Integrative Cancer Therapies
2018, Vol. 17(3) 717–727
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1534735418766615
journals.sagepub.com/home/ict
SAGE

Results From a Pilot Study of Handheld Vibration: Exercise Intervention Reduces Upper-Limb Dysfunction and Fatigue in Breast Cancer Patients Undergoing Radiotherapy: VibBRa Study

Sarah Kneis, MA[1*], Anja Wehrle, MA[2*], Anne Ilaender, MA[3], Natalja Volegova-Neher, MD[4], Albert Gollhofer, PhD[3], and Hartmut Bertz, MD[1]

Abstract

Purpose: Although there is evidence that breast cancer patients benefit from exercising during treatment, exercising during radiotherapy and especially the effects on upper-limb dysfunctions have been infrequently assessed. Therefore, we primarily aimed to confirm our interventions' feasibility and secondarily aimed to affect upper-limb dysfunctions and fatigue.
Methods: Twenty-two breast cancer patients scheduled for radiotherapy were allocated to an intervention (IG) or a passive control group (CG) as they preferred. IG exercised 3×/week during 6 weeks of radiotherapy: cycling endurance, handheld vibration, and balance training. We documented adverse events and training compliance (feasibility) and assessed the range of shoulder motion (ROM), isometric hand grip strength, vibration sense on the first metacarpophalangeal joint of the affected upper limb, and fatigue.
Results: We observed no adverse events and a training compliance of 98 %. IG's ROM improved significantly (abduction: 11°; 95% confidence interval [CI] 5 to 20; external rotation: 5°, 95% CI 0 to 10), as did the hand grip strength (1.6 kg, 95% CI −0.6 to 3.1), while CG's ROM did not change. CG's vibration sense worsened (−1.0 points, 95% CI −1.5 to −0.5), while IG's remained stable. Changes in general fatigue levels between IG (−2.0 points, 95% CI −3.0 to −1.0) and CG (0.5 points, 95% CI −1.0 to 4.5) revealed significant differences ($P = .008$)
Conclusions: Our intervention proved to be feasible and provides novel findings: it reduced fatigue levels and interestingly, handheld vibration exercises improved upper-limb function due to shoulder ROM, hand grip strength, and vibration sense.

Keywords
breast cancer, radiotherapy, fatigue, upper-limb dysfunction, handheld vibration, range of motion, vibration, exercise therapy, postural balance

Submitted August 2, 2017; revised February 11, 2018; accepted February 11, 2018

Introduction

Most women with breast cancer (BC) undergo surgery and chemotherapy and/or radiotherapy.[1] These treatments trigger various side effects, for example, shoulder immobility, numbness or tightness, and lymphedema of the arm.[1] As are other cancer patients, many BC patients are affected by fatigue[2,3] and poorer overall physical and psychological function.[2] To manage these impairments, there is evidence of the beneficial effects of physical activity and exercise already during treatment.[4,5] However, few studies have investigated exercising specifically during BC radiotherapy.[6]

---

[1]Department of Medicine I, Faculty of Medicine and Medical Center – University of Freiburg, Germany
[2]Institute for Exercise- and Occupational Medicine, Faculty of Medicine and Medical Center – University of Freiburg, Germany
[3]Department of Sport and Sport Science, University of Freiburg, Germany
[4]Department of Radiation Oncology, Faculty of Medicine and Medical Center – University of Freiburg, Germany

[*]Both authors contributed equally to this work.

Corresponding Author:
Hartmut Bertz, Department of Medicine I, Medical Center, University of Freiburg, Hugstetterstr. 55, Freiburg 79106, Germany.
Email: hartmut.bertz@uniklinik-freiburg.de

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Table 1. Patient Characteristics of Completers (n = 21).[a]

	IG (n = 11)	CG (n = 10)[b]	P
Age (years), median (min-max)	52 (39-72)	64 (48-79)	**.043**
BMI (kg/m^2), median (min-max)	24.0 (20.9-28.8)	26.7 (20.2-35.5)	.152
Stage of breast cancer (n)[c]			
0	2	0	
I	3	6	
II (A/B)	6	4	
Surgery, n (%)	11 (100)	10 (100)	
Breast conserving	10 (91)	10 (100)	
Mastectomy	1 (9)	0 (0)	
Chemotherapy, n (%)	5 (46)	5 (50)	
Antibody therapy, n (%)	1 (9)	1 (10)	
Compliance (%), mean ± SD	98 ± 5		

Abbreviations: IG, intervention group; CG, control group; BMI, body mass index.
[a] Significant results are highlighted in boldface $P < .05$.
[b] No postintervention data were available for one patient.
[c] According to UICC TNM staging system.

BC patients after surgery often suffer from less shoulder mobility that can substantially worsen during radiotherapy[7]; range of shoulder motion (ROM) is known to be expandable via stretching and strengthening exercises[8] even during radiotherapy.[9-11] Besides shoulder immobility, BC treatment can cause peripheral neuropathy symptoms[12,13] expressed as sensoric and/or motor dysfunctions.[14,15] There are indications that vibration exercises might help alleviate neuropathy-induced lower-body sensory and motor dysfunction.[16-18] This knowledge might also apply to upper-body function: upper-body–induced vibration exercises might also affect the sensorimotor system, as there are indications of enhanced elbow and wrist joint position sensation.[19,20] Furthermore, improved shoulder ROM was also demonstrated after upper-body vibration exercises.[21,22] The literature on hamstring flexibility strengthens the use of whole body vibration (WBV) to expand ROM.[23] Additionally, vibration exercise is known to serve as resistance training[24] and therefore might counteract impaired muscle strength in the affected limb of BC patients.[15,25] Despite the knowledge on upper-limb dysfunction, interventions including resistance training or targeting specific impairments like shoulder immobility are less frequent,[6,26] especially during treatment.[8,27] Most studies during BC radiotherapy focused only on fatigue modulation, mainly via endurance exercises.[28-31] However, endurance exercises during radiotherapy appear insufficient to address functional deficits induced by BC treatment.[9,32] Diminished strength and functional performance in general thus lead to significant impairments in daily life[33] and are associated with mortality.[34] Considering that balance training may serve as an additional component to alleviate functional deficits[35] and to enhance muscular power output,[36] though it has been infrequently described for cancer patients.[37-39]

We implemented a nonrandomized controlled pilot study to primarily assess the feasibility of a novel exercise intervention in BC patients during radiotherapy including handheld vibration training that aims to affect 3 relevant aspects of upper-limb function (shoulder ROM, strength, and sensorimotor function). Furthermore, being aware of the aforementioned functional impairments, the intervention also included balance training to improve functional performance and endurance training, targeting fatigue reduction.

