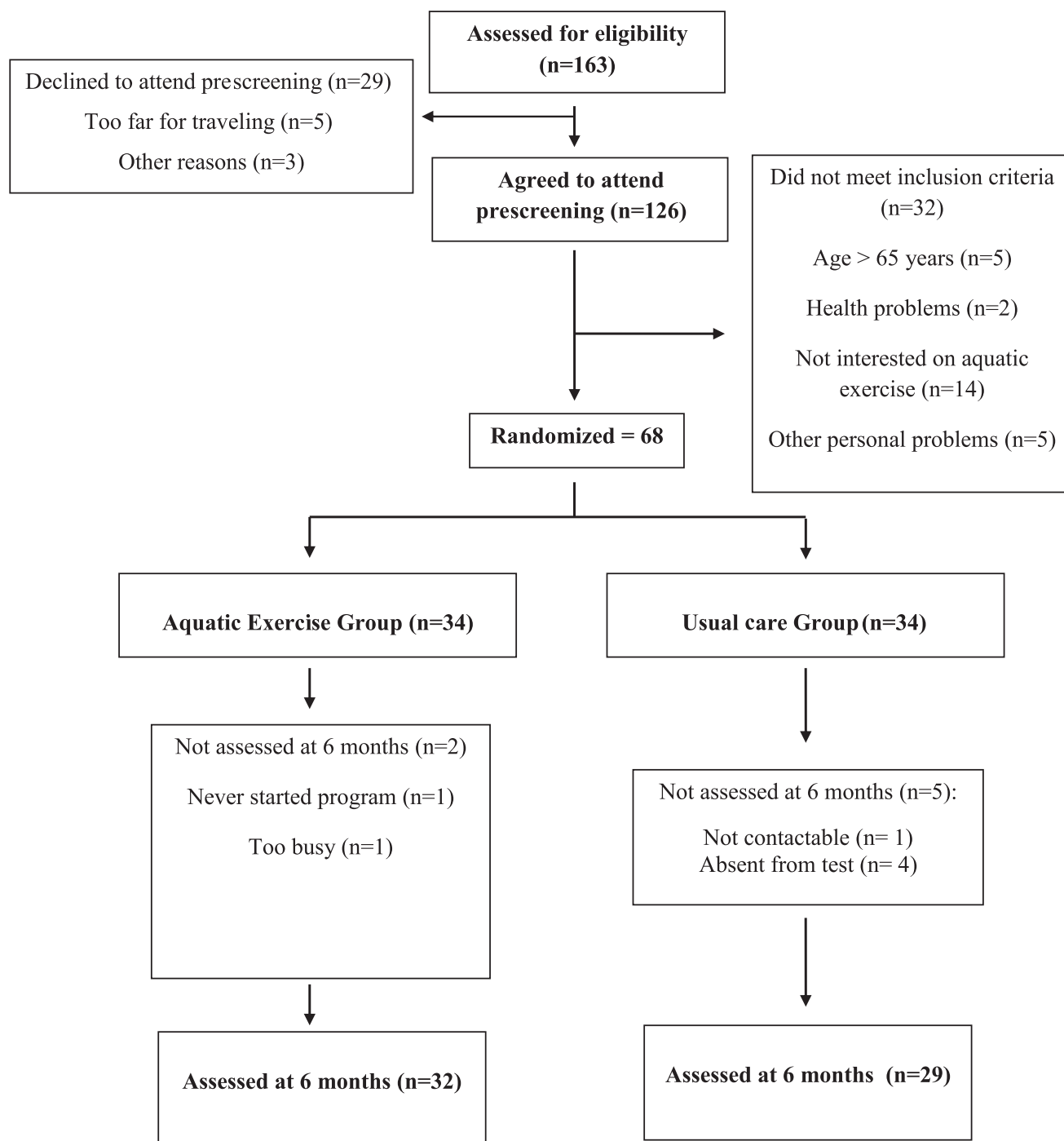


Fig 1 Flow diagram of subject recruitment and retention throughout the course of the study.

Cancer-related fatigue

The PFS score was used as the primary outcome.²⁹ The PFS consists of 22 numerical items assessing fatigue experienced by the patient. The PFS total score has a theoretical range from 0 to 10, with higher scores indicating greater fatigue. Using a 0 to 10 numerical scale, PFS measures 4 dimensions of subjective fatigue: behavioral/severity, affective meaning, sensory, and cognitive/mood. The total fatigue score is calculated by adding the 4 subscale scores and dividing by 4. The PFS total score has a theoretical range from 0 to 10, with higher scores indicating

greater fatigue. A minimally important difference (ie, a change of 2 points) on the PFS total score represents a clinically significant improvement in fatigue.²⁹

Mood state

The Spanish version of the Profile of Mood States contains 63 adjectives rated by participants on a 5-point scale. The questionnaire has 6 factors: tension, depression, anger, fatigue, vigor, and confusion. Subscale scores were converted into T scores for the analysis. A high reliability has been reported for the Profile of Mood States.³⁰

