RESEARCH REPORT

OPEN

A Prospective Observational Pilot Study of Young Women Undergoing Initial Breast Cancer Treatment and Their Biopsychosocial Profile

Niklas Paul Grusdat, MSc[1]*; Alexander Stäuber, Dr. rer. nat.*[2]*; Marion Tolkmitt, Dr. med.*[3]*; Jens Schnabel, Dr. med.*[4]*; Birgit Schubotz, Dipl.-ing.*[5]*; Peter Richard Wright, PhD*[6]*; Henry Schulz, Dr. med.*[7]

[1]Research Assistant, Professorship of Sports Medicine/Sports Biology, Chemnitz University of Technology, Chemnitz, Germany; [2]Research Assistant, Professorship of Sports Medicine/Sports Biology, Chemnitz University of Technology, Chemnitz, Germany; [3]Senior Physician, Red Cross Hospital, Rotes Kreuz Krankenhaus, Chemnitz-Rabenstein, Germany; [4]Chief Physician, Red Cross Hospital, Rotes Kreuz Krankenhaus, Chemnitz-Rabenstein, Germany; [5]Head, Clinical Cancer Registry, Tumorzentrum Chemnitz e.V., Chemnitz, Germany; [6]Programme Lead, Department of Sport, Health Sciences and Social Work, Oxford Brookes University, Oxford, United Kingdom; and [7]Professor, Professorship of Sports Medicine/Sports Biology, Chemnitz University of Technology, Chemnitz, Germany

Background: Breast cancer in young women can be a major challenge for those affected. To offer support, the establishment of a biopsychosocial profile may be beneficial. **Methods:** For this prospective observational pilot study, we collected data of 19 women with a mean age of 42.8 ± 5.4 years (30.0-49.0 year) before (T0) and after (T1) initial breast cancer treatment. The handgrip strength (HGS), 6-minute walk test (6MWT), and bioimpedance analysis for the detection of phase angle (PhA) and bioimpedance vector analysis (BIVA) were used. Assessments included the Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Cancer Therapy-Breast (FACT-B), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). **Results:** Women (age <50 years) with breast cancer showed impaired functional status (HGS, 6MWT, and PhA), abnormal physiologic findings (BIVA), decreased health-related quality of life (HRQoL), and cancer-related fatigue (CRF) after breast cancer diagnosis prior to the onset of cancer treatment with significant deterioration following cancer treatment. This was accompanied by a potentially higher risk of mortality and impaired function due to the prevalence of values below a critical threshold (PhA: T0 = 11%, T1 = 42%;

Rehabilitation Oncology

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Chemnitz University of Technology (reference number: V-182-17-AS-Tumor-20012017). The "Return" study is registered with the German Clinical Trials Register (ID: DRKS00014263).

The authors declare no conflicts of interest.

Online Publication date: February 8, 2022
Received: January 26, 2021; Accepted: November 23, 2021

Correspondence: *Niklas Paul Grusdat, MSc, Professorship of Sports Medicine/Sports Biology, Institute of Human Movement Science and Health, Faculty of Behavioral and Social Sciences, Chemnitz University of Technology, Chemnitz, Germany (Niklas.grusdat@hsw.tu-chemnitz.de).*

DOI: 10.1097/01.REO.0000000000000298

HGS: T0 = 21%, T1 = 32%). In addition, there was evidence of anxiety (47%) and depression (32%) at T0. **Conclusion:** Routine assessment of biomarkers of physical function, mental health, HRQoL, and CRF may lead to individual risk stratification and multidisciplinary intervention in young patients with breast cancer, which could help to personalize and optimize survivorship care plans. **(Rehab Oncol 2022;0000:1–10)** *Key words: mental health, physical functioning, survivorship*