Materials and Methods

Study Design and Patients

Within 5 months, we consecutively allocated 22 BC patients planned for radiotherapy at the Department of Radiation Oncology to either an intervention group (IG) or passive control group (CG) (according to their preference) to primarily assess the feasibility of our exercise intervention in a pilot study. Assessments were undertaken at pre- and postintervention time points to evaluate additional group differences. Baseline assessments took place within 1 week before starting radiation (T0) and postassessments within 1 week after 6 weeks of radiotherapy or intervention (T1), respectively. Inclusion criteria were a BC diagnosis, after surgery, and scheduled radiotherapy. Exclusion criteria were instable bone metastasis and/or severe cardiovascular diseases.[40] Table 1 summarizes patients' characteristics. The study was approved by the ethics committee, conducted according to the Declaration of Helsinki, and all patients gave written informed consent to study participation.

Intervention

The one-on-one training sessions took place in the Division of Sports Oncology in the Clinic of Internal Medicine I, 3 times per week for 60 minutes over 6 weeks during radiotherapy following Hwang et al.[9]

The intervention protocol included 3 units lasting 20 minutes: first, endurance training on a stationary bicycle with 60% to 75% of the maximum heart rate; second, handheld vibration training with the Galileo UpX vibrating dumbbell (Novotec, Pforzheim, Germany; 2.6 kg; 5-40 Hz; 2 mm amplitude). The handheld vibration training aims to enhance shoulder mobility and upper limb strength, and thus consisted of 3 sets of 5 partially assisted exercises: a passive muscle relaxing part (8-12 Hz), active coordination part (16-20 Hz), and an active resistance part (22-30 Hz). Active exercises included abduction and anteversion as well as rotation movements in different planes of the shoulder and followed intensity prescription of 14 to 16 on the perceived exertion rating scale.[40,41] For safety reasons and to support weaker or already tired patients, exercises were assisted by a pulley system. During passive relaxing, the pulley system carried the dumbbell's weight for passive vibrating over the shoulder level. Third, patients performed balance training (3 sets of 3-6 exercises) involving progressively increasing exercise difficulty by reducing the support surface and visual input, adding motor/cognitive tasks, and instability induction.[42,43] We controlled each patient's blood pressure and heart rate during each training session and documented vital parameters and training progress.

Outcome Measures

Feasibility. The primary endpoint "feasibility" was assessed by documenting exercise-related adverse events, reasons for missed sessions, and calculating training compliance in percentage (completed training sessions divided by planned training sessions).

Upper-Limb Function. All measurements of upper-limb function were assessed on the affected extremity, meaning the right or left upper extremity according to BC site.

Shoulder ROM was tested using a manual goniometer for active movements of abduction (standard value 180°), external rotation (standard value 40° to 60°), and hand-behind-back position: this means the distance (cm) between the vertebra prominens (C7) and thumb tip when subjects reach upward and toward the midline to the highest vertebral level. For these assessments, patients stood in a neutral upright position with their feet shoulder-width apart. The same examiner performed pre- and post-ROM.

Maximum isometric hand grip strength (kg) was measured using a hand grip dynamometer (DigiMax S, DigiMax Systems, Hamm, Germany). Patients sat in a stable position with the shoulder in adduction, elbow at 90° flexion, and completed 3 trials each lasting 3 to 5 seconds with 60-second rest between trials.[44] The examiner provided verbal encouragement. The highest value among 3 trials was used for analysis.[44]

Symptoms of peripheral neuropathy were evaluated by determining the vibration sense on the first metacarpophalangeal joint via a Rydel-Seiffer tuning fork with a graduating scale from 0 (no sensitivity) to 8 (highest sensitivity).

Functional Performance. All measurements were taken on a force plate (Leonardo Mechanograph GRFP, Novotec Medical GmbH, Pforzheim, Germany), which determined dynamic ground reaction forces in its local and temporal progress.

The static balance assessment took place without shoes and during 3 different conditions to determine the center of force (COF) displacement in anterioposterior and mediolateral direction: semi-tandem stance with eyes open (EO) and eyes closed (EC), and one-leg stance in EO condition. Patients were asked to stand upright and comfortably and direct their gaze onto a marked spot located at eye level on the wall. Sway path (mm) of COF was recorded over 30 seconds with a sample rate of 800 Hz. The 3 trials' mean value was used for analysis.

To evaluate the lower body's muscle power, patients performed a maximum counter-movement jump (CMJ) with freely moving arms and were instructed to jump as high as possible. Outcomes were defined as maximum power output during take-off per kilogram body weight (P_{max_jump}; W/kg) and jumping height (cm). The best of 2 trials was used for analysis.

Data were analyzed using Leonardo Mechanography Research-Software (Novotec Medical GmbH, Pforzheim, Germany).

Cardiorespiratory Fitness. Cardiorespiratory fitness was determined by peak oxygen consumption ($\dot{V}O_{2peak}$),[45] peak workload (P_{max_CPET}; Watt), and performance at the individual anaerobic threshold (IAT; Watt) measured during the maximum cardiopulmonary exercise test (CPET)[46] on an electronically braked cycle ergometer (Ergoline 900, Bitz, Germany) in recumbent position. The exercise protocol started at 20 Watts and workload increased stepwise by 10 Watts every minute until exhaustion.[40] Gas exchange and ventilation was continuously recorded via a breath-by-breath gas analysis system (Oxycon Delta, Jaeger, Hochberg, Germany). $\dot{V}O_{2peak}$ was determined as the averaged values of the last 30 seconds of exercise. The electrocardiograms (ECG) were continuously recorded; blood pressure was measured every 3 minutes. Analyzing the lactate concentration per step enabled us to determine IAT via special software (Ergonizer, Freiburg, Germany).