Table 2 Patients' characteristics and comparisons between both breast cancer survivor groups

Variable	Usual Care Group (n=29)	Aquatic Exercise Group (n=32)	P
Age (y), mean \pm SD	47 \pm 8	49 \pm 7	.350
Time posttreatment, n (%)			
<12mo	24 (82.7)	22 (69)	.176
>12mo	5 (17.3)	10 (31)	
Marital status, n (%)			
Married	19 (65.5)	20 (62)	.228
Unmarried	6 (20.7)	5 (16)	
Divorced	4 (13.8)	7 (22)	
Educational level, n (%)			
Primary school	11 (38)	11 (34)	.709
Secondary school	4 (13.8)	8 (25)	
University level	14 (48.2)	13 (41)	
Employment status, n (%)			
Home employed	6 (20.6)	7 (22)	.153
Employed	12 (41.4)	10 (31)	
Nonemployed	11 (38)	15 (47)	
Tumor stage, n (%)			
I	10 (34.4)	4 (12.5)	.145
II	14 (48.3)	23 (72)	
IIIA	5 (17.3)	5 (15.5)	
Type of surgery, n (%)			
Lumpectomy	21 (72.4)	21 (65.5)	.596
Mastectomy	8 (27.6)	11 (34.5)	
Type of treatment, n (%)			
Radiation	1 (3)	1 (3)	.991
Chemotherapy	3 (10.8)	3 (9)	
Radiation + chemotherapy	25 (86.2)	28 (88)	
Menopause, n (%)			
Yes	20 (69)	24 (75)	.197
No	9 (31)	8 (25)	
Physical activity level* (min/d), mean \pm SD	32.3 \pm 22.6	38.2 \pm 21.3	.220
Hormone therapy			
Tamoxifen	19	24	.703
Aromatase inhibitors	6	5	
Others	4	3	

NOTE. P values for comparisons among group based on χ^2 and analysis of variance tests.

* Minutes dedicated to physical activity per day.

Lower-body muscular strength

The "multiple sit-to-stand test" involves counting the time in seconds needed by the patients to rise until they reach full knee extension and sit back 10 times as fast as possible. Participants rise to a full stand from a seated position with the back straight and feet flat on the floor, without pushing off with the arms. The test-retest reliability of the multiple sit-to-stand test is good to high in most populations and settings (intraclass correlation coefficient = .81).³¹

Muscular endurance of abdominal muscles

The trunk curl static endurance test was used. This test requires a wedged piece of wood to support the patient at a fixed angle of 60°. The patients fold their arms across their chest and move the top of

their head at a fixed angle of trunk flexion (60°). The feet are maintained flat on the floor and held by the therapist. The participants hold the isometric posture as long as possible. A coefficient of >.97 for repeated measures demonstrates adequate reliability of this test.³² The mean endurance for young, healthy men and women is 134 seconds.³³

Interventions

The intervention group attended water-based sessions 3 times per week for 8 weeks in a heated deep swimming pool measuring 25 \times 12.5 meters with a depth ranging from 1.40 to 2.00 meters. The water temperature was 28°C, the room temperature was 30°C, and the relative humidity was 90%. Sessions lasted 60 minutes in duration: 10 minutes of warm-up, 40 minutes of aerobic and endurance exercises, and 10 minutes of cool-down exercises (table 1). The intensity of the aerobic exercise was maintained according to the recommendations of the American College of Sports Medicine and the American Heart Association^{9,34} and through the use of the revised Borg Rating of Perceived Exertion scale. The endurance exercises were considered moderate as the parameters set for each exercise included 2 to 3 sets of 8 to 12 repetitions. The program was supervised by a fitness specialist and by 2 physical therapists with clinical experience in the management of patients with different cancer conditions in both groups with groups of 10 to 12 women. Participants who were unable to swim were assisted by the physiotherapists.

Patients allocated to the usual care group followed the oncologist recommendations for maintaining a healthy lifestyle based on adequate nutrition, energy balance, and maintaining usual activities.

The primary outcome variable in the current study was CRF. A power calculation was conducted to determine the sample size necessary to detect changes; in the PFS based on a previous study,²⁶ a decrease of 2.5 points, with an SD of 2.0 (15%), was regarded as clinically important and achievable in breast cancer survivors. Using an alpha of .05 and a power of 80%, a sample size of at least 22 patients per group was estimated. To account for possible participant dropouts, we recruited 64 participants.

Statistical analysis

To examine the differences in baseline characteristics between included-excluded patients and compliers-dropped out, we used *t* tests and chi-square tests. The Kolmogorov-Smirnov test showed a normal distribution of the data ($P > .05$). To examine the effect of the aquatic exercise program in different outcomes, a 2 \times 3 factorial design was used. The between-subjects factor was intervention (aquatic exercise program, usual care), whereas the within-subjects factor was time in relation to intervention (before intervention, after intervention, 6 months after discharge). Data were analyzed using the SPSS^a software. Statistical significance was set at alpha levels of <.05, 2-tailed. Effect sizes were reported as negligible difference, between $\geq .25$ and ≤ 0.5 a small difference, between ≥ 0.5 and ≤ 0.8 a moderate difference, and ≥ 0.8 a large difference.

