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# Cardiopulmonary fitness and quality of life in breast cancer patients and the influence of a six month exercise program

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# I. List of abbreviations

| | |
|---|---|
| AET | Aerobic exercise training |
| AI | Aromatase inhibitor |
| BMI | Body mass index |
| CHF | Congestive heart failure |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| CPF | Cardiopulmonary fitness |
| CPET | Cardiopulmonary exercise test |
| ECG | Electrocardiogram |
| Gy | Gray |
| HER 2/neu | Human Epidermal Growth Factor Receptor |
| KPS | Karnofsky performance scale |
| LVEF | Left ventricular ejection fraction |
| MET | Metabolic equivalent task |
| MWD | Meter walking distance |
| QoL | Quality of life |
| RCT | Randomized controlled trial |
| RER | Respiratory Exchange Ratio |
| RET | Resistance exercise training |
| TNM | Tumor (Lymph-)node Metastasis |
| $VO_2$ | Oxygen uptake |
| $VO_{2peak}$ | Peak oxygen uptake |
| VE | Ventilation |
| $VT_1$ | Ventilatory threshold 1 |
| $VT_2$ | Ventilatory threshold 2 |

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# 1. Introduction

## 1.1. Breast cancer epidemiology and treatment

### Epidemiology

Breast cancer as the most common malignant disease in women is diagnosed about 70,000 times in Germany every year (status 2014). About 18,000 of them die from this disease every year, but for years mortality has been decreasing. In 2014/2013 the relative survival rates in Germany were 88% over five and 82% over ten years (Robert Koch-Institut (Hrsg.) und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg), 2017). In particular women with a low tumor stage and grade show a better prognosis in terms of survival rate (Jones, Haykowsky, Pituskin et al., 2007).

Between the years 1999 and 2009 the incidence increased and will probably increase further leading to a higher number of breast cancer survivors (Berkemeyer, Lemke, & Hense, 2016).

### The disease

Breast cancer is categorized as a solid tumor histologically originating either in the epithelia of the lactiferous duct (ductal) or the lobule of the lactiferous gland (lobular).

A distinction is made between precancerous lesions, intraductal proliferative lesions and papillary lesions in contrast to invasive carcinomas. The most common precancerous lesion is the ductal carcinoma in situ (DCIS).

Most invasive carcinomas are specified as invasive carcinoma of no special type (NST). There are further pathomorphological analyses conducted for invasive

carcinomas. The following parameters are especially important for prognosis and treatment: Firstly, grading of the tumor, a scoring evaluating the malignancy as degree of cellular differentiation. Secondly, immunohistochemical analysis of the hormone receptor status and the human epidermal growth factor receptor (HER2/neu) status. Hormone receptor status here means the presence of progesterone and estrogen receptor expression of the tumor cells. The HER2/neu receptor is a target for antibody therapy. Thirdly, Ki 67 proliferation index which is an indicator for the growth of the tumor, detecting actively dividing cells in a tissue.

As a lot of tumor entity breast cancer is categorized by the TNM-classification, and the UICC-classification. This classification is based on size of the tumor (T), lymph node invasion (N) and remote metastases (M). A special classification is made for carcinoma in situ (DCIS; TCIS; Tis Paget). (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft & AWMF), 2017; Sinn & Kreipe, 2013)

### Treatment

The regime for breast cancer therapy is depending on grading and staging of the tumor as well as tumor hormone receptor status (estrogen, progesterone receptor), HER2/neu expression, and menopausal status.

Therapy can be composed of surgery (e.g., mastectomy, breast-conserving therapy, axillary lymph node dissection), radiation, chemotherapy and/or hormonal therapy.

Chemotherapy regimes are often based on taxanes and anthracyclines. Commonly used combinations of substances include doxorubicin and cyclophosphamide (AC) / epirubicin and cyclophosphamide (EC) followed by

paclitaxel. Other agents used in either neoadjuvant or adjuvant settings are e.g. cyclophosphamide with doxetacel, platinum-containing agents, capecitabine, metothrexate and fluoruracil. In HER2/neu -positive tumors the anti-body agent trastuzumab (Herceptin; Genentech, South San Francisco, CA) is added to the mentioned chemotherapy regimes.

To treat hormone receptor positive tumors tamoxifen and aromatase inhibitors (AI) are applied depending on menopausal state: pre-menopausal patients usually receive tamoxifen, post-menopausal ones AIs. Endocrine therapy can be combined with radiation, but it should start after chemotherapy. Regular treatment duration is five to ten years.

Radiotherapy is especially recommended for patients after breast-conserving surgery. However, after mastectomy radiotherapy of the remaining chest wall can be conducted, too. (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft & AWMF), 2017; Liedtke, Thill, Jackisch et al., 2017).

### 1.2. Treatment and disease related impairments

#### Impairments of the cardiovascular system

Unfortunately, some of the above-mentioned drugs are potentially cardiotoxic. Anthracyclines seem to have the most severe cardiotoxic effect. The mechanism of action of these drugs is to inhibit DNA-synthesis, transcription and replication. As a side-effect, free radicals emerge which cause oxidative stress and inhibit the mitochondrial function. This process eventuates in myocyte apoptosis and hereby leads to cardiac damage (Ewer & Lippman, 2005; Smith, Cornelius, Plummer et al., 2010).

This damage manifests in various ways: supraventricular and ventricular arrhythmias, myopericarditis and cardiomyopathy with subsequent reduced left ventricular function and related electrocardiogram (ECG) changes all together potentially summing up in congestive heart failure (CHF) and death. The clinical manifestation of anthracycline-induced cardiomyopathy may occur acute, subacute or late after treatment. The combination of anthracyclines with other chemotherapeutic drugs, such as trastuzumab, cyclophosphamide and paclitaxel – all used in breast cancer therapy – may aggravate cardiomyopathy further (Floyd, Nguyen, Lobins et al., 2005).

Trastuzumab is a humanized monoclonal antibody binding to the extracellular domain of the human epidermal growth factor receptor (HER2/neu) protein. Up to 30% of breast cancer patients present with an amplification or overexpression of HER2/neu (Slamon, Clark, Wong et al., 1987). In larger clinical trials trastuzumab led to cardiac dysfunction as a severe side effect, especially, when applied in combination with doxorubicin/cyclophosphamide (Slamon, Leyland-Jones, Shak et al., 2001; Tan-Chiu, Yothers, Romond et al., 2005).

Contrary to anthracyclines, the underlying pathophysiology to these side effects is not fully understood. There are different theories trying to explain the cardiotoxicity of trastuzumab: HER2/neu signaling seems to be important for survival of the myocytes and their protection from cardio-toxins. Because the HER2/neu is blocked by trastuzumab, the myocytes can more easily be injured. Another theory suggests that trastuzumab may lead to loss of contractility caused by cellular stunning (Nowsheen, Viscuse, O'Sullivan et al., 2017).

In contrast to anthracyclines, trastuzumab-induced cardiotoxicity seems to be reversible after terminating therapy with trastuzumab and/or initiating treatment with supportive medication for CHF (Perez & Rodeheffer, 2004; Tan-Chiu, Yothers, Romond et al., 2005).

Other chemotherapeutical agents used in breast cancer therapy have been assessed regarding their cardiotoxicity by Floyd et al. (Floyd, Nguyen, Lobins et al., 2005):

Paclitaxel (an agent from the taxane group) can cause cardiac arrhythmias, even a complete heart block. The incidence for cardio-toxic events is about 0.1%, most of them asymptomatic and spontaneously declining. Used in combination with anthracyclines taxanes can have an additive cardiotoxic effect.

Fluorouracil seems to cause cardio-toxic events, including myocardial ischemia, atrial arrhythmias, ventricular dysfunction, and cardiogenic shock. But after termination of treatment most symptoms are reversible.

Cyclophosphamide only seems to be cardio-toxic when applied in high doses. Additive effects with anthracyclines are not definite, but have been observed.

The next therapeutical option, irradiation to the chest may cause cardiovascular injury, too. Regarding patients treated by radiotherapy in the 1970ies and early 80ies adverse cardiac effects were reported. Thus, alternative approaches, that minimized lung and heart exposure, were developed. Consequently, cardiac damage decreased but was still evident (Jones, Haykowsky, Swartz et al., 2007). Radiotherapy potentially harms all cardiac tissue leading to cardiomyopathy, coronary artery disease, valvular disease, and conduction anomalies and furthermore. The injury is dependent on dose and volume, as well as technique

of radiotherapy. Patients who underwent chest irradiation have a lifelong risk of heart diseases. As damage might occur as a subclinical abnormality at first, implementing long-term screening regimes appears crucial (Adams, Hardenbergh, Constine et al., 2003).

Aside from the effects of therapy, breast cancer seems to be associated with physical inactivity and obesity. 62% of all breast cancer patients are overweight or obese and 36% lead a sedentary lifestyle. These are risk factors for cardiovascular disease (CVD) as well. Conclusively, breast cancer patients may be at greater risk for CVD than the general population (Jones, Haykowsky, Swartz et al., 2007).

### Impairments of quality of life

Not only the physical well-being of patients is impaired by breast cancer, but also the psychological. Several dimensions of quality of life (QoL) are affected by the disease and treatment.

A severe and common symptom of cancer and side effect of cancer therapy is fatigue, so called cancer related fatigue. All different options of therapy, chemotherapy, radiation and surgery, can cause fatigue or worsen preexisting fatigue. While the pathophysiology of fatigue is not fully understood, it seems to be related to anxiety, depression, pain and sleep disturbances as well as a lower QoL. In cancer survivors moderate to severe fatigue is associated with poor performance status and a history of depression. High levels of fatigue can even be a predictor of survival (Arndt, Stegmaier, Ziegler et al., 2006; Wang & Woodruff, 2015).