Fatigue. Estimating fatigue, the Multidimensional Fatigue Inventory (MFI) scored from 0 to 20 was used. This 20-item self-report instrument represents fatigue syndrome's multidimensionality by covering general, physical, and mental fatigue as well as reduced motivation and activity.[47]

Statistics

All variables were included in nonparametric analysis as the assumption of normal distribution (Shapiro-Wilk test) was not satisfied (Table 2). Differences between our 2 subject subpopulations at T0 (including age and body mass index) and T1 and differences of groups' delta (T1-T0) were assessed by Mann-Whitney *U* test. Intragroup differences over time were computed by Wilcoxon signed-rank test. The level of significance was set to $P < .05$. Group data are presented as median and 95% confidence interval (CI). To estimate the effect of the treatment the point estimate and 95% CI of the Hodges-Lehmann's median differences for paired groups were used. Bivariate correlations between fatigue dimensions and cardiorespiratory fitness and upper-limb function variables were calculated as Spearman ρ (Table 3). All statistical analyses were conducted using IBM SPSS Version 22 software (SPSS Inc, Chicago, IL).

Results

No adverse events were observed during the study period; one CG patient dropped out after T0 for personal reasons. All the IG patients completed the exercises according to the study protocol, and we observed excellent training compliance (mean ± SD 98 ± 5%). We noted comparable baseline values in the IG and CG, except in the balance task, where IG patients performed better than the CG patients (Table 2). Note that the groups differed significantly in age (Table 1).

Fatigue

The MFI questionnaire revealed significant differences between the IG and in general fatigue-level changes (IG: −2.0 points, 95% CI −3.0 to −1.0, $P = .049$; CG: 0.5 points, 95% CI −1.0 to 4.5, $P = .395$; delta: $P = .008$). Furthermore, IG patients significantly reduced their physical (−1.5 points, 95% CI −3.0 to 0.0, $P = .040$) and mental fatigue level (4.2 points, 95% CI −0.0 to 16.7, $P = .023$) during the intervention (Figure 1A). The dimensions "reduced activity and motivation" were not affected.

Upper-Limb Function

IG patients' shoulder mobility improved (Figure 1B), meaning that ROM of abduction (11°; 95% CI 5 to 20, $P = .012$) and external rotation (5°, 95% CI 0 to 10, $P = .026$) increased significantly. The postintervention performance of hand-behind-back position revealed significant intergroup differences (IG: 10.0 cm, 95% CI 8.5 to 14.0; CG: 16.0 cm, 95% CI 11.8 to 18.8; $P = .029$). Correlations between changes in fatigue and shoulder ROM revealed a significantly negative correlation between the mental fatigue level and range of external rotation ($r = −.485$; $P = .026$).

Furthermore, the IG patients' upper-limb strength improved descriptively, represented by isometric hand grip performance (1.6 kg, 95% CI −0.6 to 3.1, $P = .050$), while the CG exhibited no change. Changes in hand grip strength correlated negatively with changes in 3 dimensions of fatigue significantly: general ($r = −.485$; $P = .026$) and physical fatigue ($r = −.594$; $P = .006$) and reduced motivation ($r = −.459$; $P = .036$; Figure 2).

Additionally, IG preserved their vibration sense, while the CG patients' sensation decreased significantly (−1.0 points, 95% CI −1.5 to −0.5, $P = .011$), leading to a significant group difference ($P = .010$; Figure 3). We noted a significantly negative correlation between changes in vibration sensation and general and physical fatigue ($r = −.529$; $P = .016$; $r = −.449$; $P = .047$, respectively).

Functional Performance

IG and CG started with significantly different balance values in both semitandem stance conditions at T0 (EO: $P = .01$; EC: $P = .001$) as IG revealed a shorter sway path. This difference persists at T1 (EO: $P = .036$; EC: $P = .005$). Both groups reduced their sway path in the one-leg condition at T1 (IG: −185 mm, 95% CI −409 to 15, $P = .050$; CG: −207 mm, 95% CI −412 to −4, $P = .043$). While the IG demonstrated no after-intervention change in both semitandem stance conditions, the CG significantly reduced their sway path in the EC condition (−187 mm, 95% CI −301 to −14, $P = .038$).

Furthermore, the IG patients improved their lower body muscle power descriptively, represented by maximum jump height (1.6 cm, 95% CI −0.1 to 3.2, $P = .050$), while the CG's jump height did not change leading to a significant difference in groups' delta ($P = .020$). Pmax_jump revealed no intergroup or intragroup differences.

Cardiorespiratory Fitness

Sub-maximum values, that is, the performance at IAT, revealed no significant intergrou or intragroup differences, while groups' delta of P_{max_CPET} (IG: 7 Watt, 95% CI −3 to 15, $P = .138$; CG: −5 Watt, 95% CI −10 to 0, $P = .080$) differed significantly ($P = .016$); the $\dot{V}O_{2peak}$ induced no significant intergroup or intragroup difference. We detected a significant negative correlation between the change in maximum-achieved performance and mental fatigue ($r = −.489$; $P = .029$) during the intervention period, meaning that an

Table 2. Outcome Parameters Pre (T0) and Post (T1) Intervention in the Intervention Group (IG, n = 11) and Control Group (CG, n = 10).[a]