Results

During the study period, 126 women with cancer agreed to attend the prescreening session (fig 1). No differences between 68 patients (54%) included and 58 patients (46%) who were excluded or declined to participate were found, except that the excluded group was older (48 vs 55y; $P < .05$). Furthermore, no differences in sociodemographic and medical features between the patients assigned to exercise and

Table 3 Comparison of study variables between the aquatic exercise group and the usual care group at baseline

Variables	Aquatic Exercise Program (n=32)	Usual Care Group (n=29)	P
PFS			
Behavioral/severity	5.38±2.04	6.16±2.13	0.20
Affective/meaning	6.32±1.87	6.79±2.01	0.74
Sensory	6.18±1.82	5.79±1.81	0.49
Cognitive/mood	5.33±1.66	5.01±2.19	0.48
Total fatigue score	5.78±1.60	5.89±1.6.3	0.98
Muscle strength tests			
McQuade test (s)	30.73±14.78	27.81±18.94	0.60
Multiple sit-to-stand test (s)	26.48±4.40	27.72±7.28	0.43
Profile of Mood States			
Tension-anxiety	46.72±10.09	49.18±10.68	0.51
Depression-dejection	48.55±9.31	52.25±11.55	0.99
Anger-hostility	52.41±9.81	55.46±12.26	0.53
Vigor	49.68±7.91	50.84±7.54	0.52
Fatigue	52.58±8.01	53.68±9.76	0.24
Confusion	40.13±10.09	42.84±9.64	0.53
Disturbance of mood	-18,631.0±5,467.76	-20,037.5±4,885.18	0.61

control groups were identified (table 2). There were also no differences in variables at baseline between groups (table 3). Seven patients were not assessed at 6 months for different reasons (see fig 1). Thirty-four patients finished the aquatic exercise program and completed 84% of the 24 physical therapy sessions (mean ± SD, 20±4 sessions). Adverse effects reported during the study included discomfort or low-intensity pain/stiffness after an exercise session in 3 patients; nevertheless, they continued the program.

Effects of aquatic exercise program in CRF

The analysis of variance (ANOVA) found significant Group×Time interactions for all dimensions of the PFS: affective ($F=13.7265$; $P<.001$), sensory ($F=20.714$; $P<.001$), cognitive ($F=12.848$; $P<.001$), severity ($F=3.399$; $P=.040$), and total fatigue score ($F=16.998$; $P<.001$). The aquatic exercise group experienced a greater decrease in fatigue than did the control group in all dimensions and the total score (table 4). The intergroup effect size after treatment was large for affective ($d=1.36$; 95% confidence interval [CI], .90–1.82), sensory ($d=1.54$; 95% CI, 1.0–1.85), cognitive ($d=1.10$; 95% CI, .59–1.60), and total fatigue ($d=1.51$; 95% CI, 1.13–1.90) scores. The intergroup effect size for the severity dimension was moderate ($d=.68$; 95% CI, .14–1.22). The aquatic exercise group maintained the improvements in fatigue in affective, sensory, cognitive, and total scores of the PFS after 6-month follow-up (see table 4). The intergroup effect size after 6-month follow-up was large for affective ($d=.90$; 95% CI, .46–1.34), sensory ($d=1.19$; 95% CI, .78–1.61), and cognitive ($d=.98$; 95% CI, .58–1.38) dimensions and the total fatigue score ($d=.87$; 95% CI, .48–1.26) related to pre-intervention values. The intergroup effect size after 6-month follow-up was negligible for the severity dimension ($d=.24$; 95% CI, .20–.76).

Effects of aquatic exercise program in leg and abdominal endurance

A significant Group×Time interaction for the multiple sit-to-stand test ($F=20.011$; $P<.001$) and the trunk curl static endurance test ($F=10.091$; $P<.001$) was also found (table 5). Intergroup effect sizes were large for the multiple sit-to-stand ($d=1.10$; 95% CI, -.55 to 2.76) and trunk curl static endurance ($d=.92$; 95% CI, -1.97 to 3.83)

tests at postintervention, but moderate (multiple sit-to-stand test, $d=.50$; 95% CI, .27–.90) and small (trunk curl static endurance test, $d=.25$; 95% CI, .20–.47) at 6-month follow-up (see table 5).

