Doctoral thesis submitted to
the Faculty of Behavioural and Cultural Studies
Heidelberg University
in partial fulfillment of the requirements of the degree of
Doctor of Philosophy (Dr. phil.)
in Sport Science

Title of the thesis

Impact of exercise therapy in patients undergoing breast cancer treatment

presented by
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year of submission
2015

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Danksagung

Mein besonderer Dank gilt Dr. Joachim Wiskemann. Als Leiter der Gruppe “Bewegung und Krebs” der Forschungsabteilung Präventive Onkologie am Nationalen Centrum für Tumorerkrankungen hat er meine Promotion in allen Projektphasen intensiv betreut, mich beraten und mir stets die beste Unterstützung zukommen lassen.

Mein herzlicher Dank gilt auch Prof. Dr. Gerhard Huber, der diese Doktorarbeit seitens des Instituts für Sport und Sportwissenschaft der Universität Heidelberg in einer für mich schwierigen Situation angenommen hat und mir bei Fragen sehr hilfreich zur Seite stand.

Mein Dank gilt allen Mitarbeitern der Forschungsabteilung Präventive Onkologie am Nationalen Centrum für Tumorerkrankungen/Deutschen Krebsforschungszentrum, die mir die erfolgreiche Arbeit dort ermöglichten. Insbesondere möchte ich mich bei Prof. Dr. Friederike Scharhag-Rosenberger bedanken. Sie hat mich stets in wichtigen Projektphasen beratend unterstützt.

Ein besonderes Anliegen ist es mir, den Teilnehmern der Trainingsstudien zu danken. Ich habe bei meiner Arbeit viel von ihnen lernen und erfahren dürfen. Die Schicksale der Patienten haben mich oft sehr berührt und ich hoffe, dass Sie von unserer Forschung persönlich weiterhin profitieren.

Ich danke meiner Familie und meinen Freunden, die mich gestützt haben. Zutiefst dankbar bin ich meiner Ehefrau Mareike, die mit mir den sehr spannenden und teilweise etwas ungewissen Weg nach Heidelberg gegangen ist. Sie war in jeder Lebenslage an meiner Seite und hat mir alle Kraft gegeben, die Arbeit zu einem erfolgreichen Ende zu bringen. Liebe Mareike – herzlichen Dank dafür.

Wichtig ist nicht die Menge des Wissens, sondern die Güte. Man kann sehr viel wissen, dabei aber nicht einmal das Nötigste.

Lew Tolstoi (* 1828 - † 1910)

List of publications in peer-reviewed journals

I. Publication
Klassen, Oliver, [Schmidt, M.E. & Scharhag-Rosenberger, F.] (2014). Cardiorespiratory Fitness in Breast Cancer Patients Undergoing Adjuvant Therapy. *Acta oncologica, 16*, 1. http://www.ncbi.nlm.nih.gov/pubmed/24837860

II. Publication
Klassen, Oliver, [Schmidt, M.E. & Ulrich C.M.] (2015). Muscle Strength in Breast Cancer Patients receiving different Treatment Regimes. submitted

III. Publiaction
Scharhag-Rosenberger, Friederike, [Kühl, R. & Klassen, O.] (2015). Exercise Training Intensity Prescription in Breast Cancer Survivors: Validity of Current Practice and Specific Recommendations. *Journal of cancer survivorship.* http://www.ncbi.nlm.nih.gov/pubmed/25711667

IV. Publication
Steindorf, Karen*, [Schmidt, M.E*. & Klassen, O.] (2014). Randomized Controlled Trial of Resistance Training in Breast Cancer Patients Receiving Adjuvant Radiotherapy. Results on cancer-related fatigue and quality of life. *Annals of Oncology*. http://www.ncbi.nlm.nih.gov/pubmed/25096607

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List of abbreviations

ACSM	American college of sports medicine
ADS	German depression scale based on Center for Epidemiological Studies
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
$APHR_{max}$	Age-predicted maximum heart rate
BC	Breast cancer
BEATE	German acronym for “Bewegung und Entspannung als Therapie gegen Erschöpfung”
BEST	German acronym for “Bewegung und Entspannung für Brustkrebspatientinnen unter Strahlentherapie”
BIA	Bioelectrical Impedance analysis
BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence interval
CPET	Cardiopulmonary exercise test
CRF	Cancer related fatigue;
CT	Chemotherapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ES	Effect size
EX	Exercise group
FAQ	Fatigue Assessment Questionnaire
FI	Muscular fatigue index
FITT	Frequency, intensity, time and type
Hb	Haemoglobin
HR50	Heart rate during exercise at 50 watts
HR_{peak}	Peak heart rate
HR_{max}	Maximal heart rate

HRR	Heart rate reserve
INVEST	INVestigation of the Effects of Strength Training
IQR	Interquartile range
ITT	Intent-to-treat
MD	Mean differences
MET	Metabolic equivalent
MIPT	Maximal isokinetic peak torque
MVIC	Maximal voluntary isometric contraction
N•m	Newton meter
NCI	National Cancer Institute
NCT	National Center for Tumor Diseases
PEACE	Physical Exercise Across the Cancer Experience
PMR	Progressive muscle relaxation
PPO	Peak power output
QoL	Quality of life
RC	Relaxation control group
RCT	Randomized controlled trial
RER	Respiratory exchange ratio
RM	Repetition maximum
ROM	Range of motion
VE/VO_2	Ventilatory equivalent for oxygen
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake
VO_2R	Oxygen uptake reserve
VT	Ventilatory threshold

Preliminary remark

This cumulative dissertation is classified in the interface area of sports science and oncology. To a large extent the work is based on two large randomized, controlled intervention studies BEST and BEATE and a healthy cohort study INVEST (term 2011-2014). All studies have been approved by the ethics committee of the University of Heidelberg, Germany. The author of this work was the recipient of a PhD scholarship from German Cancer Research Center, Heidelberg, Germany. He was significantly responsible for BEST study coordination, including recruitments, collection of all clinically relevant data, anthropometric assessments, execution and evaluation of physical performance tests. In the BEATE and INVEST studies he eminently participated in data collection, execution and evaluation of physical performance tests.

For his research the author was awarded the “2014 American College of Sports Medicine (ACSM) International Student Award“ at the 61st ACSM Annual Meeting in Orlando, Florida, USA in May 2014. At the 23rd Rehabilitation Research Colloquium, Karlsruhe, Germany in March 2014 he received the Second Poster-Award for presentation of cardiorespiratory fitness in breast cancer patients. From German Cancer Society he received a Travel Award to the 31st Annual German Cancer Congress, Berlin, Germany in February 2014. German Sport University Cologne awarded him for the Best Poster as recognition for an outstanding scientific contribution at the “3rd International Symposia on Exercise and Physical Activity in Oncology”, Cologne, Germany in May 2012.

1. General introduction

1.1. Epidemiology of breast cancer

With approximately 70,000 new cases per year, breast cancer is by far the most common cancer in women (Figure 1) in Germany ("Krebs in Deutschland 2009/2010," 2013). Additionally, there are about 6,500 ductal carcinomata in situ, a pre-cancer form of breast cancer. Based on current incidence rates, about one in eight women is diagnosed with breast cancer during their lifetime. Approximately every fourth patient is younger than 55 at diagnosis; one in ten is under 45 years old. Despite the increase in incidence rates, today fewer women die from breast cancer.

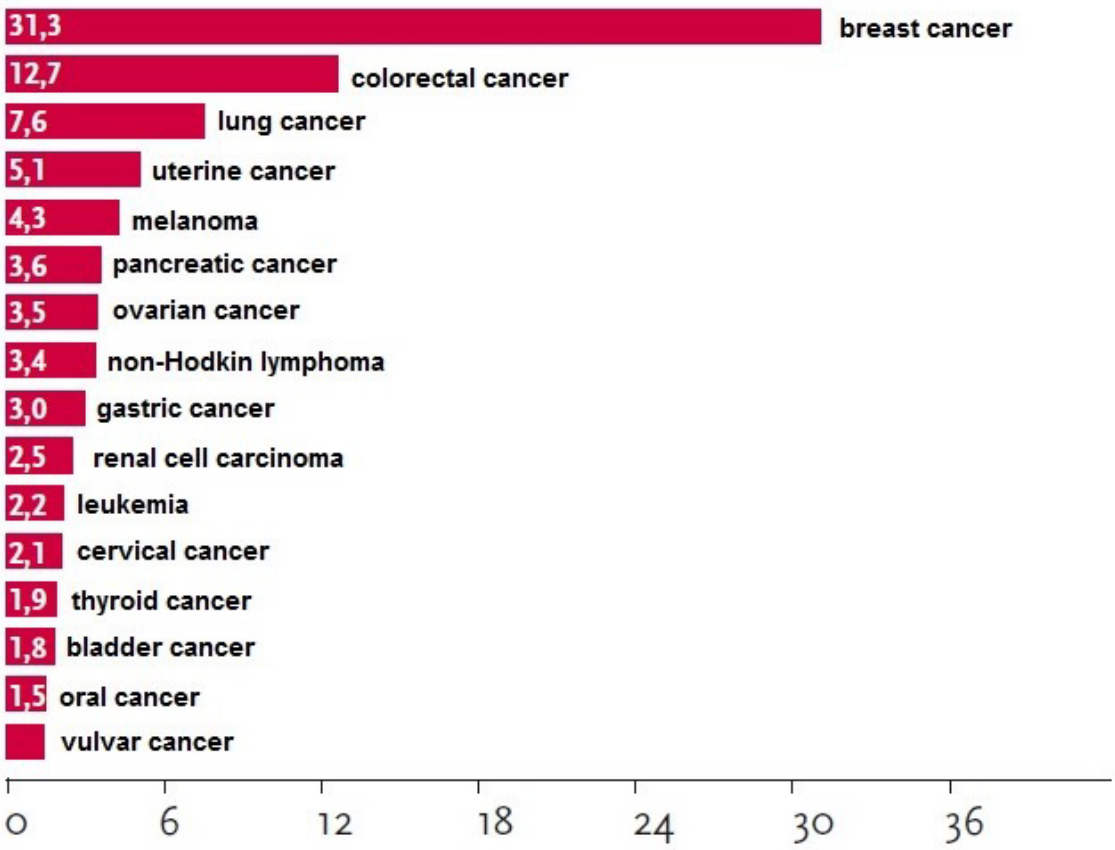

Figure 1. Percentage of the most common tumor types of women in all new cancer cases in Germany 2010 (adapted from Krebs in Deutschland 2009/2010. (2013))

Overall, the age-standardized 5-year relative survival rate was 83%, based on data

from the Cancer Registry of several states, which included female patients diagnosed with invasive breast cancer between 2000 and 2009 (Figure 2).

In 30 European countries breast cancer mortality has declined in median of 19% in the years from 1989 to 2006 (Autier et al., 2010). The chances of survival have improved significantly due to advances in cancer therapy. But these treatments leave patients with many side effects that affect their quality of life, and a persistently unhealthy lifestyle (e.g. smoking, alcohol consumption, low physical activity, obesity) can lead to earlier non-breast-cancer-specific and breast-cancer-specific mortality (Villasenor et al., 2012). Some side effects can be solved with the help of targeted medicine. But there are many adverse effects which can best be solved by physical exercise. This must be tested in exercise-oncology research.

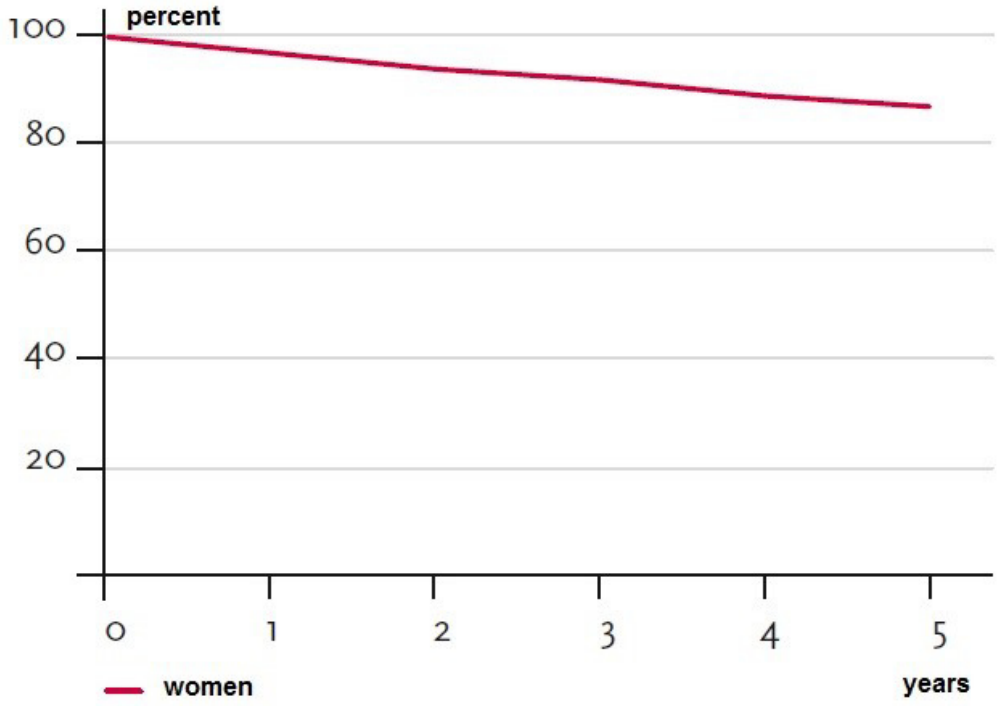

Figure 2. Relative survival rate after primary breast cancer diagnosis, Germany 2009-2010 (adapted from Krebs in Deutschland 2009/2010. (2013))

1.2. Exercise-oncology research

Significant progress has been made in the field of exercise-oncology research over the past three decades. Epidemiological studies observed that physical activity has salutary benefits in patients undergoing cancer therapy, producing improvements in their quality of life (Ulrich, Steindorf, & Berger, 2012). Additionally, observational studies in this field show a reduced risk of recurrence, and they associate physical activity with improved overall survival before the diagnosis and even after (see Figure 3) (Ballard-Barbash et al., 2012; Schmidt, Chang-Claude, et al., 2013). However, a systematic review showed some evidence that breast cancer specific survival rates can be associated with exercise only after diagnosis (Ibrahim & Al-Homaidh, 2011). Schmid and Leitzmann's meta-analysis (Schmid & Leitzmann, 2014) indicated that

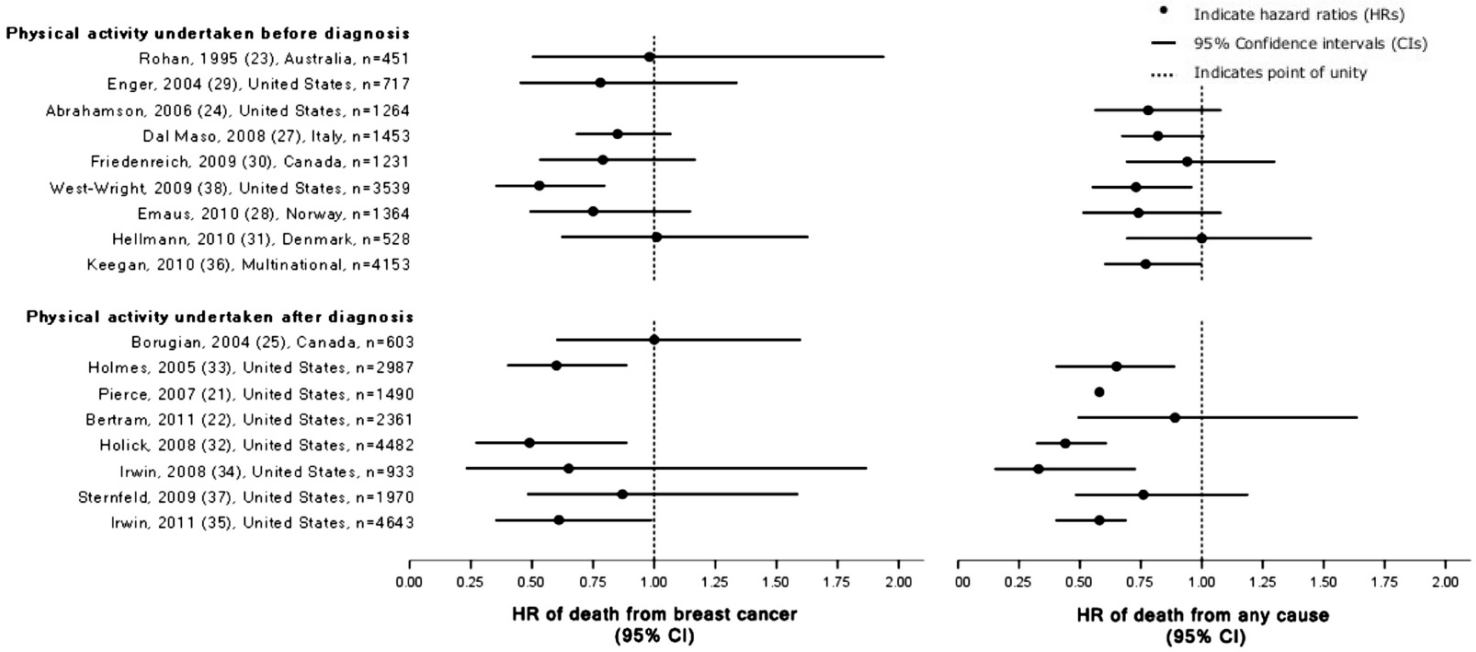

Figure 3. Forest plot of risk estimates from observational studies of physical activity and mortality outcomes in breast cancer survivors. (Ballard-Barbash 2012)

moderate physical activity of 150 min/week after diagnosis is associated with a 24% reduction in total mortality among breast cancer survivors and a 28% decreased risk of total mortality. So far we had aforementioned observational studies that provided information about survival outcome. But only intervention trials are able to show proof

of causality and explain the underlying mechanisms and benefit of exercise therapy in cancer patients. According to Friedenreich et al. (2001) recommendations for more evidence, which can be emerged from randomized controlled trials (RCT) in this field, in the last decade more RCT have been done, which give the next level of scientific evidence to develop public health recommendations on exercise therapy for cancer patients. Overall the study quality needs to be improved. Jones and Alfano (2013) summarized and listed future prospects in a recent review about the ongoing studies examining exercise across the cancer experience in this field.

Based on a framework entitled Physical Exercise Across the Cancer Experience (PEACE) time point (Figure 4) (Courneya & Friedenreich, 2001), the authors mention some major gaps in current knowledge. They identified a total of 82 independent clinical studies. Most ongoing studies are being conducted either during or following adjuvant therapy in women with breast cancer, with exercise interventions following standard exercise prescription guidelines consisting of moderate exercise training three days per week. But many of the studies were poorly designed. Several randomized trials in this field have compared an exercise intervention with standard care. Some of them have a small sample size, do not measure with gold standard methods, and have relatively heterogeneous sub-groups of patients in terms of cancer type and current or prior anticancer therapy, which is of course dependent on the primary study question. The biggest limitation in the majority of these studies is that they did not adequately design the exercise prescription in accordance with the principles of exercise training, nor did they adequately report the components of the exercise prescription or adherence to the exercise prescription (K. L. Campbell, Neil, & Winters-Stone, 2012).

To understand the potential benefits of exercise-oncology research during cancer therapy, one must consider the adverse effects of cancer treatment. During the coping phase and at the beginning of the rehabilitation phase, the side effects of the cancer therapy play the most important role (see Figure 4). Adverse effects may be acute, resolving over a period of days, weeks, or months, or they may be persistent, lasting years after treatment is completed or even for the remainder of the patient's life. Some adverse effects can begin during treatment and persist long after treatment has finished. There are five types of breast cancer therapy (Chemotherapy treatment, radiation, surgery, hormonal therapies, and targeted therapies). The therapy chosen is dependent on cancer type and size, and the age and fitness of the patient. The cancer treatment can have many side effects, directly or indirectly, on breast cancer patients' fitness and quality of life (see Figure 5), where especially cancer related fatigue is the most reported side effect during and after treatment (Mustian et al., 2007).

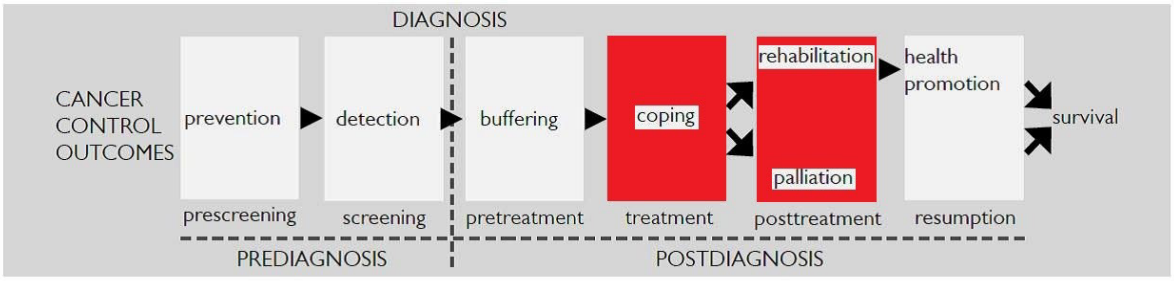

Figure 4. The Framework PEACE: an organizational model for examining physical exercise across the cancer experience (adapted from Courneya and Friedenreich 2001). Contribution of my thesis is labeled with red areas.

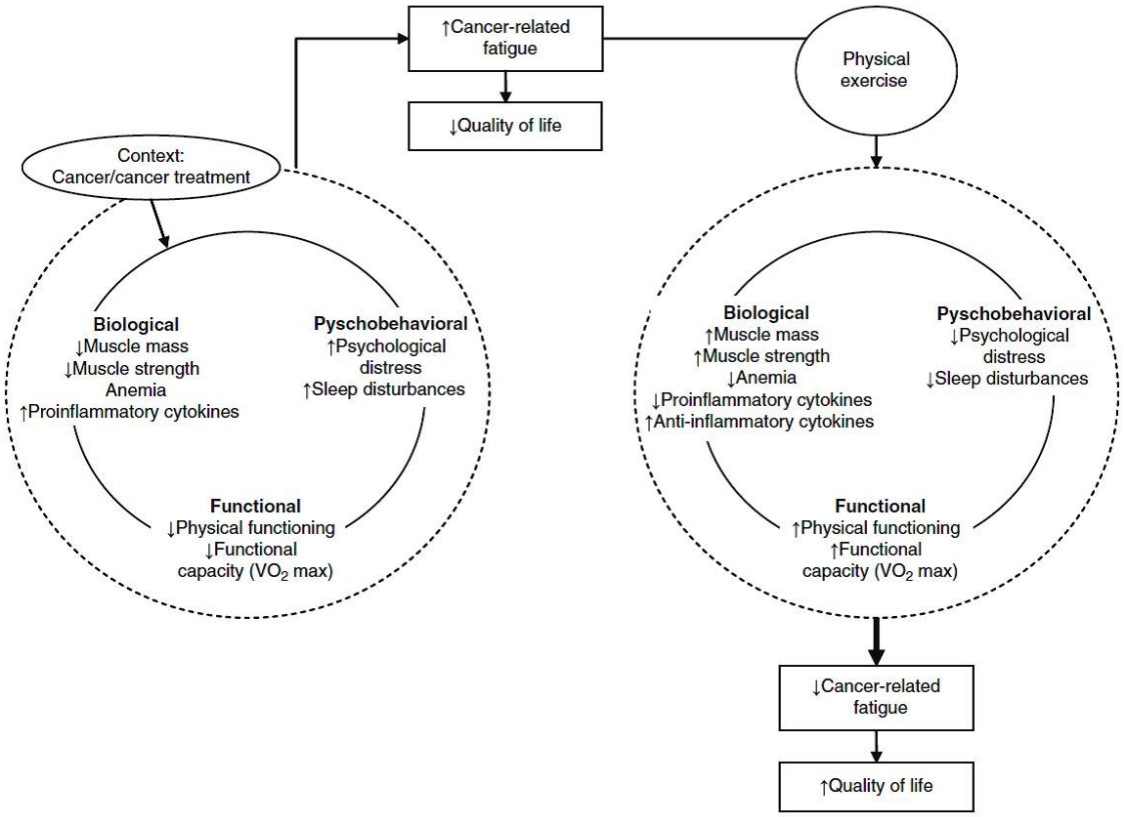

Figure 5. A biobehavioral model for the study of exercise interventions for cancer-related fatigue (adapted from Al-Majid and Gray, 2009)

Some of the acute and persistent effects of cancer treatments can be positively influenced by physical exercise. It has positive effects on the cardiovascular, musculoskeletal, nervous, endocrine, and immune systems and additionally, a number of beneficial factors like body composition, body weight, cancer related fatigue, pain, sleep disturbance, and positive influence on the symptoms of lymphedema have already been shown in cancer patients (Baumann et al., 2013). Exercise training and physical activity also have a positive psychosocial effect, which can decrease adverse effects, such as depression, anxiety, low self-esteem, and the psychological components of cancer-related fatigue. Here, most studies of cancer survivors analyzed the effect of aerobic exercise training, some a combination of aerobic exercise and resistance training (Mishra et al., 2012). A

minority of them performed resistance training (Strasser, Steindorf, Wiskemann, & Ulrich, 2013).

1.3. Exercise & breast cancer research overview

In first decades of research in "exercise and breast cancer" the main knowledge was provided by observational epidemiological studies. One of the leading research group was around C. M. Friedenreich, who also reviewed the association between physical activity and breast cancer risk in studies of the last three decades (Lynch, Neilson, & Friedenreich, 2011). They found that physical activity is associated with decreased breast cancer risk via multiple interrelated biologic pathways that may involve adiposity, sex hormones, insulin resistance, adipokines, and chronic inflammation. The evidence of observational studies was important, but since the year around 2000 it was argued that for additional progress to be made in this field, there need to be a bigger focus on intervention studies of physical activity and breast cancer (Friedenreich, 2001). The limitations of observational studies include crude and incomplete exercise supervision and assessment, lack of consideration of the underlying biological mechanisms that are operative, as well as a lack of adequate control for confounding and effect modification.

A recent review of Battaglini et al. (2014) describes the development of research in the field of breast cancer and exercise training from its beginnings in the year 1989. Twenty-five years ago, intervention trials started to examine the role of exercise in breast cancer patients and survivors. Early studies (MacVicar, Winningham, & Nickel, 1989; Mock et al., 1994; Mock et al., 1997; Schwartz, 1999; Winningham, MacVicar, Bondoc, Anderson, & Minton, 1989) were conducted with

breast cancer patients during adjuvant therapy. Most of them were home-based intervention trials that analyzed the effect of aerobic training. The major modes of aerobic exercise included walking, swimming, and cycling.

Since the year 2000, more studies have been designed which met the criteria of randomized controlled trials, and the outcomes during cancer therapy were more focused (A. Campbell, Mutrie, White, McGuire, & Kearney, 2005; Cheema & Gaul, 2006; Courneya et al., 2003; Herrero et al., 2006; Hutnick et al., 2005; Kim, Kang, Smith, & Landers, 2006; Kolden et al., 2002; Pinto, Frierson, Rabin, Trunzo, & Marcus, 2005; Schwartz, 2000; Segal et al., 2001; Turner, Hayes, & Reul-Hirche, 2004). Over the following years, study design shifted to focus on a combination of aerobic and resistance training. But in the first two decades of exercise oncology research, no study was designed that focused exclusively on resistance training. The first studies that used resistance exercise training as the main mode of exercise were performed after 2007. From that time on, more supervised studies were performed. For studies that used resistance training, weight machines, free weights, elastic bands, tubing, therapeutic balls, and resistance-training circuits were used. In most studies, weight machines were applied, and the resistance training consisted of exercises for all major muscle groups. Exercises to strengthen the upper body included bench press (pectoralis), chest cross (horizontal flexion of the shoulder joint), shoulder press (trapezius), pull downs (latissimus dorsi), biceps curls, triceps extensions, and exercises for the abdominal muscles (sit-ups). Lower body exercises included the leg press (quadriceps femoris). There is as yet a limited number of studies evaluating the efficacy of resistance training. I am aware of 11 RCT studies that use resistance training alone or as part of the study design (Ahmed, Thomas, Yee, & Schmitz, 2006; C. Battaglini et al., 2007; Cormie et al., 2013; Courneya et al.,

2007; Musanti, 2012; Schmitz, Ahmed, Hannan, & Yee, 2005; Schmitz, Ahmed, et al., 2010; Schwartz & Winters-Stone, 2009; Schwartz, Winters-Stone, & Gallucci, 2007; Winters-Stone et al., 2012; Winters-Stone et al., 2011a; Winters-Stone et al., 2013), aside from the BEST- (Potthoff et al., 2013) and BEATE-Studies (Schmidt, Wiskemann, et al., 2013). The average frequency of training was 3 days per week, ranging from 2-5 training sessions per week, with an overall training duration average of 23 weeks (in a range of 3-48 weeks). Each training session lasted 46 min on average, with training sessions ranging from 15-90 min. In those studies also applying aerobic training the intensity varied from 40%-85% of maximum heart rate, 40%-90% of VO_{2peak}, while the intensity for resistance training ranged from 55%-85% of 1RM. The most commonly evaluated variables in breast cancer and exercise studies were cardiorespiratory function, body composition, muscular strength, depression, overall quality of life, and (cancer-related) fatigue. Follow up studies several years after an intervention and survival data is rare. A first follow up investigation by Courneya et al. (2014) supports the findings of the observational studies that physical activity after a breast cancer diagnosis is associated with improved cancer outcomes.