Other symptoms often found in cancer patients are depression and anxiety. Compared with the general population, rates of anxiety and depression are twice as high with anxiety being more present than depression (Hinz, Krauss, Hauss et al., 2010; Hopwood, Sumo, Mills et al., 2010).

A further problem regarding especially premenopausal women is early-onset menopause caused by ovarian failure leading to hot flashes, night sweats, sleep disturbances, and resulting in depression and impaired QoL (Couzi, Helzlsouer, & Fetting, 1995; Shapiro & Recht, 2001).

Studies investigating the impact of treatment on overall QoL showed the following: active treatment (including surgery, chemotherapy, radiotherapy and hormone therapy) impairs QoL of female cancer patients. Some dimensions, such as global QoL, role functioning, and emotional functioning, were even affected up to one year after the end of treatment (Greimel, Thiel, Peintinger et al., 2002).

Radiotherapy seems to have a relatively small impact on QoL in breast cancer patients, but higher dosage and more fractions are associated with poorer QoL (Lee, Kilbreath, Refshauge et al., 2008).

Further, QoL is also affected by cancer stage. Meaning patients with earlier cancer stages had better QoL than patients with more advanced stages before starting treatment (Greimel, Thiel, Peintinger et al., 2002).

### 1.3. CVD as primal cause of death

The side effects of the disease and of therapy on the cardiopulmonary fitness are objectivated in a reduced peak oxygen uptake ($VO_{2peak}$), the measurement unit for cardiopulmonary fitness (CPF) or aerobic capacity. CPF is determined by

multiple components of oxygen transport, such as cardiac and pulmonary function, muscle and hematologic function. It acts as a strong indicator for cardiovascular function, efficiency of oxygen transport and potentially compensated abnormal cardiac function (Peel, Thomas, Dittus et al., 2014).

Different studies observed that, a 50-year old breast cancer patient achieves almost the same $VO_{2peak}$ as a healthy, sedentary 60-year (or even 70 or 80 year) old female. Also, patients before therapy have better $VO_{2peak}$ values than patients during or after therapy confirming the negative impact of cancer therapy on CPF (Jones, Courneya, Mackey et al., 2012; Peel, Thomas, Dittus et al., 2014).

Such an impaired $VO_{2peak}$, representing an impaired CPF, is a predictor of CVD and inversely related to risk of all-cause and cardiovascular death in various populations (Jones, Courneya, Mackey et al., 2012; Jones, Eves, Haykowsky et al., 2009).

It has been observed that the most common cause of death in breast cancer patients over 66 years at first diagnosis became CVD. This means, that the older a breast cancer survivor gets, the more likely she dies from another cause than the disease itself (Patnaik, Byers, DiGuiseppi et al., 2011). Further, women with a low stage and grade of tumor and ER-receptor positive status have a high survial rate of the initial disease and have to face the long-term side-effects of cancer therapy (Jones, Haykowsky, Pituskin et al., 2007). This gets more and more relevant: While breast cancer is detected earlier, treatment has improved, leading to a decreased mortality rate. (Chapman, Meng, Shepherd et al., 2008).

## 1.4. Exercise as safe and effective treatment

### Implementation of exercise as treatment

Since the 1960ies exercise has been tested as treatment for CVDs and has been proven to be effective. It is now established as standard treatment in cardiac rehabilitation programs in many countries. These programs improve or stabilize physical and psychological health of these patients, reducing mortality and risk of cardiovascular events (Mampuya, 2012).

The first studies investigating the impact of exercise in cancer patients were conducted in the late 1980ies (MacVicar, Winningham, & Nickel, 1989; Winningham, MacVicar, Bondoc et al., 1989). During the 1990ies the effects were further investigated in patients who received stem cell transplants (Dimeo, Tilmann, Bertz et al., 1997). But the first large clinical trial did not take place until the beginning of this century: in 2001 a study allocated breast cancer patients (n = 99) to usual care, self-directed or supervised exercise for 26 weeks. Results showed that aerobic capacity increased significantly comparing supervised exercise to the control group and that regarding some dimensions of QoL self-directed exercise was superior to supervised exercise (R. Segal, Evans, Johnson et al., 2001).

### Advantages for cancer patients undergoing exercise

Since then there have been a large number of trials in multiple settings, with different exercise regimes and in various cancer entities. Trials have been conducted pre-, during and post treatment addressing various problems: mitigating the acute and late effects of therapy on physical and psychological health, supporting the efficiency of therapy, and improving cancer as well as non-

cancer related mortality. Most of the studies observed breast cancer patients, followed by prostate, colorectal and lung cancer patients (Jones & Alfano, 2013). For example, in colorectal cancer survivors increased fitness seems to improve QoL and mitigate anxiety (Courneya, Friedenreich, Quinney et al., 2003). Furthermore, by increasing their level of exercise after diagnosis, all-cause and cancer specific mortality is diminished (Meyerhardt, Giovannucci, Holmes et al., 2006). They also showed that women with colorectal cancer who were physically active after the diagnosis were at significantly lower risk of all-cause mortality as well as cancer-specific death (Meyerhardt, Giovannucci, Holmes et al., 2006).

Similar findings were observed in prostate cancer patients: physical activity, especially vigorous activity was associated with reduced overall and prostate cancer related mortality (Kenfield, Stampfer, Giovannucci et al., 2011). During androgen deprivation therapy, resistance training is associated with better QoL, lower fatigue and higher muscular strength (R. J. Segal, Reid, Courneya et al., 2003).

Also, in lung cancer patients an exercise intervention positively affects several cardiopulmonary parameters and QoL while reducing levels of fatigue. Results were even more significant regarding patients who did not receive chemotherapy (Jones, Eves, Peterson et al., 2008).

### Beneficial effects of exercise in breast cancer patients

Exercise has several beneficial effects on breast cancer patients, too. Physical performance and aerobic capacity are improved by exercise, especially by supervised exercise training. In particular, breast cancer patients undergoing chemotherapy or radiotherapy during the intervention seem to profit more from

supervised than from self-directed exercise. Also, perceived fatigue is mitigated by exercise training (Gebruers, Camberlin, Theunissen et al., 2019).

As mentioned above, breast cancer patients are at higher risk of dying of CVD. Exercise reduces risk of CV events and CV death in early-stage breast cancer patients. Furthermore, breast cancer patients who are older than 70 years and those with a history of CVD showed a significant reduction of CV events. This appears even more significant considering the ongoing aging of society and the following increase in patients with risk factors or history of CVD (Jones, Habel, Weltzien et al., 2016).

In addition, breast cancer patients being already physical active before diagnosis, but also starting physical activity post-diagnosis reduce their risk of all-cause death and breast cancer related death (Lahart, Metsios, Nevill et al., 2015).

Moreover, exercise training and higher exercise capacity is associated with reduced side effects of cancer therapy, has shown to improve compliance to therapy and leads to higher chemotherapy completion rate without causing adverse events (Courneya, Segal, Gelmon et al., 2014; Courneya, Segal, Mackey et al., 2007).

### 1.5. Aim of this study

To summarize, it can be noted, that breast cancer is a disease with growing incidence and declining mortality. Hence, there will be more breast cancer survivors in the future. Since the treatment of breast cancer is cardiotoxic in multiple ways, breast cancer survivors have an impaired CPF and face a higher cardiac risk. However, not only the cardiopulmonary capacity of breast cancer patients is impaired, but also their QoL. An approach considering both problems

is exercise training. Exercise has been shown to be a safe treatment by ameliorating cardiopulmonary capacity and QoL in breast cancer patients.

However, data evaluating the role of exercise training in larger cohorts in 'real world' outpatient setting over a prolonged time period are still scarce. Especially, trials with measurement of oxygen capacity at different thresholds, levels of lactate and investigation of different dimensions of QoL are rarely conducted.

Therefore, the department of Prevention, Rehabilitation and Sports Medicine at Klinikum rechts der Isar of the Technical University Munich initiated a tailored lifestyle intervention program in cancer patients including nutritional counseling and supervised exercise training for six months assessing physical fitness as well as QoL. We included patients independent of therapy regime. We hypothesized that breast cancer patients improve their CPF during this exercise rehabilitation program over six months independently of their regime of therapy. We assumed that a standardized exercise training is more effective in those patients without chemotherapy than in those under chemotherapy and metastatic disease.

Further, we hypothesized that the QoL of breast cancer patients is ameliorated by our six-month exercise program. We supposed that not only different dimensions of QoL like physical and emotional functioning are positively influenced, but also that symptoms of therapy and the disease itself can be reduced, e.g. fatigue and pain. In addition, we expected patients show lower levels of emotional distress after taking part in the program.

In conclusion, the aim was to create a program accessible to everyone which demonstrably ameliorates their CPF and QoL. Further, we aimed to identify ideal

timeframes regarding the status of therapy to start such a program to maximize breast cancer patients benefit from such a program.

# 2. Methods

In 2008, the department of Prevention, Rehabilitation and Sports Medicine at Klinikum rechts der Isar of the Technical University Munich initiated a program providing exercise and nutritional counselling for cancer patients (“Exercising with Cancer”). The program is offered to all cancer patients from the hospital as well as for patients with external referral.

Throughout the six-month program, patients are prescribed physiotherapy as well as supervised endurance and resistance exercise three times a week. They are also encouraged to increase their leisure time activity. Medical examinations and nutritional counseling are covered by health insurances, whereas exercise training is only partly covered depending on the individual patient´s insurance contract.

Patients are seen for medical examination and exercise testing at baseline, after three months and after six months of intervention. This schedule is added by a consultation by a physician specialized in internal medicine and exercise physiology/internal sports medicine four weeks after starting the program in order to evaluate logistical as well as medical problems after the first weeks of exercise training.