Effects of aquatic exercise program on mood state

The ANOVA found a significant Group×Time interaction for tension ($F=3.142$; $P=.048$), depression ($F=3.759$; $P=.029$), anger ($F=4.626$; $P=.014$), and mental fatigue ($F=6.765$; $P=.002$). Intergroup effect sizes were moderate for tension ($d=.65$; 95% CI, -1.23 to 2.54), depression ($d=.60$; 95% CI, -1.21 to 2.43), and anger ($d=.79$; 95% CI, -1.43 to 3.01) subscales at postintervention (table 6). Intergroup effect sizes were negligible for tension ($d=.23$; 95% CI, -1.94 to 2.61), depression ($d=.24$; 95% CI, -.96 to 1.97), and anger ($d=.21$; 95% CI, -1.92 to 2.35) subscales at 6-month follow-up. Intergroup effect sizes were large for the mental fatigue scale ($d=.81$; 95% CI, -.61 to 2.20) at intervention and moderate ($d=.73$; 95% CI, -.89 to 2.37) at 6-month follow-up (see table 6).

In addition, the ANOVA found no significant Group×Time interactions for vigor ($F=1.057$; $P=.353$), confusion ($F=1.006$; $P=.372$), and mood disturbance ($F=1.717$; $P=.189$) (see table 6) scores. Intergroup effect sizes were negligible for vigor, confusion, and mood disturbance after treatment and 6 months after discharge ($d<.25$).

Discussion

This study found that an 8-week supervised aquatic exercise program in deep water decreased fatigue and improved leg-abdominal muscle endurance and several aspects of mood state such as tension, depression, anger, and mental fatigue in breast cancer survivors suffering moderate CRF. The effects were maintained at 6 months after discharge except for mood state.

Our results are similar to findings of previous research examining the effects of exercise on fatigue^{13,35,36} and confirm suggestions provided by clinical guidelines about the effects of exercise on fatigue.^{9,37,38} However, we reported a large effect size that is not consistent with a previous meta-analysis reporting small to moderate effect sizes.^{12,39} The larger effect size in the current trial could be related to our selected population that had a moderate to high level of

Table 4 Preintervention, postintervention, 6-mo follow-up, and change scores for mean values of the PFS score

Group	Aquatic Exercise Program	Usual Care Group	Between-group Differences
Behavioral/severity			
Preintervention	5.38±2.04	6.16±2.13	
Postintervention	3.78±1.95	6.05±1.82	
6-mo follow-up	4.04±2.22	5.45±2.38	
Within-group change scores			
Pre-post intervention	-1.59 (-2.38 to -0.80)	-0.11 (-0.72 to 0.94)	-1.48 (-0.35 to -2.61)*
Preintervention to 6-mo follow-up	-1.33 (-2.31 to -0.35)	-0.71 (-1.29 to -0.12)	-0.62 (-1.71 to 0.47)
Affective/meaning			
Preintervention	6.32±1.87	6.79±2.01	
Postintervention	3.82±2.31	6.81±2.02	
6-month follow-up	4.42±2.42	6.47±2.20	
Within-group change scores			
Pre-post intervention	-2.50 (-3.33 to -1.68)	0.02 (-0.54 to 0.58)	-2.52 (-3.48 to -1.56)*
Preintervention to 6-mo follow-up	-1.90 (-2.80 to -1.01)	-0.32 (-0.68 to 0.03)	-1.57 (-2.48 to -0.66)†
Sensory			
Preintervention	6.18±1.82	5.79±1.81	
Postintervention	3.92±1.88	6.25±2.06	
6-mo follow-up	4.08±2.25	5.68±1.93	
Within-group change scores			
Pre-post intervention	-2.26 (-2.98 to -1.53)	0.46 (-0.15 to 1.08)	-2.72 (-3.64 to -1.80)*
Preintervention to 6-mo follow-up	-2.10 (-2.87 to -1.33)	-0.11 (-0.59 to 0.36)	-1.98 (-2.88 to -1.09)†
Cognitive/mood			
Preintervention	5.33±1.66	5.01±2.19	
Postintervention	3.75±1.87	5.66±2.25	
6-mo follow-up	3.69±1.97	5.09±2.37	
Within-group change scores			
Pre-post intervention	-1.58 (-2.35 to -0.84)	0.65 (-0.13 to 1.64)	-2.23 (-3.29 to -1.17)*
Preintervention to 6-mo follow-up	-1.63 (-2.37 to -0.90)	0.08 (-0.36 to 0.52)	-1.73 (-2.54 to -0.79)†
Total fatigue score			
Preintervention	5.78±1.60	5.89±1.63	
Postintervention	3.78±1.78	6.23±1.72	
6-mo follow-up	4.01±2.08	5.47±1.82	
Within-group change scores			
Pre-post intervention	-2.00 (-2.63 to -1.37)	0.34 (-0.19 to 0.87)	-2.34 (-3.14 to -1.53)*
Preintervention to 6-mo follow-up	-1.77 (-2.49 to -1.05)	-0.42 (-0.86 to 0.01)	-1.33 (-2.15 to -0.53)†

* Values are expressed as mean ± SD for pre- and postintervention data and as mean (95% CI) for within- and between-group change scores.