Overall the exercise training in studies of the past 25 years appears to be safe for most breast cancer patients and improvements in physiological, psychological, and functional parameters can be attained with regular participation in moderate intensity exercise. Regarding efficacy a significant improvement in cardiorespiratory function was observed for the exercise group, when using estimated measurements derived from a submaximal treadmill testing protocol or directly using a cycle ergometer. Significant decrease in meters walked during a 6 min and 2 km walk tests was observed in the control group while improvements in a 12 min walk test

approached significance in the exercise group (C. L. Battaglini et al., 2014). To detect the cardiorespiratory fitness outcome of breast cancer survivors the estimated and/or submaximal treadmill VO_{2peak} or 12-min walk test were used in most of the studies. Regarding a quick overview about the endurance performance the 12-min walk test is enough. But in order to be able to describe the cardiorespiratory fitness more precisely there are important disadvantages of the treadmill tests with patients. First of all patients have to get used to walk or run on a treadmill, before testing. The second point is that there is a bias of patient selection. Patients, whose fitness is bad, are physically not able to perform the test on a treadmill. And finally the estimation of VO_{2peak} after submaximal test is not valid enough for breast cancer patients, because the VO_{2peak} data is based on calculations out of healthy individuals.

Therefore, we used the cardiorespiratory fitness test on a bicycle to solve the mentioned difficulties in the I. Publication (Klassen et al., 2014). With one of the biggest study population (N=222) in this research field we were able to measure with gold standard method the cardiorespiratory fitness of breast cancer patients during adjuvant treatment.

This review also reports that in the exercise group also positive body composition changes were observed, with the most notorious changes in significant decrease in body fat and increase in lean body mass, whereas control group experience significant increases in body fat and a trend toward an increase in overall body mass. There is also a clear trend towards greater improvement in quality of life, reduction in (cancer-related) fatigue and depression in the exercise group when compared to the control group.

Unfortunately, very limited and no definite conclusion could be drawn until now regarding the effects of resistance training programs as the main mode of exercise

training (Cormie et al., 2013; Winters-Stone et al., 2012; Winters-Stone et al., 2011b; Winters-Stone et al., 2013) and those that used resistance training as an arm part of the study design (Courneya et al., 2007; Musanti, 2012; Schwartz et al., 2007). Regarding the effects of resistance training on changes in body composition, a significant increase in body mass and lean body mass was observed in the exercise group. Upper body strength significantly increased in the exercise group while for lower body, strength significantly increased in both, exercise and control groups with a greater increase observed in the exercise group. No significant changes in quality of life were observed in either the exercise and control groups. Very limited and no definite conclusion can be drawn at this time regarding the effects of resistance training on fatigue, depression, and overall quality of life in breast cancer patients.

This is why we did the research in this area with better design quality (controlling for many variables that can confound study results such as type, frequency, intensity of exercise, different types of cancer treatments, age of patients, previous fitness levels, and other co-morbidities that can further diminish the tolerability for exercise participation and large samples sizes) to be able to do more precise exercise guidelines (Potthoff et al., 2013).

Furthermore, muscle function in these studies is mostly measured in a pragmatic way with commonly estimated one repetition maximum strength test (1-RM) (Strasser et al., 2013). The advantage is that it can be carried out for most muscle groups, but the limitation is a strong risk of praxis adaption. The most precise form to measure the strength is with an isokinetic device, but it is expensive and needs an expert to handle with this device (Christensen et al., 2014). In our BEST and BEATE study we were able to use this gold standard strength testing procedure and we reported this strength results in both studies at the baseline of the recruitment

(II. Publication) and summarized them in the IV publication (Steindorf et al., 2014) after completion of the intervention in the BEST study.

Furthermore in breast cancer research there is a lack of knowledge about the training prescriptions and the intensity. The roundtable of the American College of Sports Medicine (Schmitz, Courneya, et al., 2010) recommend the 150 min/wk with moderate or 75 min/wk with vigorous intensity for endurance and/or resistance training, taking into account the individual possibility for cancer patients. But no one investigated the moderate or vigorous intensity for breast cancer patients during adjuvant therapy adequately. Consequently, it is unknown which objective measured intensity needs to be recommend for breast cancer patients. The ACSM's guidelines for exercise prescription in healthy adults offers intensity classifications in percentages of oxygen uptake reserve (%VO_2R), heart rate reserve (%HRR), maximal oxygen uptake (%VO_{2max}), and maximal heart rate (%HR_{max}). Therefore, we used these parameters to investigate whether the ACSM's exercise intensity classification is valid for breast cancer survivors (III. Publication) (Scharhag-Rosenberger et al., 2015).

Cancer related fatigue, as one of the most debilitating multidimensional symptoms was not completely understood yet. Many breast cancer patients receive radiotherapy. During and after radiotherapy breast cancer patients often suffer from cancer-related fatigue which frequently impairs quality of life (QoL) (Lee et al., 2008; Noal et al., 2011; Taunk et al., 2011). Physical activity for breast cancer patients has been reported to decrease fatigue, to improve emotional well-being and to increase physical strength. Our study adds to the current knowledge with respect to three understudied areas: (1) exercise was performed during radiotherapy; (2) the type of training was resistance exercise, and (3) the control group also received a group-

based program so that physiological effects beyond psychosocial group-related effects were studied. Our aim was to assess the effects of a 12-week supervised resistance training on fatigue and physical fitness in breast cancer patients during adjuvant radiotherapy within a randomized controlled trial (BEST study). With my contribution the results are expected to enlarge more concrete exercise guidelines for breast cancer patients in the IV. Publication (Steindorf et al., 2014). Overall, with my contributions we addressed the aforementioned gaps in the framework PEACE, especially during breast cancer treatment.

2. Background of the included data and work for the thesis

The BEST study (clinicaltrials.gov: NCT01468766) is a randomized, controlled intervention trial investigating the effects of a 12-week supervised progressive resistance training program in 160 patients with breast cancer undergoing adjuvant radiotherapy. BEST is an acronym derived from the German term „Bewegung und Entspannung für Brustkrebspatientinnen unter Strahlentherapie“. To exclude a possible group dynamic psycho-social bias, a group-based progressive muscle relaxation training (PMR) was offered at the same temporal extent (see Figure 6) as a control intervention. The BEST study has six assessment time points (T0-T5), beginning several weeks after surgery and ending with follow-up measurements after one year for each patient. The primary endpoint is cancer-related fatigue; secondary

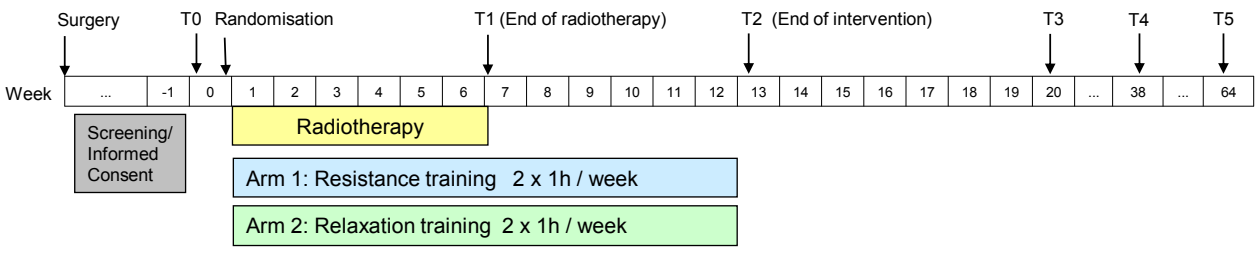

Figure 6. Design of the BEST-study

endpoints include cardiorespiratory fitness and isokinetic versus isometric performance. Additionally, immunological and inflammatory parameters, quality of life (QoL), depression, and cognitive capacity were analyzed. Biomarkers located in serum, plasma, PBMCs, urine and saliva have been collected and Tregs have been analyzed (week 0, 7, 13). Cardiopulmonary exercise tests and comprehensive strength measures (IsoMed2000), as well as bioelectrical impedance analysis (BIA), were performed pre- and post-intervention and at 6 and 12 months after. Additionally, comprehensive clinical, socio-demographic and lifestyle data has been collected.

The recruitment goal of n=160 patients was successfully reached by March 2013. Only four patients dropped out of the trial before the post-intervention assessment. Primary endpoint data is available in 95% of participants. The follow-up period ended in September 2014 with a participation rate of 90% six months post-intervention, and an expected 82% after one year. These results contribute to a

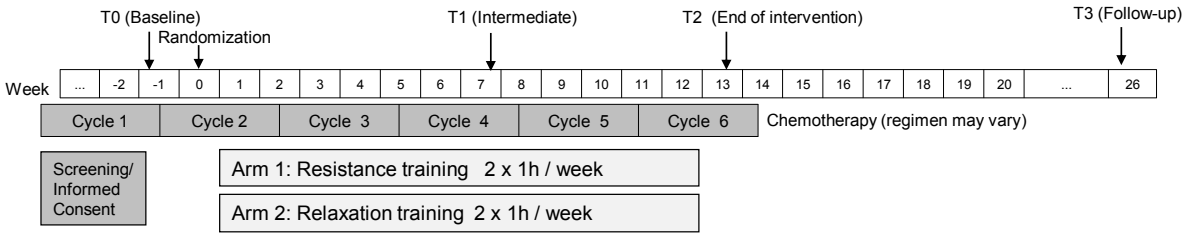

Figure 7. Design of the BEATE-study

better understanding of the physiological and psychosocial effects and the biological mechanisms of resistance training and the impact of diverse cancer treatment regimes and types. The ultimate goal is the implementation of optimized intervention programs to reduce fatigue, improve quality of life, and potentially improve the prognosis.

The second part of my data was from the patients enrolled in a second randomized controlled trial, the BEATE-study with the german acronym “Bewegung

und Entspannung als Therapie gegen Erschöpfung" (ClinicalTrials.gov NCT01106820), which has a similar study design (Figure 7) and equal intervention form, but focuses on breast cancer patients under adjuvant chemotherapy with four assessment time points (T0-T3), with the last follow-up measurement after 6 months. More details of the study are presented elsewhere (Schmidt, Wiskemann, et al., 2013). The safety of the resistance training during chemotherapy is monitored in the same way as in the BEST-study during radiotherapy.

For comparisons 26 healthy women from with matched age range were recruited from Rhein-Neckar area, Germany for the INVEST study. This study name is an acronym for INVestigation of the Effects of Strength Training. The participants performed the same tests and resistance training program.

As a study coordinator and doctoral candidate, I was responsible for the BEST study for three years and managed most of the organizational aspects of the trial. Furthermore, I recruited most of the patients with the help of the oncologists and did most of the physical performance assessments (about 700 cardiopulmonary exercise tests and 700 isokinetic strength tests, including BEATE and INVEST study). Clinical assessments like bioelectrical impedance analysis, waist-to-hip-ratio measuring, trial making tests, and anthropometrical measurements were also a part of my work. Regular phone calls for appointments and motivational aspects were needed to complete the intervention and assessments of the patients in order to get the best possible adherence rate. My responsibility included the distribution and mailing of the Fatigue Assessment Questionnaire (FAQ) and questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30). I was also involved in the development and implementation of new study-related standard operating procedures of the group "Physical Activity and Cancer".

Two peer-reviewed publications authored by me, and two which I co-authored, have been submitted or already accepted. For the co-authored articles, beyond patient recruitments in the BEST study and my data collection, I supported the first authors with my ideas, data cleansing to establish a uniform and improved data quality, and/or verified the regression analysis and created graphs and wrote comments for the manuscripts.

2.1. Aim and objectives of the thesis

The main objective of the studies presented in this thesis is to provide further insight into the impact of breast cancer during therapy on cancer related fatigue, physical fitness, benefits of resistance exercise during cancer treatment and how exercise prescriptions can be adapted for breast cancer patients. To meet this aim the first publication describes the cardiorespiratory fitness in breast cancer patients at different time points of anti-cancer treatment. The second publication investigates the muscle strength in breast cancer patients in different adjuvant treatment settings and compares it with data from healthy individuals. The third publication investigated whether and how intensity prescriptions for healthy adults by guidelines of the American College of Sports Medicine need to be adapted for breast cancer survivors. The fourth publication evaluates the efficacy of the randomized controlled trial of resistance training beyond the psychosocial benefits associated with group-based relaxation intervention on cancer-related fatigue and quality of life in breast cancer patients receiving adjuvant radiotherapy. After the manuscripts the studies and results are discussed.

2.1.1. Main research questions

- How is the cardiorespiratory fitness affected in breast cancer patients at different time points of cancer treatment? (I. Publication)
- How is the muscular strength affected in breast cancer patients during cancer treatment? (II. Publication)
- Does moderate and vigorous intensity aerobic exercise prescription of the American College of Sports Medicine guidelines fit for patients after breast cancer treatment? (III. Publication)
- Is the 12-week resistance training more effective on cancer related fatigue beyond possible psychosocial effects of a group-based intervention among breast cancer patients during adjuvant radiotherapy? (IV. Publication)

2.1.2. Secondary questions

- Are the physical fitness tests (I. & II. Publication) and progressive resistance training during radiotherapy safe and are they feasible for breast cancer patients (III. & IV. Publication)?
- Which factors might be responsible for the cardiorespiratory fitness and muscular strength breast cancer patients undergoing cancer therapy? (I. & II. Publication)?
- Is resistance training more beneficial for quality of life, depression, cognitive function, and early radiotoxicity, as well as on physical fitness, including muscle strength, cardiorespiratory fitness and flexibility? (IV. Publication)

2.2. Interrelation and the context for my research framework

For my thesis, data from two randomized controlled clinical exercise intervention trials and from a healthy control trial with resistance training intervention were used: the BEST, BEATE (ClinicalTrials.gov ID NCT01468766 and NCT01106820) and INVEST study. The high quality of the study designs, the use of gold standard measurement methods and identical surveys helped to get a better validity and reliability for my publication. The following four publications address questions about the impact of exercise therapy and physical fitness in breast cancer patients during or shortly after completion of different cancer treatments. In the first two publications, muscular function and cardiorespiratory fitness were investigated to understand the impact of cancer treatment on fitness and how clinically relevant breast cancer patient groups differ from each other. This data was compared with healthy individuals to determine their physical limitations. These results imply an analysis, presented in the third publication, which evaluated the required adaptations for endurance training intensity prescription in breast cancer patients immediately after cancer treatment, taking the American College of Sports Medicine's exercise guidelines into account. These guidelines must be proved, because their intensity recommendations for breast cancer patients are based on data for healthy individuals. The last article raised the question of how cancer-related fatigue can be improved beyond the psychosocial group effects, which was a lack in previous studies. Therefore a randomized controlled trial with progressive resistance training vs. relaxation training (control group) was analyzed in order to provide a non-biased effect of the resistance training. All of the studies presented aim to give physicians, sport scientists, and all other therapists involved the ability to inform their patients about the importance of fitness status and the benefits of exercise therapy during

cancer treatment. Furthermore, the purpose of my thesis is to provide more knowledge for an optimal exercise therapy as an integral part of cancer treatment for breast cancer patients.

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4. Cardiorespiratory fitness in breast cancer patients undergoing adjuvant therapy

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Acta oncologica 2014 Oct;53(10):1356-65.

Abstract

Purpose

The aim of this work was to investigate cardiorespiratory fitness in breast cancer patients at different time points of anti-cancer treatment.

Patients and Methods

Non-metastatic breast cancer patients (n=222, mean age 55 years) were categorized into four subgroups according to their treatment status. Cardiopulmonary exercise testing (CPET) was used to measure patients' cardiorespiratory fitness, including oxygen delivery and metabolic muscle function. Testing was performed by bicycle ergometry, and maximal oxygen uptake (VO_{2peak}) was measured. Heart rate during exercise at 50 watts (HR50) was assessed as a cardiocirculatory parameter and ventilatory threshold (VT) was used as an indicator of the O_2 supply to muscle. Analysis of covariance was used to estimate the impact of different cancer treatments on cardiorespiratory fitness with adjustment for clinical factors.

Results

Submaximal measures were successfully assessed in 220 (99%) and 200 (90%) patients for HR50 and VT, while criteria for maximal exercise testing were met by 176 patients (79%), respectively. The mean VO_{2peak} was 20.6±6.7 ml/kg/min, mean VT 10.7±2.9 ml/min/kg and mean HR50 112±16 beats/min. Chemotherapy was significantly associated with decreased VO_{2peak}, with significantly lower adjusted mean VO_{2peak} among patients post adjuvant chemotherapy compared to patients with no chemotherapy or those who just started chemotherapy regime (all $p<0.01$). Patients post adjuvant chemotherapy reached only 63% of the VO_{2peak} level expected for their age- and BMI-category (mean VO_{2peak} 15.5±4.8 ml/kg/min). Similarly, HR50

was significantly associated with treatment. However, VT was not associated with treatment.

Conclusion

Breast cancer patients have marked and significantly impaired cardiopulmonary function during and after chemotherapy. Hereby, chemotherapy appears to impair cardiorespiratory fitness by influencing the oxygen delivery system rather than impacting metabolic muscle function. Our findings underline the need of exercise training in breast cancer patients to counteract the loss of cardiorespiratory fitness during the anti-cancer treatment.

Background

Breast cancer–specific survival has substantially improved over the past decades. In the United States, the relative survival rate is about 89% at 5 years after breast cancer diagnosis (Howlader et al., 2011). Nevertheless, there are concerns about morbidity and mortality, particularly related to cardiovascular fitness. To date, cardiovascular disease mortality is more common among breast cancer survivors than breast cancer-related mortality among women who were 66 years or older (Patnaik, Byers, DiGuiseppi, Dabelea, & Denberg, 2011). An important predictor of cardiovascular events and all-cause mortality is cardiorespiratory fitness, as shown in healthy individuals and clinical populations including breast cancer patients after anti-cancer treatment (Blair et al., 1996; Peel et al., 2009). Poor cardiorespiratory fitness also has direct consequences on the performance of everyday tasks and thus impacts quality of life.

The gold standard of measuring cardiorespiratory fitness is cardiopulmonary exercise testing (CPET) (American Thoracic & American College of Chest, 2003). This method determines the overall cardiovascular and respiratory function during exercise, yielding the peak oxygen uptake (VO_{2peak}) as a maximal performance measure. In cancer patients, the oxygen system can be adversely affected by chemotherapy. Effects of chemotherapeutic agents on the respiratory, cardiac, blood, vascular, or skeletal muscle functions have been observed or hypothesized, potentially contributing to the impairment of cardiorespiratory fitness (Lakoski, Eves, Douglas, & Jones, 2012). Cardiorespiratory function is not routinely measured at any stage of breast cancer treatment, and CPET is scarcely used in clinical settings (L. W. Jones, Eves, Haykowsky, Joy, & Douglas, 2008). Although low VO_{2peak} measures have been observed in intervention studies across the breast cancer survivorship

continuum (Bourke et al., 2013), to our knowledge, there is very limited information on the impact of cancer therapy on cardiorespiratory fitness using gold standard testing methods.

Therefore, this study investigated maximal and submaximal cardiorespiratory fitness parameters among 222 non-metastatic breast cancer patients at the beginning of chemotherapy, after completion of chemotherapy, or without chemotherapy, using the gold standard for cardiorespiratory measurement. We compared cardiorespiratory capacity of these patient groups adjusted for clinical relevant parameters and compared them to healthy women with the same age and BMI. The role of cancer therapy was investigated.

Patients and Methods

Setting and Participants

The data for this analysis were data at enrollment into two randomized controlled exercise trials (baseline testing), the BEATE-Study and the BEST-Study (Potthoff et al., 2013; Schmidt et al., 2013). The studies investigated the effects of a 12 week progressive resistance vs. relaxation training in breast cancer patients undergoing chemotherapy (BEATE-Study) or radiotherapy (BEST-Study). Besides the different treatment modalities, the inclusion/exclusion criteria were equal in both studies. Exact inclusion and exclusion criteria and more details of the trials are presented elsewhere (Potthoff et al., 2013; Schmidt et al., 2013). Included in this analysis were all participants who had completed the baseline assessment by November 2012 (n=222). Both trials were conducted with parallel designs at the National Center for Tumor Diseases (NCT) in Heidelberg, Germany. The University of Heidelberg Ethics Committee has approved both trials and written informed

consent was obtained for all procedures. Women with histologically confirmed stage 0-III primary breast cancer after lumpectomy or mastectomy were eligible for the study. Participants recruited in the BEST-Study had the baseline CPET within 14 days before start of radiotherapy. Of these participants, a majority had not received chemotherapy (n=87), while some had received chemotherapy in the adjuvant (n=25) or neo-adjuvant (n=23) chemotherapy setting. Patients enrolled in the BEATE-Study (n=87) performed baseline CPET at the end of the first or second chemotherapy cycle. Based on the different treatment histories, four subgroups (see Figure 1) could be identified and were analyzed: (1) no chemotherapy, (2) started adjuvant chemotherapy, (3) post neo-adjuvant chemotherapy, (4) post adjuvant chemotherapy.

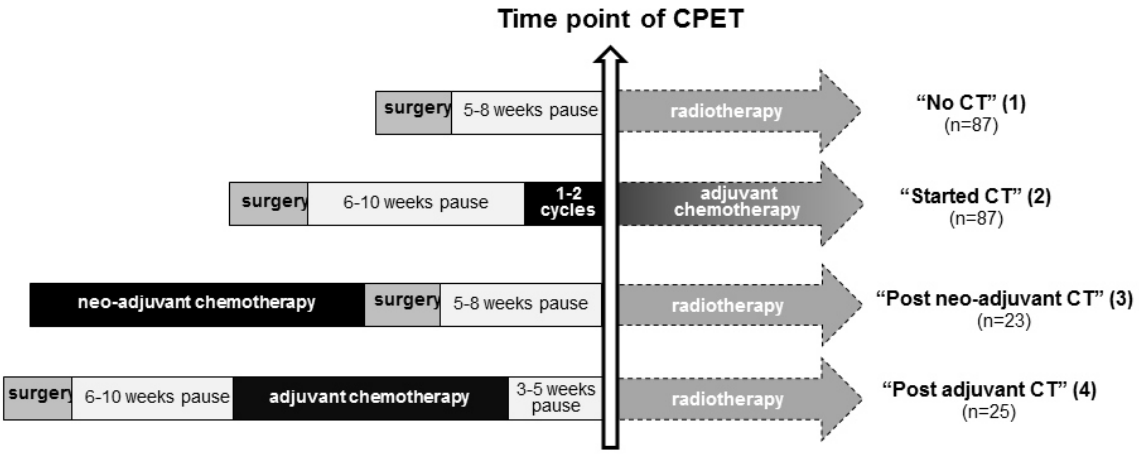


Figure 1: Stratification of study population with respect to breast cancer treatment at time point of cardiopulmonary exercise testing (CPET)

Cardiorespiratory Fitness

CPET was performed using an electronically braked cycle ergometer (ergoselect 100, ergoline, Bitz, Germany). A stepwise incremental exercise protocol was applied starting at 50 watts with increments of 25 watts every two minutes until volitional exhaustion or medical reasons for exercise termination (see below) were reached. Gas exchange was measured using a breath-by-breath gas analysis system (ergostik, Geratherm Respiratory, Bad Kissingen, Germany) which was calibrated according to the instructions of the manufacturer before each test. To monitor patient safety, a 12-lead electrocardiogram (ECG) was applied (CardioPart 12 Blue, amedtec, Aue, Germany) and blood pressure was measured with a standard cuff sphygmomanometer at rest, in the middle of each exercise stage, and three times during the 5 min recover period. Exercise was terminated prematurely in the case of major ECG abnormalities, severe dyspnea or excessive RR increase (> 230 mmHg systolic and/or >110 mmHg diastolic).

VO_{2peak} values were included in the analyses that satisfied at least one of the following criteria for maximal effort was fulfilled: Respiratory Exchange Ratio (RER) >1.1 or Peak Heart Rate (HR_{peak}) ±10% beats of the age-appropriate reference value (Howley, Bassett, & Welch, 1995; Midgley, McNaughton, Polman, & Marchant, 2007). VO_{2peak} values were considered in relation to body weight (ml/min/kg). In addition, absolute values (ml/min) were also given. Peak work rate, defined by the maximal power output (in watt) reached at the end of the highest exercise level, was interpolated if the last exercise stage was not maintained for 2 min. Peak oxygen uptake (VO_{2peak}) and peak respiratory exchange ratio (RER_{peak}) were assessed as the highest 30 second average during exercise.

Submaximal exercise measures during CPET included the ventilatory threshold (VT) and heart rate at 50 watts (HR50). The VT was determined using the V-slope method according to Beaver et al. (Beaver, Wasserman, & Whipp, 1986) as primary criterion and the first rise in the ventilatory equivalent for oxygen (VE/VO_2) as a secondary criterion (Meyer, Lucia, Earnest, & Kindermann, 2005). VT was rated independently by two experienced investigators; in case of different results, the raters re-evaluated the threshold together. The VT was also independently rated as "easily determinable", "difficult to determine" or "indeterminable". In the latter case, VT was not included in the analysis. In the analyses, VT values were considered relative to body weight (ml/min/kg). Resting HR and HR50 were obtained from the ECG recordings as 5 second averages in a sitting position before the start of exercise and at the end of the 50 watt stage, respectively.

Medical and patient demographics

Medical characteristics and treatment modalities were abstracted from medical records. Overall performance status was determined by the attending oncologist using the ECOG (Eastern Cooperative Oncology Group) performance score system at the time of enrollment. Weight and height were measured at baseline. Exercise behavior in the year before breast cancer diagnosis was assessed through self-developed surveys abstracted from the International Physical Activity Questionnaire. Participants were asked about the type, frequency, and duration of exercise (e.g. walking, cycling, and intentional exercise). Furthermore, exercise behavior during adolescence was also recorded classified as "competitive exercise" (for at least 3 years), "non-competitive exercise", or "none".

Statistical Analysis

Clinical and patient demographics, as well as fitness parameters were investigated by descriptive analyses for the entire study population, and also stratified by the four treatment subgroups. Between-group differences were assessed using χ^2 or Fisher's exact test for categorical variables, and using one-way ANOVA for continuous variables. Expected VO_{2peak} values were calculated for each woman from the regression formula presented by Koch et al. (Koch et al., 2009), according to her BMI (<25, ≥25 kg/m^2) and age (in 5-year categories). Differences between the measured and the expected VO_{2peak} values were investigated using paired t-tests. For each patient, the proportion of the observed versus expected VO_{2peak} values was calculated.

Analyses of covariance (ANCOVA) models were used to test different fitness outcomes (i.e. VO_{2peak}, VT, and HR50) with the categorical treatment variable (no chemotherapy / started chemotherapy / post neo-adjuvant chemotherapy / post adjuvant chemotherapy) as independent exposure of interest. The assumptions of homoscedasticity, normality of the residuals, and homogeneity of regression slopes were not violated. The models were adjusted for covariates selected on the basis of the theory of directed acyclic graphs (Textor, Hardt, & Knuppel, 2011), i.e. age at diagnosis, pre-diagnosis BMI (17 to <25, 25 to <30, ≥ 30 kg/m^2), smoking status at diagnosis (current, former, never), sports in the year before diagnosis (none, >0-15 MET*h/wk, >15-35 MET*h/wk, >35 MET*h/wk), sports during adolescence (none, non-competitive, competitive), walking (0-1 5h/wk, >1-3 5h/wk, >3-5 5h/wk, >5h/wk) and cycling (none, >0-1 h/wk, >1-3 h/wk, >3 h/wk) in the year before diagnosis, use of beta-blockers, or pre-existing cardiac diseases. Sensitivity analyses were performed by including hemoglobin level, trastuzumab treatment, hormone treatment,

or type of chemotherapy (taxanes, anthracyclines), where the causal direction of the association with cardiopulmonary fitness is unclear. We also checked the parsimonious models including only significant covariates and those that changed the treatment estimate by >10%, but there were no substantial changes in the results. In addition, type of chemotherapeutic agent was further evaluated among patients who have started chemotherapy using a model that included categorized the variable as taxane use only, anthracycline use only, or use of both.

Results

A total of 222 breast cancer patients with a mean age of 54.8±9.3 years were included in the analyses. Characteristics of the population are presented in Table 1. Patients who received no chemotherapy were slightly older than those in the other treatment groups. Mean hemoglobin (Hb) values were within the normal range, of above 12 g/dl, with the exception of the group post adjuvant chemotherapy, where the mean Hb was 11.4 g/dl indicating NCI-grade 1 anemia. Overall, only 2 patients had a Hb value slightly below 10 g/dl, which is defined as NCI-grade 2 anemia.