Only data from those who have given written informed consent were eligible to participate in the statistical analysis. This study protocol was approved by the ethics committee of the Klinikum rechts der Isar of the Technical University Munich, Munich, Germany; registration number 460/16 s. All medical data were obtained from medical records.

## 2.1. Patient Recruitment and Setting

Retrospectively, data from cancer patients who had been included in the “Exercising with Cancer” program between June 2010 and October 2016 were included in this analysis. Overall, 547 patients diagnosed with various cancers took part in this program, 231 of whom had been diagnosed with breast cancer. Patients maturely discontinued the program and patients with missing data were excluded. Reasons for patient drop-outs were generally social (lack of time or relocation), medical (related or unrelated to their cancer diagnosis), death before the trial was finished, or therapy-related. Reasons for missing data were due to patients not performing exercise testing at one or more visits, refusal or intolerance of gas exchange analysis, or technical in nature. Patients actively fulfilling their six-month nutrition and exercise plans at the point of data collection were also excluded from this analysis, since data of at least one timepoint was not yet collected.

Following these criteria, 174 patients (75%) finished the program, while 57 (25%) dropped out. Of these 174 patients, complete data was available for 84 patients, which comprised 36% of all 231 breast cancer patients who participated in the program (Figure 1).

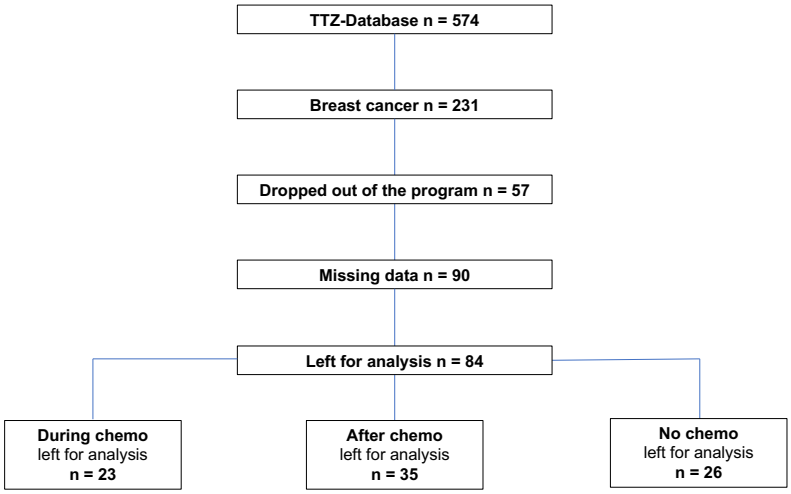


**Figure 1: Selection process of patients for analysis**
(TTZ = Tumor Therapie Zentrum)

## 2.2. Group assignment

Breast cancer patients were divided into the following groups: 1) those who received chemotherapy during the six months of intervention (*During chemotherapy*, n = 69; drop-out rate n = 20). 2) those who had completed chemotherapy (*After chemotherapy*, n = 86; drop-out rate n = 17), and 3) those who did not receive chemotherapy (*No chemotherapy*, (n = 73; drop-out rate n= 18). Drop-out rate remained relatively constant between the three therapy groups (p = 0.330).

## 2.3. Cardiopulmonary Fitness

Incremental cardio-pulmonary Exercise Testing (CPET) with a 12-lead ECG (Custo med GmbH, Ottobrunn, Germany) was performed on an electronically braked cycle ergometer (Ergoline, Bitz, Germany; Custo med GmbH, Ottobrunn, Germany) with breath-by-breath expired gas analysis (Cortex/Custo). In addition,

lactate was measured from earlobe capillary blood (BIOSEN C-line, EKF Diagnostic, Cardiff, United Kingdom). Before exercise, resting metabolic data were collected for three minutes. Patients started cycling at 25 or 50 Watts depending on general condition with increments of workloads of 25 Watts every three minutes until exhaustion or symptom limitations. $VO_{2peak}$ was assessed like all other ventilatory parameters e.g., VE, $VE/CO_2$. All tests were supervised by certified exercise physiologists.

### 2.4. CPET as gold standard and $VO_{2peak}$ as primary endpoint

CPET including gas analysis is the gold standard to assess CPF. The parameters generated by this test provide information on oxygen transport and utilization in the body and can point to asymptomatic cardiovascular abnormalities. The most significant parameter is $VO_{2peak}$ described as product of cardiac output and arteriovenous oxygen difference. The oxygen transport chain describes the transport of oxygen from the atmosphere to the mitochondria. A change in any link of the oxygen transport chain is reflected in a change of $VO_{2peak}$. Pulmonary system, cardiovascular system, blood and blood cells, and skeletal muscle are part of the oxygen transport chain. If any of these components is impaired, CPF is lowered (Jones, Courneya, Mackey et al., 2012; Jones, Eves, Haykowsky et al., 2009; Jones, Eves, Haykowsky et al., 2008).

### 2.5. Secondary endpoints

#### Exercise behavior

On every visit participants reported their exercise behavior over the last weeks:

We asked participants about the amount of time spend exercising and what kind of exercise they pursued. Exercise behavior was counted in metabolic equivalent tasks (MET) and documented as MET*h/week.

Each activity gets assigned a MET value, whereas a MET value of one equates the energy a person expends sitting at rest. For example, dancing has a MET value of 5 and bicycling a value of 8.5. These values are multiplied by the average duration of each session and times of session per week (Ainsworth, Haskell, Herrmann et al., 2011).

Further endpoints

Other endpoints of cardiopulmonary testing were maximum lactate, maximum workload (workload at the peak of exercise lasting for at least one minute), maximum heartrate, oxygen consumption ($VO_2$) at ventilatory threshold 1 ($VT_1$, formerly known as aerobic threshold), $VO_2$ at ventilatory threshold 2 ($VT_2$, formerly known as respiratory compensation point), and workload at the ventilatory threshold 1 and at the ventilatory threshold 2.

## 2.6. Quality of life

Assessment via questionnaires

At each of the three visits we asked our patients to fill out three quality of life (QoL) questionnaires: the Hospital anxiety and depression Score (HADS), the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QLQ C30) and the 36-Item Short Form Survey Instrument (SF-36).

HADS is a questionnaire composed of 14 questions, seven regarding anxiety and seven regarding depression. Each question scores from 0 (not present) to 3

(maximal present). Each subscale of HADS ranges between 0 (no anxiety or depression) to 21 (maximum level of anxiety or depression). Further, patients can be categorized: a score from 0 to 7 indicating no case, 8 to 10 indicating borderline case and over 11 indicating definite case (Hinz, Krauss, Hauss et al., 2010). In 1983 Zigmond and Snaith developed the HADS to detect anxiety and depression in patients in non-psychiatric clinics (Zigmond & Snaith, 1983). The HADS has been proven to be a valid instrument for measuring mental distress in cancer patients and has been used in many trails (Bjelland, Dahl, Haug et al., 2002; Moorey, Greer, Watson et al., 1991). In comparison with other questionnaires the HADS identified anxiety and depression best in patients with stable disease or on active treatment (Ibbotson, Maguire, Selby et al., 1994).

EORTC QLQ C30 exists of 30 questions and divides in 15 subscales: global health status; functioning scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning) and symptom scales/items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). Each scale scores from 0 to 100, calculated with the scoring system of the EORTC. A good QoL is represented as high scores in the global health status and the functioning scales, whereas higher symptom scales imply a worse symptomatology. The validity and reliability of the EORTC have been verified not only through a test/retest study (Hjermstad, Fossa, Bjordal et al., 1995; Kaasa, Bjordal, Aaronson et al., 1995). Thus, the EORTC QLQ C30 has often been used to assess quality of life in cancer patients (Gerlich, Schuler, Jelitte et al., 2016; Mehnert, Veers, Howaldt et al., 2011;

Steindorf, Schmidt, Klassen et al., 2014; Thorsen, Skovlund, Stromme et al., 2005).

SF-36 consists of 36 items and comprises eight scales: physical functioning, role functioning/physical, role functioning/emotional, energy/fatigue, emotional well-being, social functioning, pain and general health. Each scale ranges between 0 (no functioning) to 100 (full functioning). The validity of the SF-36 has been verified (McHorney, Ware, & Raczek, 1993). SF-36 has been used in many trials to measure quality of life in cancer patients (Cadmus, Salovey, Yu et al., 2009; Courneya, McKenzie, Mackey et al., 2013; Courneya, McNeil, O'Reilly et al., 2017; Mehnert, Veers, Howaldt et al., 2011).

Karnofsky performance status scale

Physical performance status was assessed at baseline, three months and six months using the Karnofsky performance status scale (KPS). This scale measures ability to maintain selfcare, activity and mobility of cancer patients raging from 100% ( no limitations) to 0 % (death) (Greimel, Thiel, Peintinger et al., 2002).

## 3. Statistical analysis

Quantitative data are described by mean and standard deviation [mean ± SD], categorical data by absolute and relative frequencies [n (%)]. For assessment of mean changes over time, repeated measurement analysis of variance (ANOVA) was conducted in consideration of the values at baseline, prior to execution of the nutrition and exercise program, as well as after three and six months of the program's implementation, respectively. If the null hypothesis of equal mean values at all three time-points could be rejected, pairwise comparisons of time-points using paired sample t-tests were performed (closed testing principle). Mean values of quantitative variables were compared using univariate analysis of variance (ANOVA) between patient groups (therapy stages). For example, ANOVA was used comparing the change of $VO_{2peak}$ from baseline to 6 months for all three groups (no chemo, during chemo and after chemo). The null hypothesis states that all changes in $VO_{2peak}$ over 6 months are the same.