† Significant Group×Time interaction (factorial repeated-measures ANOVA test; *P*<.05).

Table 5 Preintervention, postintervention, 6-mo follow-up, and change scores for mean values of strength

Group	Aquatic Exercise Program	Usual Care Group	Between-group Differences
Trunk curl static endurance test (s)			
Preintervention	30.73±18.88	27.81±14.94	
Postintervention	81.93±20.14	49.82±32.79	
6-mo follow-up	59.92±36.10	32.82±25.11	
Within-group change scores			
Pre-post intervention	51.19 (40.53–61.85)	22.00 (9.29–34.71)	29.19 (12.75–45.62)*
Preintervention to 6-mo follow-up	29.18 (16.42–41.95)	5.01 (-0.88 to 10.91)	24.17 (10.85–37.50)†
Multiple sit-to-stand test (s)			
Preintervention	26.48±4.40	27.72±7.28	
Postintervention	13.33±1.91	21.88±6.57	
6-mo follow-up	19.45±3.76	28.02±7.33	
Within-group change scores			
Pre-post intervention	-13.15 (-15.25 to -11.05)	-5.83 (-8.59 to -3.07)	-7.32 (-10.77 to -3.87)*
Preintervention to 6-mo follow-up	-7.03 (-9.03 to -5.04)	0.30 (-1.19 to 1.80)	-7.34 (-9.75 to -4.95)†

* Values are expressed as mean ± SD for pre- and postintervention data and as mean (95% CI) for within- and between-group change scores.

† Significant Group×Time interaction (factorial repeated-measures ANOVA test; *P*<.05).

Table 6 Preintervention, postintervention, 6-mo follow-up, and change scores for mean values of Profile of Mood States

Group	Aquatic Exercise Program	Usual Care Group	Between-group Differences
Tension			
Preintervention	46.72±10.09	49.18±10.68	
Postintervention	42.51±8.60	49.93±11.66	
6-mo follow-up	43.97±9.47	48.84±11.17	
Within-group change scores			
Pre-post intervention	-4.20 (-7.74 to -0.66)	0.75 (-1.35 to 2.85)	-4.95 (-8.89 to -1.01)*
Preintervention to 6-mo follow-up	-3.44 (-8.30 to 1.41)	-0.34 (-1.72 to 1.04)	-3.10 (-7.83 to 1.61)
Depression			
Preintervention	48.55±9.31	52.25±11.55	
Postintervention	45.58±9.68	53.71±11.60	
6-mo follow-up	46.03±9.01	52.68±11.84	
Within-group change scores			
Pre-post intervention	-2.96 (-5.77 to -0.15)	1.46 (-1.34 to 4.28)	-4.43 (-8.33 to 0.52)*
Preintervention to 6-mo follow-up	-2.51 (-5.32 to 0.29)	0.43 (-1.13 to 2.00)	-2.95 (-6.02 to 0.11)
Anger			
Preintervention	52.41±9.81	55.46±12.26	
Postintervention	48.17±9.44	58.25±12.58	
6-mo follow-up	50.00±10.16	54.90±12.06	
Within-group change scores			
Pre-post intervention	-4.24 (-7.38 to -1.09)	2.78 (-0.70 to 6.26)	-7.02 (-11.65 to -2.39)*
Preintervention to 6-mo follow-up	-2.41 (-6.61 to 1.78)	-0.56 (-2.50 to 1.38)	-1.85 (-6.24 to 2.53)
Vigor			
Preintervention	49.68±7.91	50.84±7.54	
Postintervention	51.62±7.15	50.46±7.63	
6-mo follow-up	50.27±9.42	51.06±8.15	
Within-group change scores			
Pre-post intervention	-1.93 (-0.43 to 4.29)	-0.37 (-2.55 to 1.80)	2.30 (-0.84 to 5.45)
Preintervention to 6-mo follow-up	0.58 (-2.39 to 3.57)	0.22 (-1.16 to 1.60)	0.36 (-2.75 to 3.48)
Fatigue			
Preintervention	52.58±8.01	53.68±9.76	
Postintervention	47.79±8.11	53.34±9.82	
6-mo follow-up	47.41±10.61	53.31±9.84	
Within-group change scores			
Pre-post intervention	-4.79 (-6.67 to -2.90)	0.34 (-2.62 to 1.93)	-4.44 (-7.38 to -1.51)*
Preintervention to 6-mo follow-up	-5.17 (-8.60 to -1.70)	-0.37 (-1.43 to 0.68)	-4.79 (-8.20 to -1.31)†
Confusion			
Preintervention	40.13±10.09	42.84±9.64	
Postintervention	37.93±8.48	43.03±10.01	
6-mo follow-up	37.75±7.34	42.02±11.31	
Within-group change scores			
Pre-post intervention	-2.20 (-4.95 to 0.54)	0.18 (-1.93 to 2.30)	-2.39 (-5.75 to 0.96)
Preintervention to 6-mo follow up	-2.37 (-6.05 to 1.29)	-0.84 (-2.74 to 1.05)	-1.53 (-5.45 to 2.40)
Total disturbance of mood			
Preintervention	-18,631±5,467	-20,037±4,885	
Postintervention	-17,175±4,279	-20,390±6,113	
6-mo follow-up	-17,306±4,501	-19,915±4,966	
Within-group change scores			
Pre-post intervention	1,445 (-160 to 3,070)	-353 (-1,617 to 911)	1808 (-180 to 3,796)
Preintervention to 6-mo follow-up	1,324 (-735 to 3,383)	121 (-490 to 734)	-1,202 (-812 to 3,217)