TABLE 1: Characteristics of the study population

	TOTAL		No CT		Started CT		Post neo. CT		Post adj. CT		p*
TOTAL n,%	222	100%	87	100%	87	100%	23	100%	25	100%	
Age [years], mean (SD)	54.8	(9.3)	57.3	(8.7)	53.5	(9.6)	51.8	(10.0)	53.5	(7.7)	0.011
Weight [kg], mean (SD)	71.7	(14.1)	73.1	(14.2)	69.6	(12.7)	70.9	(11.4)	74.6	(19.5)	0.28
Height [cm], mean (SD)	165.5	(6.6)	164.7	(7.1)	165.8	(6.5)	165.7	(4.9)	167.4	(6.4)	0.29
BMI at baseline, mean (SD)	26.2	(4.9)	27.0	(5.2)	25.3	(4.4)	25.9	(4.5)	26.5	(5.9)	0.16
Hemoglobin [g/dl], mean (SD)	12.8	(1.2)	13.5	(0.9)	12.3	(1.1)	12.8	(0.9)	11.4	(1.0)	<.0001
Resting HR, mean (SD)	82.6	(14.5)	77.9	(12.8)	85.3	(14.2)	80.8	(10.3)	91.6	(18.3)	<.0001
Days since surgery, mean (SD)	66.6	(51.2)	44.2	(13.0)	58.9	(29.1)	59.2	(55.5)	177.8	(51.8)	<.0001
Days since CT end, mean (SD)	54.8	(49.1)	n.a.		n.a.		80.2	(55.5)	27.1	(15.9)	0.0001
Stage, n (%) 0	15	6.8%	12	13.8%	1	1.1%	2	8.7%	0	0.0%	<.0001
1	101	45.5%	57	65.5%	29	33.3%	8	34.8%	7	28.0%	
2	80	36.0%	18	20.7%	43	49.4%	9	39.1%	10	40.0%	
3	26	11.7%			14	16.1%	4	17.4%	8	32.0%	
ECOG, n (%) 0	190	85.6%	77	88.5%	74	85.1%	19	82.6%	20	80.0%	0.21
1	24	10.8%	8	9.2%	7	8.0%	4	17.4%	5	20.0%	
2	1	0.5%	1	1.1%	0	0.0%	0	0.0%	0	0.0%	
missing	7	3.2%	1	1.1%	6	6.9%	0	0.0%	0	0.0%	
Taxane therapy, n (%)	82	36.9%	n.a.		34	39.1%	23	100.0%	25	100.0%	<.0001
Anthracycline therapy, n (%)	119	53.6%	n.a.		74	85.1%	22	95.7%	23	92.0%	0.43
Herceptin therapy, n (%)	28	12.6%	n.a.		19	21.8%	4	17.4%	5	20.0%	0.89
Hormone therapy, n (%)	65	29.3%	47	54.0%	0	0.0%	8	34.8%	10	40.0%	<.0001
Beta-blocker use, n (%)	35	15.8%	15	17.2%	10	11.5%	4	17.4%	6	24.0%	0.45
Smoking before diagnosis, n (%)	38	17.1%	16	18.4%	16	18.4%	5	21.7%	1	4.0%	0.31
Walking before diagnosis, n(%)											0.052
0-1 h/wk	46	20.7%	14	16.1%	24	27.6%	5	21.7%	3	12.0%	
>1-3 h/wk	70	31.5%	26	29.9%	25	28.7%	10	43.5%	9	36.0%	
>3-5 h/wk	46	20.7%	14	16.1%	25	28.7%	3	13.0%	4	16.0%	
>5h/wk	47	21.2%	27	31.0%	10	11.5%	4	17.4%	6	24.0%	
missing	13	5.9%	6	6.9%	3	3.4%	1	4.3%	3	12.0%	
Cycling before diagnosis, n(%)											0.26
none	77	34.7%	33	37.9%	25	28.7%	10	43.5%	9	36.0%	
>0-1 h/wk	76	34.2%	26	29.9%	32	36.8%	7	30.4%	11	44.0%	
>1-3 h/wk	42	18.9%	17	19.5%	18	20.7%	6	26.1%	1	4.0%	
>3h/wk	19	8.6%	8	9.2%	10	11.5%	0	0.0%	1	4.0%	
missing	8	3.6%	3	3.4%	2	2.3%	0	0.0%	3	12.0%	
Sports before diagnosis, n (%)											0.048
none	75	33.8%	38	43.7%	19	21.8%	11	47.8%	7	28.0%	
>0-9 MET*h/wk	53	23.9%	23	26.4%	19	21.8%	5	21.7%	6	24.0%	
>9-21 MET*h/wk	45	20.3%	13	14.9%	25	28.7%	4	17.4%	3	12.0%	
>21 MET*h/wk	43	19.4%	12	13.8%	21	24.1%	3	13.0%	7	28.0%	
missing	6	2.7%	1	1.1%	3	3.4%	0	0.0%	2	8.0%	
Sports in adolescence, n (%)											0.078
no sports	83	37.4%	35	40.2%	29	33.3%	8	34.8%	11	44.0%	
non-competitive	87	39.2%	41	47.1%	30	34.5%	10	43.5%	6	24.0%	
competitive	47	21.2%	10	11.5%	26	29.9%	5	21.7%	6	24.0%	
missing	5	2.3%	1	1.1%	2	2.3%			2	8.0%	

Abbreviations: BMI, body mass index; HR, heart rate; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group (performance status); MET, metabolic equivalent; SD, standard deviation.

* One-way ANOVA for continuous variables, Chi^2 or Fisher's exact test for categorical variables.

The mean duration of exercising in the CPET was 6 min 53 s, which is valid to determine the VO_{2peak} (Midgley, Bentley, Luttikholt, McNaughton, & Millet, 2008). Of the sample population, 176 patients (79.3%) exercised until exhaustion and fulfilled the criteria for maximal effort, therefore were included in the analysis of maximal exercise measures. On the other hand, 46 patients (20.7%) did not fulfill the criteria for maximal effort. In 18 cases (8.1%), exercise was terminated prematurely for medical reasons: 7 patients (3.2%) demonstrated an excessive increase in blood pressure, 3 patients (1.4%) demonstrated new ECG abnormalities, 1 (0.5%) patient experienced severe dyspnea, and 7 patients (3.2%) experienced orthopedic problems, such as knee or back pain. However, no major adverse event occurred. An additional 28 patients (12.6%) reported problems with the face mask, had poor compliance or experienced other volitional reasons to terminate the CPET before exhaustion was reached. VT was indeterminable in 22 out of 222 cases (9.9%) as a result of high/low ventilation or due to above mentioned medical abort criteria. In 109 cases (49.1%), VT was easily determinable, while 91 (41.0%) were deemed difficult to determine.

The peak and submaximal exercise measures are summarized in Table 2. The mean VO_{2peak} was lowest among patients post adjuvant chemotherapy (15.5±4.8 ml/min/kg) and highest among patients who had just started chemotherapy (23±7.1 ml/min/kg). The VT was also highest among patients who had just started chemotherapy (11.4±3.4 ml/min/kg), but did not differ substantially between the other three groups (p=0.21).

Table 2: Maximal (peak) and submaximal fitness parameters, mean (SD)

		TOTAL		No CT		Started CT		Post neo. CT		Post adj. CT	
Peak fitness measures	**n**	**mean**	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**
VO_{2peak} relative [ml/min/kg]	176	20.6	(6.7)	19.8	(5.4)	23.0	(7.1)	19.2	(6.8)	15.5	(4.8)
VO_{2peak} absolute [ml/min]	176	1416	(415)	1405	(374)	1544	(424)	1312	(353)	1076	(340)
Peak work rate [W]	176	111	(28)	112	(27)	118	(27)	107	(24)	87	(24)
Peak RER	176	1.18	(0.09)	1.15	(0.08)	1.17	(0.07)	1.22	(0.09)	1.23	(0.11)
Peak HR [beats/min]	176	157	(18)	154	(16)	161	(17)	157	(22)	151	(20)
Submaximal fitness measures											
VT relative [ml/min/kg]	200	10.7	(2.9)	10.3	(2.4)	11.4	(3.4)	10.3	(2.8)	10.0	(2.1)
VT absolute [ml/min]	200	748	(163)	742	(145)	769	(196)	721	(137)	721	(115)
HR at 50 watts [beats/min]	220	112	(16)	107	(13)	115	(15)	114	(16)	119	(19)

Abbreviations: CT, chemotherapy; RER, respiratory exchange ratio; SD, standard deviation; VO_{2peak}, peak oxygen consumption; VT, ventilatory threshold; HR, heart rate

The mean HR50 was highest among those post adjuvant chemotherapy with a tendency of tachycardia in this group (see Table 1) and lowest in the group without chemotherapy. The biggest increases from resting HR to HR50 were observed among patients in post neo-adjuvant and adjuvant chemotherapy groups.

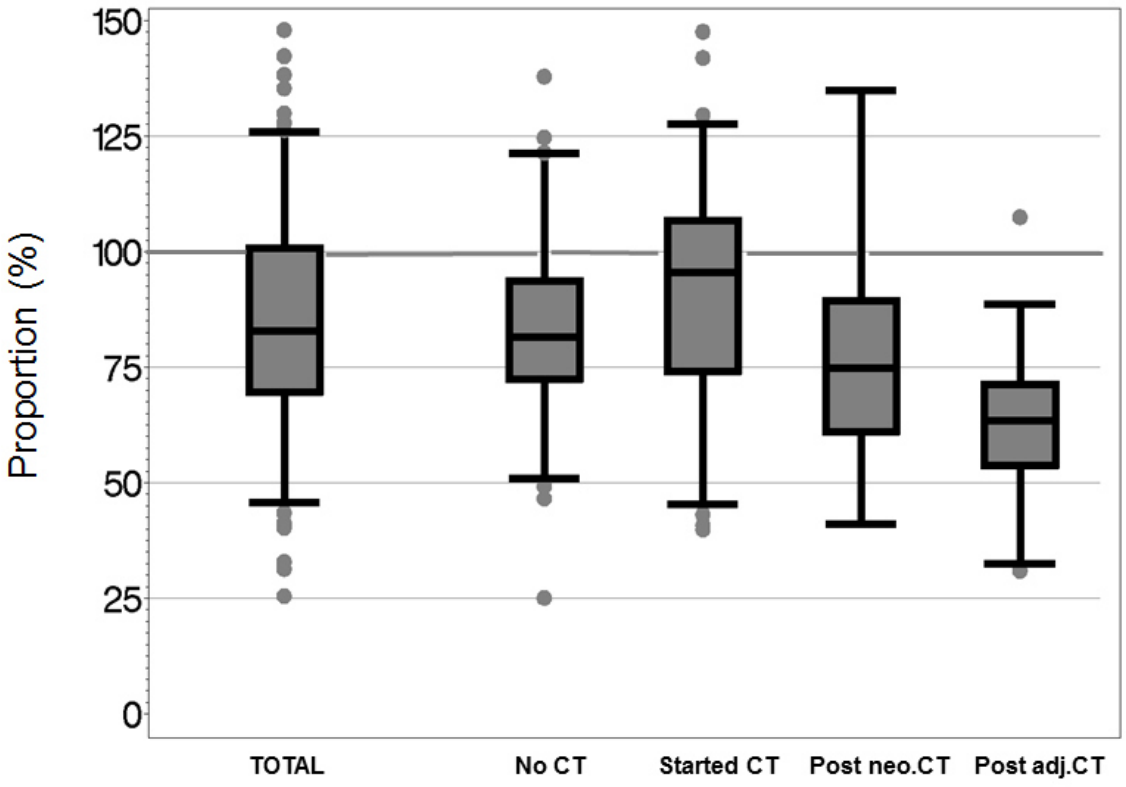
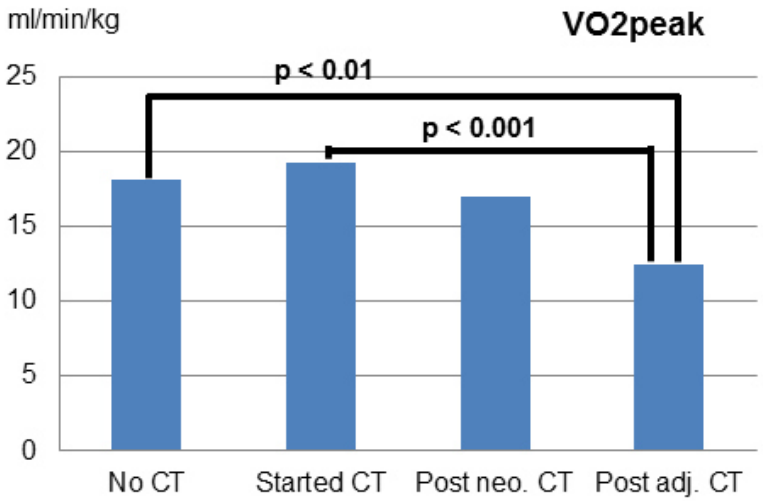
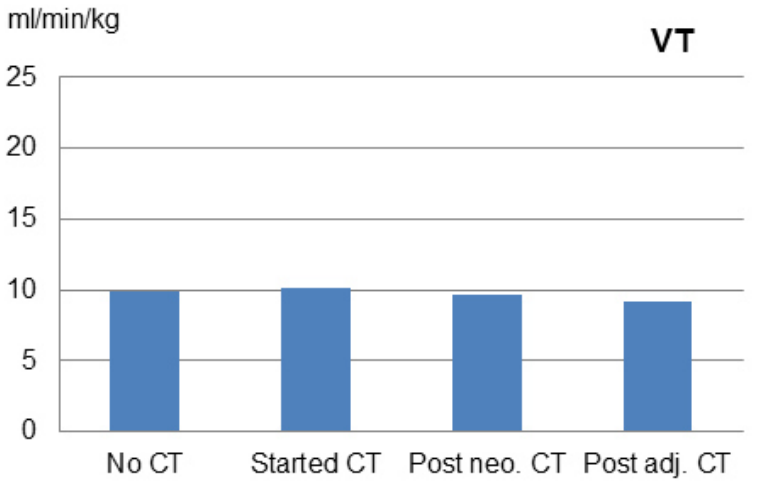
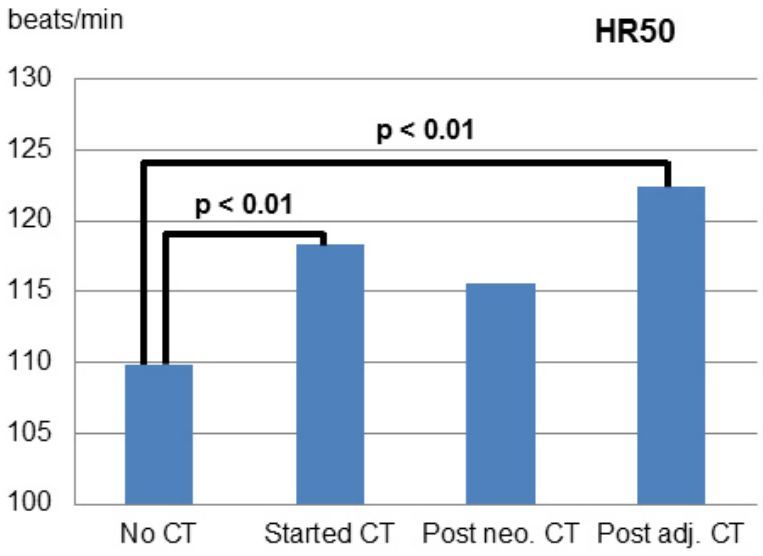


Figure 2: Distribution of VO_{2peak}, presented as percentage of expected values for healthy women with the same age and BMI. The boxes present the 1st and 3rd quartiles, the middle line the medians, and the Whisker-ends the 5th and 95th percentiles.

The median VO_{2peak} values in our patient population were significantly lower than the expected cardiorespiratory values according to the age- and BMI-related prediction formula (Koch et al., 2009) (Figure 2). Patients post adjuvant or neo-adjuvant chemotherapy reached only a median of 63% or 75% of expected VO_{2peak}, respectively. In contrast, patients who just started chemotherapy reached 96% of expected VO_{2peak}.







In ANCOVA models the categorical treatment variable was significantly associated with VO_{2peak} ($p<.01$, Figure 3), when adjusted for influencing factors such as age ($p<.01$), BMI ($p<.01$), cycling ($p=.03$), and smoking before diagnosis ($p=.07$). Hereby, the adjusted mean VO_{2peak} among patients who had just started chemotherapy did not differ from those with no chemotherapy; however the adjusted means of those two groups were significantly higher compared to post adjuvant chemotherapy. The group which just started the chemotherapy and which had

Figure 3: Adjusted mean values of each treatment category regarding VO_{2peak}, VT, and HR50. Least square means were calculated using analyses of covariance models adjusted for age, BMI, smoking before diagnosis, walking, cycling, and sports before diagnosis, sports during adolescence, use of beta-blocker, and pre-existing heart diseases. Differences between categories were tested using Tukey-Kramer tests and all statistically significant differences ($p < 0.05$) are indicated in the figures.

no chemotherapy had a more favorable VO_{2peak} compared to those who completed treatment. Notably, the VO_{2peak} was even more reduced among those who finished adjuvant chemotherapy compared to those prescribed neo-adjuvant chemotherapy. There was no significant association between the type of anti-cancer treatment and VT in the final adjusted model. The only significant determinant of VT was BMI ($p<.01$). However, treatment was found to be borderline significant ($p=.057$) in the model without adjustment for walking, cycling, and sport activities, with highest VT values among those who had started chemotherapy (data not shown).

In contrast, HR50 was significantly associated with treatment ($p<.01$) with significantly lower adjusted mean resting HR in patients with no chemotherapy compared to patients during or post adjuvant chemotherapy ($p<.01$). The only other covariate that showed a borderline significant association with HR50 in the adjusted model was use of beta-blockers ($p=0.055$) with lower HR among users. The adjusted models explained 46.1%, 31.8%, and 18.7% of the variance of VO_{2peak}, VT, and HR50, respectively.

Receipt of chemotherapy was also associated with decreased Hb-level, especially after completion of adjuvant chemotherapy ($p<.0001$). However, Hb-level showed no significant association with VO_{2peak}, VT, or HR50, or any association between treatment regimes. These fitness measures did not alter when the models were adjusted additionally for Hb. Therefore, Hb was not a significant mediator of the effects of chemotherapy on cardiorespiratory fitness.

Among patients who had just started adjuvant chemotherapy, 85% had received anthracyclines and only 39% had received taxanes. In contrast, nearly all patients post adjuvant or neo-adjuvant chemotherapy had received both, anthracyclines and taxanes, during the course of their chemotherapy (see Table 1).

Thus, the independent effects of those chemotherapeutic agents on VO_{2peak} could not be determined. However, aforementioned treatment effect on VO_{2peak} did not alter substantially when adjusting the model for taxane and anthracycline regimen. When investigating the subgroup of patients who had started adjuvant chemotherapy, the adjusted means of VO_{2peak} were nearly identical for anthracycline use only, taxane use only, and combined therapy (data not shown). Similar results were found for the adjusted means of HR50. Adjustment for trastuzumab or hormone therapy was not found to alter the results.

Discussion

The present study of 222 non-metastatic breast cancer patients revealed alarmingly low cardiorespiratory fitness in breast cancer patients across the treatment continuum. The mean VO_{2peak} among our sample population was 20.6±6.7 ml/min/kg, compared to the expected mean VO_{2peak} of 24.3±5.5 ml/min/kg among healthy population of comparable age and BMI distribution (Koch et al., 2009).

Cardiorespiratory fitness was significantly associated with type and stage of cancer treatment, with lower adjusted mean VO_{2peak} among patients post adjuvant chemotherapy compared to patients with no chemotherapy or who had just started chemotherapy. On average, patients who had just started chemotherapy (i.e. had one or two cycles of chemotherapy) were capable of reaching 96% of the VO_{2peak} level that is expected for their age- and BMI-category; however, among patients receiving post adjuvant chemotherapy (i.e. about 4 weeks after completion of chemotherapy), fitness levels were only 63% of the expected level.

Cardiopulmonary Exercise Testing (CPETs) have been universally utilized in several randomized exercise trials (Bourke et al., 2013; L. W. Jones et al., 2012),

however, there have been few systematic investigations of effects of cancer therapy on cardiorespiratory fitness among breast cancer patients. To our knowledge, there has been only one study comparing VO_{2peak} at various points of chemotherapy treatment and compared with the expected capacity in healthy women. Our study expands on previous methods by assessing submaximal exercise measures in addition to peak measures. This enabled analyses of patients who could not perform maximal exercise testing until exhaustion, which is a limitation of exercise testing in an oncology setting.

The considerable reduction in VO_{2peak} compared to healthy individuals is in accordance with the findings of Jones et al. (L. W. Jones et al., 2012). It therefore appears to be of good external validity, bur still needs confirmation in future studies. Jones and colleagues (2012) found that breast cancer patients during chemotherapy reached 73% of age-expected capacity of healthy sedentary women with a mean VO_{2peak} of 17.4±4.3 ml/min/kg. This is consistent with our results, which revealed a mean VO_{2peak} of 15.5±4.8 ml/kg/min about 4 weeks post adjuvant chemotherapy. Several intervention trials demonstrated VO_{2peak} measures in breast cancer patients or survivors ranging between 18 to 26 ml/min/kg (Bourke et al., 2013). All published comparable studies that we know of, reported similar results to our findings (Courneya et al., 2007; Drouin, Armstrong, Krause, & Orr, 2005; L. W. Jones et al., 2012; Kim, Kang, Smith, & Landers, 2006; Segal et al., 2001). In Jones et al. (L. W. Jones et al., 2012), marginally lower VO_{2peak} values were described in partly metastatic breast cancer patients. Slightly higher values in other referenced studies (Courneya et al., 2007; Kim et al., 2006; Segal et al., 2001) might be attributable to a younger population; differences in the test method, namely higher VO_{2peak} values, can be expected when using treadmill tests. The lower VO_{2peak} values in Drouin et al.

(Drouin et al., 2005) can be explained due to recruitment of only sedentary population. However, these results lack adjustment for age, BMI or other potentially influencing factors, and had large heterogeneity in the time since or end date of chemotherapy; therefore, these studies could not be properly compared to the results of the present study. Notably, the average VO_{2peak} in patients post chemotherapy showed similar impairment in cardiac capacity as that observed among 1052 women with a myocardial infarction (15.4±4.0 ml/kg/min, measured about 14 weeks after the event) (Kavanagh et al., 2003). The study population of these cardiac patients was of comparable age (58.5±9.8 years) and BMI (26.7±5.1 kg/m^2) and followed a similar testing protocol on a cycle ergometer as the present study.

Interestingly, in contrast to the objective measures of cardiorespiratory function, our attending oncologists (without being aware of the CPET results) assessed the performance of the majority of patients as ECOG=0, i.e. as fully active, able to carry on all pre-disease activities of daily living without restrictions. These results emphasize that impaired cardiorespiratory fitness is prevalent among breast cancer patients, and should be monitored and counteracted to avoid further negative consequences. Low exercise levels after breast cancer treatment should be avoided, because lack of exercise is an established predictor of mortality in both breast cancer patients and healthy women (Blair et al., 1996; Peel et al., 2009). Furthermore, low cardiorespiratory fitness has been observed as significant determinant of dependence and functional limitations in daily living among older adults (Sweeney et al., 2006).

Furthermore the impact of cancer treatment on the complex oxygen cascade, which involves several components of the respiratory and cardiovascular systems, is only marginally understood (Lakoski et al., 2012). The inclusion of three different

fitness parameters in our analysis provides further insight into the impact of chemotherapy on specific organs and functions within the cardiorespiratory system. VO_{2peak} was chosen as a global parameter, which is influenced by oxygen uptake in the lung (ventilation and gas exchange), oxygen delivery (heart and blood), and peripheral oxygen extraction (metabolism on muscular level) (American Thoracic & American College of Chest, 2003). Because VO_{2peak} depends on maximal effort and not all patients are willing or able to spend maximal effort, submaximal parameters, such as VT and HR50, are considered. VT provides insight into energy metabolism (aerobic vs. anaerobic) in the muscle and is defined as the point during graded exercise at which ventilation increases disproportionately to O_2 uptake. Heart rate at 50 Watts (HR50) or at a given submaximal work load provides information regarding the heart rate response, an important contributor to exercise intolerance. Our multiple regression analyses revealed that chemotherapy treatment has a significant impact on VO_{2peak}, independent of other influencing factors such as age, BMI, or previous regular aerobic exercise. Effects of chemotherapeutic agents on different organ components of the oxygen system (e.g. the respiratory, cardiac, blood, vascular, or skeletal muscle functions) have been observed or hypothesized, potentially contributing to impaired cardiorespiratory fitness (Lakoski et al., 2012). Our adjusted regression analyses showed that HR50 was significantly affected by chemotherapy treatment. One can speculate that this observation is related to an impaired oxygen transportation of the blood which is compensated by a higher heart rate. VT was not significantly associated with chemotherapy, suggesting that there is no substantial impairment in skeletal muscle function as a result of chemotherapy treatment.

However, the direct effects of cancer therapy are not easy to distinguish from indirect effects of therapy, such as detraining or changes in body weight and

composition as consequence of physical inactivity. Reduced physical activity may also be a potential consequence of poor cardiorespiratory fitness post cancer therapy. Cancer-related fatigue, which often persists during and after anti-cancer therapy and lack of knowledge of the benefits of effects of exercise, might increase sedentary behavior. Among breast cancer patients, a significant reduction in physical activity during cancer therapy has been observed, with a large proportion of women remaining inactive or demonstrating reductions in physical activity level post therapy compared to pre-diagnosis (Huy, Schmidt, Vrieling, Chang-Claude, & Steindorf, 2012).

To counteract this vicious cycle (i.e. low fitness leading to decreased activity leading to further decreased fitness), physicians and health professionals should encourage breast cancer patients to be physically active during therapy and to engage in exercise programs. There is strong evidence from randomized intervention studies that even strenuous exercise, including aerobic as well as resistance training, is feasible and can be safely performed in breast cancer patients during and after therapy (Cheema, Gaul, Lane, & Fiatarone Singh, 2008). A meta-analysis of endurance exercise interventions in breast cancer patients reported an average 14.8% increase in VO_{2peak} (Kim, Kang, & Park, 2009). A recent meta-analysis by Jones and colleagues reported similar cardiorespiratory fitness benefits among cancer patients participating in exercise programs (L. W. Jones et al., 2011).

There are several limitations to this study. The investigated size of the treatment groups was unequal, because the studies (BEST and BEATE) were not primarily designed for these comparisons. Additionally, the cross-sectional design (i.e. using the baseline measurements only) limits causal inferences. Measurements of cardiorespiratory fitness are repeated at several time points in our intervention

trials, therefore longitudinal investigations are possible in the future. A methodological issue is that our exercise protocol started at a relatively high load level (50 watts). VT was reached at an average of 47 watts, which is within the first exercise stage. The VT would be more easily identifiable and determined better if at least one complete exercise stage was achieved below the anticipated VT or by using a ramp incremental test protocol. Therefore the VT results must be interpreted with caution. Given the problems with VT, future studies should elucidate to importance of measuring VT in cancer patients by evaluating the suitability of different testing protocols to detect VT more precisely.

Strengths of our study include the use of the gold standard of cardiorespiratory fitness testing for the assessment of overall cardiorespiratory function. The additional investigation of submaximal measures, (i.e. VT and HR50) provides insight into the effects on muscular metabolic function and cardiocirculatory values. Submaximal parameters are independent of maximal effort. Because 46 of 222 participants could not reach the criteria for maximal effort, the submaximal data still provided relevant information on the patients' cardiorespiratory fitness. In the absence of maximal exertion results, this data can be used to advise patients on endurance training prescriptions. Furthermore, the present study utilized information from a relatively large patient group and assessed many cofactors, which enabled adjusted regression modeling. Various breast cancer treatment characteristics were explored. These subgroups were recruited under comparable conditions from the same population source resulting in reliable findings.

In conclusion, breast cancer patients had marked and significantly impaired cardiorespiratory function during and post chemotherapy. The impact on VO_{2peak} appears to accumulate over the course of chemotherapy, while HR was already

impaired during the first chemotherapy cycles. However, there was no significant association between chemotherapy treatment and VT. Overall, our data suggest that chemotherapy may adversely affect cardiorespiratory fitness by negatively influencing the oxygen delivery system rather than impacting metabolic muscle function.

These findings underline the need of systematic exercise training to counteract the loss of cardiorespiratory fitness during the anti-cancer treatment in breast cancer patients. In conjunction with the recommendations of other studies (S. B. Jones et al., 2013; Strasser, Steindorf, Wiskemann, & Ulrich, 2013), exercise therapy should become a substantial and integrative part of supportive oncology therapy, with the ultimate goal to mitigate treatment-related side effects and improve quality of life and survival after breast cancer.

Conflict of interests

The authors declare no conflicts of interest.