Female breast cancer is the most commonly diagnosed cancer worldwide, with an estimated 2.3 million new cases (11.7%) in 2020.[1] In the European Union, it accounts for 29.2% of all cancers in women.[2] About 70 000 new cases are diagnosed in Germany every year. Around 30% of all breast cancer cases in Germany occur in women younger than 50 years.[3] In women aged 40 to 49 years, a trend to advanced stage incidence can be observed.[4] In comparison to older patients, an increased risk of recurrence and lower survival is emerging.[5-7] Breast cancer treatment can be associated with experiences of limitations in (physical) function,[8,9] neurological disorders,[10] effects on the musculoskeletal[11] and cardiovascular system.[12] Handgrip strength (HGS)[13] and the 6-minute walk test (6MWT)[14] have gained scientific credibility in the clinical setting as biomarkers of physical function. In addition, the use of the bioimpedance analysis (BIA) in combination with bioimpedance vector analysis (BIVA) has also led to scientific interest because they provide detailed information on body composition, general health,[15] and cell membrane integrity.[16] Moreover, these measures are of prognostic value in mortality,[17] disease progression,[18,19] and the incidence of postoperative complications[20] in various clinical fields. Besides the physiologic effects, breast cancer has a significant effect on mental health, and patients often are overwhelmed, resulting in various concerns.[21] Despite the underrepresentation in scientific research, experiences of severe psychosocial stress,[22] depression,[23] debilitating fears,[24] cancer-related fatigue (CRF),[25] and decreases in health-related quality of life (HRQoL) were observed in women with breast cancer at a young age. Especially for women who develop breast cancer at an early stage in life, the ability to function in the workplace and employment issues are of great concern.[26,27] Close monitoring of patients' needs, using patient-orientated indicators, can predict outcomes in a more differentiated manner. More studies that provide information on the biopsychosocial status of breast cancer patients, including biological/clinical, psychological, and social-emotional factors, are needed and may lead to a more holistic approach in subsequent oncological rehabilitation.[28-30] To date, little scientific data are available to establish critical threshold values of function and body composition in combination with anxiety, depression, CRF, and HRQoL of young women with newly diagnosed breast cancer prior to and after initial cancer treatment (surgery, chemotherapy, and radiation therapy). The purpose of the present study was to find out the extent to which biopsychosocial parameters of young women (<50 years) with breast cancer change throughout treatment.

METHODS

Between April 2018 and August 2020, a total of 130 women with breast cancer were recruited within the research project "Return" (trial acronym) approved by the Ethics Committee of the Chemnitz University of Technology (V-182-17-AS-Tumor-20012017), and registered to the German Clinical Trials Register (ID: DRKS00014263). All patients were recruited in the Red Cross Hospital in Chemnitz-Rabenstein, Germany. Within 1 week after the diagnosis of breast cancer, women were invited by their medical doctor for consultation and informed about possible participation in the present study. Participants had the opportunity to read and consider the research information leaflet. A sufficient time (>24 hours) to reflect on the implications of participating in the study was provided. There was no pressure to take part in the research. Inclusion criteria included the patients' written informed consent, recent diagnosis of untreated female breast cancer, no defibrillator or cardiac pacemaker, or no orthopedic restrictions for participating in the tetra-polar BIA and HGS assessments. Patients were excluded after completing a medical history interview for eligibility concerning research on tumor treatment and rehabilitation effects if they had a previous invasive malignancy, other malignant tumors, untreated pulmonary hypertension, diagnosed dementia, or chronic obstructive pulmonary disease. Eighty-four participants met the inclusion criteria, and only 19 patients (<50 years) who had not initiated cancer treatment were enrolled and completed the allocated assessments and medical interventions for statistical analysis of this prospective observational pilot study. Further restrictions recorded are presented in Figure 1. Details of personal characteristics, tumor pathology, disease stage, treatment received, estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 status were provided by the clinical cancer registry.

Measurements

All assessments were carried out prior to the onset of any cancer treatment at pretest (T0) and within 1 week after completing conventional cancer treatment (surgery, chemotherapy, and radiation therapy) at posttest (T1). Cases with long-term endocrine therapy continued beyond T1. Based on the variable duration of breast cancer treatment for each woman, repeated testing (T0 and T1) was performed on different intervals.

The Functional Status. The standardized assessment consisted of an HGS test, following the Southampton protocol[31] with a hydraulic hand dynamometer (Baseline,