		T0, Median (95% CI)	T1, Median (95% CI)	Median Difference[b] (95% CI)	T1 − T0 *P*
Range of shoulder motion					
Abduction (°)	IG	165 (134 to 169)	175 (148 to 180)	11 (5 to 20)	**.012**
	CG	160 (135 to 169)	168 (139 to 178)	5 (0 to 15)	.168
	P	1.000	.557	.132	
External rotation (°)	IG	55 (80 to 63)	60 (55 to 68)	5 (0 to 10)	**.026**
	CG	60 (47 to 64)	52 (49 to 60)	−1 (−8 to 6)	.671
	P	.654	.720	.051	
Hand-behind-back position (cm)[c]	IG	13.0 (10.2 to 15.3)	10.0 (8.5 to 14.0)	−1.0 (−4.5 to 1.0)	.200
	CG	14.5 (10.3 to 19.1)	16.0 (11.8 to 18.8)	0.5 (−0.5 to 2.0)	.282
	P	.605	**.029**	.132	
Hand grip strength (kg)	IG	26.2 (22.6 to 31.2)	28.6 (24.4 to 32.3)	1.6 (−0.6 to 3.1)	.050
	CG	26.1 (23.7 to 29.4)	26.6 (23.5 to 30.1)	0.3 (−2.8 to 3.8)	.799
	P	1.000	.654	.426	
Vibration sense (scale 0-8)	IG	7.0 (6.7 to 7.5)	7.0 (6.4 to 7.6)	−0.13 (−0.5 to 0.3)	.469
	CG	6.5 (5.4 to 7.3)	5.4 (4.3 to 6.5)	−1.0 (−1.5 to −0.5)	**.011**
	P	.132	.060	**.010**	
COF displacement					
Semitandem EO (mm)	IG	471 (427 to 569)	487 (433 to 542)	−12 (−65 to 44)	.594
	CG	644 (542 to 845)	565 (500 to 733)	−70 (−180 to 17)	.114
	P	**.010**	**.036**	.251	
Semitandem EC (mm)	IG	859 (726 to 997)	805 (676 to 956)	−22 (−152 to 45)	.424
	CG	1259 (1055 to 2009)	1167 (984 to 1694)	−187 (−301 to −14)	**.038**
	P	**.001**	**.005**	**.046**	
One-leg stance EO (mm)	IG	1172 (1038 to 1595)	1103 (931 to 1316)	−185 (−409 to 15)	.050
	CG	1591 (956 to 2008)	1382 (899 to 1644)	−207 (−412 to −4)	**.043**
	P	.791	.659	.724	
Counter movement jump					
Jump height (cm)	IG	22.3 (19.8 to 27.0)	26.7 (21.4 to 28.3)	1.6 (−0.1 to 3.2)	.050
	CG	19.8 (15.8 to 26.1)	19.4 (15.3 to 25.1)	−0.6 (−1.7 to 0.2)	.114
	P	.387	.990	**.020**	
P_{max_jump} (Watt/kg)	IG	27.25 (22.00 to 29.49)	27.92 (23.06 to 30.62)	0.44 (−0.59 to 1.31)	.374
	CG	22.02 (16.51 to 29.02)	22.64 (17.79 to 26.55)	−0.04 (−1.81 to 1.28)	.878
	P	.251	.132	.654	
Cardiorespiratory fitness					
VO_{2peak} (L/min)	IG	1.53 (1.25 to 1.65)	1.40 (1.26 to 1.59)	−0.04 (−0.18 to 0.10)	.594
	CG	1.49 (1.06 to 1.84)	1.42 (1.06 to 1.85)	0.02 (−0.11 to 0.12)	.859
	P	.710	.882	.412	
P_{max_CPET} (Watt)	IG	100 (85 to 116)	110 (90 to 124)	7 (−3 to 15)	.138
	CG	100 (64 to 125)	88 (58 to 121)	−5 (−10 to 0)	.080
	P	.456	.112	**.016**	
IAT (Watt)	IG	70 (61 to 81)	72 (61 to 87)	2 (−5 to 7)	.721
	CG	65 (50 to 94)	72 (49 to 102)	0 (−5 to 6)	1.000
	P	.780	.717	.965	
MFI20 dimensions of fatigue (score max. 20)					
General fatigue	IG	13.0 (9.1 to 14.1)	11.0 (7.1 to 13.3)	−2.0 (−3.0 to −1.0)	**.049**
	CG	9.5 (6.5−12.3)	12.0 (7.7 to 13.7)	0.5 (−1.0 to 4.5)	.395
	P	.132	.557	**.008**	
Physical fatigue	IG	12.0 (9.1 to 14.2)	10.0 (8.2 to 12.0)	−1.5 (−3.0 to 0.0)	**.040**
	CG	8.0 (6.2 to 12.0)	10.0 (8.2 to 11.9)	1.5 (−1.5 to 3.0)	.292
	P	.132	.863	.080	

(continued)

Table 2. (continued)

		T0, Median (95% CI)	T1, Median (95% CI)	Median Difference[b] (95% CI)	T1 − T0 *P*
Reduced activity	IG	12.0 (8.9 to 13.5)	11.0 (7.9 to 13.7)	−0.5 (−3.0 to 2.0)	.677
	CG	10.5 (7.3 to 13.0)	11.0 (8.0 to 12.6)	0.0 (1.0 to 1.5)	.762
	P	.756	.973	.670	
Reduced motivation	IG	10.0 (7.7 to 11.2)	8.0 (5.6 to 10.2)	−1.3 (−3.5 to 0.5)	.106
	CG	7.5 (5.8 to 10.6)	8.5 (7.2 to 11.6)	1.5 (−0.5 to 3.0)	.073
	P	.468	.314	.183	
Mental fatigue	IG	11.0 (8.1 to 13.3)	9.0 (6.6 to 10.5)	4.2 (−0.0 to 16.7)	**.023**
	CG	7.5 (5.5 to 10.3)	8.0 (6.2 to 10.6)	8.3 (−4.2 to 20.8)	.435
	P	.099	.973	.086	

Abbreviations: CI, confidence interval; COF, center of force; EO, eyes open; EC, eyes closed; P_{max_jump}, maximum power output during countermovement jump; P_{max_CPET}, maximum workload during cardiopulmonary exercise test; $\dot{V}O_{2peak}$, peak oxygen consumption; IAT, individual anaerobic threshold; MFI20, Multidimensional Fatigue Inventory.

[a] Significant results are highlighted in boldface $P < .05$.

[b] Prescribes the treatment effect by point estimation and 95% confidence interval of the Hodges-Lehmann's median differences for paired groups.

[c] Lower value means a higher range of motion.

Table 3. Correlation Coefficients of Changes in Dimensions of Fatigue and Changes in Cardiorespiratory Fitness and Upper Limp Function.[a]

Δ MFI20 Dimensions of Fatigue (Score Max. 20)	Δ P_{max_CPET} (Watt)	Δ $\dot{V}O_{2peak}$ (mL/min)	Δ IAT (Watt)	Δ Abduction (°)	Δ External Rotation (°)	Δ Hand Behind Back Position (cm)	Δ Hand Grip Strength (kg)	Δ Vibration Sense (Scale 0-8)
General fatigue	−.191	.019	.091	−.311	.019	−.132	**−.501***	**−.529***
Physical fatigue	−.289	.251	.409	.020	−.298	.340	**−.594****	**−.449***
Reduced activity	.076	.329	.014	.130	−.104	−.115	−.401	−.355
Reduced motivation	−.179	.096	.376	−.077	−.218	.042	**−.459***	−.101
Mental fatigue	**−.489***	.250	−.220	.223	**−.485***	.357	−.012	−.420

Abbreviations: Δ, T1 − T0; MFI20, Multidimensional Fatigue Inventory; P_{max_CPET}, maximum workload during cardiopulmonary exercise test; $\dot{V}O_{2peak}$, peak oxygen consumption; IAT, individual anaerobic threshold.