Acknowledgements

The BEST-Study is funded by the Interdisciplinary Research Funding Program (intramural) of the National Center for Tumor Diseases (NCT), Heidelberg. The authors thank the study participants who willingly spent their time to complete the study procedures, the breast cancer centers supporting the recruitment, Petra Armbrust, Dr. Tilla Ruf, Renate Schoenmakers, Dr. Sabine Wessels, Sandra Gollhofer, Simone Stefaniszyn and Marina Sumic for study coordination and assistance and Werner Diehl for data management.

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5. Muscle strength in breast cancer patients receiving different treatment regimes

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Abstract

Aim

Muscle strength has been associated with a decreased mortality risk and reduced side-effects in oncologic patients. However, little is known about how muscle strength is affected by cancer therapy. We investigated muscle strength in breast cancer patients during treatment and also compared it with healthy individuals.

Methods

Breast cancer patients (N=255), staged 0-III, aged 54.4±9.4 years, were categorized into four groups according to their treatment status. Their muscle function was assessed with gold standard method by maximal isokinetic peak torque (MIPT) (60°/s, 180°/s) and maximal voluntary isometric contraction (MVIC) tests in lower and upper extremity muscle groups. Additionally, muscular fatigue index (FI%) and shoulder flexibility was evaluated. Healthy women (N=26), aged 53.3±9.8 were tested using the same method. Analysis of covariance was used to estimate the impact of different cancer treatments on muscle function with adjustment for various clinical and socio-demographic factors.

Results

Consistently lower muscle strength and higher FI% was measured in knee strength in patients after chemotherapy. On average, patients had up to 25% lower strength in lower extremities and 12-16% in upper extremities in MVIC and MIPT during cancer treatment compared to healthy women. No substantial difference between patient groups in shoulder strength, but significantly lower shoulder flexibility in patients with radical mastectomy was measured. No serious adverse events were reported.

Conclusions

Patients showed markedly impaired muscle strength after adjuvant therapy. The clinically relevant decrease underlines the need of exercise therapy as early as possible in order to prevent or counteract the loss of muscle function.

Keywords

isokinetic, isometric, multi-joint, muscle function, chemotherapy

Introduction

Cancer-related muscle dysfunction is a broad clinical challenge, which is not restricted to palliative or advanced stage patients as it has also been observed in newly diagnosed patients with low tumor burden (Christensen et al., 2014; Villasenor et al., 2012). Many factors can affect skeletal muscle function including age, comorbidities, malnutrition, physical inactivity, tumor-derived factors, systemic and local cancer treatments, and supportive care medication (Lakoski, Eves, Douglas, & Jones, 2012). A prospective cohort study (HEAL) revealed a high prevalence of sarcopenia and its association with a higher all-cause mortality hazard ratio (HR) of 2.86 in breast cancer (BC) survivors (Villasenor et al., 2012). Low muscle strength and physical inactivity can be a predictor for persistent fatigue in older, long-term BC survivors (Winters-Stone, Bennett, Nail, & Schwartz, 2008). BC patients undergoing adjuvant chemotherapy (CT) reduce their daily energy expenditure during therapy, which is associated with a loss of muscle mass (Demark-Wahnefried et al., 2001; Huy, Schmidt, Vrieling, Chang-Claude, & Steindorf, 2012). Furthermore, it was shown that skeletal muscle status is of clinical relevance since it is associated with treatment complications and time-to-tumor progression (Prado et al., 2009). With regard to healthy older individuals, muscle strength, but not mass, was identified as a strong independent predictor of all-cause mortality (Newman et al., 2006).

Based on the current knowledge of treatment related side-effects, it can be assumed that muscle function is affected by different cancer treatments, but the role of muscle strength during cancer treatment has been insufficiently investigated (Strasser, Steindorf, Wiskemann, & Ulrich, 2013). Since we recently reported that cardiorespiratory performance varies between patient groups defined by cancer treatment (Klassen et al., 2014) we would like to provide an overall picture of the

performance status and the different impact of several types of cancer treatment among BC patients by analyzing various muscle strength parameters.

Methods

Population

For this analysis, baseline data of two randomized controlled exercise trials (RCTs) in BC patients were used, i.e. the BEATE-Study and the BEST-Study (ClinicalTrials.gov NCT01106820 and NCT01468766, respectively) (Potthoff et al., 2013; Schmidt et al., 2013; Steindorf et al., 2014). These two RCTs investigated the effects of 12-week progressive resistance training in comparison to relaxation training in BC patients undergoing adjuvant CT (BEATE-Study) or adjuvant radiotherapy (BEST-Study). Women with histologically confirmed stage 0-III primary BC after lumpectomy or mastectomy were eligible for the studies. Further inclusion and exclusion criteria and more details of the RCTs are presented elsewhere (Potthoff et al., 2013; Schmidt et al., 2013). In a parallel intervention study (INVEST-Study) with identical surveys, 26 healthy age-matched control women participated in the same 12-week progressive resistance training protocol to obtain comparison data.

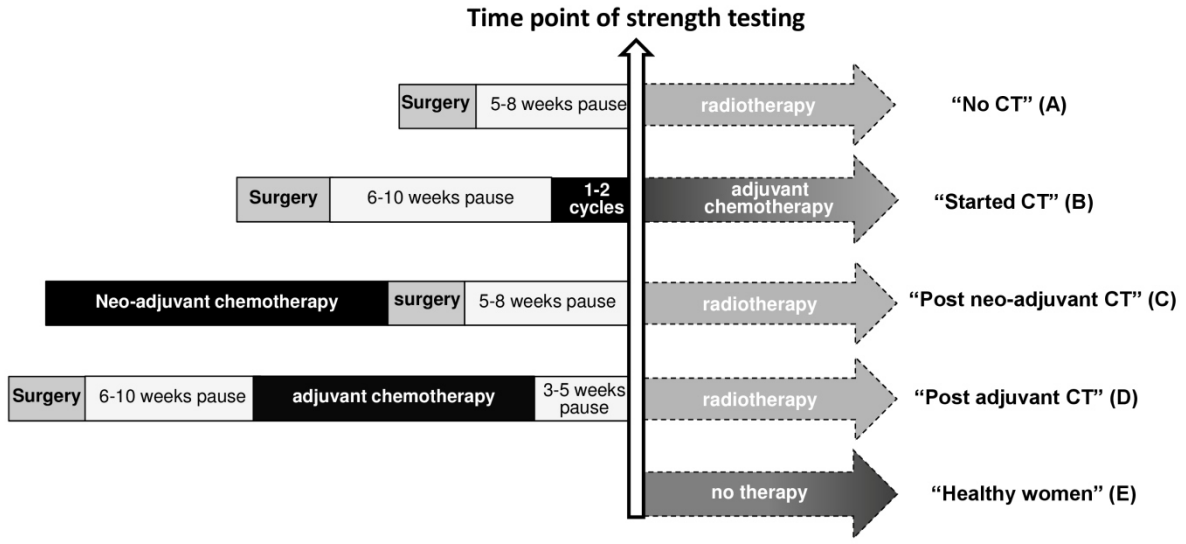

Figure. 1: Time point of the strength testing in clinically important treatment groups of BC patients and healthy women

Both RCTs were conducted with parallel designs at the National Center for Tumor Diseases (NCT) in Heidelberg, Germany. Based on the different clinically important treatment histories and the healthy subjects, five subgroups were defined: No CT, Started (adjuvant) CT, Post neo-adj. CT, Post adj. CT, and healthy women. Patients recruited in the BEST-Study had the baseline strength testing within 14 days before starting radiotherapy. Of these participants, a majority had received surgery only (No CT, n=105), while some had received CT in the adjuvant (Post adj. CT, n=28) or neo-adjuvant (Post neo-adj. CT, n=31) CT setting. Patients enrolled in the BEATE-Study (Started CT, n=91) performed baseline strength testing at the end of the first or second CT cycle (see Figure 1).

Assessment of muscle function

Test system

Isokinetic and isometric muscle strength were measured by using IsoMed 2000-system B-series version (D&R Ferstl GmbH, Hemau, Germany). The use of

isokinetic dynamometer is valid and reliable (Dirnberger, Wiesinger, Kosters, & Muller, 2012) and considered a gold standard method to evaluate strength in cancer patients (Christensen et al., 2014)' (Jones et al., 2010; Kilgour et al., 2010; Weber et al., 2009).

Muscle function parameters

Maximal isokinetic peak torque (MIPT) was tested for shoulder external and internal rotation, and for knee extensors and flexors at the angular velocities of 60°/s and 180°/s. The range of motion (ROM) for isokinetic knee measurement was limited between the angles from 10° to 90°. The position of dynamometer for shoulder rotation was tilted at 40° of abduction. The ROM for isokinetic testing was from 10° external rotation to 70° internal rotation. The MIPT for shoulder rotation was calculated for dominant side.

With this device we also measured the maximal voluntary isometric contraction (MVIC) for shoulder internal rotator in the position of 43° and knee extensor muscles in the position of 35° (0° is straight leg), which sustainably were the strongest angle positions. For BC patients we calculated MVIC on the operated and non-operated side. For healthy women we calculated MVIC from the mean of left and right side.

Muscular fatigue was determined by the calculation of the peak torque decline at 60°/s in knee extensors of the dominant leg. Therefore we used the muscular fatigue index: FI% = [(peak torque of initial three repetitions –peak torque of final 3 repetitions) / peak torque of initial three repetitions] × 100, an adapted formula as described by Kannus (Kannus, 1994) to define the ability of an individual to maintain a level of performance. A high FI% indicates that muscles fatigue quickly. The peak torque of the first repetition overall was markedly lower than that of the second

repetition, and it was considered as a first “attempt” for the patient, it was omitted from the calculation of the initial peak torque values.

Additionally, we measured the ROM in the arm elevation with a goniometer in a standardized supine lying position to elicit the flexibility limitations after surgery in both the operated and healthy sides.

Testing protocol

Participants were secured using thigh, pelvic and torso straps to minimize extraneous body movements. The subjects were permitted to use the handlebars on both sides of the IsoMed 2000 chair for additional stability during leg testing, but not for shoulder testing. For the MVIC testing, the participants were instructed to push as hard as possible against the fixed lever arm. Contraction time for MVIC was restricted to six seconds for each position. Each subject performed 10 maximal reciprocal contractions in both angular velocities for MIPT. During testing, both the subject and the instructor were able to see the strength curve on the monitor. Subjects were given verbal encouragement to generate the highest possible strength. Each torque artifact resulting from deceleration, which often exceeds the true peak torque, was removed by using a filter; only gravity corrected data was used for analysis.

Data analysis

Clinical and sociodemographic data were investigated by descriptive analyses for the entire study population. Between-group differences were assessed using $\chi 2$ or Fisher’s exact test for categorical variables, and using one-way analysis of variance (ANOVA) for continuous variables. Analyses of covariance (ANCOVA) models were used to test whether the muscle function parameters differed between the four cancer treatment groups and in comparison with healthy individuals. We

calculated models adjusted for covariates that seemed biologically reasonable influencing factors. The included covariates are reported within the results section. Presented here are the parsimonious models including the significant covariates and those that changed the treatment estimate by >10%. Sensitivity analyses with different adjustment sets were performed to investigate the stability of the models.

The ROM in the shoulder of the operated side was adjusted for the operation type (radical mastectomy and partial mastectomy). All statistics were performed using SAS 9.3 (SAS Institute Inc. NC, USA). The level of significance was set at $p < 0.05$.

Results

Participant characteristics

Participant characteristics stratified by treatment groups are presented in Table 1. All patients underwent surgical resection with mean (±SD) time to strength assessment of 65.2 ± 49 days. According to the different treatment settings, there were significant group differences in the timeframe between patients' surgery and the strength assessment ($p < .001$). The longest time period from surgery to muscle strength testing was 180.1 ± 50.5 days in the Post adj. CT group. The shortest period was 45.5 ± 12.7 days in the No CT group. Muscle strength testing was 76.4 ± 48.2 days after CT in the Post neo-adj. CT group and 27.6 ± 15.4 days in the Post adj. CT group. The group with No CT was older (57.1 ± 8.7 years) than the group Post neo-adj. CT (51.1 ± 9.3 years), Started CT group (52.6 ± 9.9 years) and Post adj. CT group (54.3 ± 7.9 years). Healthy controls had a mean age of 53.3 ± 9.8 years. There were no significant differences between the treatment groups in weight, height, body mass index (BMI) and in the Eastern Cooperative Oncology Group (ECOG) status

classified by the oncologists. Furthermore, no substantial differences in sport activity pre-diagnosis were observed between patient groups. The healthy controls had a higher level of moderate physical activity.

Table 2: Characteristics of the population

				Breast cancer treatment groups						
		TOTAL		No CT	Started CT	Post neo-adj. CT	Post adj. CT	P*	Healthy women	P**
Number of women		281		105	91	31	28		26	
Age, mean (SD)		54.3	(9.4)	57.1 (8.7)	52.6 (9.9)	51.1 (9.3)	54.3 (7.8)	0.0011	53.3 (9.8)	0.0027
Weight, mean (SD)		72.2	(13.9)	73.6 (13.6)	71.7 (14.0)	71.0 (11.3)	74.6 (18.4)	0.60	67.3 (11.4)	0.24
Height, mean (SD)		165.9	(6.6)	164.9 (6.9)	166.3 (6.7)	166.1 (4.8)	167.3 (6.9)	0.26	166.9 (6.7)	0.33
BMI, mean (SD)		26.3	(5.0)	27.1 (5.1)	25.9 (4.9)	25.8 (4.3)	26.5 (5.5)	0.33	24.2 (4.2)	0.077
Menopausal status, n (%)	pre	67	26%	19 18%	37 41%	5 16%	6 21%	0.0035	n.a.	n.a.
	peri	29	11%	10 9%	8 9%	7 23%	4 14%			
	post	147	58%	73 69%	39 42%	18 58%	17 61%			
	missing	12	5%	3 4%	7 8%	1 3%	1 4%			
Days since surgery, mean (SD)		65.2	(49.0)	45.5 (12.7)	56.8 (22.7)	55.9 (48.2)	180.1 (50.5)	<.001	n.a.	n.a.
Days since CT end, mean (SD)		55.1	(44.6)	n.a.	n.a.	76.4 (48.2)	27.6 (15.4)	<.001	n.a.	n.a.
Mastectomy, n (%)	yes	55	22%	4 4%	33 37%	11 36%	7 25%	<.001	n.a.	n.a.
Partial mastectomy, n (%)	yes	197	77%	101 96%	55 60%	20 64%	21 75%			

		TOTAL		Breast cancer treatment groups				P*	Healthy women	P**
				No CT	Started CT	Post neo-adj. CT	Post adj. CT			
	missing	3	1%		3 3%					
Lymph nodes dissected, n (%)	none	11	4%	10 9.5%	1 1.1%			<.001	n.a.	n.a.
	sentinel	147	58%	76 72%	48 52%	14 45%	9 32%			
	axillary	94	37%	18 17%	40 44%	17 55%	19 68%			
	missing	3	1%	1 1%	2 2%					
Stage, n (%)	0	15	6%	13 12%		2 7%		<.001	n.a.	n.a.
	1	118	46%	65 62%	36 40%	10 32%	7 25%			
	2	94	37%	26 25%	43 47%	15 48%	10 36%			
	3	27	11%	1 1%	11 12%	4 13%	11 39%			
	missing	1	<1%		1 1%					
Taxane, n (%)	yes	90	35%	n.a.	32 35%	31 100%	27 96%	<.001	n.a.	n.a.
	missing	1	<1%		1 1.%					
Anthracycline, n (%)	yes	131	51%	n.a.	77 85%	29 96%	25 89%	0.23	n.a.	n.a.
	missing	3	1%		1 1%	1 3%	1 4%			
Herceptine treatment, n (%)	yes	16	6%	0 0%	4 4%	6 19%	6 21%	<.001	n.a.	n.a.
	missing	1	<1%		1 1%					
Hormone therapy, n (%)	yes	79	31%	55 52%	0 0%	13 42%	11 39%	<.001	n.a.	n.a.
ECOG, n (%)	0	222	87%	93 89%	79 87%	27 87%	23 82%	0.49	n.a.	n.a.
	1	25	10%	10 9%	6 6%	4 13%	5 18%			

	TOTAL		Breast cancer treatment groups					Healthy women	P**
			No CT	Started CT	Post neo-adj. CT	Post adj. CT	P*		
2	1	<1%	1	1%					
missing	7	3%	1	1%	6	6%			
FAQ physical fatigue, mean (SD)	39.4	(27.1)	35.0	(26.9)	44.0	(25.5)	45.0 (25.5)	56.7 (24.5)	<.001	16.4 (18.3)	<.001
Depression (ADS), mean (SD)	25.1	(16.7)	26.6	(17.1)	25.6	(16.2)	28.9 (18.5)	26.0 (14.7)	0.83	11.8 (11.4)	<.001
Sports before diagnosis[1], n (%) none	98	35%	46	44%	21	23%	14 45%	9 32%	0.14	8 31%	0.0045
>0-9 MET·h/wk	77	27%	25	23%	24	26%	7 23%	7 25%		14 54%	
>9-21 MET·h/wk	55	20%	19	18%	24	26%	6 19%	4 14%		2 8%	
>21 MET·h/wk	46	16%	14	13%	21	23%	4 13%	7 25%			
missing	5	2%	1	1%	1	1%		1 4%		2 8%	
Cycling[a], n (%) none	98	35%	38	36%	28	31%	14 45%	10 36%	0.87	8 31%	0.26
>0-1 h/wk	85	30%	32	31%	31	34%	9 29%	11 39%		2 8%	
>1-3 h/wk	60	21%	22	21%	20	22%	6 19%	3 11%		9 34%	
>3 h/wk	31	11%	10	9%	12	13%	2 7%	2 7%		5 19%	
missing	7	3%	3	3%				2 7%		2 8%	

BMI body mass index, *CT* chemotherapy, *ECOG* Eastern Cooperative Oncology Group, *MET* metabolic equivalent, *SD* standard deviation, *FAQ* Fatigue Assessment Questionnaire with items for physical fatigue, *ADS* German depression scale based on Center for Epidemiological Studies Depression Scale (CES-D),

[a] Exercise behavior in the year before breast cancer diagnosis with self-developed surveys abstracted from the International Physical Activity Questionnaire (IPAQ)

* P-value for one-way ANOVA for continuous variables, Chi2 or Fisher's exact test for categorical variables only for breast cancer patient groups

** P-value for one-way ANOVA for continuous variables, Chi2 or Fisher's exact test for categorical variables for all groups

Maximal voluntary isometric contraction (MVIC)

The adjusted means and 95% confidence intervals (CI) for knee extensors and internal rotators in the operated and non-operated shoulder for MVIC are presented in Table 2.

Table 3: Maximal voluntary isometric contraction (MVIC) in N·m in different treatment groups and healthy subjects

	Breast cancer treatment groups						
Measure/Treatment	**No CT** (n = 105) A	**Started CT** (n = 91) B	**Post neo-adj. CT** (n = 31) C	**Post adj. CT** (n = 28) D	Significant differences between patient groups	**Healthy women** (n = 26) E	Significant differences to healthy women
Knee Extension[a]	126.8 (120.2, 133.5)	125.4 (118.1, 132.7)	119.0 (108.1, 129.9)	122.8 (111.5, 134.1)	n.s.	138.5 (127.4, 149.5)	n.s.
Shoulder internal rotation (op)[b]	28.5 (27.3, 29.7)	29.7 (28.3, 31.0)	28.3 (26.0, 30.6)	29.4 (27.0, 31.7)	n.s.	33.8 (31.4, 36.2)[1]	A/E, B/E, C/E
Shoulder internal rotation (non-op) [b]	30.1 (28.8, 31.3)	30.9 (29.5, 32.3)	28.8 (26.4, 31.1)	29.1 (26.5, 31.6)	n.s.	33.8 (31.4, 36.2)[c]	A/E, B/E, C/E, D/E

Data presented as adjusted mean with 95% confidence intervals (CI)
[a] Model for knee extension is adjusted for age, BMI (17-<25, 25-30, >30 kg/m^2), weight, drugs which influence the muscle tonus, antidepressants, regular cycling and previous experience in resistance training
[b] Model for shoulder rotation is adjusted for age, BMI (17-<25, 25-30, ≥30 kg/m^2) and previous experience in resistance training
[c] In healthy women: mean of left and right arm
MVIC maximal voluntary isometric contraction*, N·m* Newton meter, *op* operated side

Concerning MVIC of knee extensors, the BC treatment groups had impairments of 9-14% in strength in comparison to healthy women, but these differences did not reach statistical significance. There were also no statistically significant differences between the BC patients groups in shoulder MVIC, neither for the operated nor for the non-operated side. However, healthy women had 12-16% higher MVIC in shoulder internal rotators which is significantly different in comparison to the BC patient groups.

Maximal isokinetic peak torque (MIPT)

Adjusted means and 95% CI of MIPT in knee and shoulder muscles in two speeds for the treatment groups and healthy women are reported in Table 3. BC patient groups had, on average, 5-20% decreased MIPT in knee extensors and a 7-25% decrease in knee flexors compared to healthy women measured with 60°/s (see Figure 2). The most impaired groups were those with completed chemotherapies. Isokinetic shoulder internal rotator strength was significantly impaired in all cancer treatment groups when compared to healthy controls.

Table 3: Maximal isokinetic peak torque (MIPT) in N·m in different treatment groups and healthy subjects

	Breast cancer treatment groups						
Measure/Treatment	**No CT** (n = 105) A	**Started CT** (n = 91) B	**Post neo-adj. CT** (n = 31) C	**Post adj. CT** (n = 28) D	Significant differences between patient groups	**Healthy women** (n = 26) E	Significant differences to healthy women
Knee Extension[a] in 60°/s	88.6 (83.2, 94.1)	92.6 (86.5, 98.7)	84.0 (76.1, 91.9)	77.7 (69.9, 85.5)	A/D, B/D	97.5 (89.5, 105.6)	A/E, C/E, D/E
Knee Flexion[a] in 60°/s	57.2 (53.7, 60.8)	64.5 (60.6, 68.4)	53.1 (47.3, 58.9)	51.9 (45.9, 57.9)	A/B, A/C, B/C, B/D	69.2 (63.3, 75.1)	A/E, C/E, D/E
Knee Extension[a] in 180°/s	56.6 (53.3, 59.9)	58.4 (54.7, 62.1)	51.5 (46.7, 56.3)	47.2 (42.5, 51.9)	A/D, B/C, B/D	63.5 (58.6, 68.3)	C/E, D/E
Knee Flexion[a] in 180°/s	48.9 (46.2, 51.7)	53.5 (50.5, 56.5)	43.2 (38.7, 47.7)	43.4 (38.8, 48.1)	A/B, B/C, B/D,	59.6 (55.0, 64.1)	A/E, B/E, C/E, D/E

Shoulder internal rotation[b] in 60°/s	25.6 (24.6, 26.6)	26.9 (25.8, 28.0)	26.0 (24.1, 27.9)	25.6 (23.7, 27.5)	n.s.	30.4 (28.4, 32.3)	A/E, B/E, C/E, D/E
Shoulder external rotation [b] in 60°/s	8.7 (8.0, 9.4)	8.8 (8.0, 9.5)	9.2 (7.9, 10.5)	8.3 (7.0, 9.6)	n.s.	10.8 (9.4, 12.2)	n.s.
Shoulder internal rotation [b] in 180°/s	23.7 (22.6, 24.7)	22.4 (21.4, 23.4)	22.8 (21.0, 24.6)	21.7 (19.9, 23.6)	n.s.	26.3 (24.3, 28.2)	n.s.
Shoulder external rotation [b] in 180°/s	6.0 (5.4, 6.7)	5.6 (5.0, 6.2)	5.7 (4.7, 6.8)	5.5 (4.4, 6.6)	n.s.	7.4 (6.3, 8.6)	n.s.

Data presented as adjusted mean with 95% confidence intervals (CI)
[a] Model for knee extension and flexion is adjusted for age, BMI (17-<25, 25-30, ≥30 kg/m^2), weight, drugs which influence the muscle tonus, antidepressants, regular cycling and previous experience in resistance training
[b] Model for shoulder rotation is adjusted for age, BMI (17-<25, 25-30, ≥30 kg/m^2) and previous experience in resistance training
MIPT maximal isokinetic peak torque*, N·m* Newton meter

Shoulder internal rotators of the dominant side were 12-16% weaker among the treatment groups in comparison to healthy controls, but within cancer patients, no between-group differences were found. There were no significant differences in shoulder MIPT between BC patients with regard to the operated side (data not shown).

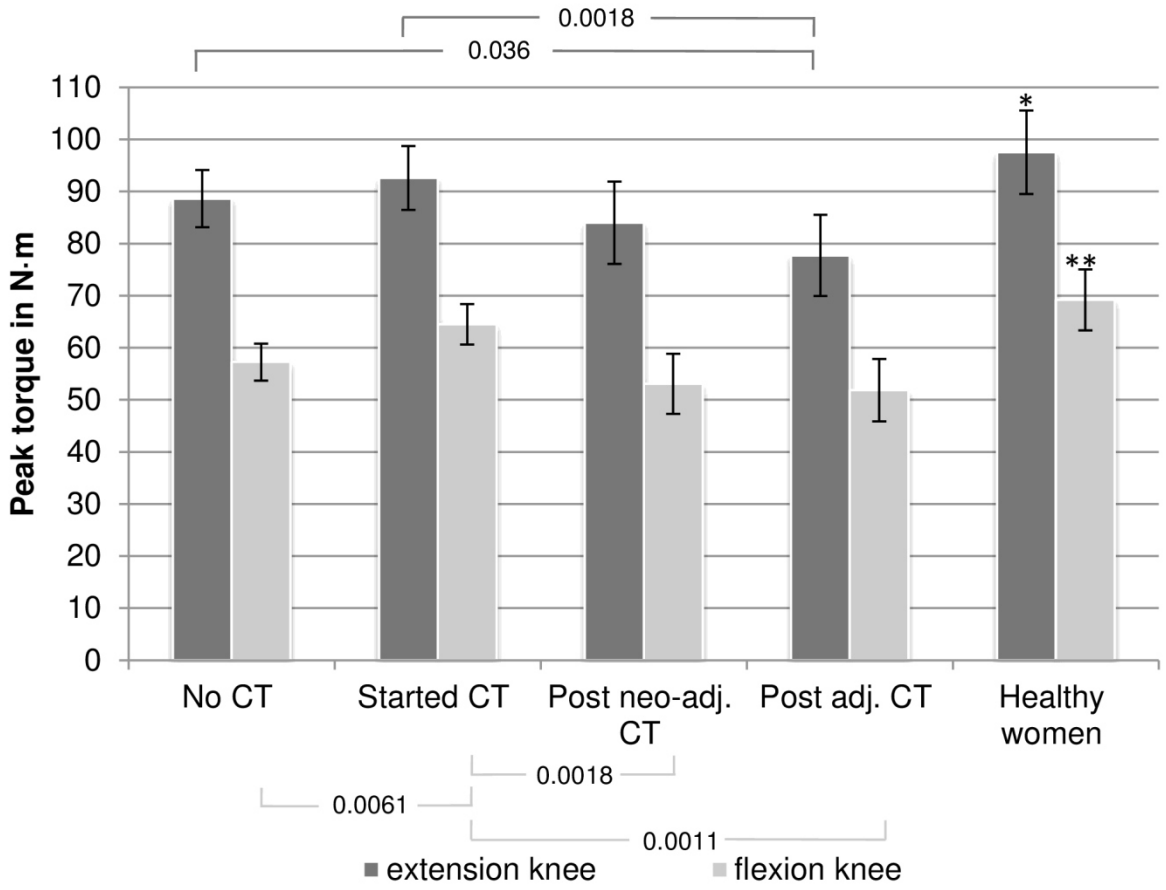

Figure 2: Adjusted means of maximal isokinetic peak torque (MIPT) at 60°/s of extension/flexion knee with 95% confidence intervals (CI),

* Significant differences to Post neo-adj. CT (p=0.037) and Post adj. CT (p<0.001),

** Significant differences to No CT (p=0.0023), Post neo-adj. CT (p<0.001) and Post adj. CT (p<0.001)

Models adjusted for age, BMI (17-<25, 25-30, >30 kg/m^2), weight, drugs which influence the muscle tonus, antidepressants, regular cycling and previous experience in resistance training

In the ANCOVA model, the covariates which had a significant impact on the strength of lower extremities were cancer treatment, age, BMI, weight, drugs which influence muscle tonus and mood (antidepressants), previous experience in resistance training and regular cycling (Table 2, 3). Other potential confounding

factors like orthopedic dysfunctions, cardiovascular restrictions, cancer-related physical fatigue (assessed by the Fatigue Assessment Questionnaire), ECOG and tumor stage showed no significant impact on muscle strength and no confounding on the group effect.

Significant covariates in the model for strength of the operated shoulder were cancer treatment, age, weight and previous experience in resistance training (Table 2, 3). Operation type, number of dissected lymph nodes, preexisting injuries in shoulder/arm and time since BC surgery had no significant impact.