For comparisons of two groups, two-sample t-tests were used. For example, comparing $VO_{2peak}$ at baseline and 6 months for the whole sample. The null hypothesis would be that $VO_{2peak}$ has the same value at baseline and 6 months.

Categorical data were compared between patient groups using Pearson's-Chi-squared test. For example, Pearson's-Chi-squared test was used comparing how many patients quit the program in each group (no chemo, during chemo and after chemo). The null hypothesis states that drop-out rate was the same in all three groups (no chemo, during chemo and after chemo).

Linear regression (Figure 2) was applied to assess the relationship between age and $VO_{2peak}$ at baseline and after six months, in comparison to the $VO_{2peak}$

expected for sedentary women without a history of breast cancer (Fitzgerald, Tanaka, Tran et al., 1997). Correlation between continuous data points was assessed using Pearson's correlation coefficient. All statistical tests were two-tailed, with a significance level of $\alpha$=5%.

# 4. Results

## 4.1. Patients' characteristics

84 breast cancer patients (mean age 49±9 years, all female, curative n = 77, metastatic n = 7; KPS score: 90±5) were included in this analysis (Table 1, Figure 1). Most patients had stage I or IIA breast cancer (34.5% and 33.3%, respectively). 77 had non-metastatic and seven had metastatic disease. 79 (94%) women underwent surgery. 64 patients received radiation therapy while taking part in this program. Of the 26 patients who did not receive any chemotherapy, 21 received hormone therapy (tamoxifen or aromatase inhibitors).

Patients whose treatment plan did not include chemotherapy were significantly older than the other two groups, however, no significant differences in weight or body mass index between groups were present.

KPS changed significantly over six months from a mean of 90% to 92% (p=0.001).

**Table 1 - Patients' charcateristics**

| | Overall | | During Therapy | | After Therapy | | No Therapy | |
|---|---|---|---|---|---|---|---|---|
| Variable | No. | % | No. | % | No. | % | No. | % |
| No Patients | 84 | 100 | 23 | 27.4 | 35 | 41.7 | 26 | 31.0 |
| Age, years baseline | | | | | | | | |
| Mean | 49 | | 46 | | 46 | | 55 | |
| SD | 9 | | 7 | | 9 | | 8 | |
| Anatomic stage baseline | | | | | | | | |
| 0 | 3 | 3.6 | 1 | 4.3 | 0 | 0 | 2 | 7.7 |
| I | 29 | 34.5 | 5 | 21.7 | 12 | 34.3 | 12 | 46.2 |
| IIA | 28 | 33.3 | 9 | 39.1 | 10 | 28.6 | 9 | 34.6 |
| IIB | 11 | 13.1 | 2 | 8.7 | 7 | 20.0 | 2 | 7.7 |
| IIIA | 1 | 1.2 | 0 | 0 | 1 | 2.9 | 0 | 0 |
| IIIB | 1 | 1.2 | 0 | 0 | 1 | 2.9 | 0 | 0 |
| IIIC | 2 | 2.4 | 1 | 4.3 | 1 | 2.9 | 0 | 0 |
| IV | 7 | 8.3 | 3 | 13.0 | 3 | 8.6 | 1 | 3.8 |
| No data | 2 | 2.4 | 2 | 8.7 | 0 | 0 | 0 | 0 |
| Status baseline | | | | | | | | |
| curative | 77 | 92 | 20 | 87 | 32 | 91 | 25 | 96 |
| metastatic | 7 | 8 | 3 | 13 | 3 | 9 | 1 | 4 |
| KPS baseline | | | | | | | | |
| Mean | 90 | | 87 | | 91 | | 91 | |
| SD | 5 | | 5 | | 6 | | 4 | |
| KPS 3 months | | | | | | | | |
| Mean | 91 | | 89 | | 92 | | 92 | |
| SD | 5 | | 3 | | 6 | | 4 | |
| KPS 6 months | | | | | | | | |
| Mean | 92 | | 90 | | 92 | | 93 | |
| SD | 5 | | 4 | | 5 | | 5 | |
| Radiation | | | | | | | | |
| baseline | 52 | 62 | 5 | 22 | 28 | 80 | 19 | 73 |
| 3 months | 57 | 68 | 10 | 44 | 27 | 77 | 20 | 77 |
| 6 months | 63 | 75 | 14 | 61 | 29 | 83 | 20 | 77 |
| Surgery | | | | | | | | |
| baseline | 71 | 85 | 15 | 65 | 31 | 89 | 25 | 96 |
| 3 months | 77 | 92 | 19 | 83 | 32 | 91 | 26 | 100 |
| 6 months | 79 | 94 | 21 | 91 | 32 | 91 | 26 | 100 |

## 4.2. Changes of cardiopulmonary fitness over time

### Resting data

Resting exercise data are shown in Table 2. Mean resting heart rate was 78±11 beats/min at baseline and did not change significantly over the six months of the trial (p = 0.108). Two patients (2%) presented with tachycardia at the beginning of the trial; at six months the number had increased to 5%. Systolic blood pressure, diastolic blood pressure and lactate did not change significantly over the six months.

**Table 2 - Exercise data**

| Variable | **Baseline** Mean±SD | **3 months** Mean±SD | **6 months** Mean±SD | **p-value*** |
|---|---|---|---|---|
| Weight, kg | 69±12 | 68±12 | 68±12 | 0.754 |
| BMI, kg/m$^2$ | 24±4 | 24±4 | 24±4 | 0.709 |
| MET-h*wk | 27±22 | 34±21[c] | 33±27[g] | 0.045 |
| **Resting Data** | | | | |
| HR, beats/min | 78±11 | 77±12 | 76±11 | 0.250 |
| Systolic blood pressure, mmHg | 115±14 | 114±13 | 113±12 | 0.326 |
| Diastolic blood pressure, mmHg | 75±9 | 73±7 | 75±8 | 0.114 |
| Lactate, mmol/L | 0.78±0.32 | 0.8±0.29 | 0.8±0.27 | 0.696 |
| **Peak Exercise Data** | | | | |
| HR, beats/min | 160±17 | 164±16[c] | 165±14[i] | <0.001 |
| Cardiac reserve, beats /min | 82±18 | 87±16[c] | 89±18[d, i] | <0.001 |
| Systolic blood pressure, mmHg | 177±29 | 176±26 | 178±24 | 0.659 |
| Diastolic blood pressure, mmHg | 80±10 | 78±9 | 81±8[f] | 0.008 |
| $VO_{2peak}$, mL/kg/min | 24.53±6.22 | 25.37±6.07[a] | 26.06±6.40[d, i] | 0.002 |
| $VO_{2peak}$ predicted, mL/kg/min | 26.79±3.19 | 26.70±3.19 | 26.60±3.16 | |
| $VO_{2peak}$, L/min | 1.66±0.36 | 1.71±0.38[a] | 1.75±0.36[d, i] | 0.002 |
| RER | 1.10±0.10 | 1.12±0.09[a] | 1.11±0.08 | 0.148 |
| Workload, Watts | 122±31 | 130±30[c] | 136±30[f, i] | <0.001 |

| | | | | |
|---|---|---|---|---|
| Lactate, mmol/L | 6.26±1.95 | 6.95±2.15[c] | 7.25±2.13[d, i] | <0.001 |
| **During Exercise Data** | | | | |
| $VO_2$ at $VT_1$, L/min n = 50 | 0.97±0.22 | 0.95±0.20 | 1.04±0.25[e, g] | 0.21 |
| $VO_2$ at $VT_2$, L/min n = 59 | 1.37±0.31 | 1.46±0.32[c] | 1.46±0.34[i] | 0.004 |
| Workload at $VT_1$, Watts n = 34 | 54±21 | 56±18 | 66±23[e, h] | |
| Workload at $VT_2$, Watts n = 34 | 99±27 | 103±23 | 111±29[e, h] | |
| HR at $VT_1$, beats/min n = 48 | 112±18 | 110±16 | 115±15[d] | |
| HR at $VT_2$, beats/min n = 50 | 142±19 | 147±19[b] | 146±18[g] | |
| Time p-value (baseline to three months) a: p<0.1; b: p< 0.05; c: p<0.01<br>Time p-value (three months to six months) d: p<0.1; e: p< 0.05; f: p<0.01<br>Time p-value (baseline to six months) g: p<0.1; h: p< 0.05; i: p<0.01<br>* p-value from repeated measurement ANOVA | | | | |

Primary endpoint

Peak exercise data are presented in Table 2. $VO_{2peak}$ was 24.53±6.22 mL/kg/min (1.66±0.36 L/min, respectively) at baseline and increased to 25.37±6.07 mL/kg/min at three months. After six months of exercise $VO_{2peak}$ reached 26.06±6.40 mL/kg/min (1.75±0.36 L/min, respectively), showing a highly significant change (p = 0.001). $VO_{2peak}$ was 93% of the age predicted $VO_{2peak}$ at baseline and 96% at six months.

Secondary endpoints

MET*h/wk (reported in Table 2) increased significantly in the first three months from 27±22 MET*h/wk to 34±21 MET*h/wk (p = 0.004). Afterwards MET*h/wk decreased to 33±27 MET*h/wk at six months; in conclusion we see a tendency to a significant improvement over time (p = 0.063). The correlation between change of MET*h/wk and change of $VO_{2peak}$ over six months was not significant (p = 0.291; correlation coefficient r = 0.117).

A highly significant improvement is also shown in maximal workload (baseline: 122±31 Watts; six months: 130±30 Watts; $p < 0.001$), maximal lactate (baseline 6.26±1.95 mmol/L; six months 7.25±2.13 mmol/L; $p < 0.001$) and maximal heart rate (baseline 160±17 beats/min; six months 165±14 beats/min; $p < 0.001$). Maximal heart rate was 92% of age predicted heart rate at baseline and 95% at six months. Contrary to our expectations, we saw no significant change in RER ($p = 0.289$).