* Values are expressed as mean ± SD for pre- and postintervention data and as mean (95% CI) for within- and between-group change scores.

† Significant Group×Time interaction (factorial repeated-measures ANOVA test; $P<.05$).

CRF, allowing for a greater margin of improvements. This study helps to reduce the gap in the literature about the effectiveness of supervised exercise programs in a subgroup of patients with special requirements or at risk to develop other symptoms associated with CRF.⁶ It has recently been reported that there was no benefit from a water exercise program in a chest-high pool for CRF in breast cancer survivors

suffering from hormone therapy-associated arthralgia pain.²¹ Current results were obtained with an exercise program in a deep water pool including aerobic/endurance exercise as a principal component (70% of each session), which could require more exertion than exercises in a chest-high pool with reduced cardiovascular demands (20% of each exercise session). It is possible that the decreased stress on

weight-bearing joints and decreased axial loading facilitated aquatic exercise. Aquatic exercise could improve the fitness level of participants, which is known as one of the pillars to attenuate CRF.^{5,7} Hydrostatic pressure during water exercise redistributes blood from the limbs to the thoracic cavity; this redistribution may have reduced the heart rate and transiently increased the blood pressure.⁴⁰ Unfortunately, we did not use a heart rate monitor during immersion to provide support to these speculations. Future studies in a larger and multisite sample are recommended to determine the physiological adaptations during water exercise in breast cancer survivors.

The results of the current study also showed significant and clinical improvements in leg and abdominal muscle strength. The decreased muscle function in cancer survivors during and after the oncology treatment is well known.^{6,41,42} This reduced force had been associated with an increase in CRF and reduction in quality of life.^{17,18} Recent research provides support to the positive influence of aerobic and strength training exercise interventions in breast cancer survivors mediated by different physiological responses such as decreases in insulin levels,⁴³ reduction in C-reactive protein levels,⁴⁴ or an increase in the adiponectin/leptin ratio.⁴⁵ Large effect sizes in muscle strength were reported in our study and could possibly be linked to the resistance effects offered by water. We used an increase in the velocity of movement during the exercises as a major component of progression with intensity of the exercise with less joint stress as compared with land-based exercise.⁴⁶ Future studies should be carried out to determine the effect of these types of programs on muscle metabolism (ie, adenosine triphosphate and cytokines dysregulation, deprivation of satellite cells) associated with oncology treatment⁴⁷ to promote the maintenance of muscle mass.

The reduction in CRF and the increase in strength reported in the current study are similar to recent studies that have demonstrated that fitness improves quality of life by reducing CRF in breast cancer survivors.⁴⁸ Our results give preliminary support to the implementation of aquatic exercise programs to promote the recovery of functional limitations following initial breast cancer treatment that have been associated with an important reduction in all-cause and competing-cause survival.⁴⁹

The current results on mood state partially agree with the results from previous studies using a land-exercise approach.²⁶ The reported psychological positive effects of aquatic exercise could help to explain the reduction in CRF of our population. Exercise facilitators were included in this aquatic exercise program being group-based, high therapist/patient supervision ratio (1 therapist for each 5–7 patients), individually tailored, and gradually progressed. These exercise motivators can be related to self-perceived exercise benefits.⁸ Relief of CRF and improvement in strength reported in this study may improve the patients' ability to perform daily activities and to interact with others.⁵⁰ These improvements in the relationship between survivors and proxy environment could help to improve several aspects of mood state as identified in this trial.

Study limitations

Although this study obtained relevant clinical findings, some limitations need to be considered when interpreting the results. First, this study examined women with stages I to IIIA breast cancer without limitations to practice water exercise referred by oncologists from a metropolitan hospital. These selection criteria resulted in a smaller population of potentially eligible patients. Therefore, it may be difficult to generalize these results to all patients with breast cancer. Second, it is difficult to assess muscle function and heart rate during

the water exercises. Third, different resources such as a deep water pool and a high ratio of supervision of the exercise program can reduce the cost-effectiveness of the trial. Fourth, intention to treat and responder analysis to explore the characteristics of those patients most likely to derive benefit were not included in this study. Finally, it is unknown whether participants continued any type of physical training after the intervention. Influences of previous exercise programs on the physical activity level of cancer survivors should be clarified in future studies. Nevertheless, the structured aquatic exercise program and the use of validated objective outcomes enhance the methodologic quality of the trial. Knowledge about safe and effective exercise programs has influenced choices regarding physical activity and exercise in cancer survivors,⁵¹ and no serious adverse effects of this program give preliminary support to the use of aquatic exercise in cancer survivors.