Muscular fatigue (FI %)

The greatest fatigue in muscular performance within 10 repetitions could be shown in the Post adj. CT group, followed by the groups Post neo-adj. CT and No CT. All patient groups fatigued faster compared to the healthy individuals, except those patients in the Started CT group (Figure 3).

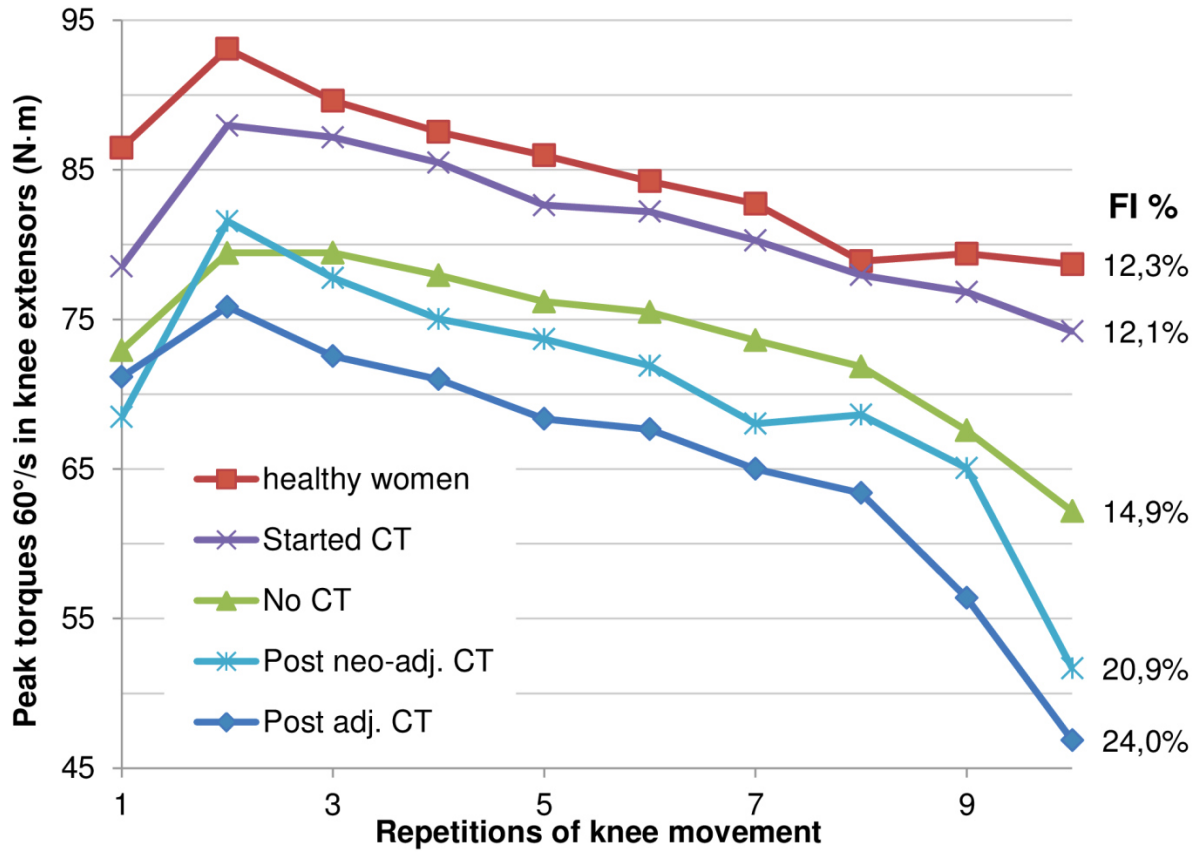

Figure 3: Muscular fatigue over a set and muscular fatigue index (FI % = [(peak torque of initial 3 repetitions –peak torque of final 3 repetitions) / peak torque of initial 3 repetitions] × 100) in different treatment groups in knee extensors of the dominant leg. Presented are the unadjusted group means. First repetition omitted from analysis of FI%

Shoulder flexibility

The ANCOVA model showed no significant association with the treatment groups. However, they indicated that the type of surgery and the length of time elapsed since BC surgery was independently influencing factors for shoulder flexibility. The operated side was, on average, 12% less flexible in patients with radical mastectomy compared to partial mastectomy. Furthermore, there was a significant difference in flexibility of the arm elevators in patients <6 weeks post-surgery (mean of 83°) and those who were tested 6-12 weeks post-surgery (mean of 90°). No significant differences were identified in patients who were tested >12 weeks

post-surgery (mean of 95°) in comparison to those tested between 6-12 weeks post-surgery.

Discussion

The performed isokinetic and isometric tests were safe and feasible. No adverse events were observed; only sporadic muscle soreness was reported by a few patients. Overall, we observed that BC patients undergoing acute cancer treatment had remarkably impaired strength capacity in both isokinetic and isometric values as well as in muscular fatigue compared to healthy individuals. Specifically, patients who had received chemotherapy in their treatment history were the most affected.

To our knowledge, this is the first study investigating isometric and isokinetic strength performance in different clinically important BC patient groups. Therefore, our results provide new insights into muscle strength performance of BC patients from several perspectives.

Our findings are in line with other studies showing an impaired muscle status in cancer patients. Most published studies in the field assessed strength performance via hand-grip (Kilgour et al., 2013; Platt, Gross, & Davis, 2014; Schneider, Hsieh, Sprod, Carter, & Hayward, 2007) or hand-held dynamometry (Harrington et al., 2011; Hummler et al., 2014), with functional tests (Schneider et al., 2007; Winters-Stone et al., 2008) or by using the one repetition maximum method (Courneya et al., 2007; Galvao et al., 2009; Ruiz et al., 2009). There are also studies using isokinetic testing procedures, but these studies had low sample sizes, and focused on other research questions (Fong et al., 2013; Kilgour et al., 2010; Wilcock et al., 2008).

Regarding the reported performance differences between cancer patients and matched healthy controls, the studies mentioned above reported larger differences in strength performance than we observed in our studies. For example, we detected mean differences between 12-16% in MVIC for the internal shoulder rotators, whereas a study published by Harrington et al. (Harrington et al., 2011) reported a 26% reduction in a comparable patient group. Lastly, differences with regard to strength testing procedures might be of importance. Hand-held dynamometry is known to be a valid and reliable testing procedure, but relatively large measurement errors can occur based on an insufficient standardization of the testing position (Knols, Stappaerts, Fransen, Uebelhart, & Aufdemkampe, 2002). Computer-based stationary dynamometry with fixed and therefore highly standardized testing positions will therefore provide more accurate testing values (Kannus, 1994).

One of the new insights of this study comes along with the isokinetic testing protocol. Since we included two different testing speeds in the protocol, we were able to draw conclusions in relation to muscle fiber activation. Research has shown that at lower angular velocities, muscle fibers I and II can be maximally activated, whereas with increasing speed, less slow twitch fiber (type I) will be recruited (Kannus, 1994). With regard to our findings, our results suggest that chemotherapy treatment does not have an impact on fiber activation since the isokinetic strength differences between the chemotherapy groups and the non-CT/started CT groups as well as the control group are comparable in both angular velocities.

New insights could be also reported with regard to the interaction of CT and fatigue resistance of skeletal muscles. We observed that patients having received chemotherapy (nearly all treated with anthracycline) had less strength and greater muscular fatigue compared to BC patients without CT or just at the beginning of CT.

An explanation for these findings could be an inactivity-related shift of muscle fibers and a CT-induced change in mitochondrial capacity of muscle cells (Bonifati et al., 2000). This is supported by the observation that CT caused severe reductions in myofiber size, neurogenic alterations and mitochondria-related damages in mice as well as in humans (Christensen et al., 2014; Scott et al., 2011). Furthermore, it is well known that BC patients reduce their physical activity level during the period of cancer treatment (Huy et al., 2012). Moreover, our patients reported less activity in the year before. These circumstances potentially lead to a loss of muscle strength, which can be supported by our objective data. In general, individual strength performance in cancer patients may be influenced by various contextual factors. Some of those factors are independent from the cancer setting (e.g. age or motivation of the patient) and some not (e.g. locoregional and systemic therapies, cancer related fatigue) (Knols et al., 2002). Receiving chemotherapy might be one of the most important factors as we already reported for cardiorespiratory fitness (Klassen et al., 2014), but the mechanisms (Bonifati et al., 2000; Gilliam & St Clair, 2011; Scott et al., 2011) and pathways (Egerman & Glass, 2014) of cancer treatment influences on muscle structure and function are not completely understood.

Aside from reduced strength capacity, upper-body mobility restrictions represent a stressful physical limitation in patients undergoing BC surgery (Hayes et al., 2012). We measured a loss of shoulder mobility and decreased shoulder internal rotator strength, resulting in an impaired shoulder function, which was a result of mastectomy. Impaired shoulder function has been reported in many BC survivors even several years after surgery (Kootstra et al., 2013). Interestingly, the time difference between surgery and testing, type of surgery and pain are considered to

have no impact on shoulder strength; only flexibility, which was dependent on the type and time since surgery, was impaired.

Strengths and limitations

Our study has several strengths. We performed stationary isokinetic strength testing, which is the gold standard procedure for functional skeletal muscle assessment. Furthermore, we report data on a very large sample size (n=255) of early stage BC patients in a well-defined and clinically relevant time frame. Moreover, we were able to assess many relevant cofactors and include them in adjusted regression models on strength performance in clinically relevant subgroups. Lastly, the current study is the first which reports information about muscular fatigue in relation to different treatment settings and all patient data could be compared with an age matched healthy control group.

This study did include some limitations. The sizes of the groups were unequal because the studies (BEST, BEATE and INVEST) were not primarily designed for these comparisons. Additionally, the cross-sectional design limits causal inferences. Furthermore, the healthy women were a convenience sample and despite matching by age-groups, differences need to be interpreted with caution. Nevertheless, the strength performance of our healthy participants was in line with comparably aged healthy women (Frontera, Hughes, Lutz, & Evans, 1991).

Conclusions

Our study showed that isometric and isokinetic strength testing appears to be safe in a large cohort of BC patients. We reported about significantly impaired isometric and isokinetic strength capacity with higher muscular fatigue in low

extremities and dysfunctions in shoulder mobility in our patients. Overall, receiving chemotherapy treatment seems to have the greatest impact on muscular strength.

Based on these findings, the prevention of muscle dysfunction should be an important goal during cancer treatment and underlines the importance for the implementation of resistance training regimens during cancer treatment to mitigate or reverse muscle dysfunction. To further understand the mechanisms of muscular dysfunction in cancer patients, there is a need for the assessment of cellular muscle structure and biomarkers combined with accurate (gold standard) strength testing procedures.

Acknowledgments

The authors thank the study participants who willingly spent their time to complete the study procedures, the BC centers supporting the recruitment, Dr. Jan Oelmann and Dr. Andrea Koffka for medical advice and examinations, Petra Armbrust and Dr. Tilla Ruf for study coordination and assistance, Werner Diehl for data management, and Michael Paskow for free linguistic editing.

Footnotes

Funding

The BEST trial was partially funded by the Interdisciplinary Research Funding Program (intramural) of the National Center for Tumor Diseases (NCT), Heidelberg. The training for all three trials (BEST, BEATE and INVEST) was supported by the Foundation “Stiftung Leben mit Krebs”. Dr. Wiskemann was personally supported by the Manfred-Lautenschlaeger-Foundation.

Competing interests None.

Ethics approval The University of Heidelberg Ethics Committee has approved the trials.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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6. Exercise training intensity prescription in breast cancer survivors: validity of current practice and specific recommendations

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Journal of cancer survivorship 2015 March; DOI 10.1007/s11764-015-0437-z.

Abstract

Purpose

Cancer survivors are recommended to perform 150 min/week of moderate or 75 min/week of vigorous aerobic exercise, but it remains unclear how moderate and vigorous intensities can be prescribed. Therefore, it was investigated whether and how intensity prescriptions for healthy adults by the American College of Sports Medicine (ACSM) need to be adapted for breast cancer survivors.

Methods

52 breast cancer survivors (stage 0-III, age 52±9 years, BMI 25.4±3.5 kg/m^2) performed cardiopulmonary exercise tests at the end of primary-therapy. Intensity classes defined as percentages of maximal heart rate (HR_{max}), heart rate reserve (HRR), and maximal oxygen uptake (VO_{2max}) were compared to the ACSM's intensity classes using oxygen uptake reserve as reference.

Results

The prescriptions for moderate and vigorous exercise intensities were significantly different between breast cancer survivors and healthy adults when using VO_{2max} (moderate 50–66 vs. 46–63 and vigorous 67–91 vs. 64–90 %VO_{2max}) or HRR (moderate 26–50 vs. 40–59 and vigorous 51–88 vs. 60–89 %HRR), but not when using HR_{max} (moderate 65–76 vs. 64–76 and vigorous 77–94 vs. 77–95 %HR_{max}).

Conclusions

In breast cancer survivors, intensity prescriptions for healthy adults result in considerably too intense training if HRR is used as guiding factor. Prescriptions using VO_{2max} result in a slightly too low exercise intensity, whereas recommendations in percentages of HR_{max} appear valid.

Implications for Cancer Survivors

Cancer survivors should not uncritically adopt exercise intensity prescriptions for healthy adults. Specific prescriptions for the studied population are provided.

Introduction

Exercise training in breast cancer survivors has been demonstrated to be safe and to elicit numerous beneficial effects on the physiological and psychological level (Schmitz et al., 2010). These include improvements in aerobic fitness and muscular strength (evidence category A), quality of life, fatigue, anxiety, body composition, and body size (evidence category B) (Schmitz et al., 2010). Furthermore, increasing evidence from observational studies suggests that regular physical activity may extend survival (Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005; Irwin & Mayne, 2008). Therefore, exercise training is recommended by expert panels worldwide (Hayes, Spence, Galvao, & Newton, 2009; Rock et al., 2012; Schmitz et al., 2010) and has become a recognized part of supportive therapy. However, knowledge is still scarce about how to prescribe exercise training for cancer survivors. Especially the definition of adequate training intensities remains unclear (Jones, 2011).

The American College of Sports Medicine's (ACSM's) exercise guidelines for cancer survivors recommend to follow the exercise prescriptions for healthy adults, with specific adaptations based on the disease and treatment-related adverse effects (Schmitz et al., 2010). These prescriptions include 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity endurance exercise, adapted based on the abilities of cancer survivors (Physical Activities Guidelines Advisory Committee, 2008; Schmitz et al., 2010). However, this adaptation is not specified and it remains unclear how moderate and vigorous exercise intensities can be defined in cancer survivors. Brisk walking might be moderate for one but near-maximal for another individual and, therefore, relative intensity prescriptions by means of heart rates, walking velocities or work rates on the cycle ergometer are needed. The ACSM provides such exercise intensity prescriptions for apparently healthy adults (Garber et

al., 2011) and in the absence of cancer-specific data this is also widely used for breast cancer survivors. Physicians and coaches can use various data of cardiopulmonary exercise tests (CPET) to look up prescriptions for different intensity classes in this table. For example, moderate intensity is classified as 64–76 % of maximal heart rate (HR_{max}) (Schmitz et al., 2010). If no measured HR_{max} is available, age-predicted maximum heart rate ($APHR_{max}$, 220 minus age) is often applied (Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997; Musanti, 2012). Further options are to use percentages of maximal oxygen uptake (VO_{2max}) or heart rate reserve (HRR, difference between resting heart rate and HR_{max}) (Garber et al., 2011). Some authors also prefer to derive exercise intensities from peak power output (PPO) which is not part of the ACSM's intensity classification (Courneya et al., 2012).

However, these intensity prescriptions for healthy individuals might not be valid for breast cancer survivors. Chemotherapy and thoracic radiation may impact the cardiac, pulmonary and vascular system, hemoglobin concentration, and skeletal muscle oxidative capacity (Lakoski, Eves, Douglas, & Jones, 2012). As a result, for example, 50 % of breast cancer survivors were observed to present with resting sinus tachycardia 20 months after anthracycline-taxane containing chemotherapy and/or therapy with the monoclonal antibody trastuzumab (Jones et al., 2006). An elevated resting heart rate reduces HRR and, therefore, intensity prescription in percentages of HRR might need to be adjusted. Similarly, VO_{2max} is markedly reduced in breast cancer survivors compared to healthy individuals (Jones et al., 2012; Klassen et al., 2014; Schneider et al., 2014), which might affect intensity prescription in percentages of VO_{2max}. For training prescription, the interpretation of previous exercise intervention studies, and the design of future studies it is essential

to know whether and how intensity classification for healthy adults (Garber et al., 2011) needs to be adapted for breast cancer survivors.

Therefore, CPETs in breast cancer survivors were analyzed in the present study to (i) evaluate whether the exercise intensity classification for apparently healthy adults by the ACSM (Garber et al., 2011) is valid in breast cancer survivors and (ii) provide an adapted exercise intensity prescription table for breast cancer survivors to facilitate training recommendations and comparisons of previous training intervention studies that used different parameters for exercise prescription. Breast cancer survivors were investigated at the end of primary therapy to represent a point in time typical for the beginning of endurance training.

Materials and Methods

General design

For the present analysis, data from two randomized controlled clinical exercise intervention trials were used: the BEST and BEATE study (ClinicalTrials.gov ID NCT01468766 and NCT01106820). In these studies, the effects of relaxation training (non-exercising social attention control group) vs. exercise training were investigated in breast cancer patients undergoing radiation and chemotherapy, respectively (for study design see (Potthoff et al., 2013) and (Schmidt et al., 2013)). Both studies were approved by the Ethics Committee of the Medical Faculty Heidelberg and respected human rights according to the Declaration of Helsinki. Written informed consent was obtained from all patients before enrolment. CPETs of the relaxation control group participants at the end of primary therapy were analyzed. Oxygen uptake reserve (VO_2R, difference between resting and maximal oxygen uptake representing the individual range of exercise capacity) served as the reference to define intensity

classes (Garber et al., 2011). Individual linear regression equations were calculated from the CPET data with percentages of VO_2R as the independent variable and percentages of HRR, $HR_{max,}$ $APHR_{max}$, VO_{2max}, and PPO as dependent variables to derive the intensity classes for the other parameters. The results were compared to the exercise intensity classification for apparently healthy adults by the ACSM (Garber et al., 2011).

Participants

Female patients with histologically confirmed primary breast cancer, stage 0 to III, age ≥18 years, and BMI ≥18 $kg \cdot m^{-2}$ were included. Participants belonged to the non-exercising relaxation control group and were tested once 2 weeks before to 12 weeks after the end of the primary therapy, i.e. surgery plus chemotherapy and/or radiation. Exclusion criteria were (i) acute infectious diseases, severe neurological, cardiovascular, respiratory or renal diseases, or other concurrent malignant diseases, (ii) intake of beta blockers or calcium channel blockers, (iii) premature cessation of the CPET due to medical reasons (e.g. ECG abnormalities or high blood pressure) or lack of spending maximal effort (respiratory exchange ratio (RER) <1.10 or HR_{max} <200 minus age (Midgley, McNaughton, Polman, & Marchant, 2007)), and (iv) completion of <2 exercise stages in the CPET to enable calculation of a regression equation. Eligibility for maximal exercise testing was approved by a study physician. Of 89 eligible patients, a total of 37 patients had to be excluded (beta or calcium channel blockade: *n* = 18, <2 exercise stages in the CPET: *n* = 5, premature cessation of the CPET due to medical reasons: *n* = 2, and lack of spending maximal effort: *n* = 12), resulting in a study population of *n* = 52. Patients' characteristics are given in **Table 1**.

Table 1: Patients' characteristics (primary therapy included surgery plus chemotherapy and/or radiation; n = 52).

Anthropometric data	
Age [years], mean ± SD	52 ± 9
Height [cm], mean ± SD	168 ± 7
Weight [kg], mean ± SD	71 ± 11
BMI [$kg \cdot m^{-2}$], mean ± SD	25.4 ± 3.5
Breast cancer stage	
0, *n* (%)	2 (4%)
I, *n* (%)	27 (52%)
II, *n* (%)	15 (29%)
III, *n* (%)	8 (15%)
ECOG	
0, *n* (%)	49 (94%)
1, *n* (%)	3 (6%)
Therapy	
Surgery, *n* (%)	52 (100%)
Chemotherapy, *n* (%)	32 (62%)
Anthracyclines, *n* (%)	31 (60%)
Taxanes, *n* (%)	31 (60%)
Radiotherapy, *n* (%)	51 (98%)
Targeted therapy, *n* (%)	8 (15%)
Trastuzumab, *n* (%)	8 (15%)
Hormone therapy, *n* (%)	31 (60%)
Time since end of primary therapy [wk], mean ± SD	5 ± 3

Determination of patients' characteristics

Height and body weight were measured in sportswear without shoes using a calibrated scale and a yardstick. Breast cancer stage, performance score (ECOG), and medication were derived from the patient's medical records. Present medication was additionally asked prior to CPET.

Cardiopulmonary exercise tests

The CPETs were performed on an electronically braked cycle ergometer (Ergoselect 100, Ergoline, Bitz, Germany). All participants were familiar with the

CPET procedure from previous testing. The tests were preceded by a resting period of >3 min in a sitting position on the cycle ergometer to obtain resting values. The stepwise incremental exercise protocol started at 50 W and work rate was increased every 2 min by 25 W until voluntary exhaustion or occurrence of medical reasons for premature exercise cessation. Cadence was kept constant around 60 or 65 revolutions per minute and participants were encouraged to spend maximal effort. A 12-lead ECG was recorded continuously and blood pressure was measured every 2 min. Gas exchange measurements were performed continuously using a breath-by-breath system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). The metabolic device was calibrated before each test according to the instructions of the manufacturer using a 3 l syringe and gas of known concentration.

Derived variables

Gas exchange data and heart rate (HR) were time averaged over 30 s. Resting oxygen uptake (VO_2) and HR were considered the last 30 s average value of the resting period. It was previously demonstrated that resting VO_2 assessment in a sitting compared to a supine position does not affect the intercept and slope of %HRR-%VO_2R relationship (Cunha, Midgley, Monteiro, & Farinatti, 2010). PPO was linearly interpolated if the last stage of the stepwise incremental protocol was not completed. VO_{2max} and HR_{max} were determined as the highest 30 s average values during or immediately post exercise, respectively. RER_{max} was considered the highest 30 s average value during exercise. $APHR_{max}$ was calculated using the formula 220 minus age (Dimeo, Fetscher, et al., 1997). VO_2R was calculated as difference between VO_{2max} and resting VO_2. HRR was calculated as difference between HR_{max} and resting HR. Over the course of the exercise test, VO_2 and HR

were averaged over the last 30 s of each exercise stage and the last 30 s of the test and were expressed in %VO_2R, %VO_{2max}, %HRR, %HR_{max}, and %$APHR_{max}$.

Statistical analysis

For each participant, individual linear regression equations were calculated using percentages of VO_2R as independent variable and percentages of HRR, VO_{2max}, HR_{max}, $APHR_{max}$, and PPO as dependent variables. From these individual equations, intensity classes according to the intensity classification for apparently healthy adults by the ACSM (Garber et al., 2011) were calculated for breast cancer survivors using percentages of VO_2R as reference. Obtained values were compared with the ACSM's values for 30, 40, 60, and 90 % VO_2R by means of one-sample *t*-tests. To control for the familywise error, a sequential Bonferroni correction was applied and $p < 0.017$ was considered significant for this analysis. Slopes and intercepts of the individual linear regression equations were averaged across participants to receive mean regression equations. In addition to the data of the whole group, subgroup data for participants with and without chemotherapy were analyzed. Slopes and intercepts of the regression equations as well as values for 30, 40, 60, and 90 % VO_2R were compared between subgroups using unpaired Student's *t*-tests. Data are presented as means ± standard deviations (SD) and 95 % confidence intervals (95% CI).

Results

CPET outcomes

Resting and maximal CPET data are given in Table 2. The relationships between different CPET variables observed in breast cancer survivors compared to those in healthy adults given by the ACSM data are displayed in Figure 1. The regression between percentages of PPO and VO_2R (not part of the ACSM's intensity classification) averaged % PPO = 1.08 ± 0.26 %VO_2R - 7.45 ± 25.03 (*n* = 52). Slopes and intercepts of the regressions were not significantly different between breast cancer survivors with and without chemotherapy (all $p \geq 0.18$, HR: *n* = 31 with chemotherapy vs. *n* = 20 without chemotherapy; VO_2: *n* = 32 with chemotherapy vs. *n* = 20 without chemotherapy).

Table 2: Resting and maximal data of the cardiopulmonary exercise test (n = 52, VO_2: oxygen uptake, HR: heart rate, PPO: peak power output, VO2max: maximal oxygen uptake, RERmax: maximal respiratory exchange ratio, HRmax: maximal heart rate, APHRmax: age-predicted maximal heart rate).

Parameter	Mean ± SD
Resting VO_2 [ml·min^{-1}]	247 ± 60
Resting VO_2 [ml·min·kg^{-1}]	3.5 ± 0.7
Resting HR [min^{-1}]	83 ± 12
Resting sinus tachycardia [*n* (%)]	4 (8%)
PPO [W]	123 ± 26
PPO [W·kg^{-1}]	1.7 ± 0.4
VO_{2max} [ml·min^{-1}]	1580 ± 390
VO_{2max} [ml·min·kg^{-1}]	22.6 ± 6.3
RER_{max} [ ]	1.18 ± 0.09
HR_{max} [min^{-1}]	158 ± 14
$APHR_{max}$ [min^{-1}]	168 ± 9

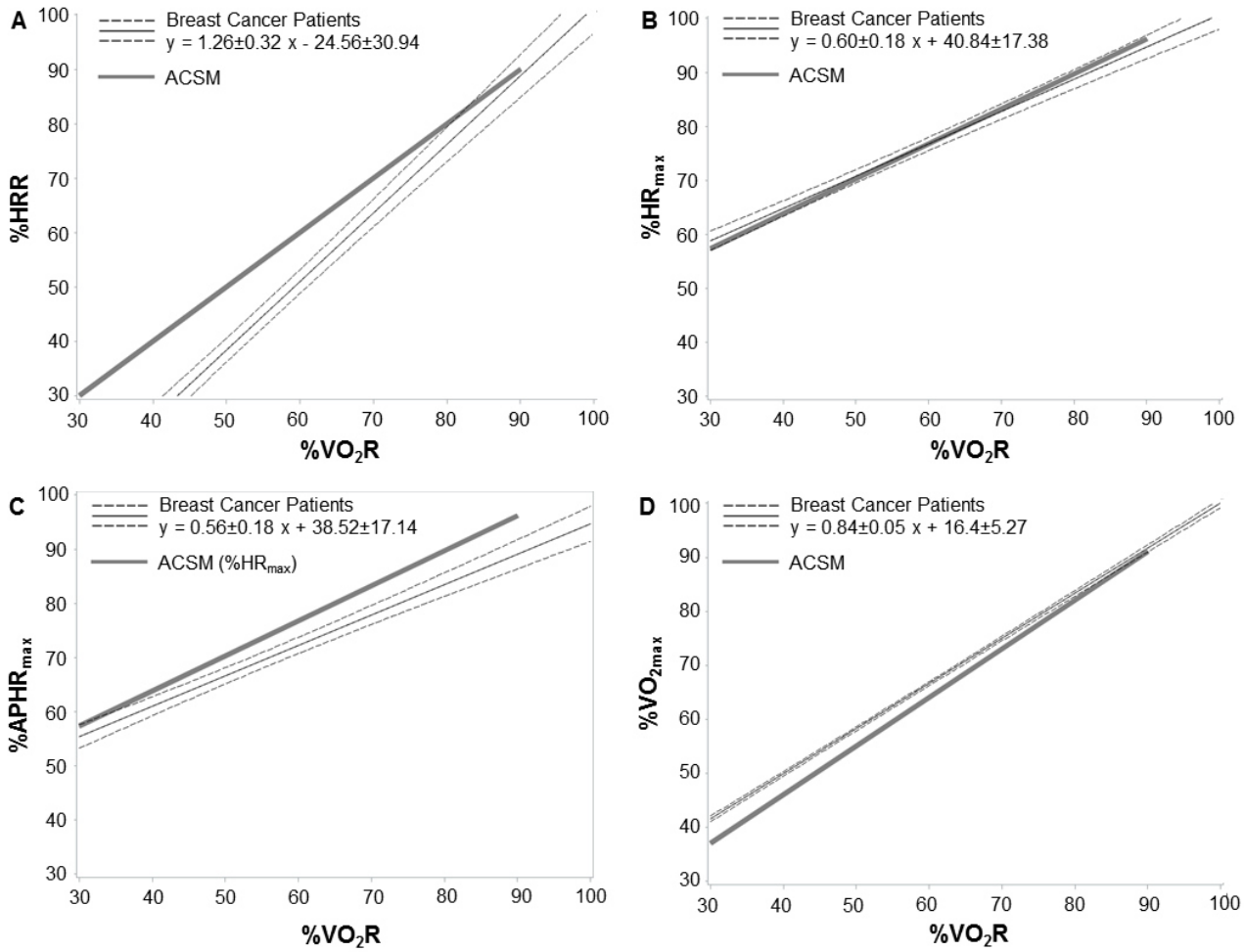

Figure 1: Linear regressions between percentages of VO2R and percentages of (A) HRR, (B) HRmax, (C) APHRmax, and (D) VO2max in breast cancer survivors at the end of primary therapy (observed data, means and 95% confidence bands) and healthy individuals (data provided by the ACSM, mean regression lines, n = 51 for HR, n = 52 VO2).