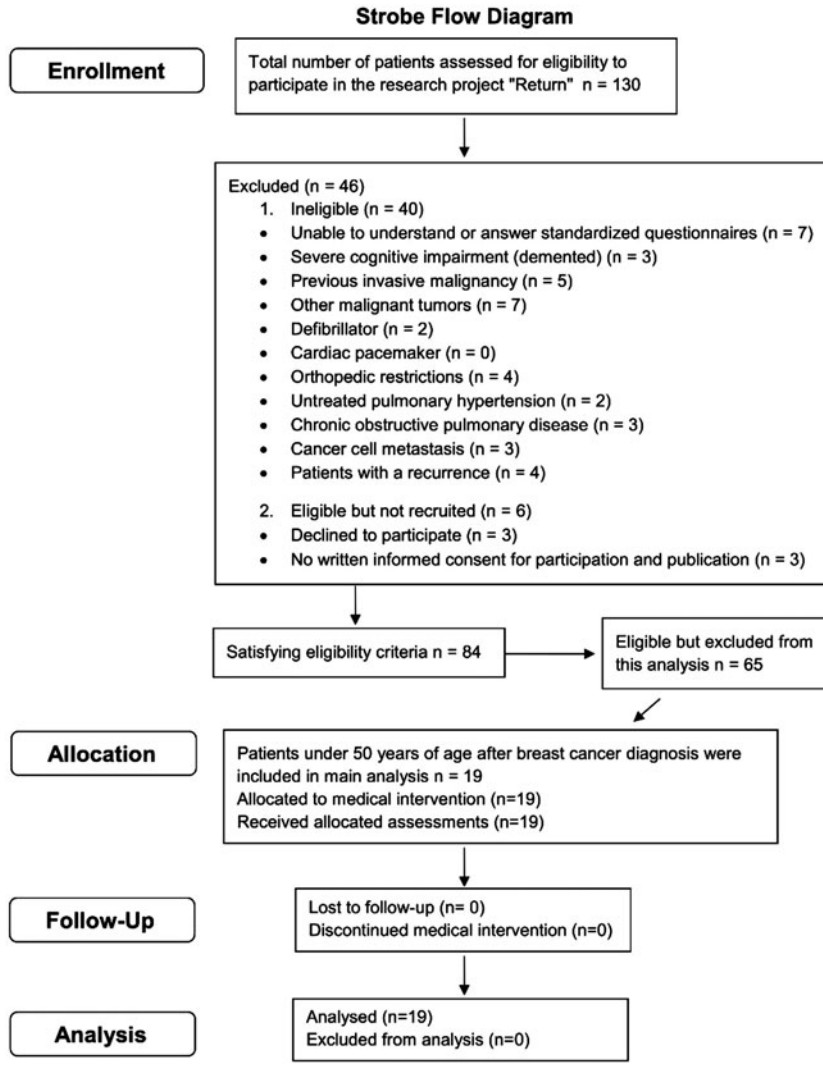

Fig. 1. STROBE flow diagram of the prospective observational study in young women with breast cancer.

HIRes, Gauge ER, USA). Only the peak value of 3 attempts of the HGS test was used to assess muscular strength. According to Enright, submaximal endurance performance was measured on a 20-m track with the 6MWT.[14] For body composition measurement, a BIA was performed (BIA 5 Series multifrequency, EgoFit GmbH, Germany). After resting 10 minutes in a supine position, the associated biosignals of cell resistance (R), cell reactance (Xc), and the phase angle (PhA) were recorded on the subject's right side of the body, between the wrist and ankle on a nonconductive surface at a fixed frequency of 50 kHz. Height and weight were recorded with footwear and headwear removed using a standard stadiometer and weigh scale. This protocol allows the calculation of body mass index (BMI). All assessments were performed by personnel trained in densitometry and blinded to the assignment.

The Questionnaires. The mental health of participants was investigated by the Hospital Anxiety and Depression Scale (HADS). The HADS consists of 14 thematically alternately listed questions (points per question: 0-3; total score 0-21). The HADS is scored separately for anxiety and depression and interpreted as follows: 0 to 7 = normal, 8 to 10 = mild case, 11 to 14 = moderate case, and 15 to 21 = severe case. Higher values represent a more pronounced mental impairment.[32]

The Functional Assessment of Cancer Therapy-Breast questionnaire (FACT-B) was administered to evaluate the HRQoL. The FACT-B includes Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB) plus a 9-item Breast Cancer Subscale (BCS) addressing specific concerns. Items were added to evaluate the respective total score (FACT-G total score, FACT-B total score). To derive the FACT-B Trial Outcome Index (TOI), the sum of the Physical Well-Being (PWB), Functional Well-Being (FWB), and Breast Cancer Subscale (BCS) was computed, which represents a summary index of the physical functional outcome.[33] For detection of self-reported CRF and its effect on daily activities and function, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), which contains 13 items, was applied.[34] For FACT-B and FACIT-F, higher scores (negative items were reverse-scored) indicate a subjectively perceived better HRQoL and nonfatigued status. All patients completed the

questionnaires with qualified personnel available to answer any questions or clarify any meaning.