$VO_2$ at ventilatory threshold $VT_1$ increased from 0.97±0.22 L/min (baseline) to 0.95±0.20 L/min (three months) and then further to 1.04±0.25 L/min (six months); indicating a significant change between three and six months ($p = 0.011$). $VO_2$ at $VT_2$ was significantly higher at six months (1.46+0.34 L/min) than at baseline (1.37±0.31 L/min) ($p =0.007$). The workload at $VT_1$ was 54±21 watts at baseline and increased to 66±23 at six months ($p = 0.025$). A similar development is seen for workload at $VT_2$: at baseline workload was 99±27 watts and at six months it was 111±29 ($p = 0.005$). Heartrate at $VT_1$ stayed nearly the same over the six months (baseline 112±18 beats/min; three months 110±16 beats/min; six months 115±15 beats/min, $p = 0.443$). Heartrate at $VT_2$ does change significantly over time as well (baseline 142±19 beats/min; three months 147±19 beats/min; six months 147±18 beats/min; $p = 0.042$).

Age-related decline in $VO_{2peak}$

Baseline correlation analysis between age and $VO_{2peak}$ showed the expected decline with age, as identified in previous studies (Jones, Courneya, Mackey et al., 2012). Intervention after six months revealed a mean improvement of $VO_{2peak}$

by 1.5 ml/kg/min, irrespective of age (Figure 2). Breast cancer patients older than 55 years even reached mean values above the expected $VO_{2peak}$ decline of healthy sedentary women (Figure 2).

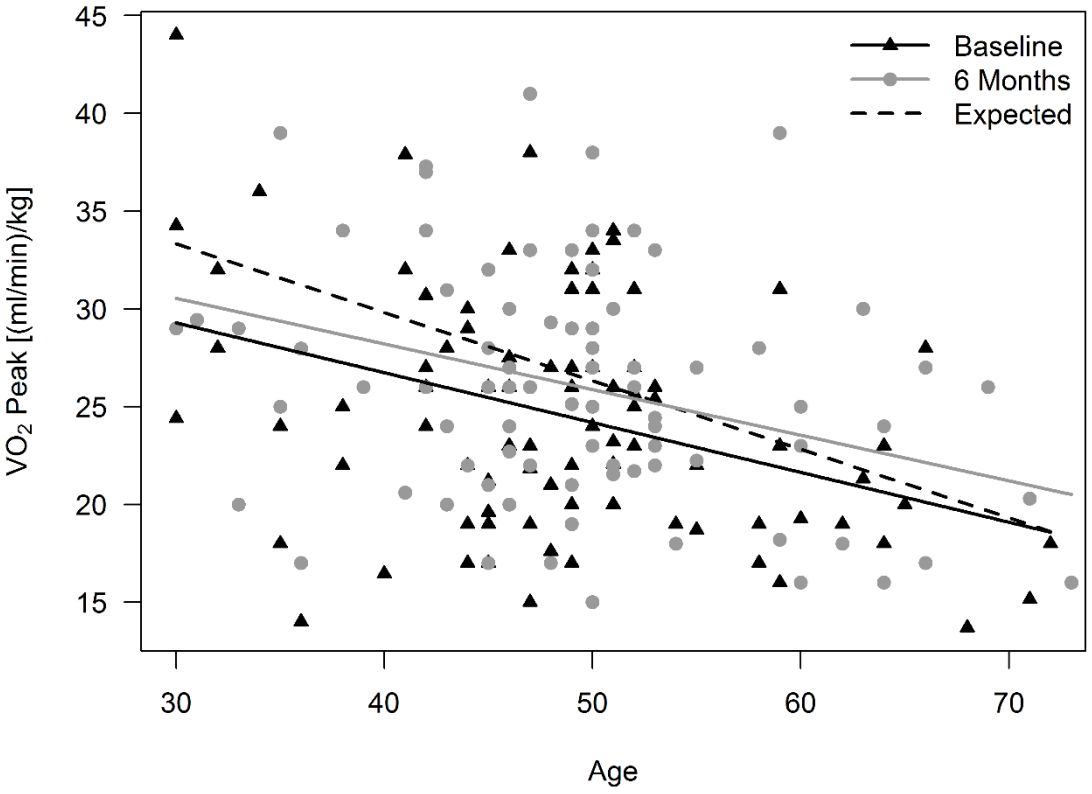


**Figure 2: Age related decline of VO2peak, comparison before and after exercise training**
Relationship between age and $VO_{2peak}$:
expected $VO_{2peak}$ decline of healthy sedentary women (black dashed line: y = 43.82 – 0.35 · age)
$VO_{2peak}$ decline measured at baseline (black line: y = 36.931 – 0.255 · age)
$VO_{2peak}$ decline measured at six months (grey line: y = 37.537 – 0.233 · age)

### 4.3. Differences of cardiopulmonary fitness between groups

All exercise parameters did not show a significant difference between the groups. As presented in Figure 3 all three groups improved their $VO_{2peak}$ after six months of exercise training.

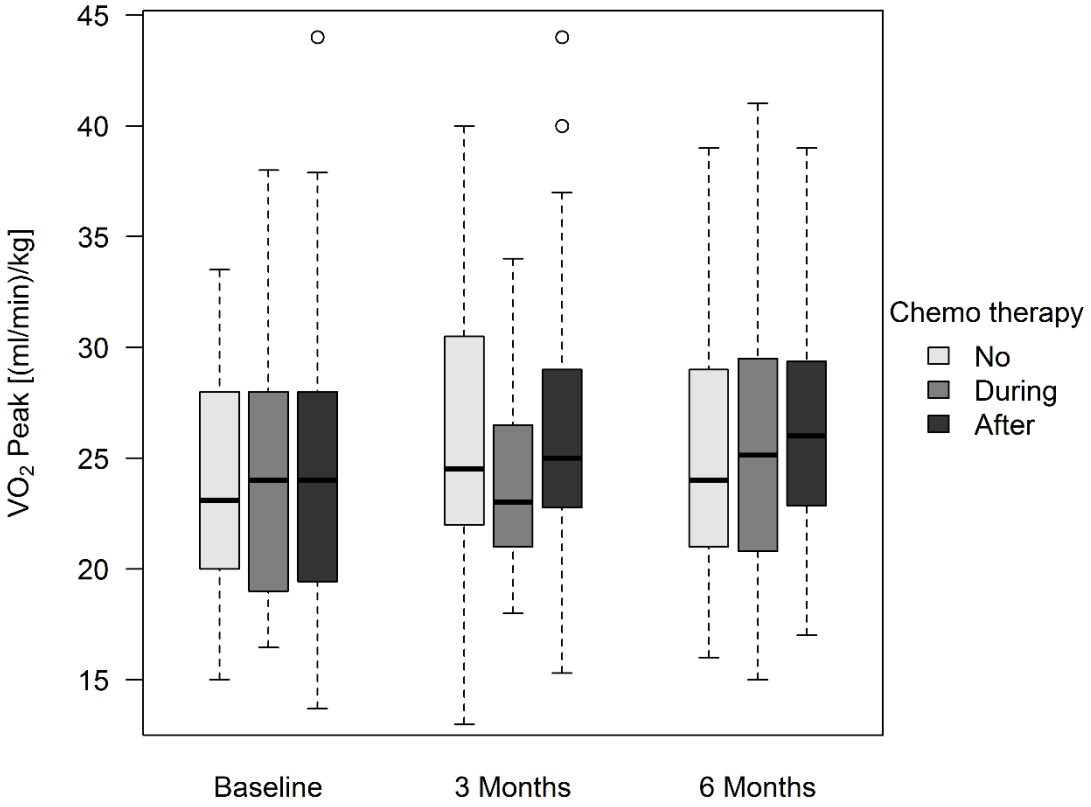


**Figure 3: Differences of $VO_{2peak}$ between therapy groups**
$VO_{2peak}$ measured for every therapy group seperatly at all three time points showing no significant differences at any timepoint (baseline p = 0.992; three months p = 0.657; six months p = 0.824)

Comparing the three therapy groups the value of $VO_{2peak}$ did not differ significantly at any time point (baseline p = 0.992; three months p = 0.657; six months p = 0.824 and the change of $VO_{2peak}$ from baseline to six months did not differ significantly, too (p = 0.359).

The *During chemotherapy group* started with a $VO_{2peak}$ of 24.56±5.94 mL/kg/min, the value decreased to 23.89±4.76 mL/kg/min and afterwards increased up to 25.55±6.06 mL/kg/min (baseline to six months: p = 0.210). Maximal workload and maximal lactate improved constantly over the six months. In the first three months the group incremented their MET*h/wk from 27±23 to 34±25 and over the six months up to 38±39 (baseline to six months: p = 0.156).

For the *After chemotherapy group* $VO_{2peak}$ was 24.86±6.81 mL/kg/min at baseline and increased to 27.00±6.61 mL/kg/min after six months (baseline to six months: p = 0.001). Maximal workload and maximal lactate increased constantly. In this group the MET*h/wk were the highest to start with: 31±22; after three months the exercise activity increased to 34±24 MET*h/wk and remained at this level until the end of the program (baseline to six months: p = 0.493).

The *No chemotherapy group* was the oldest group and had the lowest $VO_{2peak}$ (24.32±5.90 mL/kg/min) and the lowest MET*h/wk (23±21) at baseline. These patients achieved the highest values of $VO_{2peak}$ (25.56±6.25 mL/kg/min) and MET*h/wk (35±16) after the first three months. In the following months $VO_{2peak}$ decreased to 25.33±6.48 mL/kg/min and MET*h/wk decreased to 28±16 ($VO_{2peak}$ baseline to six months: p=0.252; MET*h/wk baseline to six months: p = 0.317). In contrast maximal workload and maximal lactate improved continuously.