Exercise intensity classification

Intensity classes observed in breast cancer survivors compared to the data of healthy adults provided by the ACSM (Garber et al., 2011) are given in Table 3. Percentages of HRR were significantly lower in breast cancer survivors than in healthy adults within the range of intensities relevant for training prescription of 30, 40, and 60 % VO_2R (all $p < 0.001$, $n = 51$). Percentages of HR_{max} corresponding to 30, 40, and 60 % VO_2R were not significantly different between breast cancer survivors and healthy adults (all $p \geq 0.29$, $n = 51$). Percentages of $APHR_{max}$ in breast cancer survivors corresponding to 30 and 40 % VO_2R were also not significantly

different from HR_{max} in healthy adults (all $p \geq 0.07$), but percentages of $APHR_{max}$ corresponding to 60 % VO_2R were significantly lower (all $p < 0.001$, $n = 51$). Percentages of VO_{2max} for given percentages of VO_2R were all significantly higher in breast cancer survivors than in healthy adults (all $p < 0.001$, $N = 52$). Subgroup analyses for patients with and without chemotherapy revealed no significant differences for any value within all intensity classes (all $p \geq 0.15$, $n = 51$ for HR, $n = 52$ for VO_2).

Table 3: Values observed in breast cancer survivors at the end of primary therapy compared to the values for apparently healthy adults provided by the ACSM (Garber et al., 2011).

Reference	**Healthy Adults**	**Cancer Survivors**	**Healthy Adults**	**Cancer Survivors**	**Cancer Survivors**	**Healthy Adults**	**Cancer Survivors**
%VO_2R	**%HRR**	**%HRR**	**%HR_{max}**	**%HR_{max}**	**%$APHR_{max}$#**	**%VO_{2max}**	**%VO_{2max}**
Mean	Mean	Mean ± SD (95% CI)	Mean	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean	Mean ± SD (95% CI)
30	30	13.2 ± 21.5 * (7.1 – 19.3)	57	58.8 ± 12.0 (55.4 – 62.1)	55.4 ± 12.8 (51.8 – 59.0)	37	41.5 ± 3.7 * (40.5 – 42.5)
40	40	25.8 ± 18.3 * (20.7 – 31.0)	64	64.8 ± 10.3 (61.9 – 67.7)	61.0 ± 11.5 (57.8 – 64.2)	46	49.9 ± 3.2 * (49.0 – 50.7)
60	60	51.0 ± 12.3 * (47.6 – 54.5)	77	76.7 ± 6.9 (74.8 – 78.7)	72.2 ± 9.4 * (69.6 – 74.9)	64	66.6 ± 2.1 * (66.0 – 67.2)
90	90	88.8 ± 5.5 (87.3 – 90.3)	96	94.7 ± 2.7 * (93.9 – 95.5)	89.1 ± 8.6 * (86.6 – 91.5)	91	91.6 ± 0.5 * (91.5 – 91.8)

Asterisks indicate significant differences (Bonferroni adjusted p < 0.017, n = 51 for HR, n = 52 for VO2, # compared to the ACSM's %HRmax values for healthy adults).

Training prescriptions

A specific exercise intensity prescription table for breast cancer survivors at the end of primary therapy in the style of the ACSM's table for healthy adults (Garber et al., 2011) but derived from the observed data is given in Table 4. This table can be used for exercise intensity prescription in this specific population.

Table 4: Exercise intensity prescriptions for breast cancer survivors at the end of primary therapy based on observed data in the style of the ACSM's exercise intensity classification for apparently healthy adults (Garber et al., 2011) with percentages of VO2R as reference (n = 51 for HR, n = 52 for VO2).

Intensity Class	%VO_2R	%HRR	%HR_{max}	%$APHR_{max}$	%VO_{2max}	%PPO
Very light	< 30	< 13	< 59	< 55	< 42	< 25
Light	30 - 39	13 - 25	59 - 64	55 - 60	42 - 49	25 - 35
Moderate	40 - 59	26 - 50	65 - 76	61 - 71	50 - 66	36 - 57
Vigorous	60 - 89	51 - 88	77 - 94	72 - 88	67 - 91	58 - 89
Near-max. to maximal	≥ 90	≥ 89	≥ 95	≥ 89	≥ 92	≥ 90

Discussion

The present study for the first time evaluated whether and how the widely used ACSM's exercise intensity classification for apparently healthy adults (Garber et al., 2011) needs to be adapted for breast cancer survivors at the end of primary therapy. This investigation is highly important because endurance training is recommended for breast cancer survivors due to its numerous beneficial effects (Hayes et al., 2009; Rock et al., 2012; Schmitz et al., 2010), but it remains unclear how to adequately prescribe exercise training intensities in this population. The analysis demonstrates that if exercise intensity in breast cancer survivors at the end of primary therapy is prescribed in percentages of HRR according to the ACSM's intensity classification for apparently healthy adults (Garber et al., 2011), exercise is considerably more intense than intended. In contrast, the use of percentages of VO_{2max} leads to slightly lower exercise intensities than intended. Only the use of percentages of HR_{max} according to the ACSM appears to be valid in breast cancer survivors within the relevant range of intensity classes. Therefore, exercise intensity prescriptions for healthy adults should not be uncritically adopted for breast cancer survivors. Especially, common prescriptions in percentages of HRR should not be

used. Instead, specifically adapted exercise training intensity prescriptions are recommended as provided in Table 4 for middle-aged breast cancer survivors at the end of primary therapy.

The observed differences in intensity classes defined as percentages of HRR and VO_{2max} between breast cancer survivors and healthy adults provided by the ACSM appear to be attributable to some differences in resting and maximal values. As expected (Schneider et al., 2014), mean VO_{2max} was reduced by about 17 % when compared to age and sex specific reference values (Koch et al., 2009). However, resting oxygen uptake exactly met the standard value for healthy individuals of 3.5 $ml \cdot min^{-1} \cdot kg^{-1}$ (Glass & Dwyer, 2007), which together resulted in a reduced VO_2R reflecting the smaller performance capacity in breast cancer survivors. Percentages of VO_2R served as reference for intensity classification (Garber et al., 2011) and the relationship between percentages of VO_2R and VO_{2max} only slightly differed from that in healthy individuals because of the absence of differences in resting oxygen uptake. In terms of percentages of HRR, the average resting heart rate was about 15 min^{-1} higher than that reported for healthy untrained females of similar age participating in the HERITAGE Family Study (Wilmore et al., 2001). Furthermore, average HR_{max} was about 10 min^{-1} lower than expected in 52 year old healthy women according to a meta-analysis (Tanaka, Monahan, & Seals, 2001) which is not associated with a lack of spending maximal effort as indicated by the high RER_{max}. Thus, HRR was severely reduced, leading to an altered relationship between percentages of VO_2R and HRR.

Interestingly, there were no significant differences between breast cancer survivors with and without chemotherapy for any of the regressions or intensity classifications. This suggests that about five weeks after the end of primary therapy,

the relationship between the observed variables in response to incremental exercise is not affected in a different way from chemotherapy than from other cancer related factors like deconditioning due to physical inactivity, radiotherapy, targeted or hormone therapy. However, this finding should be interpreted cautiously. First, the time between the end of chemotherapy and the CPET varied between patients. They had received neoadjuvant or adjuvant chemotherapy regimens, and all but one of them had received radiation thereafter which means that the acute effects of chemotherapy might have already been washed out. Second, the subpopulations with and without chemotherapy were relatively small for statistical comparisons. Therefore, while the present analysis reflects a point in time typical for the beginning of exercise training and the sample size was sufficient for overall analyses, it may not be ideal to investigate the specific effects of chemotherapy on exercise intensity classification.

Following the style of the ASCM's table for exercise intensity classification for apparently healthy adults, we present a table for exercise intensity prescription in breast cancer survivors at the end of primary therapy (Table 4). This table can be used for training prescription in this specific population. The easiest way is to calculate $APHR_{max}$ as 220 minus age and to prescribe aerobic activities with an exercise heart rate of 61–71 % $APHR_{max}$ for 150 min/week (or with an exercise heart rate of 72–88 % $APHR_{max}$ for 75 min/week). However, it should be noted that inaccuracies in age-predicted $APHR_{max}$ may occur. Tanaka et al. (Tanaka et al., 2001) report a range in HR_{max} of about 40 min^{-1} in healthy women at the age of 50 years. In the present study, measured HR_{max} differed from $APHR_{max}$ by -42 to 19 min^{-1} (data not shown) supporting these concerns (2001). Therefore, while the use of $APHR_{max}$ is a feasible way for exercise prescription in practice, measured instead of

age predicted values appear preferable in exercise intervention studies. In these studies, measured values ideally come from maximal CPET which is feasible and safe in breast cancer survivors at the end of primary therapy (Jones, Eves, Haykowsky, Joy, & Douglas, 2008; Lakoski et al., 2012).

Most of the observed variables demonstrated high standard deviations for given percentages of VO_2R, indicating individual variability in exercise intensity classification. In healthy individuals, points of criticism in the use of fixed percentages of maximal values for training prescription have been raised before. For example, there is considerable variation in percentages of VO_{2max} and HR_{max} at the individual anaerobic threshold, a reference point in the blood lactate curve reflecting the individual metabolic situation (Meyer, Gabriel, & Kindermann, 1999). Furthermore, prolonged exercise at given percentages of VO_{2max} resulted in highly variable blood lactate responses between individuals demonstrating an unpredictable metabolic exercise response (Scharhag-Rosenberger, Meyer, Gassler, Faude, & Kindermann, 2010). Consequently, exercise prescription by means of individual thresholds, i.e. gas exchange or blood lactate thresholds, might be superior. In lung cancer patients, the ventilatory threshold has already been used for training prescription (Jones, Eves, Spasojevic, Wang, & Il'yasova, 2011; Jones et al., 2007). The lactate threshold has also been used in a population affected by different types of cancer (Dimeo, Tilmann, et al., 1997), but so far there are no systematic comparisons of different methods for exercise intensity prescription in cancer survivors. Threshold determination requires some additional measurements or analyses in the CPET and might therefore remain reserved for research. But this approach appears worth investigation to further improve exercise intensity prescription in cancer survivors.

Besides practical training prescription for breast cancer survivors, Table 4 also enables comparisons of pervious training studies in which different parameters were used to define exercise intensity. For example, in a study by Dolan et al. (2010) breast cancer patients initially trained for 15 min at 60 % VO_{2max} and in a study by Musanti et al. (2012) they initially trained for 15–30 min at 40–65 % $APHR_{max}$. Comparing this by means of Table 4 or Figure 2, it is apparent that participants in the study by Dolan et al. (2010) trained at a moderate intensity (52 % VO_2R) and the patients in the study by Musanti et al. (2012) trained in wide range of very light to moderate intensity (3–47 % VO_2R). In two other studies by Vincent et al. (2013) and MacVicar et al. (1989) breast cancer patients initially performed interval training at 50–60 % HR_{max} and 60–85 % HRR, respectively. This corresponds to the very light to light (15–32 % VO_2R) and the vigorous intensity class (67– 87 % VO_2R), respectively. Thus, Table 4 and Figure 2 allow converting endurance training intensities defined by means of different parameters into comparable intensity classes or % VO_2R values, respectively. This for the first time enables comprehensive reviews and meta-analyses focusing on the effects of different endurance training intensities in breast cancer survivors.

A strength of the present study is that individual linear regression equations were calculated for each participant instead of working with averaged data. This enhances accuracy of the findings. Furthermore, compared with similar analyses in individuals with type 2 diabetes (n = 23) (Colberg, Swain, & Vinik, 2003), obesity (three BMI groups with *n* = 22–23 in each group) (Pinet, Prud'homme, Gallant, & Boulay, 2008), myocardial infarction or chronic heart failure (*n* = 65 and *n* = 72, respectively) (Brawner, Keteyian, & Ehrman, 2002), the sample size of 52 appears adequate. However, there are also some weaknesses that should be addressed: A

relatively homogeneous group of middle-aged non-obese breast cancer survivors at the end of primary therapy was investigated, which limits generalizability of the data. The present findings might therefore be considered preliminary supporting the need of further studies in patients with different types of cancer and at different points in the cancer continuum. Another critical point is that the exercise protocol started relatively high at 50 W. Although the regression equations are based on a reasonable number 4 ± 1 (min–max: 2–6) data points, the values for very light or light exercise intensity classes occurred below 50 W in some instances and, therefore, the regression equations do not perfectly reflect these intensity classes. Furthermore, resting VO_2 and resting HR for the calculation of VO_2R and HRR were not assessed according to gold standard methods in the morning in a supine position after a defined period of rest. Instead, we used pre-exercise resting data which might be higher but reflect routine CPETs in a more realistic way. A previous study compared different methods for assessing resting values and although differences in resting values were observed, the relationship between percentages of VO_2R and HRR was not affected (Cunha et al., 2010). Therefore, it is unlikely that the results of the present study were relevantly affected by the method of resting measurements.

Conclusions

Exercise guidelines for cancer survivors recommend 150 min/week of moderate or 75 min/week of vigorous aerobic exercise and suggest adaptations of exercise prescriptions based on the disease and treatment-related adverse effects (Schmitz et al., 2010). The present study for the first time quantifies the required adaptations for endurance training intensity prescription in middle-aged non-obese breast cancer survivors at the end of primary therapy.

Analyses of CPETs revealed that if intensity prescriptions for healthy adults (Garber et al., 2011) are applied in breast cancer survivors at the end of primary therapy, exercise prescribed in percentages of HRR is considerably more intense than intended. The use of percentages of VO_{2max} results in a slightly lower intensity than intended and the use of HR_{max} appears adequate. Therefore, exercise training intensity prescriptions for healthy adults should not be uncritically used for cancer survivors. Instead, we recommend specifically adapted exercise training intensity prescriptions as provided here for the investigated population. Further studies in patients with different types of cancer and at different points in the cancer continuum are needed for more generalizable recommendations.

From a scientific perspective, the variability of the observed data suggests that more individualized ways of intensity prescription might be superior. Future research should therefore address the use of ventilatory or blood lactate thresholds for intensity prescription in cancer survivors.

Acknowledgements

The BEST study was funded by the Interdisciplinary Research Funding Program (intramural) of the National Center for Tumor Diseases (NCT) Heidelberg and supported by the Foundation “Stiftung Leben mit Krebs”. Dr. Wiskemann was personally supported by the Manfred-Lautenschlaeger-Foundation.

Conflict of interests

The authors declare that they have no competing interests.

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7. Randomized controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life

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Annals of oncology 2014 Nov;25(11):2237-4.

Abstract

Background

Exercise has been reported to decrease cancer-related fatigue and to increase quality of life (QoL) in various breast cancer populations. However, studies investigating exercise during radiotherapy or resistance training are scarce. We conducted a randomized controlled trial (BEST study) to assess the efficacy of 12-week resistance training on fatigue beyond possible psychosocial effects of a group-based intervention.

Patients and methods

One-hundred-sixty patients with breast cancer stage 0-III were randomly assigned to a 12-week progressive resistance training (2 times/week) or a 12-week relaxation control (2 times/week). Both interventions were group-based. The primary endpoint fatigue was assessed with a 20-item multidimensional questionnaire, QoL with EORTC questionnaires. Statistical analyses were based on analysis of covariance models for the individual changes from baseline to week 13.

Results

Adherence to the intervention program as well as the completion rate (97%) for the primary outcome variable fatigue were high. In intention-to-treat analyses for the *N*=155 patients, significant between-group mean differences (MD) favoring the exercise group were observed for general fatigue (*P*=0.044), especially for the subscale physical fatigue (MD= -0.8; 95% confidence interval = (-1.5, -0.2), *P*=0.013), but not for affective (*P*=0.91) or cognitive fatigue (*P*=0.65). For QoL, significantly larger improvements regarding the role function (*P*=0.035) and pain (*P*=0.040) were noted among exercisers compared to relaxation controls. Future perspective improved significantly stronger in the relaxation control group compared to the exercise group (*P*=0.047).

Conclusions

The 12-week resistance training program was a safe, feasible and efficacious strategy to improve cancer-related fatigue and components of QoL in breast cancer patients during adjuvant radiotherapy. As exercise was compared to another group-based intervention, results indicate that resistance training effects on fatigue and QoL go beyond psychosocial benefits, and that the clinically relevant overall benefit of resistance exercise compared to usual care can be assumed to be higher.

Key Messages

This randomized controlled trial evaluated the efficacy of 12-week resistance training beyond the psychosocial benefits associated with a 12-week group-based relaxation intervention on cancer-related fatigue and quality of life in 160 breast cancer patients receiving adjuvant radiotherapy. Between-intervention comparisons showed that the resistance training was an efficacious strategy to reduce the primary and clinically meaningful endpoint fatigue.

Additionally uploaded online-only Supplementary Material:

Figure S1

Introduction

Many breast cancer (BC) patients receive radiotherapy and are thus confronted with cancer-related fatigue as the most frequent side effect, with severe impact on quality of life (QoL) (Noal et al., 2011). Despite increasing evidence that exercise may be an effective treatment for fatigue, exercise during radiotherapy has rarely been investigated (Brown et al., 2011). To our knowledge, only one small randomized exercise trial (*N*=46) specifically investigated BC patients during radiotherapy (Mock et al., 1997). Four other exercise trials reported on mixed patient populations, including BC patients during adjuvant radiotherapy (Mock et al., 2005; Mustian et al., 2009; Mutrie et al., 2007; Segal et al., 2001).

Further clarification is also needed on which types of exercise are beneficial. Benefits of both aerobic and resistance training on fatigue and QoL have been reported (Brown et al., 2011; Ohira, Schmitz, Ahmed, & Yee, 2006; Strasser, Steindorf, Wiskemann, & Ulrich, 2013). Yet, the majority of randomized exercise trials investigated pure aerobic or combined aerobic and resistance training. Thus, the effects of muscle strengthening exercise are still understudied (Al-Majid & Gray, 2009).

In addition, it is still unclear whether exercise interventions reduce fatigue and improve QoL primarily through psychosocial effects. It has been shown that group-based, supervised exercise produces positive psychosocial “side effects” due to social interactions, improved self-efficacy, and attention from a trainer (Faller et al., 2013), which potentially contribute to lower fatigue and higher QoL. As most previous studies compared exercise interventions to usual care, physiological effects beyond psychosocial group-related effects could not be studied. Thus, the BEST study aimed to evaluate the efficacy of resistance training beyond the psychosocial benefits

associated with a group-based non-exercise intervention on fatigue and QoL in 160 BC patients receiving adjuvant radiotherapy.

Methods

Study design

The BEST study is a prospective, randomized, controlled intervention trial evaluating a 12-week resistance training in stage 0-III BC patients during adjuvant radiotherapy. To determine the effect of exercise per se, the control group received a supervised group-based muscle-relaxation program. Both interventions began parallel to the first radiotherapy. Endpoints were assessed before start of radiotherapy (baseline, T0), post-radiotherapy (week 7, T1), and post-intervention (week 13, T2). The study was approved by the ethics committee of the University of Heidelberg and registered at ClinicalTrials.gov (NCT01468766). Details of the study design are described elsewhere (Potthoff et al., 2013).

Patients

Eligibility criteria were: histologically confirmed primary BC; stage 0-III after lumpectomy or mastectomy; scheduled for radiotherapy; age ≥18 years; body mass index (BMI) ≥18 kg/m^2; ability to understand and follow the study protocol; and willingness to come to the exercise facilities. Patients with contraindications for resistance training (e.g., acute infectious disease, severe cardiac disease, severe respiratory insufficiency), patients with other concomitant malignant diseases (except carcinoma in situ of skin or cervix), and patients who were currently participating in systematic intense exercise training (at least 1h twice/week) or who had previously

participated in an exercise intervention trial were excluded on screening. All participants gave written informed consent.

Recruitment and randomization

Eligible patients scheduled for adjuvant radiotherapy at the University of Heidelberg Medical Center between February 2011 and March 2013 were contacted in clinic. Interested patients were informed in detail by the BEST study physicians and study coordinators. Patients who signed the written informed consent underwent, within 21 days prior to the start of radiation, a baseline assessment at the National Center for Tumor Diseases (NCT), including a check for contraindications. Eligible participants were randomly allocated 1:1 to the exercise group (EX) or relaxation control group (RC). Allocation was done by a biometrician who was not involved in the recruitment procedure, based on predetermined lists with random block size, stratified by age and baseline physical fatigue level. Study personnel did not have access to the randomization lists.

Interventions

Both interventions were administered for about 60 minutes twice weekly over a 12-week period together with other cancer patients under the supervision of trained and experienced physiotherapists in specific training facilities at the study center. The intervention started at the day of the first radiotherapy treatment. Physical status, adverse events and adherence were recorded for each training session by the participants and the trainers. The progressive exercise intervention comprised 8 different machine-based resistance exercises (3 sets, 8-12 repetitions at 60–80% of

1-RM) (Potthoff et al., 2013). The control group performed progressive muscle relaxation without any aerobic or muscle strengthening components.

Outcome measures

The primary endpoint was change of cancer-related fatigue from baseline to week 13. Fatigue was assessed with the Fatigue Assessment Questionnaire (FAQ), a 20-item, self-assessment questionnaire validated for a German-speaking population (Glaus & Muller, 2001). It covers the physical, affective and cognitive fatigue dimensions. Scores are on a 0-100 scale, with higher scores indicating worse fatigue.

Quality of life (QoL) was assessed with the validated, 30-item self-assessment questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30, version 3.0) (Aaronson et al., 1993). In addition, the 23-item BC-specific EORTC QLQ-BR23 was applied.

Depressive symptoms were self-assessed with the 20-item CES-D scale, a validated instrument for cancer patients (Schroevers, Sanderman, van Sonderen, & Ranchor, 2000). Cognitive function was estimated with the trail-making-test, a reliable and valid measure used in neuropsychological diagnostics (Sanchez-Cubillo et al., 2009).

Muscle strength was measured for isometric and isokinetic muscle capacity of representative muscle groups for upper and lower extremity (Potthoff et al., 2013). Endurance performance (VO_{2peak}) was measured on a bicycle ergometer. The procedure was also used to identify exercise-contraindicating cardiac impairments.

Safety

Potential adverse effects (e.g., lymphedema, pain, muscle soreness, nausea, dyspnea, tachycardia) were recorded by the participants at each training session, using standardized questionnaires. Adverse events reported spontaneously by the patient or observed by therapists were also recorded.

Sample size and statistical analyses

The study was designed to detect a standardized effect size of 0.5 for total fatigue with a two-sided t-test of power of 80% at 5% significance level. Thus, 64 patients per arm were needed for analysis. Assuming a maximal drop-out rate of 20%, 80 patients were recruited per arm.

Data were analyzed on the intent-to-treat-basis (ITT). Analysis of covariance (ANCOVA) was used with pre- to post-intervention change as dependent variable, the intervention group as independent variable, and the baseline measure as covariate. To fulfill the normality assumption, fatigue parameters were square-root transformed. Transformation of EORTC parameters was not needed. As the number of missing fatigue values was very low (3%), we performed complete-case analyses. Confounding and effect modification by potential influencing factors, such as age, baseline BMI, and treatment characteristics, were investigated. Further sensitivity analyses were performed, using ordinal logistic regression, to investigate robustness of results for the EORTC symptoms that are based only on single items. Results did not differ substantially from the ANCOVA results. We made no adjustment for multiple comparisons for the secondary outcomes, which were considered to be explorative analyses.

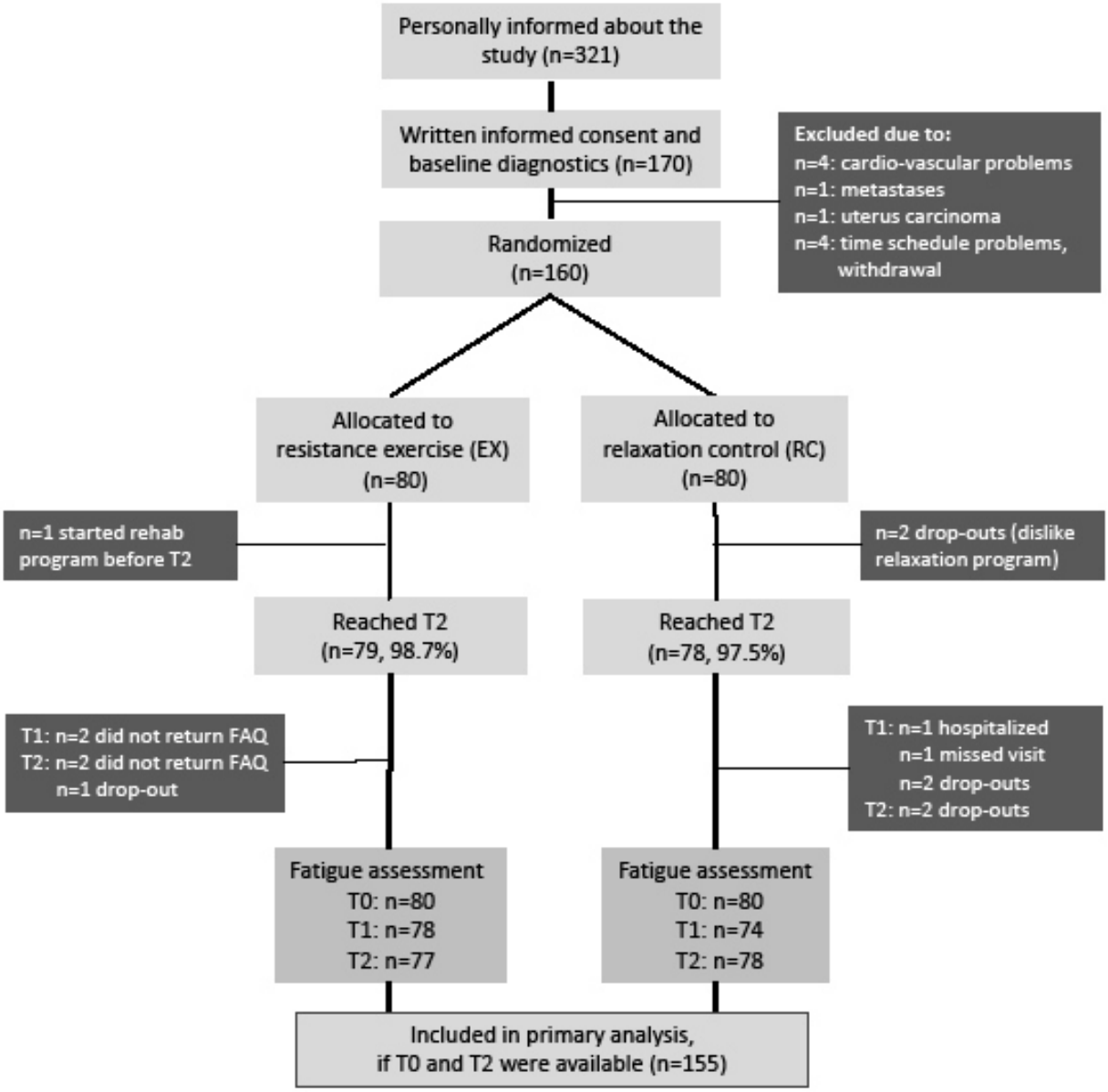

Figure 1. CONSORT diagram
Abbreviations: FAQ, Fatigue Assessment Questionnaire; T0, before start of radiotherapy and intervention (baseline); T1, post radiotherapy (week 7); T2, post intervention (week 13)

Standardized effect sizes (ES) were calculated for all outcomes by dividing the between-group difference of the post-intervention means (adjusted for baseline values) by the pooled baseline standard deviation. For ease of presentation, ES in favor of EX received a positive sign and in favor of RC a negative sign. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant. SAS Version 9.3 was used for all analyses.

Results

A total of 321 BC patients were personally informed about the study, 170 gave written informed consent and underwent baseline diagnostics, out of which 160 patients were randomized for the BEST study, 80 to EX and 80 to RC (Figure 1). Pre- and post-intervention assessment of the primary endpoint was available in a total of 155 (97%) participants, 77 in EX and 78 in RC. Demographics and treatment characteristics did not differ significantly between both intervention groups (Table 1). Mean age was 56 years (range 29-75). The majority of patients had not received any chemotherapy before radiotherapy (64%). Neo-adjuvant chemotherapy had been completed by 19% of the patients (median time to baseline: 9 weeks, 1st to 3rd quartile range (QR): 8-11 weeks). The other patients (16%) had completed adjuvant chemotherapy shortly before baseline (median: 3.5 weeks, QR: 2.7–5.0). All primary and secondary outcome variables were equally distributed in EX and RC at baseline (all $P>0.05$), except for the EORTC symptom dry mouth ($P=0.033$).