[a] Significant results are highlighted in boldface $^{**}P = .01$. $^{*}P = .05$.

increase in maximum performance is accompanied by a decrease in the mental fatigue level and vice versa. Other tested fatigue dimensions were associated with neither maximum nor submaximum CPET values.

Discussion

The aim of this pilot study was to assess the feasibility and effects of handheld vibration training in BC patients during radiotherapy and to evaluate further exercise effects of our intervention.

The excellent training compliance (98%) we observed with no adverse events confirms the feasibility and provides interesting results about handheld vibration training for BC patients' upper limb function: it seems to improve shoulder mobility and hand grip strength and may inhibit the deterioration of vibration sense during radiotherapy. Furthermore, our intervention possesses the potential to reduce the level of fatigue, while functional performance and cardiorespiratory fitness were less affected.

The IG's upper-limb function improved on 3 levels. First, vibration exercises enhanced the affected limb's shoulder mobility. Our results are thus in line with those of Tripp et al,[21] who reported improved glenohumeral internal rotation after acute handheld vibration at 15 Hz. Also, Ferguson et al[22] enhanced shoulder flexibility after upper-body exercises on a vibrating platform at a frequency of 30 Hz. Scarring after surgery, pain-induced nonuse of the joint, and skin irritation during radiotherapy often restrict shoulder ROM.[11] Thus, the shoulder joint benefits merely from using the surrounding muscles becoming re-accustomed to such movements. Vibration within 8 to 12 Hz may relax muscle tension and loosen scarred adhesions due to the wobbling. Furthermore, reports about vibration-induced (25-44 Hz) lower-body flexibility propose that enhanced ROM after vibration exposure may be attributable to mechanisms based on a thermoregulatory effect, increased pain threshold, Golgi tendon organ excitation, and antagonist inhibition.[48-50] As the antagonistic co-contraction of arm muscles is described to proportionally increase with rising vibration frequency (18-42 Hz),[51] we

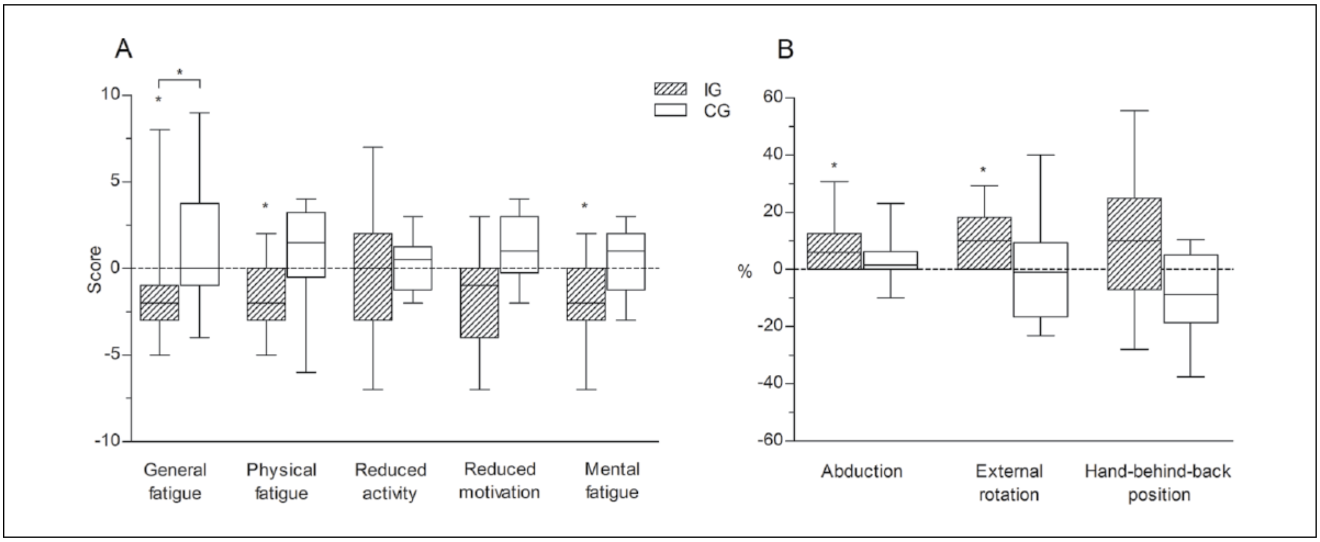

Figure 1. Distribution of changes from T0 to T1 of (A) the MFI20 dimension of fatigue and (B) range of shoulder motion of affected upper limb in IG and CG. Box-and-whisker plots showing the lower quartile (25th percentile), median (50th percentile), upper quartile (75th percentile), and degree of dispersion as 95% confidence interval (95% CI). *Indicates a significant difference (*$P < .05$).

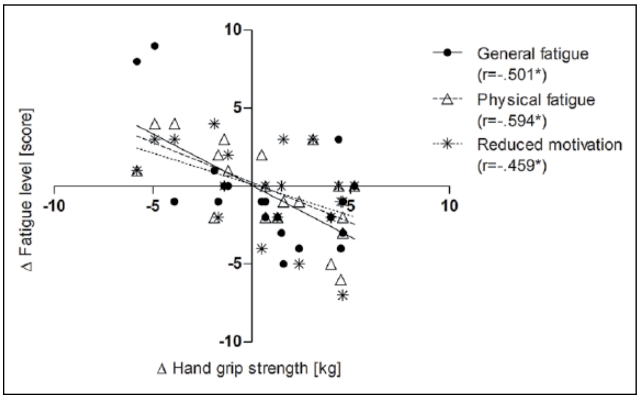

Figure 2. The scatterplot graphically represents the relationship between changes (Δ) of hand grip strength in kg (*x*-axis) versus changes (Δ) of 3 MFI20 dimensions of fatigue (*y*-axis) of IG and CG from T0 to T1. *Indicates a significant correlation (*$P < .05$).