Data Analysis

Data analysis was performed with the statistical software package IBM SPSS statistics 26 (Chicago, Illinois). Descriptive statistics are presented as mean ± standard deviation (SD), and the minimum and maximum of the outcome parameters are cited in brackets. Based on distribution (Shapiro-Wilk test), either a paired-samples *t* test or a nonparametric Wilcoxon signed rank test was used. A significance level of $P < .05$ for data analyses was set. For the paired-samples *t* test, the effect size was calculated by Cohen's *d* using the formula: $d = \frac{M_2 - M_1}{SDpooled}$. Suggested benchmarks for interpretation of the effect size by Cohen are small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$). For nonparametric testing, the Pearson correlation coefficient was calculated by the formula: $r = Z/\sqrt{N}$ and classified according to Cohen as small ($r = 0.10$), medium ($r = 0.25$), and large ($r = 0.40$).[35]

BIVA was conducted using BIVA software (Piccoli A & Pastori G, Department of Medical and Surgical Sciences, University of Padova, Padova, Italy, 2002; available by e-mail: apiccoli@unipd.it). According to the RXc graph,[15,36] raw data of R and Xc were standardized by the height (H) of patients and plotted as RXc vector (bivariate) graphs for T0 and T1 inside a gender-specific reference population plot of White females of the United States (n = 1625). Based on the BIVA reference data and the associated tolerance ellipses, a detailed classification of the body composition status (cachexia, lean/anorexic, dehydrated, athletic, obese, and overhydration/edema) is possible. Regarding the BIVA graph, a lower R leads to a shortening of the vector and thereby reflects an excess of fluid, such as occurs in edema. High or low Xc indicates an increase or decrease of soft tissue dielectric mass (membranes and tissue interfaces). Confidence ellipses of BIVA describe the area in which the 2-dimensional vectors fall within a 95% probability. Graphically, nonoverlapping 95% confidence ellipses were significantly different from each other ($P < .05$; which is equivalent to a significant Hotelling's T^2 test). Bioimpedance values within BIVA that fall outside the 75% tolerance ellipse of the reference population indicate an example of abnormal physiology.[36,37]

For the HGS,[38] PhA,[39] and 6MWT,[40] data can be interpreted and classified in terms of their clinical relevance due to existing critical threshold values as they are described in the scientific literature. A critical HGS is categorized by a value below the individual risk threshold, which lies ≥1 ± SD below the standardized mean HGS.[38] The PhA, representing the arctangent between R and Xc, is calculated by using the following equation: $PhA[^\circ] = \arctan(\frac{Xc}{R}) \times (\frac{180}{\pi})$.[41] For the analysis of the individual PhA, the fifth percentile for sex-, age-, and BMI-stratified PhA reference value appears as a cut-off for impaired functional status.[39]

The sex-specific reference equation for women—$6MWD = 2.11 \times height_{cm}) - (2.29 \times weight_{kg}) - (5.78 \times age) + 667\ m$—was used to compute the predicted 6MWT. Regarding the 6MWT performance of the study individuals, values below the calculated distance (m) are considered a critical threshold.[40]

RESULTS

Nineteen women with breast cancer were included in the present analysis. Baseline demographics and the patients' clinical characteristics are summarized in Table 1. The age at diagnosis was 42.8 ± 5.4 SD years (30.0-49.0 years). The interval between breast cancer diagnosis and initial data collection prior to starting treatment for breast cancer (T0) was 7.8 days (range 7.0-9.0 days). For completing the treatment, participants with primary disease finished their cycles of chemotherapy and treatment sessions of radiation therapy. The time for completing breast cancer treatment was 9.3 ± 2.5 SD months (range 5.5-12.7 months). After breast cancer treatment, follow-up

TABLE 1
Baseline Demographics and Clinical Characteristics of n = 19 Young Women With Breast Cancer[a]