Conclusions

In conclusion, an 8-week deep water exercise program was clinically effective for improving CRF, muscle strength, and several aspects of mood state as compared with usual treatment care at short and medium term in breast cancer survivors reporting a moderate rate of fatigue.

Supplier

a. SPSS, version 19.0; SPSS, Inc, 233 S Wacker Dr, 11th Floor, Chicago IL 60606.

Keywords

Breast; Exercise; Fatigue; Neoplasms; Rehabilitation

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References

1. Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue: implications for breast cancer survivors. *Cancer* 2012;118:2261-9.
2. de Jong N, Candel MJ, Schouten HC, Abu-Saad HH, Courtens AM. Prevalence and course of fatigue in breast cancer patients receiving adjuvant chemotherapy. *Ann Oncol* 2004;15:896-905.
3. Cella D, Davis K, Breitbart W, Curt G. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *J Clin Oncol* 2001;19:3385-91.
4. Schmitz KH, Speck RM, Rye SA, DiSipio T, Hayes SC. Prevalence of breast cancer treatment sequelae over 6 years of follow-up: the Pulling Through Study. *Cancer* 2012;118:2217-25.
5. Campos MP, Hassan BJ, Riechelmann R, Del Giglio A. Cancer-related fatigue: a review. *Rev Assoc Med Bras* 2011;57:211-9.
6. Cantarero-Villanueva I, Fernandez-Lao C, Fernández-de-las-Peñas C, Díaz-Rodríguez L, Sánchez-Cantalejo E, Arroyo-Morales M. Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment. *Eur J Cancer Care* 2011;20:632-9.
7. Mitchell SA. Cancer-related fatigue: state of the science. *PM R* 2010; 2:364-83.
8. Blaney J, Lowe-Strong A, Rankin J, Campbell A, Allen J, Gracey J. The cancer rehabilitation journey: barriers to and facilitators of exercise among patients with cancer-related fatigue. *Phys Ther* 2010;90:1135-47.

9. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 2010;42:1409-26.
10. Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. *Health Psychol* 2007;26:660-7.
11. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull* 2008;134:700-41.
12. Speck RM, Courneya KS, Mâsse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010;4:87-100.
13. Fong DY, Ho JW, Hui BP, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ* 2012;344:e70.
14. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? *Nat Rev Cancer* 2004;4:891-9.
15. Nair KS. Aging muscle. *Am J Clin Nutr* 2005;81:953-63.
16. Yavuzsen T, Davis MP, Ranganathan VK, et al. Cancer-related fatigue: central or peripheral? *J Pain Symptom Manage* 2009;38:587-96.
17. McMillan EM, Newhouse IJ. Exercise is an effective treatment modality for reducing cancer-related fatigue and improving physical capacity in cancer patients and survivors: a meta-analysis. *Appl Physiol Nutr Metab* 2011;36:892-903.
18. Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodríguez L, Fernández-de-las-Peñas C, Ruiz JR, Arroyo-Morales M. The handgrip strength test as a measure of function in breast cancer survivors: relationship to cancer-related symptoms and physical and physiologic parameters. *Am J Phys Med Rehabil* 2012;91:774-82.
19. Waller B, Lambeck J, Daly D. Therapeutic aquatic exercise in the treatment of low back pain: a systematic review. *Clin Rehabil* 2009;23:3-14.
20. Batterham SI, Heywood S, Keating JL. Systematic review and meta-analysis comparing land and aquatic exercise for people with hip or knee arthritis on function, mobility and other health outcomes. *BMC Musculoskelet Disord* 2011;12:123.
21. Cantarero-Villanueva I, Fernández-Lao C, Caro-Morán E, et al. Aquatic exercise in a chest-high pool for hormone therapy-induced arthralgia in breast cancer survivors: a pragmatic controlled trial. *Clin Rehabil* 2012 [Epub ahead of print].
22. Cuesta-Vargas AI, Heywood S. Aerobic fitness testing in chronic nonspecific low back pain: a comparison of deep-water running with cycle ergometry. *Am J Phys Med Rehabil* 2011;90:1030-5.
23. Town G, Bradley S. Maximal metabolic responses of deep and shallow water running in trained runners. *Med Sci Sports Exerc* 1991;23:238-41.
24. Segar ML, Katch VL, Roth RS, et al. The effect of aerobic exercise on self-esteem and depressive and anxiety symptoms among breast cancer survivors. *Oncol Nurs Forum* 1998;25:107-13.
25. Mock V, Dow KH, Meares CJ, et al. Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncol Nurs Forum* 1997;24:991-1000.
26. Cantarero-Villanueva I, Fernández-Lao C, Del Moral-Avila R, Fernández-de-Las-Peñas C, Feriche-Fernández-Castany MB, Arroyo-Morales M. Effectiveness of core stability exercises and recovery myofascial release massage on fatigue in breast cancer survivors: a randomized controlled clinical trial. *Evid Based Complement Alternat Med* 2012;620619.
27. Munguía-Izquierdo D, Legaz-Arrese A. Assessment of the effects of aquatic therapy on global symptomatology in patients with fibromyalgia syndrome: a randomized controlled trial. *Arch Phys Med Rehabil* 2008;89:2250-7.
28. Castro-Sánchez AM, Matarán-Peñarocha GA, Lara-Palomo I, Saavedra-Hernández M, Arroyo-Morales M, Moreno-Lorenzo C. Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. *Evid Based Complement Alternat Med* 2012;2012:473963.
29. Piper BF, Dibble SL, Dodd MJ, et al. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. *Oncol Nurs Forum* 1998;25:677-84.
30. Andrade EM, Arce C, Seoane G. Adaptación al español del cuestionario "Perfil de los Estados de Ánimo" en una muestra de deportistas. *Psicothema* 2002;14:708-13.
31. Bohannon RW. Test-retest reliability of the five-repetition sit-to-stand test: a systematic review of the literature involving adults. *J Strength Cond Res* 2011;25:3205-7.
32. McGill SM, Childs A, Liebenson C. Endurance times for low back stabilization exercises: clinical targets for testing and training from a normal database. *Arch Phys Med Rehabil* 1999;80:941-4.
33. Liebenson C. Spinal stabilization—an update, part 2: functional assessment. *J Bodywork Mov Therapies* 2004;8:199-210.
34. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007;39:1435-45.
35. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2008;2:CD006145.
36. Velthuis MJ, Agasi-Idenburg SC, Aufdenkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomized controlled trials. *Clin Oncol* 2010;22:208-21.
37. Mock V, Abernethy AP, Atkinson A, et al. NCCN Clinical Practice Guidelines in Oncology™: cancer-related fatigue. 2007. Available at: http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf. Accessed August 20, 2007.
38. Mitchell SA, Friese CR. Oncology Nursing Society PEP (Putting Evidence into Practice): weight of evidence classification schema and decision rules for summative evaluation of a body of evidence. 2007. Available at: http://www.ons.org/outcomes/volume1/fatigue/pdf/fatigue_woevidence.pdf. Accessed August 20, 2007.
39. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello LS, Ferrer R, Johnson B. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2011;20:123-33.
40. Asahina M, Asahina MK, Yamanaka Y, Mitsui K, Kitahara A, Murata A. Cardiovascular response during aquatic exercise in patients with osteoarthritis. *Am J Phys Med Rehabil* 2010;89:731-5.
41. Bruera E, Brenneis C, Michaud M, Jackson PI, MacDonald RN. Muscle electrophysiology in patients with advanced breast cancer. *J Natl Cancer Inst* 1988;80:282-5.
42. Satariano WA, Ragheb NE, Branch LG, Swanson GM. Difficulties in physical functioning reported by middle-aged and elderly women with breast cancer: a case-control comparison. *J Gerontol* 1990;45:3-11.
43. Ligibel JA, Campbell N, Partridge A, et al. Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. *J Clin Oncol* 2008;26:907-12.
44. Michigan A, Johnson TV, Master VA. Review of the relationship between C-reactive protein and exercise. *Mol Diagn Ther* 2011;15:265-75.
45. Friedenreich CM, Neilson HK, Woolcott CG, et al. Changes in insulin resistance indicators, IGFs, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. *Endocr Relat Cancer* 2011;18:357-69.
46. Graef FI, Pinto RS, Alberton CL, de Lima WC, Krueh LF. The effects of resistance training performed in water on muscle strength in the elderly. *J Strength Cond Res* 2010;24:3150-6.
47. Clarkson PM, Kaufman SA. Should resistance exercise be recommended during breast cancer treatment? *Med Hypotheses* 2010;75:192-5.
48. Buffart LM, De Backer IC, Schep G, Vreugdenhil A, Brug J, Chinapaw MJ. Fatigue mediates the relationship between physical fitness and quality of life in cancer survivors. *J Sci Med Sport* 2012 Jun 30 [Epub ahead of print].
49. Braithwaite D, Satariano WA, Sternfeld B, et al. Long-term prognostic role of functional limitations among women with breast cancer. *J Natl Cancer Inst* 2010;102:1468-77.
50. Yang CY, Tsai JC, Huang YC, Lin CC. Effects of a home-based walking program on perceived symptom and mood status in post-operative breast cancer women receiving adjuvant chemotherapy. *J Adv Nurs* 2011;67:158-68.
51. Sander AP, Wilson J, Izzo N, Mountford SA, Hayes KW. Factors that affect decisions about physical activity and exercise in survivors of breast cancer: a qualitative study. *Phys Ther* 2012;92:525-36.