Karnofsky performance status was significantly different at baseline (p = 0.014), however showed a trend at three months (p = 0.051), but lost significance at six months (p = 0.208).

### 4.4. Metastatic patients

Comparison between *Non-metastatic* and *Metastatic group* revealed the following: Drop-out rate was almost the same as in *Non-metastatic group*, 23% vs 25% respectively. Regarding exercise parameters the *Non-metastatic group* started with higher $VO_{2peak}$ values than the *Metastatic group* at baseline (24.59±6.17 mL/kg/min). Over the six months the patients in this group improved constantly up to a mean of 26.19±6.51 mL/kg/min (p < 0.001). In contrast, the *Metastatic group* started at 23.85±7.28 mL/kg/min and then improved their

$VO_{2peak}$ in the first three months up to 27.29±5.74 mL/kg/min. In the following three months the $VO_{2peak}$ decreased to 24.71±5.22 mL/kg/min (p = 0.755). MET*h/wk increased from 37.1 to 46.1 in the first three months. At six months the value decreased to 30.6, since two patients were not able to exercise at all (p = 0.592).

### 4.5. Quality of life

QoL results are represented in Table 3, 4, and 5. All QoL data were analyzed for the whole patient sample, because QoL data was too scarce to compare the three groups.

#### HADS

Analyzing the item depression of the HADS revealed that 56% of our group were no cases, 10% were borderline depressive, 4% were cases at baseline. The mean score was 5.2 (SD 3.7). The allocation in the categories nearly stayed the same over the six months. The mean diminished to 4.8 (SD 3.9) and further to 4.4 (SD 3.9) after six months of exercise. The change over the six months was significant (p = 0.041).

Anxiety was spread more widely: 37% of the patients were no cases of anxiety at baseline, 20% were borderline and 11% were definite cases. The number of definite cases stayed nearly the same over the six months, the number of no cases rose. At all three time points the mean of anxiety was higher than the mean of depression. But the mean decreased from 7.3 over 7.1 (at three months) to 6.8 (at six months). This change was not significant (p = 0.184).

**Table 3 - Results HADS**

| Variable | **Baseline** Mean±SD | **3 months** Mean±SD | **6 months** Mean±SD | |
|---|---|---|---|---|
| Anxiety n = 57 | 7.3±3.4 | 7.1±4.0 | 6.8±3.5 | 0.090 |
| Depression n = 58 | 5.2±3.7 | 4.8±3.9 | 4.4±3.9 | 0.419 |
| Time p-value (baseline to three months) a: p<0.1; b: p< 0.05; c: p<0.01<br>Time p-value (three months to six months) d: p<0.1; e: p< 0.05; f: p<0.01<br>Time p-value (baseline to six months) g: p<0.1; h: p< 0.05; i: p<0.01<br>* p-value from repeated measurement ANOVA | | | | |

EORTC

Significant changes over time were achieved in global health (baseline 56±20, six months 65±20; p = 0.003), physical functioning (baseline 78±17, six months 84±16; p = 0.003), role functioning (baseline 59±33, six months 70±29; p = 0.021) and social functioning (baseline 64±32, six months 74±30; p = 0.047).

Therefore, three of the functioning scales amended and the other two (emotional functioning and cognitive functioning) nearly stayed the same over the six months of exercise training.

None of the symptom scales improved significantly, however, fatigue and nausea/vomiting showed a trend towards less symptoms. Insomnia ameliorated in the first three months, but after six months the value turned out even higher than at baseline (baseline 50±38, three months 41±35, six months 52±36).

**Table 4 - Results EORTC QLQ C30**

| Variable | **Baseline** Mean±SD | **3 months** Mean±SD | **6 months** Mean±SD | **p-value*** Mean±SD |
|---|---|---|---|---|
| **Global health status** | | | | |
| Global health status n=46 | 56±20 | 63±19[a] | 65±20[i] | 0.024 |
| **Functional scales** | | | | |
| Physical functioning n=48 | 78±17 | 82±14 | 84±16[i] | 0.014 |
| Role functioning n=49 | 59±33 | 66±27 | 70±29 | 0.05 |
| Emotional functioning n=45 | 58±24 | 62±25 | 59±26 | 0.567 |
| Cognitive functioning n=47 | 71±30 | 70±29 | 72±27 | 0.765 |
| Social functioning n=49 | 64±32 | 69±27 | 74±30 | 0.064 |
| **Symptom scales/items** | | | | |
| Fatigue n=46 | 49±23 | 44±24 | 42±28 | 0.200 |
| Nausea and vomiting n=50 | 7±13 | 3±10 | 3±9 | 0.140 |
| Pain n=46 | 35±32 | 37±31 | 36±31 | 0.860 |
| Dyspnoea n=49 | 24±29 | 27±28 | 19±26 | 0.155 |
| Insomnia n=50 | 50±38 | 41±35 | 52±36 | 0.081 |
| Appetite loss n=49 | 10±22 | 7±18 | 5±18 | 0.427 |
| Constipation n = 50 | 15±24 | 11±24 | 11±23 | 0.335 |
| Diarrhoea n=50 | 5±12 | 7±18 | 7±19 | 0.789 |
| Financial difficulties n=49 | 25±32 | 22±29 | 26±30 | 0.556 |

Time p-value (baseline to three months) a: p<0.1; b: p< 0.05; c: p<0.01
Time p-value (three months to six months) d: p<0.1; e: p< 0.05; f: p<0.01
Time p-value (baseline to six months) g: p<0.1; h: p< 0.05; i: p<0.01
* p-value from repeated measurement ANOVA

SF-36

In the eight items of the SF-36, we saw the biggest change in role functioning/physical (baseline 39±39, six months 54±37; p = 0.013) and role functioning/emotional (baseline 56±46, six months 70±40; p = 0.043). Social

functioning followed by physical functioning and energy/fatigue improved significantly by approximately 10 points over the six months of exercise. Patients felt less pain over time (baseline 61±48, six months 66±26, p = 0.235), but the change was not significant. General health ameliorated after the six months of exercise, but did not reach significance.

**Table 5 - Results SF-36**

| Variable | **Baseline** Mean±SD | **3 months** Mean±SD | **6 months** Mean±SD | **p-value*** |
|---|---|---|---|---|
| Physical functioning n = 45 | 75±18 | 81±15[b] | 83±18[i] | 0.006 |
| Role functioning/physical n = 46 | 39±39 | 49±37[a] | 54±37[h] | 0.018 |
| Role functioning/emotional n = 42 | 56±46 | 64±44 | 70±40 | 0.107 |
| Energy/fatigue n = 49 | 46±16 | 53±16[c] | 54±18[i] | 0.001 |
| Emotional well-being n = 50 | 60±15 | 65±20[b] | 65±18[h] | 0.016 |
| Social functioning n = 50 | 65±23 | 73±25[b] | 76±26[i] | 0.002 |
| Pain n = 49 | 61±28 | 64±24 | 66±26 | 0.434 |
| General health n = 48 | 59±16 | 60±16 | 64±17[d, h] | 0.069 |

Time p-value (baseline to three months) a: p<0.1; b: p< 0.05; c: p<0.01
Time p-value (three months to six months) d: p<0.1; e: p< 0.05; f: p<0.01
Time p-value (baseline to six months) g: p<0.1; h: p< 0.05; i: p<0.01
* p-value from repeated measurement ANOVA

# 5. Discussion

## 5.1. Discussion of our results - cardiopulmonary fitness

In agreement with our hypothesis we observed an improvement in cardiopulmonary capacity in all patients completing this six-month life-style intervention program. This was expressed as improvements of $VO_{2peak}$ and maximum workload as well as increases in $VO_2$ at ventilatory thresholds during spiroergometry. The significant increase in maximal lactate and maximal heartrate confirm these findings.

In contrast to our hypothesis we observed that six months of exercise training improves $VO_{2peak}$ to a comparable extent, irrespective whether patients had been treated before, were currently treated or had not been treated at all by chemotherapy.

Even patients with metastatic disease profited from the participation in this program (improvement in $VO_{2peak}$ by 0.86 mL/kg/min).

Overall, the reduced physical fitness of breast cancer patients at baseline compared to healthy sedentary women diminished over the six months of intervention. Interestingly, these improvements were independent of state of breast cancer therapy. Particularly older women beyond 55 years profited from the program reaching even higher values than average values of age-matched healthy women (Figure 2).

### $VO_{2peak}$

As mentioned above, all patients included in this analysis improved their $VO_{2peak}$ during the six months of exercise training significantly (increase by 1.6

mL/kg/min, $p < 0.01$). However, the improvements in $VO_{2peak}$ were not as high as observed in previous studies, e.g. +2.7 mL/kg/min versus our patient group +1.6 mL/kg/min, which might be explained by higher baseline levels (24.5±6.2 mL/kg/min) compared to previous studies (18.6±3.9 mL/kg/min) (Courneya, Mackey, Bell et al., 2003). This study investigated CPF before and after 15 weeks of exercise in 53 postmenopausal breast cancer patients comparing intervention and control group. In another study showing similar baseline levels as ours (24.7±4.3 mL/kg/min) patients (n = 58) improved by 2.2 mL/kg/min after ten weeks of exercise training. In contrast to our study participants had already finished therapy. This might explain the higher improvement. Analyzing the group ”after chemotherapy”, data revealed an improvement by 2.1 mL/kg/min - almost the same as in the study mentioned above (Mehnert, Veers, Howaldt et al., 2011). Both trials (Courneya, Mackey, Bell et al., 2003; Mehnert, Veers, Howaldt et al., 2011) compared intervention and waiting/usual care group and revealed that the intervention group enhanced their CPF, whilst the waiting/usual care group worsened theirs.