Anthropometric Data	Total Group n = 19
Age, y	42.8 ± 5.4 (30.0-49.0), Q_{50}: 44.0
Age, 30-35 y, n (%)	2 (10.5)
Age, 35-40 y, n (%)	3 (15.8)
Age, 41-49 y, n (%)	14 (73.7)
Height, m	1.66 ± 0.06 (1.56-1.78), Q_{50}: 1.67
Weight, kg	74.3 ± 21.3 (49.7-135.1), Q_{50}: 66.3
BMI, kg/m^2	26.5 ± 6.3 (19.6-42.6), Q_{50}: 24.4
UICC, n (%)	IA = 8 (42.1), IIA = 10 (52.6), IIB = 1 (5.3)
IDC, n (%)	Yes = 19 (100), no = 0 (0)
Her2/neu status, n (%)	Positive = 1 (5.3), negative = 18 (94.7)
ER status, n (%)	Positive = 16 (84.2), negative = 3 (15.8)
SNB, n (%)	Yes = 18 (94.7), no = 1 (5.3)
ALND, n (%)	Yes = 1 (5.3), no = 18 (94.7)
BCS, n (%)	Yes = 15 (78.9), no = 4 (21.1)
MRM, n (%)	Yes = 2 (10.5), no = 17 (89.5)
SCM, n (%)	Yes = 2 (10.5), no = 17 (89.5)
Adjuvant C, n (%)	Yes = 7 (36.8), no = 12 (63.2)
Neoadjuvant C, n (%)	Yes = 12 (63.2), no = 7 (36.8)
Anth-bC, n (%)	Yes = 4 (21.1), no = 15 (78.9)
TaxAnth-C, n (%)	Yes = 15 (78.9), no = 4 (21.1)
Adjuvant RT, n (%)	Yes = 15 (78.9), no = 4 (21.1)
ET, n (%)	Yes = 15 (78.9), no = 4 (21.1)
TMX, n (%)	Yes = 10 (52.6), no = 9 (47.4)
AIs, n (%)	Yes = 5 (26.3), no = 14 (73.7)

[a]Data are expressed as means ± standard deviation (range), median or n (%).

Abbreviations: AIs, aromatase inhibitors; ALND, axillary lymph node dissection; Anth-bC, anthracycline-based chemotherapy; BCS, breast-conserving surgery; BMI, body mass index; C, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; Her2/neu, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; MRM, modified radical mastectomy; Q_{50}, median; RT, radiation therapy; SCM, subcutaneous mastectomy; SNB, sentinel node biopsy; TaxAnth-C, anthracycline and taxane-based chemotherapy; TMX, tamoxifen; UICC, Union for International Cancer Control.

TABLE 2

Anthropometrics, Biomarkers of Physical Functional Status and the Prevalence of Critical Values of Bioimpedance Phase Angle, Handgrip Strength, and 6-Minute Walk Test of Young Women With Breast Cancer Prior to the Onset of (T0) and After Initial Cancer Treatment (T1) of n = 19 Young Women With Breast Cancer[a]

Variable	T0	T1	*P*	Effect Size
Weight, kg	74.3 ± 21.3 (49.7-135.1), Q_{50}: 66.3	76.2 ± 21.2 (52.0-138.0), Q_{50}: 68.0	.005 W	$r = 0.64$
BMI, kg/m^2	26.5 ± 6.3 (19.6-42.6), Q_{50}: 24.4	27.2 ± 6.3 (20.6-43.6), Q_{50}: 25.6	.005 W	$r = 0.65$
R 50 kHz, Ω	532.9 ± 68.6 (404.0-627.0), Q_{50}: 542.0	511.5 ± 82.4 (402.0-644.0), Q_{50}: 502.0	.021 *t*	Cohen's $d = 0.58$
Xc 50 kHz, Ω	55.7 ± 11.2 (36.0-80.0), Q_{50}: 57.0	47.7 ± 10.8 (32.0-71.0), Q_{50}: 48.0	.000 *t*	Cohen's $d = 2.09$
PhA 50 kHz, °	5.9 ± 0.8 (4.4-7.7), Q_{50}: 5.7	5.3 ± 0.7 (4.5-6.9), Q_{50}: 5.1	.000 *t*	Cohen's $d = 1.46$
HGS peak, kg	31.5 ± 6.4 (24.0-47.0), Q_{50}: 34.0	29.0 ± 5.2 (22.0-42.0), Q_{50}: 30.0	.000 *t*	Cohen's $d = 1.22$
6MWT, m	537.4 ± 72.5 (427.0-700.0), Q_{50}: 530.0	522.2 ± 74.1 (400.0-685.0), Q_{50}: 500.0	.000 *t*	Cohen's $d = 1.30$
Below risk threshold, PhA, n (%)	Yes = 2 (10.5), no = 17 (89.5)	Yes = 8 (42.1), no = 11 (57.9)		
Below risk threshold, HGS, n (%)	Yes = 4 (21.1), no = 15 (79.0)	Yes = 6 (31.6), no = 13 (68.4)		
Below reference, 6MWT, n (%)	Yes = 16 (84.2), no = 3 (15.8)	Yes = 16 (84.2), No = 3 (15.8)		

[a]Data are expressed as means ± standard deviation (range), median or n (%).