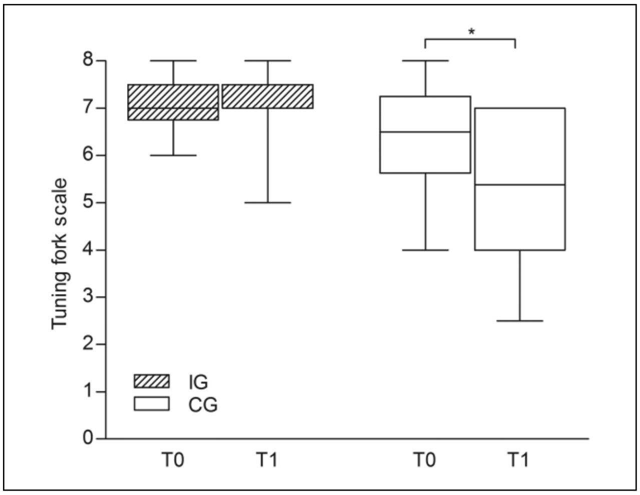

Figure 3. Distribution of IG's and CG's vibration sense at T0 and T1. *Y*-axis presents graduating scale from 0 (no sensitivity) to 8 (highest sensitivity) of tuning fork. Box-and-whisker plots showing the lower quartile (25th percentile), median (50th percentile), the upper quartile (75th percentile), and degree of dispersion as 95% confidence interval (95% CI). *Indicates a significant difference (*$P < .05$).

assume that primarily our vibration exercises ≤22 Hz caused neuromuscular-induced flexibility gains.

WBV in general is known to cause elevated EMG activation by increasing vibration frequency and thus not only lead to acute antagonistic co-contraction that operates as a safety strategy for joint stabilization[52-54] but also results in greater strength.[24] Increased EMG activity via superimposed vibration during exercise was also found for arm muscles[54,55] and seems to be muscle-tension dependent.[54] This indicates that vibration considerably affects strength when superimposed on exercises while adding an additional load.[54] We thus observed strength improvement as a secondary aspect of our intervention's impact on upper-limb function. We assume that especially the active resistance part (22-30 Hz) of the vibration exercises led to increased muscle strength, as patients performed strengthening exercises with a vibrating dumbbell weighing 2.6 kg. The dumbbell's weight may seem marginal, but considering patients' impairments, we observed the need for a pulley system to reduce the dumbbell's weight and ensure correct exercise execution. Our results are in line with Xu et al,[56] who showed improved strength in elbow flexors after 9 weeks of vibration training at 30 Hz twice a week. WBV is generally known to improve neuromuscular performance and strength due to neural adaptations comparable to effects from conventional resistance training.[24]

The third aspect of the exercise effect on upper-limb function is represented by preventing the vibration sense from deteriorating in the affected upper limb. While the CG's vibration sense decreased significantly, the IG's remained consistent. There are indications that an exercise-induced increase in blood flow enhances the overall rate of metabolism, which is associated with a higher level of neurotrophic factors[57,58] that may influence sensory function. It is common knowledge that endurance training leads to cardiovascular adaptations, but vibration exercises are also known to acutely increase blood flow.[59] Furthermore, vibration training, that is, WBV, directly affects the nervous system by inhibiting spinal reflex excitability.[59] Upper-limb vibration training also possesses the potential to stimulate the somatosensory system, as there are indications of improved elbow and wrist joint position sense after handheld vibration.[19,20] We therefore assume that especially the handheld vibration training induced adaptive processes that might have prevented a radiotherapy-caused decline in IG's sensory function as in our CG.

Functional performance may represent a key independent variable for cancer survivors, since functional impairments are associated with shorter survival.[60] In our study, balance exercises led to improved functional performance, represented by increased jump height. There is ample evidence that balance training leads to neurophysiological adaptations resulting in a greater rate of force development relevant to jumping performance.[61-63] Due to the balance tasks, our IG exhibited overall a significantly shorter sway path, both pre- and postintervention, compared to CG associated with a better balance control.[64] Although the CG improved over time and even with no intervention, they remained below the IG's level. Both groups reduced their sway path during the one-leg stance. We assume that the IG found the semitandem stance conditions too easy to trigger adaptations after exercising, while the CG may have exhibited a familiarization effect with the assessments. Overall, the IG demonstrated a better functional performance than the CG, probably due to their younger age and their stronger preference for a physically-active intervention, as we had not randomized the groups' allocation.

In line with other exercise intervention studies during radiotherapy, ours reduced the level of fatigue significantly.[28-31,43] Fatigue is a multidimensional phenomenon[65] and its underlying mechanisms have not been clarified conclusively.[66] However, specific interventions can influence fatigue, for example, exercising[67]; exercising may trigger changes in inflammatory processes and of course improve cardiorespiratory fitness.[66] Although many studies have addressed the effect of mainly endurance exercise on fatigue, few investigated the correlation between the change in fatigue levels and endurance capacity.[67] A Cochrane review identified 2 studies whose authors detected a correlation and 3 studies reporting no association.[67] We observed only a reduction in mental fatigue in our study, along with changes in maximum workload. One might assume that patients with a low mental fatigue level would be quite willing to exhaust themselves. We detected only a marginal overall effect on cardiorespiratory fitness, possibly due to the endurance exercise intensity. Other interventions provide a daily program up to 30 minutes[31] or a longer exercise period (12 weeks).[68] We assume that our intervention's endurance part was too moderate to generate cardiorespiratory adaptations and therefore too weak to affect all the fatigue dimensions. Furthermore, we detected a correlation between upper-limb function, especially hand grip strength and fatigue. In their review, Brown et al[4] conclude that moderate resistance exercises appear more effective in reducing fatigue than low intensive endurance training. This concurs with our results where improved upper-limb function is accompanied by a reduction in the fatigue level. This is an important finding, as Smets et al[69] found that the degree of post-radiation functional disability represented a relevant predictor of fatigue. Also, Cantarero-Villanueva et al[70] reported a negative relationship between handgrip strength and fatigue in BC survivors. However, we cannot exclude a psychosocial effect on fatigue due to the passive control group's having had no social contact with the sports scientists.[43] In general, supervised interventions during BC treatment have proven to be more efficient than home-based programs in terms of fatigue[71] and also in terms of upper-limb dysfunction.[6] Furthermore, supervision is said to ensure a greater adherence,[9] underlined by our excellent training compliance.

We conclude that our exercise intervention was feasible since we observed no adverse events and excellent compliance. Additionally, this pilot study may inspire further investigations, as it yields novel findings about exercising during the radiotherapy of BC patients: The present intervention program reduced the fatigue level, and interestingly demonstrated a considerable effect on upper-limb function in terms of improved shoulder ROM, hand grip strength, and sensory function possibly due to vibration-induced neuromuscular adaptations. Thus, our pilot study may provide the basis for randomized controlled trials to confirm these promising results.

Authors' Note

Research materials of this article can be accessed by contacting the corresponding author.