Our analysis showed no significant differences in improvement of exercise parameters between the therapy groups. All women had improved their CPF values at the end of the intervention even though the *After chemotherapy group* showed the biggest improvement (+2.1 mL/kg/min). There is no other trial comparing these three types of therapy regimes. Another trial comparing different therapy regimes is the one by Hsieh et al.: In this study four therapy regime (surgery; surgery and radiation; surgery and chemotherapy; surgery, radiation and chemotherapy) were compared. Patients (n = 96) took part in an individually

supervised exercise training for six months. Similar to our findings, the study revealed that all breast cancer patients improved their cardiopulmonary fitness level independent of cancer therapy, (measured by time on treadmill and predicted $VO_{2max}$) (Hsieh, Sprod, Hydock et al., 2008).

Some trials have investigated patients undergoing chemotherapy: For example, in 2007 248 breast cancer patients undergoing chemotherapy were included in a randomized controlled trial (RCT) comparing usual care, resistance (RET) and aerobic exercise training (AET). In this trial patients exercised for the duration of their chemotherapy (median 17 weeks). At the end, CPF (measured in $VO_{2peak}$) of patients in the usual care group and RET group worsened, whereas the AET group could preserve but not improve their CPF (Courneya, Segal, Mackey et al., 2007). In contrast, $VO_{2peak}$ of patients in the *During chemotherapy group* improved by 1.0 mL/kg/min in our analysis.

One study in 2007 compared women with breast cancer undergoing chemotherapy versus women "after chemotherapy": Cardiopulmonary improvement was assessed in 113 breast cancer patients taking part in a six-month individually tailored exercise program (including aerobic and resistance training, as well as stretching). The study revealed a significant improvement in predicted $VO_{2peak}$, however, only in the "after chemotherapy" group. (Schneider, Hsieh, Sprod et al., 2007).

In comparison to other studies, our findings are similar to previous studies showing improvement in CPF in breast cancer patients after exercise training. However, there has currently been no study comparing these three types of therapy regime assessing exercise capacity over a six months training program.

MET

During the program patients were encouraged to exercise even beyond the prescribed exercise sessions. This led to an increase of weekly exercise time as well as intensity of exercise expressed as metabolic equivalent task (from 27±22 MET*h/wk to 34±21 MET*h/week). Independent of therapy regime patients increased their physical activity, even though the *During chemotherapy group* showed the largest improvement (+7 MET*h/week after six months). Usually, trials investigating CPF in cancer patients have a specially tailored exercise program for the participants and therefore do not measure their physical activity (Courneya, Mackey, Bell et al., 2003; Hsieh, Sprod, Hydock et al., 2008; Mehnert, Veers, Howaldt et al., 2011). Consequently, there are not many trials for comparison.

In 2005 a study investigated physical activity in breast cancer patients after 12 weeks of telephone counseling and motivation to engage in exercise (Pinto, Frierson, Rabin et al., 2005). The study showed that patients who are regularly motivated to exercise increase their minutes of exercise per week compared to a control group. In this trial minutes of exercise were measured instead of MET*h/week, so a direct comparison is not possible. But encouraging patients to exercise seems to increase weekly time of training.

Other trials explore whether physical activity is a predictor of adverse invents or survival. Comparing these patient groups, our patients reported average high baseline exercise behavior compared to other studies:

In 2016 a trial analyzing correlation between exercise behavior and occurrence of cardiovascular events in breast cancer survivors revealed a median of 10.3

MET*h/week (compared to our findings: median 22 MET*h/week at baseline) (Jones, Habel, Weltzien et al., 2016). This trial demonstrated that a higher level of physical activity lowers the risk of a cardiovascular event in the future.

A study analyzing the correlation between exercise behavior and survival in metastatic lung cancer patients, baseline exercise behavior was 28±45 MET*h/week (Jones, Hornsby, Goetzinger et al., 2012).

A large study (n=2705) in men with prostate cancer revealed that an increase in MET*h/wk significantly lowered the risk of all-cause mortality (more than 9 MET*h/wk 33% lower risk). Further, they observed that vigorous exercise was significantly associated with lower risk of death from prostate cancer (Kenfield, Stampfer, Giovannucci et al., 2011).

A study comparing standard to high intensity aerobic exercise in breast cancer patients (n = 301) determined that the higher dose did not lead to a significantly higher $VO_{2peak}$. Standard dose consisted of 25-30 minutes of aerobic exercise and high dose of 50-60 minutes, thrice weekly. Intervention started with the onset of chemotherapy and lasted until three to four weeks after termination of chemotherapy (mean 16.4 weeks of intervention) (Courneya, McKenzie, Mackey et al., 2013). Our findings reveal a similar pattern, since all patients improved their level of exercise and fitness, but we could not find a direct correlation between changes in MET*h/week and changes in $VO_{2peak}$. Leading to the assumption that maximal CPF is not only determined by exercise in this cohort, but also by other disease-associated factors.

Metastatic patients

Our findings in metastatic patients show that also these patients improved their CPF after six months of exercise training not significantly (baseline 23.85±7.28 mL/kg/min, six months 24.71±5.22 mL/kg/min). Our program seems to be feasible regardless of therapy intention, since drop-out rate was almost the same as in non-metastatic group (23% vs 25% respectively). Metastatic patients even increased their physical activity in the first three months of training. After six months two patients weren't able to exercise due to disease related issues, such as pain. Analyzing such a small number of patients the mean of MET*h/week is diminished for all patients. Whereas in fact the other five metastatic patients were still able to exercise at a lower level.

Data on metastatic patients are scarce. A small review analyzing seven trials in patients with different cancer entities confirmed that exercise has a beneficial effect on QoL and physical performance in patients with metastatic cancer (Beaton, Pagdin-Friesen, Robertson et al., 2009).

In 2018 a RCT in metastatic breast cancer patients investigating safety and feasibility, as well as CPF and QoL allocated patients (n = 65) to either an aerobic exercise group or to attending a stretching group for 12 weeks. The analysis of the data showed that exercise training was safe, but for the most patients not feasible regarding high rate of permanent discontinuation. CPF was maintained in both groups. Baseline level of $VO_{2peak}$ was 22.5±6.7 mL/kg/min, similar to our small patient group (Scott, Iyengar, Nilsen et al., 2018).

In another trial, investigating the impact of exercise on physical functioning in metastatic breast cancer patients, participants (n = 101) allocated to the

intervention group received exercise training for 16 weeks (consisting of moderate-intensity aerobic exercise). There were no significant changes in minutes of exercise per week, but results favored the intervention group. Furthermore, QoL and time on treadmill improved in the intervention group, but results were not significant. Whereas, therapy seemed to have an impact on time on treadmill, i.e. patients undergoing less-intensive therapy were better able to attend the exercise program. No adverse events were observed. Authors concluded that exercise is safe, but not feasible for patients with advanced breast cancer (Ligibel, Giobbie-Hurder, Shockro et al., 2016).

Investigating patients with other cancer entities reveals several advantages for patients with advanced disease participating in exercise programs: A study in prostate cancer patients (curative and palliative; n = 155) showed that a 12 week resistance training lowers fatigue, improves QoL and strengthens muscular fitness regardless of intention of treatment (R. J. Segal, Reid, Courneya et al., 2003). In metastatic lung cancer patients (n = 118) exercise capacity has been shown to be a strong predictor for survival. In this study a 50 m improvement in 6-meter walking distance (MWD) equaled a 13% reduction in the risk of death. (Jones, Hornsby, Goetzinger et al., 2012).

In summary, our data showe that patients with metastatic disease are able to complete a six-month exercise program and profit from it. But our findings are limited due to the small number of patients with metastatic breast cancer. Since other studies have different findings on feasibility, more trials in metastatic patients will be needed in the future.

## 5.2. Discussion of our results - Quality of Life

Improvements induced by our life-style program were not limited to objectively measured parameters, but were also observed in improvements in the KPS, i.e. after the six months more patients felt healthier and were able to perform their general activity, although overall the score was high among the participants.

Consistent with our hypothesis we observed an amelioration of QoL throughout the whole group who completed the six-month exercise program. Different subitems of QoL and also symptoms of disease and side effects of therapy diminished significantly.

The six month exercise training led to a better global QoL (measured by the EORTC, significantly by $p < 0.01$) and general health (measured by the SF-36, significantly by $p < 0.05$). In both scales the biggest improvements were seen in role functioning (in SF-36 both subitems physical and emotional role functioning) and social functioning. Moreover, physical functioning improved significantly in both scales, too.

The symptoms nausea and vomiting, dyspnoea, loss of appetite and constipation, got better, but did not achieve statistical significance. Only a few dimensions of QoL did not improved, such as pain, insomnia, and diarrhoea.

We had inconsistent findings in fatigue, a very serious symptom in cancer patients: measured in the EORTC, fatigue did not improve significantly, but showed a positive trend; energy/fatigue measured in the SF-36 scale did reach statistically significant improvement.

Analysis of the HADS revealed, that after the trial our patients were less depressed and showed a tendency towards less anxiety.

The impact of exercise on QoL of cancer patients has frequently been investigated. Some of these studies used different scaling systems, nevertheless we can compare their outcome to ours. Most of the studies emphasize our findings, only a few report contrary results.

In 2011 one trial investigated QoL, depression and anxiety in breast cancer patients (n = 58) who had already finished therapy. After ten weeks of exercise (e.g. gymnastics, movement games, relaxation, walking, jogging) the exercise group showed similar results as we did: Patients in the exercise group had a lower anxiety and depression score than at baseline in comparison to the waiting group. Contrary to our findings, QoL did not change significantly, only the dimension social functioning improved in the exercise group (Mehnert, Veers, Howaldt et al., 2011).