Abbreviations: BMI, body mass index; HGS, handgrip strength; Ω, electrical resistance; PhA, phase angle; Φ/°, phi; Q_{50}, median; R, cell resistance; *t*, paired-samples *t* test; W, nonparametric Wilcoxon signed rank test; Xc, cell reactance; 6MWT, 6-minute walk test.

data were collected within 1 week (6.2 days, range 5.0-7.0 days).

The Anthropometrics

The longitudinal statistical comparison of the anthropometric data indicated significant differences in the anthropometric parameters for weight (kg), and BMI (kg/m^2), and BMI (kg/m^2) (Table 2).

The Biomarkers of Physical Functional Status

The biomarkers of physical functional status and the prevalence of critical threshold values are summarized in Table 2. The functional status was significantly lower at T1 than at T0, with large effect sizes in all measured parameters. At T0, 21% of the women presented a critical HGS below individual cut-off, which changed to 32% at T1. In 11% of women, a critical PhA value was detected at T0, which changed to 42% at T1. A 6MWT, lower than the individual predicted value, was found in 84% of the women at T0 with no change at T1.

The Pattern of the BIVA

At T0, the mean impedance vector with 95% confidence ellipses was located inside the 75% tolerance ellipse, within the cachectic quadrant (low body cell mass) and state of fluid overload (apparent edema). At T1, the bioimpedance values drifted outside the 75% tolerance ellipse of the same quadrant (low body cell mass) and state (apparent edema), indicating abnormal physiology. Based on the graphical overlapping of the 95% confidence ellipses, no significant difference could be detected between T0 and T1 (Figure 2).

The Perceived Health-Related Quality of Life

The FACT-B questionnaire data are presented in Table 3. At T1, a deterioration was observed in FACT-B ($P < .001$) and all subscores except for emotional well-being (EWB, $P = .08$).

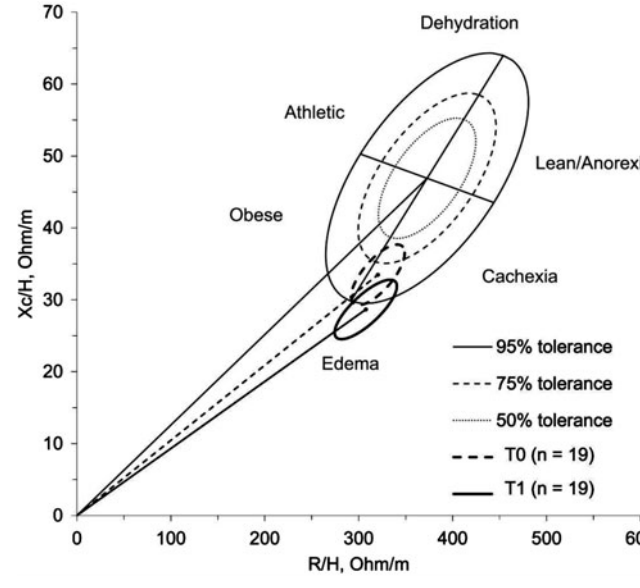

Fig. 2. The BIVA RXc graphs with 95% confidence ellipses of young women with breast cancer prior to the onset of (T0) and after initial cancer treatment (T1), reference graph based on gender-specific 50%, 75%, and 95% tolerance ellipses (gray). Optimal body composition is located at the center (50% and 75% tolerance ellipses). Bio-impedance values that fall outside the 75% tolerance ellipse of the reference population indicate an abnormal physiologic situation. BIVA indicates bioimpedance vector analysis; H, height; R, resistance; Xc, reactance.

TABLE 3

Health-Related Quality of Life (FACT-B), Fatigue (FACIT-Fatigue), Anxiety, and Depression (HADS) Prior to the Onset of (T0) and After Initial Cancer Treatment (T1) of n = 19 Young Women With Breast Cancer[a]