Acknowledgments

We acknowledge the cooperation and training implementation of sports therapists and physiotherapists of the Sports Oncology

Division in Department of Medicine I, Medical Center, University of Freiburg, and we thank all the patients and control group participants for their collaboration. We also thank J. Scholber for patient recruitment and gratefully acknowledge the cooperation with the Department of Radiation Oncology. Furthermore, we thank M. Baumstark for statistical assistance, B. Hildenbrand for his support, and Novotec Medical GmbH for providing us with their Galileo UpX vibrating dumbbell.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The authors received no financial support for the research and authorship of this article. The article processing charge was funded by the German Research Foundation (DFG) and the University of Freiburg in the funding program Open Access Publishing.

ORCID iD

Hartmut Bertz https://orcid.org/0000-0002-3805-8123

References

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*. 2012;62:220-241.
2. Ewertz M, Jensen AB. Late effects of breast cancer treatment and potentials for rehabilitation. *Acta Oncol*. 2011;50:187-193.
3. Jereczek-Fossa BA, Marsiglia HR, Orecchia R. Radiotherapy-related fatigue. *Crit Rev Oncol Hematol*. 2002;41:317-325.
4. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2011;20:123-133.
5. 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.
6. McNeely ML, Campbell K, Ospina M, et al. Exercise interventions for upper-limb dysfunction due to breast cancer treatment. *Cochrane Database Syst Rev*. 2010;(6):CD005211.
7. Senkus-Konefka E, Jassem J. Complications of breast-cancer radiotherapy. *Clin Oncol (R Coll Radiol)*. 2006;18:229-235.
8. De Groef A, Van Kampen M, Dieltjens E, et al. Effectiveness of postoperative physical therapy for upper-limb impairments after breast cancer treatment: a systematic review. *Arch Phys Med Rehabil*. 2015;96:1140-1153.
9. Hwang JH, Chang HJ, Shim YH, et al. Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. *Yonsei Med J*. 2008;49:443-450.
10. So HS, Kim IS, Yoon JH, Park OJ. Effects of aerobic exercise using a flex-band on physical functions & body image in women undergoing radiation therapy after a mastectomy [in Korean]. *Taehan Kanho Hakhoe Chi*. 2006;36:1111-1122.
11. Lee TS, Kilbreath SL, Refshauge KM, Pendlebury SC, Beith JM, Lee MJ. Pectoral stretching program for women undergoing radiotherapy for breast cancer. *Breast Cancer Res Treat*. 2007;102:313-321.
12. Grisold W, Grisold A, Löscher WN. Neuromuscular complications in cancer. *J Neurol Sci*. 2016;367:184-202.
13. Hershman DL, Lacchetti C, Dworkin RH, et al; American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32:1941-1967.
14. Pradat PF, Delanian S. Late radiation injury to peripheral nerves. *Handb Clin Neurol*. 2013;115:743-758.
15. Kibar S, Aras MD, Delialioğlu SU. The risk factors and prevalence of upper extremity impairments and an analysis of effects of lymphoedema and other impairments on the quality of life of breast cancer patients. *Eur J Cancer Care (Engl)*. 2017;26. doi:10.1111/ecc.12433.
16. Streckmann F, Zopf EM, Lehmann HC, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. *Sports Med*. 2014;44:1289-1304.
17. Verhulst ALJ, Savelberg HHCM, Vreugdenhil G, Mischi M, Schep G. Whole-body vibration as a modality for the rehabilitation of peripheral neuropathies: implications for cancer survivors suffering from chemotherapy-induced peripheral neuropathy. *Oncol Rev*. 2015;9:263.
18. Schönsteiner SS, Bauder-Mißbach H, Benner A, et al. A randomized exploratory phase 2 study in patients with chemotherapy-related peripheral neuropathy evaluating whole-body vibration training as adjunct to an integrated program including massage, passive mobilization and physical exercises. *Exp Hematol Oncol*. 2017;6:5.
19. Tripp BL, Faust D, Jacobs P. Elbow joint position sense after neuromuscular training with handheld vibration. *J Athl Train*. 2009;44:617-623.
20. Radovanovic S, Day SJ, Johansson H. The impact of whole-hand vibration exposure on the sense of angular position about the wrist joint. *Int Arch Occup Environ Health*. 2006;79:153-160.
21. Tripp BL, Eberman LE, Dwelly PM. Handheld vibration effects shoulder motion. *Int J Sports Med*. 2009;30:868-871.
22. Ferguson SL, Kim E, Seo DI, Bemben MG. Comparing the effects of 3 weeks of upper-body vibration training, vibration and stretching, and stretching alone on shoulder flexibility in college-aged men. *J Strength Cond Res*. 2013;27:3329-3334.
23. Houston MN, Hodson VE, Adams KKE, Hoch JM. The effectiveness of whole-body-vibration training in improving hamstring flexibility in physically active adults. *J Sport Rehabil*. 2015;24:77-82.
24. Rittweger J. Vibration as an exercise modality: how it may work, and what its potential might be. *Eur J Appl Physiol*. 2010;108:877-904.
25. Neil-Sztramko SE, Kirkham AA, Hung SH, Niksirat N, Nishikawa K, Campbell KL. Aerobic capacity and upper limb

strength are reduced in women diagnosed with breast cancer: a systematic review. *J Physiother*. 2014;60:189-200.