Table 1: Baseline Characteristics of the Study Population

Characteristics	TOTAL (n=155)		Exercise (n=77)		Control (n=78)	
	No.	%	No.	%	No.	%
Age, years						
Mean	55.8		55.2		56.4	
SD	9.1		9.5		8.7	
BMI						
Mean	27.2		26.9		27.6	
SD	5.1		5.4		4.8	
Days since surgery						
Mean	67.1		68.1		66.2	
SD	56.0		60.7		51.1	

Table 1: Baseline Characteristics of the Study Population

Characteristics	TOTAL (n=155)		Exercise (n=77)		Control (n=78)	
Stage						
0	14	9.0	9	11.7	5	6.4
1	81	52.3	36	46.8	45	57.7
2	45	29.0	27	35.1	18	23.0
3	15	9.6	5	6.5	10	12.8
Pre-treatment						
Neo-adjuvant chemotherapy	30	19.4	14	18.2	16	20.5
Surgery only	100	64.5	51	66.2	49	62.8
Adjuvant chemotherapy	25	16.1	12	15.6	13	16.7
Radiation technic						
3D	116	74.8	61	79.2	55	70.5
IMRT	39	25.2	16	20.8	23	29.5
Radiation boost	113	72.9	57	74.0	56	71.8
Current herceptin therapy	11	7.1	7	9.1	4	5.1
Current hormone therapy	75	48.4	41	53.2	34	43.6
Sports in the year before diagnosis						
none	66	42.6	33	42.9	33	42.3
>0-9 MET*h/wk	38	24.5	19	24.7	19	24.4
>9-21 MET*h/wk	27	17.4	15	19.5	12	15.4
>21 MET*h/wk	24	15.5	10	13.0	14	17.9
Current smokers	16	10.3	9	11.7	7	9.0

Abbreviations: BMI, Body Mass Index; IMRT, Intensity Modulated Radiation Therapy; MET, metabolic equivalent; SD, standard deviation.

Adherence was similar in both groups. Out of 24 scheduled sessions, the median attended number was 19 (QR: 13–23, range 1-24) in EX and 19 (QR: 12–22,

range 0-24) in RC. In EX, significant improvements were observed for muscle strength, e.g., in isokinetic knee flexion (P<0.0001), but not for cardiorespiratory fitness. No injuries or severe adverse events related to the interventions were reported. The frequency of reported lymphedema did not differ between groups.

Primary endpoint

Overall, from pre- to post-intervention, total cancer-related fatigue decreased significantly in EX, while in RC there was no significant change (Table 2). Correspondingly, the primary ITT analysis showed significant differences between both intervention groups (P=0.044) with ES=0.25 (Figure S1). Considering the different fatigue dimensions, the effect was significant regarding physical fatigue (P=0.013, ES=0.33), but not for the affective (P=0.91, ES=0.01) or the cognitive (P=0.65, ES=0.07) dimension.

Table 2: Fatigue at different timepoints, adjusted mean changes and between-group differences

Outcome*	Arm	N†	Mean (SD)			Adjusted‡ Mean Change (95%CI)			Adjusted‡ Between-Group Difference (95%CI)		
			Baseline (T0)	Post RT (T1)	Post Interv. (T2)	from T0 to T1	from T1 to T2	from T0 to T2	from T0 to T1	from T1 to T2	from T0 to T2
Overall											
Total fatigue	Exercise	77	5.9 (2.2)	5.9 (2.0)	5.4 (2.3)	0.0 (-0.3, 0.4)	**-0.6 (-0.9, -0.3)**	**-0.5 (-0.9, -0.2)**	-0.4 (-0.9, 0.1)	-0.1 (-0.5, 0.3)	**-0.5 (-1.0, -0.0)**
	Relaxation	78	6.0 (2.0)	6.3 (1.7)	5.9 (1.9)	**0.4 (0.1, 0.8)**	**-0.5 (-0.8, -0.2)**	-0.0 (-0.4, 0.3)			
Physical fatigue	Exercise	77	5.7 (2.7)	6.1 (2.2)	5.0 (2.8)	0.4 (-0.0, 0.8)	**-1.1 (-1.5, -0.7)**	**-0.7 (-1.2, -0.3)**	-0.3 (-0.9, 0.3)	-0.5 (-1.1, 0.1)	**-0.8 (-1.5, -0.2)**
	Relaxation	78	5.9 (2.3)	6.4 (2.0)	5.9 (2.2)	**0.7 (0.2, 1.1)**	**-0.6 (-1.0, -0.2)**	0.1 (-0.4, 0.6)			
Affective fatigue	Exercise	77	5.8 (2.7)	5.4 (2.7)	5.3 (2.6)	-0.4 (-0.8, 0.1)	-0.0 (-0.4, 0.4)	**-0.5 (-1.0, -0.0)**	-0.3 (-0.9, 0.4)	0.3 (-0.3, 0.9)	-0.0 (-0.7, 0.6)
	Relaxation	78	5.6 (2.5)	5.4 (2.5)	5.2 (2.6)	-0.1 (-0.6, 0.3)	-0.3 (-0.8, 0.1)	-0.5 (-0.9, 0.0)			
Cognitive fatigue	Exercise	77	4.9 (3.0)	4.9 (3.0)	4.9 (3.2)	-0.1 (-0.6, 0.4)	-0.2 (-0.7, 0.4)	-0.1 (-0.8, 0.5)	**-0.8 (-1.5, -0.1)**	0.4 (-0.4, 1.2)	-0.2 (-1.1, 0.7)
	Relaxation	78	5.4 (3.1)	5.9 (2.6)	5.3 (3.0)	**0.7 (0.2, 1.2)**	**-0.6 (-1.1, -0.0)**	0.1 (-0.6, 0.7)			
Patients with Preceding Adjuvant Chemotherapy											
Total fatigue	Exercise	12	7.0 (1.2)	5.2 (2.0)	5.3 (2.1)	**-1.7 (-2.6, -0.8)**	0.0 (-0.5, 0.6)	**-1.6 (-2.4, -0.8)**	-1.0 (-2.3, 0.2)	0.2 (-0.6, 0.9)	-0.8 (-1.9, 0.3)
	Relaxation	13	6.4 (2.2)	5.9 (1.6)	5.7 (1.4)	-0.6 (-1.5, 0.2)	-0.1 (-0.7, 0.4)	**-0.8 (-1.6, -0.0)**			
Physical fatigue	Exercise	12	7.7 (1.5)	5.2 (2.4)	4.8 (2.7)	**-2.2 (-3.4, -1.1)**	-0.5 (-1.2, 0.2)	**-2.7 (-3.8, -1.7)**	-1.3 (-2.9, 0.3)	-0.3 (-1.3, 0.7)	**-1.5 (-3.1, -0.0)**
	Relaxation	13	6.6 (2.7)	5.9 (1.9)	5.6 (1.7)	-1.0 (-2.1, 0.1)	-0.2 (-0.9, 0.5)	**-1.2 (-2.2, -0.2)**			
Affective fatigue	Exercise	12	5.5 (2.7)	4.6 (2.7)	5.2 (2.7)	-0.9 (-2.2, 0.3)	0.6 (-0.2, 1.3)	-0.3 (-1.6, 1.0)	-0.7 (-2.5, 1.0)	0.8 (-0.3, 1.8)	0.2 (-1.6, 1.9)
	Relaxation	13	5.5 (2.6)	5.3 (2.6)	5.1 (2.2)	-0.2 (-1.4, 1.0)	-0.2 (-0.9, 0.5)	-0.4 (-1.7, 0.8)			
Cognitive fatigue	Exercise	12	4.9 (2.7)	3.7 (3.2)	4.9 (2.9)	**-1.3 (-2.4, -0.2)**	0.7 (-0.7, 2.1)	-0.5 (-2.0, 1.1)	-0.7 (-2.3, 0.8)	0.4 (-1.6, 2.4)	-0.1 (-2.3, 2.1)
	Relaxation	13	6.1 (2.3)	5.4 (2.0)	5.4 (2.3)	-0.6 (-1.6, 0.5)	0.3 (-1.0, 1.7)	-0.4 (-1.8, 1.1)			
Patients without Preceding Adjuvant Chemotherapy											
Total fatigue	Exercise	65	5.7 (2.3)	6.1 (2.0)	5.4 (2.3)	**0.4 (0.0, 0.7)**	**-0.7 (-1.0, -0.3)**	-0.3 (-0.7, 0.0)	-0.3 (-0.8, 0.2)	-0.1 (-0.6, 0.4)	-0.5 (-1.0, 0.1)
	Relaxation	65	5.9 (1.9)	6.4 (1.7)	6.0 (2.0)	**0.7 (0.3, 1.0)**	**-0.5 (-0.9, -0.2)**	0.1 (-0.3, 0.5)			
Physical fatigue	Exercise	65	5.4 (2.8)	6.3 (2.2)	5.1 (2.9)	**0.8 (0.4, 1.3)**	**-1.2 (-1.7, -0.7)**	-0.4 (-0.9, 0.1)	-0.2 (-0.8, 0.5)	-0.5 (-1.2, 0.2)	-0.7 (-1.4, 0.0)
	Relaxation	65	5.7 (2.3)	6.5 (2.0)	6.0 (2.3)	**1.0 (0.6, 1.5)**	**-0.7 (-1.2, -0.2)**	0.3 (-0.2, 0.8)			
Affective fatigue	Exercise	65	5.9 (2.7)	5.5 (2.7)	5.3 (2.6)	-0.3 (-0.8, 0.2)	-0.2 (-0.6, 0.3)	**-0.5 (-1.0, -0.0)**	-0.2 (-0.9, 0.6)	0.2 (-0.4, 0.9)	-0.1 (-0.8, 0.6)
	Relaxation	65	5.7 (2.5)	5.5 (2.5)	5.3 (2.7)	-0.1 (-0.6, 0.4)	-0.4 (-0.9, 0.1)	-0.5 (-1.0, 0.1)			
Cognitive fatigue	Exercise	65	4.9 (3.1)	5.1 (3.0)	4.9 (3.3)	0.1 (-0.4, 0.7)	-0.4 (-1.0, 0.2)	-0.1 (-0.8, 0.6)	**-0.8 (-1.6, 0.0)**	0.4 (-0.5, 1.2)	-0.3 (-1.2, 0.7)

Outcome*	Arm	N†	Mean (SD)			Adjusted‡ Mean Change (95%CI)			Adjusted‡ Between-Group Difference (95%CI)		
			Baseline (T0)	Post RT (T1)	Post Interv. (T2)	from T0 to T1	from T1 to T2	from T0 to T2	from T0 to T1	from T1 to T2	from T0 to T2
	Relaxation	65	5.2 (3.2)	6.0 (2.8)	5.3 (3.1)	**0.9 (0.4, 1.5)**	**-0.8 (-1.4, -0.1)**	0.1 (-0.5, 0.8)			

Abbreviations: CI, confidence interval; Interv., Intervention; RT, radio therapy; SD, standard deviation.
* Fatigue scores were square-root transformed from the original 0-100 score to reach a good model fit, thus resulting in a 0-10 scale.
† Number of patients with measures at both timepoints, T0 and T2. ‡ Regression models are adjusted for baseline value.

Secondary endpoints

Investigation of the EORTC QoL scores (Table 3, Figure S1) revealed a significant increase in global QoL in EX from pre- to post-intervention but no significant change in RC, but the between-group difference was small and nonsignificant (*P*=0.37, ES=0.15). Significantly larger improvements in EX vs. RC were detected in role function (*P*=0.035, ES=0.31) and in pain (*P*=0.040, ES=0.25). Future perspective improved significantly more in RC compared to EX (*P*=0.047, ES=0.28). Emotional function, social function, and body image improved significantly in both intervention groups, without a significant between-group difference.

Further, small effects in favor of EX were observed for several QoL symptoms. However, these effects failed to reach statistical significance (Table 3). Regarding the CES-D depression score, there was no significant change from pre- to post-intervention in either of the intervention groups (Table 3, Figure S1). Overall cognitive performance improved slightly more in EX than in RC, but between-group differences were nonsignificant.

The results remained stable when adjusting the ANCOVA models for randomization strata or other potential influencing factors, such as age, previous chemotherapy, baseline BMI, baseline depression, sports in the year before diagnosis, or living status (alone/with others). No significant interactions were observed.

Table 3: Patient Reported Outcomes Pre-/Post-Intervention, Adjusted Mean Changes and Between-Group Differences

Outcome*	Arm	N†	Mean (SD) Baseline (T0)	Mean (SD) Post Intervention (T2)	Adjusted‡ Mean Change (95% CI) from T0 to T2	Adjusted‡ Between-Group Difference (95% CI) from T0 to T2	p
Global QoL	Exercise	76	59.3 (21.3)	64.3 (24.5)	**4.6 (0.1, 9.2)**	3.0 (-3.5, 9.5)	0.37
	Relaxation	72	60.8 (20.0)	62.0 (21.2)	1.6 (-3.1, 6.3)		
Quality of life - EORTC QLQ30 functions (Scale 0-100)							
Physical function	Exercise	77	80.5 (18.0)	82.5 (18.8)	2.2 (-0.8, 5.2)	1.5 (-2.7, 5.7)	0.48
	Relaxation	78	79.1 (16.7)	80.0 (16.9)	0.7 (-2.3, 3.7)		
Emotional function	Exercise	77	58.4 (23.7)	65.5 (25.5)	**7.2 (3.0, 11.5)**	-2.2 (-8.1, 3.8)	0.48
	Relaxation	78	57.3 (25.7)	66.9 (23.9)	**9.4 (5.2, 13.6)**		
Role function	Exercise	75	63.6 (27.9)	75.3 (28.3)	**11.2 (5.7, 16.7)**	**8.5 (0.6, 16.3)**	**0.035**
	Relaxation	71	66.0 (27.4)	68.1 (26.8)	2.7 (-2.9, 8.3)		
Cognitive function	Exercise	77	72.9 (27.2)	75.5 (27.3)	3.2 (-1.5, 7.8)	4.2 (-2.4, 10.8)	0.21
	Relaxation	76	69.7 (27.6)	69.3 (26.8)	-1.0 (-5.7, 3.7)		
Social function	Exercise	75	68.4 (30.7)	75.6 (27.2)	**8.0 (3.4, 12.7)**	-0.8 (-7.4, 5.7)	0.81
	Relaxation	75	64.7 (29.2)	74.4 (23.5)	**8.9 (4.2, 13.5)**		
Quality of life - EORTC QLQ30 symptoms (Scale 0-100)							
Fatigue	Exercise	77	42.4 (24.9)	34.3 (28.1)	**-8.1 (-13.0, -3.3)**	-5.9 (-12.7, 0.9)	0.09
	Relaxation	77	43.1 (26.3)	40.7 (25.1)	-2.2 (-7.1, 2.6)		
Insomnia	Exercise	76	39.0 (30.0)	39.0 (30.0)	-1.8 (-8.2, 4.5)	-8.8 (-17.8, 0.2)	0.05
	Relaxation	77	46.3 (36.3)	51.5 (34.9)	**7.0 (0.7, 13.3)**		
Dyspnea	Exercise	77	27.7 (30.3)	25.1 (29.7)	-2.9 (-9.0, 3.2)	-6.7 (-15.3, 1.9)	0.13
	Relaxation	77	29.0 (34.3)	32.5 (33.8)	3.8 (-2.3, 9.9)		
Nausea and vomiting	Exercise	76	5.7 (15.0)	5.3 (13.7)	-1.4 (-4.7, 1.9)	0.1 (-4.5, 4.8)	0.96
	Relaxation	77	7.8 (20.2)	5.4 (15.6)	-1.5 (-4.8, 1.8)		
Pain	Exercise	77	29.4 (30.2)	25.5 (26.4)	-4.0 (-8.9, 1.0)	-7.4 (-14.4, -0.3)	**0.040**
	Relaxation	75	29.8 (29.4)	33.1 (31.5)	3.4 (-1.6, 8.4)		
Appetite loss	Exercise	77	13.0 (23.7)	7.8 (18.7)	**-4.7 (-9.0, -0.3)**	-5.0 (-11.1, 1.1)	0.11
	Relaxation	77	11.3 (23.3)	12.1 (23.5)	0.3 (-4.0, 4.7)		
Constipation	Exercise	77	7.8 (17.0)	5.6 (16.6)	-3.0 (-7.5, 1.6)	-3.4 (-9.8, 3.1)	0.30
	Relaxation	77	11.7 (23.4)	11.3 (28.4)	0.4 (-4.1, 4.9)		
Diarrhea	Exercise	77	8.7 (20.5)	7.4 (15.9)	-1.4 (-6.0, 3.1)	-4.6 (-11.1, 1.8)	0.16
	Relaxation	77	9.1 (24.0)	12.1 (25.9)	3.2 (-1.4, 7.7)		
Financial difficulties	Exercise	77	23.8 (31.0)	23.4 (29.6)	-0.0 (-4.8, 4.8)	-1.8 (-8.6, 5.0)	0.60
	Relaxation	76	21.5 (33.4)	23.7 (29.7)	1.8 (-3.1, 6.6)		

Outcome*	Arm	N†	Mean (SD) Baseline (T0)	Mean (SD) Post Intervention (T2)	Adjusted‡ Mean Change (95% CI) from T0 to T2	Adjusted‡ Between-Group Difference (95% CI) from T0 to T2	p
Quality of life - EORTC BR23 functions (Scale 0-100)							
Future perspective	Exercise	71	38.0 (29.4)	49.8 (34.2)	**11.2 (5.4, 16.9)**	**-8.4 (-16.6, -0.1)**	**0.047**
	Relaxation	67	41.3 (30.2)	60.2 (26.7)	**19.5 (13.6, 25.4)**		
Body Image	Exercise	71	68.2 (32.1)	76.2 (27.7)	**7.3 (3.4, 11.1)**	0.2 (-5.4, 5.8)	0.95
	Relaxation	67	72.9 (28.5)	79.2 (25.8)	**7.1 (3.1, 11.1)**		
Sexual functioning and satisfaction	Exercise	69	33.5 (31.8)	42.8 (32.0)	**10.3 (4.9, 15.6)**	7.4 (-0.4, 15.2)	0.063
	Relaxation	62	27.6 (29.7)	31.5 (28.8)	2.8 (-2.8, 8.5)		
Quality of life - EORTC BR23 symptoms (Scale 0-100)							
Side effects (overall)	Exercise	71	26.8 (19.3)	26.8 (20.0)	-0.8 (-4.4, 2.7)	1.5 (-3.6, 6.6)	0.56
	Relaxation	67	30.8 (21.7)	27.5 (17.5)	-2.3 (-6.0, 1.3)		
Feeling sick	Relaxation	68	35.8 (26.6)	25.5 (29.4)	**-9.8 (-15.6, -4.0)**	-4.7 (-13.0, 3.6)	0.26
	Exercise	66	33.3 (28.0)	28.8 (28.6)	-5.1 (-11.0, 0.8)		
Dry mouth	Exercise	77	22.9 (30.7)**+**	21.2 (31.5)	-3.4 (-9.4, 2.7)	-3.7 (-12.3, 4.8)	0.3883
	Relaxation	78	31.2 (31.0)	29.9 (33.4)	0.4 (-5.6, 6.4)		
Taste disorders	Relaxation	77	16.9 (29.9)	17.3 (29.4)	-0.6 (-5.7, 4.4)	6.9 (-0.2, 14.0)	0.058
	Exercise	78	20.5 (31.9)	12.0 (22.1)	**-7.5 (-12.5, -2.5)**		
Eye symptoms	Exercise	77	26.4 (31.2)	27.3 (31.9)	-0.3 (-6.2, 5.6)	4.1 (-4.2, 12.4)	0.33
	Relaxation	78	30.8 (35.9)	25.2 (29.0)	-4.4 (-10.3, 1.4)		
Hair loss/upset	Relaxation	74	14.4 (29.2)	15.8 (26.6)	-1.9 (-7.3, 3.5)	7.2 (-0.4, 14.9)	0.062
	Exercise	76	22.8 (37.0)	10.5 (22.6)	**-9.1 (-14.5, -3.8)**		
Hot flashs	Exercise	71	47.4 (35.9)	54.5 (34.4)	**7.4 (0.2, 14.7)**	-3.8 (-14.2, 6.7)	0.48
	Relaxation	66	46.0 (37.8)	57.6 (35.3)	**11.2 (3.7, 18.7)**		
Head ache	Relaxation	70	19.0 (26.4)	22.4 (30.9)	3.0 (-2.6, 8.6)	-1.5 (-9.5, 6.6)	0.72
	Exercise	66	21.7 (25.8)	25.8 (29.1)	4.4 (-1.3, 10.2)		
Arm symptoms	Exercise	74	26.3 (25.5)	22.7 (25.4)	-3.0 (-7.6, 1.5)	-0.7 (-7.0, 5.7)	0.83
	Relaxation	78	23.6 (24.4)	21.8 (23.3)	-2.3 (-6.8, 2.1)		
Breast symptoms	Relaxation	74	27.7 (22.5)	27.0 (21.2)	-0.4 (-5.0, 4.1)	-6.1 (-12.4, 0.3)	0.061
	Exercise	78	26.7 (21.0)	32.6 (23.4)	**5.6 (1.2, 10.0)**		
Depression - CES-D (Scale 0-100)							
Depression score	Exercise	75	26.1 (16.8)	24.6 (17.7)	-1.6 (-4.4, 1.1)	0.7 (-3.1, 4.6)	0.71
	Relaxation	76	27.5 (17.2)	25.0 (16.6)	-2.4 (-5.1, 0.4)		
Cognitive function - Trail-Making-Test [seconds]							
Overall	Exercise	72	112.9 (45.5)	98.3 (36.9)	**-15.0 (-19.9,-10.0)**	-5.4 (-12.3, 1.5)	0.13
performance	Relaxation	73	116.0 (45.2)	106.0 (42.7)	**-9.6 (-14.4, -4.7)**		
Executive functioning	Exercise	72	77.9 (34.8)	66.9 (28.8)	**-11.5 (-15.4, -7.5)**	-3.7 (-9.2, 1.9)	0.19
	Relaxation	73	81.3 (35.8)	72.9 (30.2)	**-7.8 (-11.7, -3.9)**		

Outcome*	Arm	N†	Mean (SD) Baseline (T0)	Mean (SD) Post Intervention (T2)	Adjusted‡ Mean Change (95% CI) from T0 to T2	Adjusted‡ Between-Group Difference (95% CI) from T0 to T2	p
Cognitive processing speed	Exercise	72	35.0 (13.9)	31.4 (11.1)	**-3.6 (-5.8, -1.4)**	-1.9 (-5.0, 1.1)	0.22
	Relaxation	73	34.7 (12.0)	33.1 (14.2)	-1.7 (-3.8, 0.5)		

Abbreviations: CI, confidence interval; CES-D, Center of Diseases Depression Scale; QoL, Quality of Life; SD, standard deviation.

* Fatigue scores square-root transformed, i.e. scale 0-10.

† Number of patients with measures at both timepoints, T0 and T2.

‡ Regression models are adjusted for baseline value.

\+ Difference between both intervention groups at baseline, $p < 0.05$.

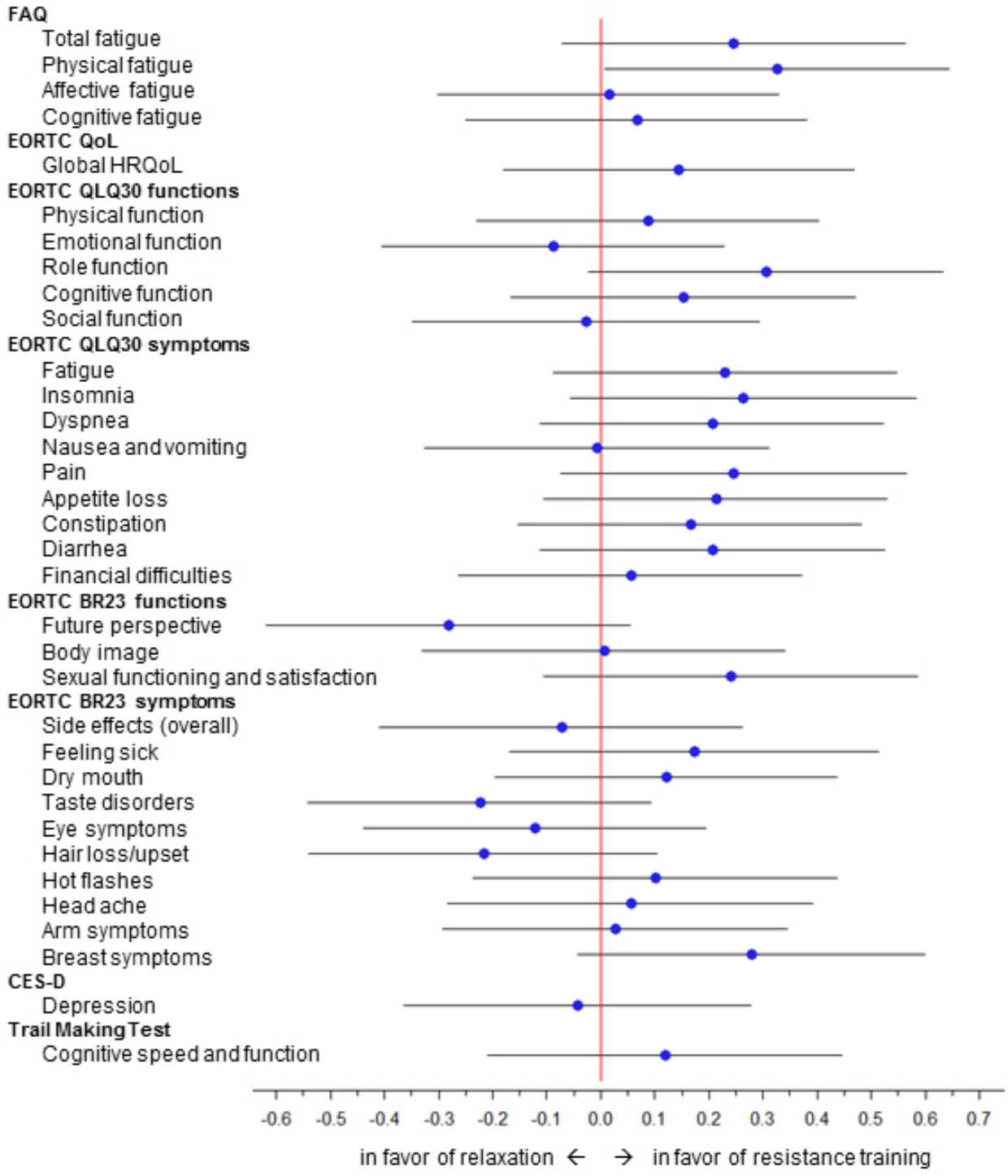

Figure S1. Effect sizes for fatigue, quality of life, depression and cognition
Effect sizes (ES), denoted by a dot, with 95% confidence intervals, for the difference between the resistance exercise intervention group and the relaxation control group, based on changes from baseline to the end of intervention (week 13) and adjusted for baseline scores. For ease of presentation, the results for some items were rescaled so that now all ES in favor of the resistance training received a positive sign, and in favor of relaxation a negative sign. Estimates expressed in units of 1 standard deviation.
Abbreviations: FAQ, Fatigue Assessment Questionnaire; EORTC, European Organisation for Research and Treatment of Cancer; QoL, quality of life; HRQoL, health-related quality of life; QLQ30, 30-item questionnaire for QoL; BR23, 23-item breast cancer specific questionnaire; CES-D, 20-item depression scale.

Discussion

We report here the results of a large randomized controlled trial in BC patients testing the effects of exercise during adjuvant radiotherapy. The 12-week resistance exercise program was an efficacious strategy to reduce the primary endpoint total fatigue, particularly physical fatigue. Furthermore, improvements in some subscales of QoL were observed. The program was safe and had good adherence. Since group-based relaxation training was chosen as the control group, our results indicate that resistance exercise provides beneficial effects beyond psychosocial effects induced by group-based programs.

Several studies have investigated the effect of exercise on fatigue in BC patients. A meta-analysis including 25 randomized exercise intervention trials reported an overall effect size of 0.39 (95% CI: 0.27-0.51) (Brown et al., 2011). Our study adds to current knowledge for BC patients with respect to two understudied areas: (1) exercise was performed during radiotherapy; and (2) the type of training was pure resistance exercise. So far, only three randomized studies analyzed resistance exercise interventions without aerobic components with respect to fatigue or QoL (Courneya et al., 2007; Ohira et al., 2006; Winters-Stone et al., 2012). One study (Courneya et al., 2007) randomly assigned 242 patients receiving chemotherapy to resistance exercise, aerobic exercise, or usual care, but did not observe significant effects, possibly due to the high variability of outcomes during chemotherapy. Another study (Winters-Stone et al., 2012) also reported no difference in fatigue among 106 postmenopausal survivors randomized to a 1-year resistance exercise or stretching program. Yet results were limited by a nonrandom drop-out rate of 37%. The third study (Ohira et al., 2006) did not investigate fatigue, but

observed significant improvements in the physical and the psychosocial QoL score among 86 survivors randomized to resistance training compared to usual care.