Variable	T0	T1	Change, %	*P*	Effect Size
FACT-B (0-156)	110.3 ± 17.0 (82.0-140.0), Q_{50}: 111.0	91.4 ± 11.3 (72.0-112.0), Q_{50}: 92.0	−17.4	.000 *t*	Cohen's $d = 2.35$
PWB (0-28)	24.3 ± 3.4 (15.0-28.0), Q_{50}: 25.0	18.6 ± 3.4 (13.0-24.0), Q_{50}: 18.0	−23.5	.000 W	$r = 0.83$
SWB (0-28)	23.4 ± 3.7 (15.1-28.0), Q_{50}: 23.3	18.0 ± 3.6 (9.0-25.0), Q_{50}: 18.0	−26.2	.000 *t*	Cohen's $d = 2.26$
EWB (0-24)	15.8 ± 5.1 (3.0-22.0), Q_{50}: 16.0	17.0 ± 2.7 (11.0-21.0), Q_{50}: 17.0	+7.6	.087 *t*	
FWB (0-28)	17.5 ± 6.4 (6.0-27.0), Q_{50}: 19.0	14.6 ± 4.7 (6.0-23.0), Q_{50}: 15.0	−16.6	.000 *t*	Cohen's $d = 0.98$
BCS	29.3 ± 4.4 (19.0-38.0), Q_{50}: 29.0	23.2 ± 4.0 (17.0-32.0), Q_{50}: 23.0	−20.8	.000 *t*	Cohen's $d = 2.70$
TOI (0-104)	71.1 ± 11.7 (50.0-92.0), Q_{50}: 69.0	56.4 ± 7.9 (42.0-72.0), Q_{50}: 57.0	−20.7	.000 *t*	Cohen's $d = 2.55$
FACT-G (0-108)	81.0 ± 14.2 (54.0-103.0), Q_{50}: 82.0	68.2 ± 9.1 (51.0-81.0), Q_{50}: 69.0	−15.8	.000 *t*	Cohen's $d = 1.63$
FACIT-F (0-52)	40.5 ± 7.9 (24.0-50.0), Q_{50}: 43.0	28.5 ± 10.3 (17.0-48.0), Q_{50}: 25.0	−29.6	.000 *t*	Cohen's $d = 1.58$
HADS-Anxiety (0-21)	10.2 ± 4.5 (3.0-19.0), Q_{50}: 10.0	8.6 ± 3.2 (5.0-15.0), Q_{50}: 8.0	−15.7	.004 W	$r = 0.666$
HADS-Depression (0-21)	7.2 ± 5.6 (0.0-19.0), Q_{50}: 6.0	7.4 ± 4.2 (0.0-16.0), Q_{50}: 7.0	+2.8	.6881 *t*	

[a]Data are expressed as means ± standard deviation (range), median or change in percent.

Abbreviations: BCS, Breast Cancer Subscale; EWB, emotional well-being; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-G, Functional Assessment of Cancer Therapy-General; FWB, Functional Well-Being; HADS, Hospital Anxiety and Depression Scale; PWB, Physical Well-Being; Q_{50}, median; SWB, Social Well-Being; TOI, Trial Outcome Index; *t*, paired-samples *t* test; W, nonparametric Wilcoxon signed rank test.

The Cancer-Related Fatigue Status

Between T0 and T1 in young women with breast cancer, a significant reduction of FACIT-F score ($P < .001$) was found (Table 3).

The HADS

At T0, 47% of women showed moderate (26%) and severe (21%) anxiety. At T1, moderate (16%) and severe (11%) anxiety decreased to 27%. Thirty-two percent (moderate 21%, severe 11%) of women showed depression at T0 with a reduction to 22% (moderate 11%, severe 11%) at T1.

Anxiety

Total HADS-Anxiety at T0 (mean 10.2) and T1 (mean 8.6) could be assigned as mild case with a significant change over time ($P = .004$) and large effect size ($r = 0.67$).

Depression

Total HADS-Depression at T0 (mean 7.2) and T1 (mean 7.4) could be assigned as normal with no significant change over time ($P = .688$) (Table 3).

DISCUSSION

Based on the preliminary data of the research project "Return," we conducted a subanalysis of biopsychosocial data of young women receiving breast cancer treatment. We monitored the parameters of biopsychosocial status, including biological/clinical, psychological, and social-emotional factors, with the help of standardized and clinically established assessment tools before and after completing breast cancer treatment.

Our main findings provide evidence that young women with breast cancer showed impaired values of the HGS, 6MWT, PhA; abnormal physiology according to the BIVA, decreased HRQoL and CRF after breast cancer diagnosis with significant deterioration following treatment. This was accompanied by a potentially higher risk of mortality and impaired function due to the prevalence of values below a critical threshold. In addition, there was evidence of anxiety and depression.