26. Fong DYT, Ho JWC, Hui BPH, et al. Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ*. 2012;344:e70.
27. Wiskemann J, Schmidt ME, Klassen O, et al. Effects of 12-week resistance training during radiotherapy in breast cancer patients. *Scand J Med Sci Sports*. 2017;27:1500-1510.
28. Aghili M, Farhan F, Rade M. A pilot study of the effects of programmed aerobic exercise on the severity of fatigue in cancer patients during external radiotherapy. *Eur J Oncol Nurs*. 2007;11:179-182.
29. Battaglini CL, Mihalik JP, Bottaro M, et al. Effect of exercise on the caloric intake of breast cancer patients undergoing treatment. *Braz J Med Biol Res*. 2008;41:709-715.
30. 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.
31. Mock V, Frangakis C, Davidson NE, et al. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. *Psychooncology*. 2005;14:464-477.
32. Potthoff K, Schmidt ME, Wiskemann J, et al. Randomized controlled trial to evaluate the effects of progressive resistance training compared to progressive muscle relaxation in breast cancer patients undergoing adjuvant radiotherapy: the BEST study. *BMC Cancer*. 2013;13:162.
33. den Ouden MEM, Schuurmans MJ, Brand JS, Arts IEMA, Mueller-Schotte S, van der Schouw YT. Physical functioning is related to both an impaired physical ability and ADL disability: a ten year follow-up study in middle-aged and older persons. *Maturitas*. 2013;74:89-94.
34. Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. *Br J Cancer*. 2015;112:194-198.
35. Granacher U, Muehlbauer T, Gruber M. A qualitative review of balance and strength performance in healthy older adults: impact for testing and training. *J Aging Res*. 2012;2012:708905.
36. Zech A, Hübscher M, Vogt L, Banzer W, Hänsel F, Pfeifer K. Balance training for neuromuscular control and performance enhancement: a systematic review. *J Athl Train*. 2010;45:392-403.
37. Streckmann F, Kneis S, Leifert JA, et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Ann Oncol*. 2014;25:493-499.
38. Tofthagen C, Visovsky C, Berry DL. Strength and balance training for adults with peripheral neuropathy and high risk of fall: current evidence and implications for future research. *Oncol Nurs Forum*. 2012;39:E416-E424.
39. Schwenk M, Grewal GS, Holloway D, Muchna A, Garland L, Najafi B. Interactive sensor-based balance training in older cancer patients with chemotherapy-induced peripheral neuropathy: a randomized controlled trial. *Gerontology*. 2016;62:553-563.
40. Scharhag-Rosenberger F, Becker T, Streckmann F, et al. Studien zu körperlichem Training bei onkologischen Patienten: Empfehlungen zu den Erhebungsmethoden. *Dtsch Z Für Sportmed*. 2014;65:304-313.
41. Borg G. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377-381.
42. Granacher U, Muehlbauer T, Taube W, Gollhofer A, Gruber M. Sensorimotor training. In: Cardinale M, Newton R, Nosaka K, eds. *Strength and Conditioning: Biological Principles and Practical Applications*. 1st ed. San Francisco, CA: Wiley-Blackwell; 2011:399.
43. Steindorf K, Schmidt ME, Klassen O, et al. Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life. *Ann Oncol*. 2014;25:2237-2243.
44. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing*. 2011;40:423-429.
45. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol*. 2008;9:757-765.
46. Wasserman K. *Principles of Exercise Testing & Interpretation: Including Pathophysiology and Clinical Applications*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.
47. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI): psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39:315-325.
48. Feland JB, Hawks M, Hopkins JT, Hunter I, Johnson AW, Eggett DL. Whole body vibration as an adjunct to static stretching. *Int J Sports Med*. 2010;31:584-589.
49. Issurin VB, Liebermann DG, Tenenbaum G. Effect of vibratory stimulation training on maximal force and flexibility. *J Sports Sci*. 1994;12:561-566.
50. Karatrantou K, Gerodimos V, Dipla K, Zafeiridis A. Whole-body vibration training improves flexibility, strength profile of knee flexors, and hamstrings-to-quadriceps strength ratio in females. *J Sci Med Sport*. 2013;16:477-481.
51. Rodríguez Jiménez S, Benítez A, García González MA, Feliu GM, Maffiuletti NA. Effect of vibration frequency on agonist and antagonist arm muscle activity. *Eur J Appl Physiol*. 2015;115:1305-1312.
52. Pollock RD, Woledge RC, Mills KR, Martin FC, Newham DJ. Muscle activity and acceleration during whole body vibration: effect of frequency and amplitude. *Clin Biomech (Bristol, Avon)*. 2010;25:840-846.
53. Ritzmann R, Gollhofer A, Kramer A. The influence of vibration type, frequency, body position and additional load on the neuromuscular activity during whole body vibration. *Eur J Appl Physiol*. 2013;113:1-11.
54. Mischi M, Cardinale M. The effects of a 28-Hz vibration on arm muscle activity during isometric exercise. *Med Sci Sports Exerc*. 2009;41:645-653.
55. Bosco C, Cardinale M, Tsarpela O. Influence of vibration on mechanical power and electromyogram activity in human arm flexor muscles. *Eur J Appl Physiol Occup Physiol*. 1999;79:306-311.
56. Xu L, Cardinale M, Rabotti C, Beju B, Mischi M. Eight-week vibration training of the elbow flexors by force modulation:

effects on dynamic and isometric strength. *J Strength Cond Res*. 2016;30:739-746.

57. Park JS, Höke A. Treadmill exercise induced functional recovery after peripheral nerve repair is associated with increased levels of neurotrophic factors. *PLoS One*. 2014;9:e90245.
58. Cooper MA, Kluding PM, Wright DE. Emerging relationships between exercise, sensory nerves, and neuropathic pain. *Front Neurosci*. 2016;10:372.
59. Games KE, Sefton JM. Whole-body vibration influences lower extremity circulatory and neurological function. *Scand J Med Sci Sports*. 2013;23:516-523.
60. Brown JC, Harhay MO, Harhay MN. Patient-reported versus objectively-measured physical function and mortality risk among cancer survivors. *J Geriatr Oncol*. 2016;7:108-115.
61. Bruhn S, Kullmann N, Gollhofer A. The effects of a sensorimotor training and a strength training on postural stabilisation, maximum isometric contraction and jump performance. *Int J Sports Med*. 2004;25:56-60.
62. Gruber M, Gollhofer A. Impact of sensorimotor training on the rate of force development and neural activation. *Eur J Appl Physiol*. 2004;92:98-105.
63. Taube W. Neurophysiological adaptations in response to balance training. *Dtsch Z Für Sportmed*. 2012;63:273-277.
64. Kneis S, Wehrle A, Freyler K, et al. Balance impairments and neuromuscular changes in breast cancer patients with chemotherapy-induced peripheral neuropathy. *Clin Neurophysiol*. 2016;127:1481-1490.
65. Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. *Oncologist*. 1999;4:1-10.
66. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11:597-609.
67. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev*. 2012;(11):CD006145.
68. Milne HM, Wallman KE, Gordon S, Courneya KS. Effects of a combined aerobic and resistance exercise program in breast cancer survivors: a randomized controlled trial. *Breast Cancer Res Treat*. 2008;108:279-288.
69. Smets EM, Visser MR, Willems-Groot AF, Garssen B, Schuster-Uitterhoeve AL, de Haes JC. Fatigue and radiotherapy: (B) experience in patients 9 months following treatment. *Br J Cancer*. 1998;78:907-912.
70. 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;91:774-782.
71. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. *Clin Oncol (R Coll Radiol)*. 2010;22:208-221.