We chose a group-based control intervention with psychosocial conditions similar to the exercise program and for which beneficial effects on fatigue were shown (Song, Xu, Zhang, Ma, & Zhao, 2013) Thus, our observed effects for resistance training likely refer to physiological effects of exercise, over and above the psychosocial benefits associated with group-based programs. The clinically relevant overall effect of resistance exercise compared to usual care can therefore be expected to be higher than the one observed in our study.

For general QoL, our observed ES of 0.15 was smaller than the ES of 0.34 (95% CI: 0.07-0.62) reported by a meta-analysis on randomized exercise studies in BC patients during adjuvant therapy (Carayol et al., 2013), presumably due to choosing an active control group in our study with psychosocial benefits too. Our analyses regarding QoL functions and symptoms suggest that resistance training also has physiological effects on QoL. Compared to RC there were improvements in role function and pain. The benefit regarding pain is especially relevant, because patients and physicians are often concerned that intense resistance exercise may increase side effects. On the other hand, patients in the relaxation group were less concerned about the future, reflecting rather psychological aspects. Although we did not correct for multiple testing so that some findings might have appeared by chance, our results strengthen observations from a Cochrane review that exercise has beneficial effects on QoL (Mishra et al., 2012). It is not surprising that no differences in emotional and social functions between EX and RC were found, because psychosocial interventions, including relaxation programs, may also have beneficial effects on emotional distress (Faller et al., 2013). Accordingly, while previous

randomized intervention trials reported reduced depression in exercise programs compared to usual care (Daley et al., 2007), we did not observe benefits of EX over RC regarding depression.

In conclusion, our large randomized controlled intervention trial indicates that resistance exercise is safe, feasible as well as efficacious in improving cancer-related fatigue and components of QoL in BC patients during adjuvant radiotherapy. With fatigue being the most frequent side effect during radiotherapy, this finding is clinically meaningful to many BC patients. The observed physiological effects of resistance exercise are over and above psychosocial benefits associated with group-based supervised programs. Our results substantiate the claim that resistance training should become an integral part of exercise prescriptions for BC patients and that these programs should begin parallel to adjuvant radiotherapy.

Acknowledgements

We would like to thank the patients who participated in this clinical trial. We also thank the Institute of Sports and Sports Science of the University of Heidelberg for providing the training facilities; Lena Kempf, Marcel Bannasch, Nadine Ungar, and Beate Biazeck for performing the interventions; Ulrike Bussas, MD, Simone Hummler, MD, Holger Hof, MD, Henrik Hauswald, MD, and Andrea Koffka, MD, for medical support and/or help with recruitment; Lin Zielske, Eva Frei, PhD, and Renate Skatula for the lab work; Sabine Wessels, PhD, Sandra Gollhofer, Simone Stefaniszyn, Marina Sumic, Petra Armbrust, Rea Kühl, Friederike Scharhag-Rosenberger, PhD, Ursula Bollow, and Tilla Ruf, PhD, for study assistance; and Werner Diehl, PhD, for data management.

Funding

This work was supported by the Interdisciplinary Research Funding Program (intramural) of the National Center for Tumor Diseases (NCT), Heidelberg, Germany [grant number IFP project VI.1]; and the foundations “Stiftung Leben mit Krebs” and the “Manfred-Lautenschlaeger-Stiftung” that partially supported our intervention programs.

Disclosures

The authors have declared no conflicts of interest. Results have partially been presented on the following conferences: oral presentation (German Cancer Society Conference 2014, Berlin, Germany); poster (American College of Sports Medicine conference 2014, Orlando, United States of America), highlighted poster session (American Society of Clinical Oncology conference 2014, Chicago, United States of America).

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8. General discussion

8.1. Summarizing the main findings

Gold standard fitness measuring methods showed markedly impaired physical performance level in breast cancer patients and the need of adjustment of the intensity prescription during treatment. In addition physical exercise, particularly strength training plays an important role in cancer prevention as well as in the prevention and treatment of cancer-related fatigue during. This chapter summarizes the main results, and considers remaining problems with the quality of the studies. Afterward, it discusses the main findings in light of the existing literature and ends with concluding remarks, implications, and suggestions for future research.

Cardiorespiratory fitness in breast cancer patients undergoing adjuvant therapy (I. Publication)

The cardiorespiratory fitness analyses of 222 breast cancer patients clearly show that their marked and significantly impaired cardiopulmonary function with mean VO_{2peak} was 20.6 ± 6.7 ml/min/kg, compared to the expected mean VO_{2peak} of 24.3 ± 5.5 ml/min/kg among a healthy population of comparable age and BMI distribution. An even lower adjusted mean VO_{2peak} was measured among patients post adjuvant chemotherapy, compared to patients with no chemotherapy or who had just started chemotherapy, with 63% of the expected level. The impact on VO_{2peak} appears to accumulate over the course of chemotherapy, while heart rate was already impaired during the first chemotherapy cycles. However, there was no significant association between chemotherapy treatment and ventilatory threshold.

Chemotherapy seems to impair cardiorespiratory fitness by influencing the oxygen delivery system, rather than impacting metabolic muscle function.

What this study adds

- These results contribute to gold standard measurements of cardiorespiratory fitness with breast cancer patients in acute cancer treatment.
- Breast cancer patients showed markedly impaired physical performance level after CT.
- The significant performance differences between CT and non-CT treatment groups underline the need for individual exercise therapy in breast cancer patients as early as possible to prevent or counteract the loss of physical performance during the anti-cancer therapy.

Muscular strength in breast cancer patients undergoing adjuvant therapy (II. Publication)

Testing with the isokinetic device was safe and practical. The analysis of 255 breast cancer patients shows that strength and muscular fatigue (the fatigue index was up to 50% higher) are strongly mediated by chemotherapy and are most impaired, with up to 25% in the lower extremities, in patients undergoing chemotherapy. On average, all of the patient groups, including those who had just started chemotherapy and those who only had breast cancer surgery, had a significantly impaired physical performance status compared with healthy controls. The strength of the upper extremities was no different between breast cancer patient groups, but the type of surgery was associated with 12% less flexibility in the shoulder after a radical mastectomy than after a partial mastectomy. The reason for

dysfunctions in upper extremities after surgery has less to do with shoulder strength and more to do with decreased shoulder flexibility.

What this study adds

- Breast cancer patients undergoing various acute cancer treatments have remarkably impaired isokinetic and isometric strength capacity, predominantly those receiving chemotherapy in their treatment history.
- Fatigue resistance of the quadriceps muscle is affected by chemotherapy treatment.
- Less shoulder strength than decreased shoulder flexibility might be the reason for dysfunctions in upper extremities after surgery.
- Identification of breast cancer patients with increased need for individual exercise rehabilitation is possible.
- Resistance exercise may also be applied as a prevention program against muscle dysfunction in breast cancer patients at high risk (= receiving chemotherapy).
- Based in the findings there is a strong need for the implementation of resistance exercises in breast cancer patients in the context of chemotherapy treatment.

Exercise training intensity prescription in breast cancer survivors: validity of current practice and specific recommendations (III. Publication)

The ACSM classification in percentages of oxygen uptake reserve (%VO_2R), heart rate reserve (%HRR), and maximal oxygen uptake (%VO_{2max}) for healthy individuals does not seem to elicit the expected exercise intensity for breast cancer patients. Prescriptions in %VO_{2max}, according to the ACSM, result in intensities slightly lower than intended. In contrast, prescriptions in %HRR, according to the

ACSM, result in exercise intensities that are markedly higher than intended, and therefore should not be used. Only percentages of maximal heart rate (%HR_{max}) can be used at the end of acute therapy. The high standard deviations of the observed percentage values indicate a high individual variability in the relationships between %VO_2R and the other parameters. However, the use of ventilatory thresholds might be better for eliciting defined metabolic strain in this population. Further research is therefore required to improve the prescription for exercise intensity in cancer survivors. These results can be used to prescribe endurance training intensities for breast cancer survivors at the end of acute therapy. They also enable us to compare previous exercise intervention trials in breast cancer survivors, in which different ways of prescribing intensity were used.

What this study adds

- The ACSM's exercise intensity classification for healthy individuals is valid for breast cancer survivors at the end of acute therapy only if %HR_{max} is used.
- Prescriptions in %VO_{2max} according to the ACSM result in exercise intensities slightly lower than intended.
- In contrast, prescriptions in %HRR according to the ACSM result in exercise intensities markedly higher than intended and therefore should not be used.
- Our results can be used to prescribe endurance training intensities for breast cancer survivors at the end of acute therapy.
- These results also enable comparisons of previous exercise intervention trials in breast cancer survivors in which different ways of intensity prescription were used.

Randomized controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: Results on cancer-related fatigue and quality of life (IV. Publication)

Adherence was similar in both intervention arms, with a median attendance number of 19 (interquartile range (IQR): 13–23, range 1-24) in the resistance training arm and 19 (IQR: 12–22, range 0-24) in the relaxation training arm. In intention-to-treat analyses, the change in peak torque of isokinetic knee extension muscle strength (speed: 60°) was significantly higher in the resistance training group (adjusted between-group mean difference of 7.14, 95% confidence interval 2.35 to 11.94, p=0.004). No significant effect was observed for VO_{2peak}.

No injuries or severe adverse events related to the interventions were reported from either group. The frequency of reported lymphedema did not differ between groups.

Overall, from pre- to post-intervention, total fatigue decreased significantly in the resistance training arm, while in the control group with relaxation training there was no significant change. Correspondingly, the primary intention-to-treat analyses showed significant differences between both intervention groups (p=0.044), with an effects size (ES) of 0.33. Considering the different fatigue dimensions, there was a significant intervention effect on physical fatigue (p=0.013, ES=0.40), but none on the affective (p=0.91, ES=0.02) or the cognitive (p=0.65, ES=0.07) dimension. Significant between-group differences favoring resistance training were noted for subscales of quality of life (Figure 3), but not for depression.

A possible mechanism for the effectiveness of resistance exercise in reducing CRF among breast cancer survivors is the attenuation of the progressive muscle wasting

and disruptions in muscle metabolism that occur with cancer and associated treatments (Ryan et al., 2007).

What this study adds

- Our large randomized controlled intervention trial indicates that resistance exercise is safe and feasible as well as efficacious in improving fatigue and important components of QoL in BC patients during adjuvant radiotherapy.
- With fatigue being the most frequent side effect during radiotherapy, this finding is clinically meaningful to many BC patients.
- The physiological effects of exercise add to the psychosocial benefits associated with group-based supervised programs.
- Our results substantiate the claim that resistance training should become an integral part of exercise prescriptions for BC patients and that these programs should begin parallel to adjuvant radiotherapy.

8.2. Considerations of the study quality

The research described in this thesis focused on four different exposures: cardiorespiratory fitness measured by cardiopulmonary exercise test, muscular functions measured by isokinetic device, endurance training prescription, and the main results of the RCT on cancer-related fatigue. Beyond the strengths and limitations of the studies, this chapter addresses additional issues related to their internal and external validity, e.g. methods, study population, outcome measurements, and generalizability.

8.2.1. Methodological discussion

RCTs (except systematic reviews) are generally considered to be the most reliable form of scientific indication in the hierarchy of evidence that influences healthcare policy and practice, because RCTs reduce spurious causality and bias. However, RCTs can yield biased results if they lack methodological precision. My presented publications tried to report complete, clear, and transparent information on the methodology and findings of the study. The descriptive research method and cross-sectional analysis used in my publications is also discussed. Therefore, I took the most important guidelines for randomized trials and observational research (Guyatt et al., 2011; Ryan R, Hill S, Prictor M, & J, 2013; Schulz, Altman, & Moher, 2010; Vandenbroucke et al., 2014), and put them in the next sections into the context of my thesis.

8.2.2. Trial design and registration

The aforementioned RCT study designs of the BEST and BEATE studies were also reported in detail in publications (Potthoff et al., 2013; Schmidt et al., 2013) for adequate transparency. Furthermore, my publications I-IV summarized the study designs of the BEST, BEATE and INVEST studies. To support the empirical evidence and to meet the requirements of journal editors, the RCTs were registered (BEST: clinicaltrials.gov: NCT01468766; BEATE: ClinicalTrials.gov NCT01106820).

8.2.3. Eligibility criteria

The eligibility criteria were reported, along with the reasons for choosing these criteria. We were able to ensure that the patients in the BEST study (IV. Publication) are similar in age, type and stage of cancer, general health, and previous treatment,

so we could be sure that the results of the study are caused by the intervention being tested and not by other factors. For the analysis of cardiorespiratory fitness and muscle strength and cancer-related fatigue in breast cancer patients (I. – IV publications), we reported the eligibility criteria.

8.2.4. Randomization and allocation concealment

Allocation was done by the biometrician, based on a predetermined list generated with a blocked randomization SAS procedure with a fixed block size, stratified by age (< 50 / ≥ 50 years) and baseline physical fatigue level (< 14 / ≥ 14). We used stratification in the randomization process, as we expect these variables to have a major influence on the outcome. To prevent possible bias, study personnel involved in the recruitment and the baseline assessment did not have access to the randomization lists and were not aware of the block size (Potthoff et al., 2013; Schmidt et al., 2013).

8.2.5. Sample size, interventions and outcome

The number of subjects assigned to control and treatment groups affect a RCT's reliability. The primary aim of the RCTs was to compare changes on the overall fatigue scale from the baseline to week 13 between the exercise and relaxation group. To detect a mean standardized effect size of 0.5 with a two-sided t-test with significance level 0.05 and a power of 80%, we needed a sample size of 80 per arm for the BEST study and 50per arm for the BEATE study: 160 or rather 100 women in total, assuming a maximal drop-out rate of 20% in the BEST study and 15% in the BEATE study (Borm, Fransen, & Lemmens, 2007). The criteria for baseline similarity of groups in the two interventions were fulfilled. We were able to

report the outcome measure from >85% of subjects, which is defined as an important methodologic quality aspect (Brown et al., 2011). For the reported cancer-related fatigue (primary outcome) and secondary outcome analysis in the BEST study, 155 (97%) patients were included (4th publication). This sample and the testing adherence were also large enough to detect clinically relevant intervention effects on the secondary outcome, like cardiorespiratory fitness or muscle function. For the cardiorespiratory fitness parameters (secondary outcome) at baseline (1st publication), we included patients from the two present RCTs (N=222), who had been tested before November 2013. For the analysis of the muscle functions (2nd publication), patients from the two RCTs and healthy women from the INVEST study (n=281) were included. For the analysis of the exercise intensity (3rd publication), a subgroup of breast cancer patients (n=52) who had finished their primary cancer treatment (surgery + chemotherapy and/or radiation), and had been in the relaxation group until November 2013 in order to exclude possible bias due to resistance training, was included from the two RCTs as a pilot study. Overall, I am not aware of any comparable studies with larger sample sizes.

All outcome measures were defined, including how and when they were assessed. The patients' fitness was measured with gold standard methods to improve the evidence and the intervention program was reported with sufficient detail to allow replication, including how and when it was actually administered. Adverse events of the tests and the side effects of the intervention were consequently reported in the studies with no serious harm overall.

8.2.6. Blinding

Blind testing was not possible to organizational reasons in our exercise studies, but participants were not shown their exercise test results until after the intervention. For organizational and financial reasons, it was also not possible to conceal the subject allocation from the intervention therapists, because they were own employees from National Center for Tumor Diseases in Heidelberg, Germany. In order to maintain or improve adherence to the training, they reported the absence of training problems to the study coordinator, who himself performed assessments.

8.2.7. Intention-to-treat analysis

We did the analysis on an intention to treat basis, in the sense that we took no account of adherence to the intervention. Furthermore, we used all available data, keeping participants in their original assigned groups (Hollis & Campbell, 1999).

8.2.8. Generalizability

The patients were recruited at the National Center for Tumor Diseases (NCT) in Heidelberg. These patients are mostly from urban areas, with a higher educational level than the population in a rural area. In general, education yields better health knowledge which is important to understand the health effects of one's actions. For instance, better educated individuals know more about the long-term health risks of overweight, consequences of smoking, alcohol drinking and positive effects of physical exercise and sport (Schneider & Schneider, 2012). Higher education and better health care infrastructure also means that a higher rate of timely preventive medical screenings is possible to detect breast cancer in early stage.

Generally, among patients in highly developed countries, the age-standardized incidence rate of breast cancer is more than twice as high as in countries with low levels of economic development (World Cancer Report 2014). Our participants (BEATE: mean 52.7±10.0 years; BEST: mean 55.8±9.1 years) are younger than average, as the mean age at diagnosis in Germany (mean 64 years) ("Krebs in Deutschland 2009/2010," 2013). One important reason was that we did not include patients with metastasized tumors or other severe diseases, because we wanted to focus on early stage breast cancer patients not receiving palliative treatment. The assessment in patients with advanced breast cancer of our primary outcomes and secondary outcomes and the realization of the intervention would not have been possible with our capabilities and was not our focus on research. Nevertheless, a few studies report benefits of exercise during advanced disease or palliative care (Stene et al., 2013).

Randomization should solve the problem of external validity, but random sampling does not guarantee complete generalizability. The generalizability in our studies of the relatively homogeneous group of middle-aged, slightly overweight primary diagnosed breast cancer patients with mean BMI of 26.3 kg/m^2 (higher prevalence of overweight and obesity among German women between 50 and 59 years with a mean BMI of 27,4 kg/m^2 (Mensink et al., 2013)) to all breast cancer patients might therefore not hold, but the internal validity is very high. However, all research suffers from limitations of external validity, whether observational or experimental, quantitative or qualitative, since it is necessarily limited by the context in which it takes place.

Our own analyses about barriers to participate in the BEST study show that elderly breast cancer patients, but also those below age 40, patients living alone, having a long travel distance, as well as those with worse cancer prognosis, recent chemotherapy, being affected by fatigue, or with more comorbidities are less willing or able to participate in a RCT (Gollhofer et al., 2015).

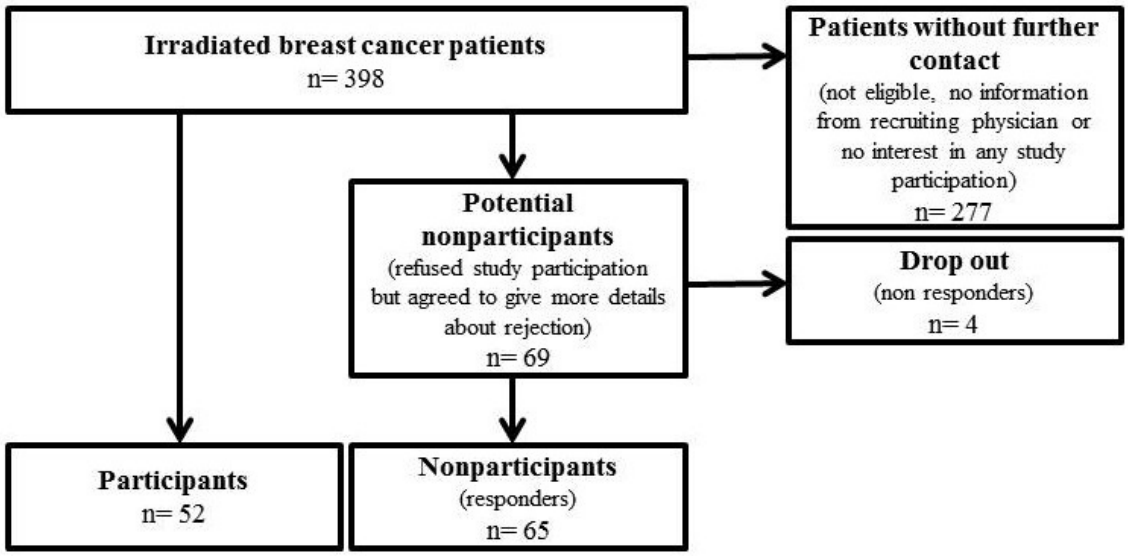

Figure 8. Recruitment flow in the BEST study from July 2011 to December 2011 (Gollhofer et al., 2015)

The authors reported that the recruitment for the BEST study in the first half year was less than 15 % of all breast cancer patients who started radiation (see Figure 11). The recruitment in breast cancer patients who started chemotherapy (BEATE study) was even lower. One explanation can be that patients with worse prognosis, more comorbidities and more intense therapy see more barriers or are not able to participate in an additional training program or study. However, it can be speculated, that they can benefit from a specific exercise program more than younger participants in a better shape.

8.3. General conclusions

The studies described in this thesis provide support for the hypothesis that exercise as a modifiable factor can provide improvements in fatigue beyond group-related psychosocial effects, cardiorespiratory fitness, muscular strength, and quality of life. It was essential to evaluate the physical and physiological status of breast cancer patients with gold standard methods in order to find the optimal future training prescriptions. Although the size of our study did not allow us to draw firm conclusions regarding the general advantages of exercise, our findings indicated that exercise with adjusted intensity may have bigger effects on health status during and potentially after cancer therapy in breast cancer patients.

8.4. Clinical implications: What is the advice for patients with breast cancer?

Cancer-related fatigue has an important role in quality of life, and physical performance plays an essential role during breast cancer treatment. These factors can be improved by a resistance exercise program, supported by the findings of the aforementioned BEST study results during radiotherapy and BEATE study results (Schmidt et al., 2014) in patients undergoing chemotherapy. Clinical trials showed that full-dose intensity in adjuvant chemotherapy for early-stage breast cancer is important for better disease-free survival and overall survival (Bonadonna, Valagussa, Moliterni, Zambetti, & Brambilla, 1995; Budman et al., 1998; Wood et al., 1994). Exercise can potentially improve the chemotherapy completion rate (Courneya et al., 2007). Since intervention trials began, about twenty five years ago, only minimal adverse effects have been reported (Battaglini et al., 2014). Our results

support these findings where no injuries or severe adverse events related to the interventions were reported.

We recommend starting an exercise program as early as possible for breast cancer patients. To maintain and/or improve cardiorespiratory fitness, our recommendations should be followed for exercise training intensity in breast cancer survivors. The considerable clinical extent and importance of muscle dysfunction should be met with a resistance training program to maintain and/or improve muscle mass, strength, and metabolism during and after cancer treatment. All breast cancer patients should have an individual exercise program integrated into their cancer therapy process, depending on their secondary illnesses, physical and psychological constitution, and different cancer treatments, as well as side effects resulting from surgery, chemotherapy, radiation, hormonal therapies, and targeted therapies.

8.5. Scientific implications and future research direction

The results show that cancer-related fatigue, low physical performance, and quality of life during cancer treatment are modifiable in the short term. But there is still less knowledge about long-term benefits of an exercise program of 12 weeks intervention. Based on the study results, new questions arise for follow-up studies. What influence does an exercise program during breast cancer treatment have on recurrence or survival rate? Courneya et al. (2014) have begun this kind of research with randomized data, and found absolute 8-year survival differences between 7% and 9%, but their sample size is clearly insufficient for any definitive conclusions. It is also not yet possible to say whether resistance training or endurance training is more beneficial for breast cancer survivors, as regards the recurrence rate. To find out,

there must be more multicenter trials with large-scale and adequate event rates organized with longer follow-ups in future.

Moreover, the exercise adherence rate in the studies with breast cancer patients during cancer treatment was 68.2% - 78.3% of the expected number of sessions attended (Courneya et al., 2008; Kim, Kang, Smith, & Landers, 2006; Swenson, Nissen, & Henly, 2010). Adherence in the BEST study was relatively high, with a rate of 79%. But exercise adherence varies greatly in studies with breast cancer survivors, with significantly lower rates after treatment (Kampshoff et al., 2014). Therefore, all exercise and cancer studies should evaluate adherence, to uncover the barriers to exercise and improve training quality.

Furthermore, the principles of exercise training and thoroughly reporting of all components of the exercise prescription should be standard for publications in this research field. Only with these requirements will it be possible to create precise recommendations for the ideal exercise regime, according the 'FITT' format (frequency (number of sessions per week), intensity (prescribed intensity of the activity), time (duration of each exercise bout) and type (aerobic and/or resistance activity)) for breast cancer patients during various treatment phases and after cancer therapy (Campbell, Neil, & Winters-Stone, 2011).

High-quality trials are necessary to understand the mechanisms of exercise training on common but currently understudied physiological toxicities, biomarkers, and therapy complications (e.g. body composition, cardiotoxicity, peripheral neuropathy, thrombosis, bone loss, tumor proliferation, arthralgia, cancer recurrence) Additionally, further high-quality studies are necessary to determine the effects of exercise on return to work or capacity for caregiving for children/aging parents (Jones & Alfano, 2013).

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Supplementary

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Current Position

since 03/2015 — **Head of department "Sports Therapy"** in an orthopedic/traumatological outpatient rehabilitation center at the Klinik Münsterland, Bad Rothenfelde, Germany

Positions

01/2015 – 03/2015 — **Research associate** of scientific projects at Institute of Sports and Sports Sciences (ISSW), Heidelberg and National Center for Tumor Disease (NCT), Heidelberg, Germany

06/2011 – 01/2015 — **PhD Student and Coordinator** of a scientific project "BEST-Study: Resistance Training vs. Relaxation during adjuvant Radiotherapy" at the Division of Preventive Oncology at the National Center for Tumor Disease (NCT) / German Cancer Research Center (DKFZ) and University Hospital Heidelberg, Germany

01/2008 – 05/2011 — **Leading Sports Scientist** at the units of the performance diagnostics (i.e. cardiopulmonary exercise and isokinetic testing), medical training therapy and workplace health promotion in cooperating ambulant rehabilitation centers in Hamm, Soest, Bad Laer, Germany

11/2007 – 01/2008 — **Internship** at the rehabilitation center at medicos.AufSchalke in the unit of performance diagnostic and the unit of cardiorespiratory and orthopedic rehabilitation in Gelsenkirchen, Germany

09/2006 – 08/2007 — **Coordinator** of the workplace health promotion at DaimlerChrysler AG with budget responsibility; Organization and implementation of projects

	related to primary prevention and ergonomics - **diploma thesis** about an evaluation of workplace safety, ergonomy and application environmental support, Sindelfingen, Germany
01/2005 – 05/2011	**Instructor, consultant and organizer** of sport- and intercultural events at one local and one regional exercise & sport association at the LandesSportBund in North Rhine-Westphalia, Germany
09/2003 – 08/2006	**Sports therapist** with a focus on medical training therapy and orthopedic disease in the rehabilitation clinic at Isomed in Kamen, Germany

Academic Education

2011-2014	Graduate Program at the Helmholtz International Graduate School for Cancer Research in Heidelberg, Germany
02/2009 – 10/2009	Advanced Training: Exercise specialist for adults with internal diseases at the National Paralympic Committee Germany
10/2009	Advanced Training: Kinesio-Taping at the K-Active Association in the rehabilitation center iuventas in Hamm, Germany
02/2008 – 10/2008	Advanced Training: Certification as a **clinical exercise specialist** at German Sport University in Cologne, Germany
2003 – 2007	Sports science (**Diploma; Sports Science/Exercise in Leisure time, Health and Training**) and Russian Culture (5 Semester Bachelor studying at the Lotman-Institute) at Ruhr University Bochum, Germany
2002	Abitur at Städtisches Gymnasium, Bergkamen, Germany

MEMBERSHIP SCIENTIFIC SOCIETIES

American College of Sports Medicine (ACSM)

German Association of Sports Psychology (asp)

AWARDS

„2014 ACSM International Student Award“ at the 61. ACSM Annual Meeting in Orlando, Florida, USA, May 2014.

Second Poster-Award at the 23. Rehabilitation Research Colloquium, Poster: „ Cardiorespiratory fitness in breast cancer patients undergoing different anti-cancer therapies“, Karlsruhe, Germany, March 2014.

DKG (German Cancer Society) Travel Award, Annual DKK (German Cancer Congress) Berlin, Germany, February 2014.
First Poster-Award at the 3rd International Symposia on Exercise and Physical Activity in Oncology, Poster: “BEST – Study: Progressive Resistance Training and Progressive Muscle Relaxation during Radiotherapy as Therapy against Cancer-related Fatigue”, Cologne, Germany, May 2012

POSTER AND PRESENTATIONS

Klassen O., Schmidt M.E., Wiskemann J., Ulrich C., Oelmann J., Hof H., Potthoff K., Steindorf K.: BEST study: progressive resistance training and progressive muscle relaxation during radiotherapy as therapy against cancer-related fatigue Publication of the abstract in (2013) 3rd international, interdisciplinary symposium “Physical activity in Oncology” at the German Sport University Cologne, Germany, May 2012

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Promotionsausschuss der Fakultät für Verhaltens- und Empirische Kulturwissenschaften der Ruprecht-Karls-Universität Heidelberg

Doctoral Committee of the Faculty of Behavioural and Cultural Studies, of Heidelberg University

Erklärung gemäß § 8 Abs. 1 Buchst. b) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften

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