Similar to our study, a trial conducted in 155 breast cancer patients undergoing radiotherapy found that fatigue, especially physical fatigue, role functioning and pain can be ameliorated by 12 weeks of exercise training (consisting of eight different machine-based resistance exercises, 60 minutes twice weekly) compared to a relaxation program. Furthermore, the exercise group achieved higher values of QoL after the intervention underpinning our results (Steindorf, Schmidt, Klassen et al., 2014).

Others especially focused on fatigue/cancer related fatigue: In different settings fatigue was significantly diminished by exercise (Hagstrom, Marshall, Lonsdale et al., 2016; Yang, Chen, & Li, 2015). In the first trial mentioned above patients after therapy underwent 16 weeks of resistance training or were allocated to a control group (n = 39). In the other trial training consisted of six weeks of AET.

Patients (n = 47) undergoing radiotherapy were allocated to an intervention or control group. Both studies showed significant reduction of fatigue in the intervention group.

On the contrary, one study showed reduced fatigue in the control group instead of the intervention group (Thorsen, Skovlund, Stromme et al., 2005): Patients after chemotherapy with breast, gynecologic or testicular cancer received 14 weeks of exercise (supervised home-based training twice weekly, patients chose their favorite activity). After the intervention fatigue had only lowered in the control group. The authors explained this finding by the timing of intervention. Intervention started just after chemotherapy was finished. At this time postchemo fatigue is said to be the highest and physical fitness to be the lowest. Hence, exercise training might be more of a burden than a support.

Another study in breast cancer patients undergoing chemotherapy for the first 18 weeks of intervention gained similar results: After 18 weeks of resistance and aerobic training control and intervention group reported severe fatigue, the exercise group showing even higher levels. QoL was diminished, too. After the 36 weeks follow up fatigue levels had gone back to baseline and QoL showed a small improvement in both groups. The patients in this trial underwent chemotherapy in the first 18 weeks of the trial. This might explain these outcomes (Travier, Velthuis, Steins Bisschop et al., 2015).

In summary, results on fatigue are inconsistent, but exercise during chemotherapy seems to worsen fatigue. Since we did not evaluate fatigue in a separate questionnaire, our findings might not have the same strength as the ones in the studies mentioned above. Furthermore, we can only compare the

findings on fatigue to our whole sample, since we had not enough data to analyze each of the three groups. Nevertheless, our results show a decrease of fatigue in both scales and confirmed the fact that fatigue can be positively influenced by exercise training.

Other investigations focused on depression and anxiety in cancer patients: A large meta-analysis of randomized controlled trials validated that depression can be reduced by exercise in cancer survivors, especially in breast cancer patients and when training is supervised (Brown, Huedo-Medina, Pescatello et al., 2012). In a 12 week exercise program with six-month follow-up in early stage breast cancer patients (n = 177) the exercise group showed a tendency towards less depression compared to the control group. These findings were stable over the six-month follow-up (Mutrie, Campbell, Whyte et al., 2007).

In conclusion, exercise seems to ameliorate depression in breast cancer patients, consistent with our results. While in our patient group global QoL improved significantly, most other studies show a positive trend, but there are also negative examples, especially regarding women undergoing chemotherapy while taking part in an exercise trial. As in our study, exercise seems to have a positive impact on social functioning and role functioning, but findings on different subscales of QoL vary.

### 5.3. Limitations

Due to the retrospective design of our study there are some limitations:

The number of patients included into the final analysis was reduced because of drop out and data loss, which allowed us to only analyze 36% of the breast cancer patients who started the program. Drop-out rate was 25%. It is possible that the

women who dropped out of the program, are the ones who were less active or more impaired by their disease. Others found that 91% of their participants were physical active people, suggesting that patients already used to exercise are more likely to participate and complete an exercise intervention (Mehnert, Veers, Howaldt et al., 2011). Thus, we cannot evaluate, if our exercise program is feasible for all breast cancer patients.

Limited data were available from 39% of all breast patients, 52% from those who finished the trial, respectively. Some data was not available for analysis because at least one exercise test was not properly documented; other was not analyzable because some patients did an exercise test without gas analysis (reason being e.g., intolerance of the mask). Since we only included patients on who data from all three exercise tests were available, in the end we had data for analysis of 36% of all breast cancer patients who started the program, 48% from those who finished the trial, respectively.

In addition, in a prospective design we would have had a specific exercise program. Whereas, in our study weekly amount of exercise and type of exercise varied between patients. Our six-month program consisted of prescribed physiotherapy as well as supervised endurance and resistance exercise. Furthermore, patients were also encouraged to increase their leisure time activity. We did not monitor attendance rate to the prescribed training sessions. This is why we chose the questionnaire to evaluate the amount of exercise per week. But measurements of exercise by questionnaire is vague and should be assessed by objective devices such as accelerometers in future studies.

In addition, we cannot recommend a special type of training, since we did not analyze exactly what kind of exercise patients pursued and most of the patients did a combination of RET and AET.

Analyzing the QoL data we were faced with the problem, that many participants missed to answer at least one question at one of the three measuring points. We decided to only include these sets of data, in which the same question was answered at all three measuring points (e.g., question six of the SF-36 was answered at baseline, three months and six months). This led to a high exclusion-rate of data sets and to a variation in number of patients in every scale and subitem. Only in this way we were able to measure changes over time. At the end, we had not enough data to compare the three groups, hence, we only could investigate the group as a whole. Due to the lack of data, our analysis of the QoL shows more of a trend, than a valid statement on breast cancer patients during exercise.

The interpretation of the impact of exercise is limited due to the lack of data on a non-exercise control group. Hence, it is not possible to evaluate, how CPF and QoL would be changed in patients not receiving an intervention.

Other limitations are caused by the nature of exercise studies: Blinding of the participants, as done in pharmacological interventions, is not possible (Jones & Alfano, 2013). Also, the social aspect of exercise, e.g., the regular contact to a physician (during follow-ups) and physiotherapist (during exercise sessions) is reported to have a positive impact and may influence especially QoL outcomes (Ferrer, Huedo-Medina, Johnson et al., 2011; Spence, Heesch, & Brown, 2011; Whitehead & Lavelle, 2009).

Another drawback is the inhomogeneity of the *During chemotherapy group*: Some of the patients in this group finished chemotherapy during the time of intervention, whilst other received chemotherapy the whole time of the intervention.

## 5.4. Conclusion

Our study is one of the largest comparing different therapy groups and one of the few using different cardiopulmonary parameters and metabolic measurements, e.g., lactate analysis. Aside from that, we investigated psychological outcomes in different scaling systems.

As mentioned above our analysis has several limitations. Nevertheless, the following can be concluded:

Within a six-month period, breast cancer patients can significantly improve their CPF. This applies for different therapy regimes (during, after and without chemotherapy), as well as for patients with advanced cancer.

An exercise program consisting of prescribed training sessions (aerobic and resistance training) and encouragement to increase exercise in their leisure time seems to be feasible and effective.

Even QoL of the participants ameliorated. This is expressed in improvement of its various dimensions (e.g., social, role, physical functioning) and several symptoms (nausea, dyspnoea, appetite loss and constipation) caused by the disease or therapy. Also, patients felt less depressed at the end of the intervention.

Taking all this in account, exercise can be recommended at all stages of breast cancer and at alle times of therapy status. However, large randomized intervention studies are needed to confirm these findings.

# 6. Summary

Breast cancer is the most common malignant disease in women in Germany. Mortality from breast cancer has decreased during the past three decades as a result of early diagnosis, and novel treatment strategies. But breast cancer survivors have significantly lower aerobic capacity, measured in peak oxygen uptake ($VO_{2peak}$) compared to age-matched sedentary women. Exercise during rehabilitation of breast cancer has been shown to have beneficial effects on $VO_{2peak}$ and quality of life. However, studies of the effects of exercise on patients in different therapeutic stages are scarce.

Using a retrospective study design, data from 84 breast cancer survivors (age 49±9 yr; curative therapy approach n=77, metastatic disease n=7, radiation therapy at baseline n=52; Karnofsky Performance Scale: 90±5), were analyzed. Subjects participated in a six-month lifestyle intervention program of nutritional counseling and supervised exercise between 2010 and 2016. Changes of cardiopulmonary exercise testing (CPET) outcomes were compared after three and six months for each of the three following patient groups: 1) Actively receiving chemotherapy 2) Finished chemotherapy, and 3) Did not receive chemotherapy. Quality of life outcomes were compared for the whole patient sample after three and six months of intervention.

Overall, peak power output and aerobic power ($VO_{2peak}$) increased from baseline to six months (Baseline: 122±31 vs. 6 mo: 136±30 W, $p<0.01$, and Baseline: 24.5±6.2 mL/kg/min vs. 6 mo: 26.1±6.4 mL/kg/min, $p<0.01$). Also, other exercise parameters improved, e.g., $VO_2$ at VT1. These improvements were similar in all three groups. Patients with metastatic disease also improved in $VO_{2peak}$, but less

than in non-metastatic disease. Some dimensions of quality of life improved significantly (global health, physical functioning, role functioning and social functioning measured by the EORTC; role physical and emotional, social functioning, physical functioning and energy/fatigue measured by the SF-36; depression measured by the HADS).

Breast cancer patients who completed this six-month exercise program improved their $VO_{2peak}$ regardless of whether or not patients had previously received chemotherapy, were currently receiving chemotherapy, or had not been treated at all by chemotherapy. Even patients with metastatic disease profited from the participation in this program. Moreover, aerobic endurance capacity, measured as the $VO_2$ at ventilatory threshold, also improved after exercise training. Furthermore, exercise improves several dimensions of quality of life and soothes depression in this patient group.

# 7. Appendix

## 7.1. Bibliography


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