Using BIA as a noninvasive technique to evaluate changes of the prognostic relevant biomarker PhA, we found that 90% of women in the present study showed an average value prior to the onset of cancer treatment. After initial breast cancer treatment, 42% of the women presented critical values below published risk thresholds, with a mean value of 5.3°.[39] A PhA less than or equal to 5.6° is associated with shorter survival in women with breast cancer, with a median age at diagnosis of 49 years (25-74 years).[18] Low PhA is also connected with impaired functional status, lower muscle strength, and reduced quality of life.[19,42] Given reference data of healthy women, mean PhA is 6.09° (age group 40-49 years, BMI 25-30) with higher values at younger ages.[39]

Changes in body cell mass and hydration status can be interpreted with the BIVA, making it in comparison with the PhA a more favorable tool for body composition assessment and monitoring. However, both components are relevant for the determination of recovery, rehabilitation, and physical function.[20,41] Our data revealed that young women with breast cancer differ significantly from population-based reference data prior to and after completion of initial breast cancer treatment, but with no significant difference over time (within-group). However,

BIVA values at T1 fell outside the BIVA reference ellipse of 75% are indicating abnormal physiology, the presence of cachexia (low body cell mass), and a state of fluid overload (apparent edema). The significant change in Xc represents the resistive effect produced by the tissue interfaces and cell membranes,[43] suggesting a reduction of cell membrane function.

Furthermore, the vector displacement was characterized by a significant decrease of R. Defining R as the flow restriction to an electrical current,[44] there was a greater water distribution between the extra- and intracellular compartments. The observed state of fluid overload may be due to secondary lymphedema, attributed to cancer-specific drug and surgical treatment.[45] Studies showed that about 40% of women with lymph node removal followed by radiation therapy develop this side effect.[46] More research is required with an extensive study group to identify how clinical characteristics including lymphedema, obesity, dietary supplements, stage and type of cancer, and side effects of chemotherapy correlate with BIA and BIVA data.

A healthy individual's 6MWT ranges from 400 to 700 m, and reflects the exercise capacity for daily physical activities.[14] This is gaining importance in patients with breast cancer during treatment and rehabilitation.[47] The 6MWT has been used for the outcome evaluation of aerobic capacity in cancer research.[48,49] However, there is a lack of reference data for different cancers. In our study, a 6MWT lower than the individual predicted value[40] was shown in 84% of women prior to and post-cancer treatment. A mean 6MWT of 537.4 m (T0) and 522.2 m (T1) may indicate a lower capacity during everyday life.[50] Although speculative, the low 6MWT observed prior to cancer treatment may be attributable to certain lifestyle factors (eg, diet, physical activity, smoking, and alcohol consumption) and could potentially have influenced the risk of developing breast cancer.[51]

Evidence for an elevated mortality risk[52,53] and concurrent cancer-related symptoms[54] HGS warrants closer examination. Referring to available risk threshold values,[38] 21% of women in our study presented a critically low HGS at T0, which increased to 32% at T1. When considering the age of patients (mean 42.8 years), the overall HGS (T0 = 31.5 kg, T1 = 29.0 kg) was below the mean value (34.8 kg) of a large German reference population of healthy women aged 40 to 44 years[38] indicating a weak muscle strength status.

Besides the potentially life-threatening danger, women diagnosed with breast cancer face various concerns of possible future challenges (eg, familial, professional, sexuality, body image, fertility, financial, and logistical).[21] Considering associations between the stressful life event and the occurrence of low performance in the HGS and the 6MWT gives rise to the potential for bias, as physical performance may be affected by emotional and motivational aspects and lack of psychological health.[55,56] To understand the modifying effects, future studies need to compare the subject's status before and after diagnosis. Nevertheless, early implementation of routine physical function tests may help health care professionals provide feedback and educated advice about the benefits of physical activity.

Threats linked to women experiencing breast cancer may be highly individual, and patients can get overwhelmed by functional changes and social-emotional challenges. Limiting consequences in the HRQoL have predictive value for shorter survival[57] and disease progression.[58] The significantly reduced HRQoL with lower reported physical, social, and functional well-being of women in the present study might reflect greater attentional demands needed to compensate for the side effects of breast cancer treatment throughout the different stages of therapy. A reduction of 2 to 3 points in the PWB, FWB, and BCS subscales is considered a meaningful change that patients perceive as harmful, leading the clinician to modify the patient's management.[59,60] A notable observation was the consistency for the TOI (−14.7 points, −21%) between PWB (−5.7 points, −24%), FWB (−2.9 points, −17%), and BCS (−6.1 points, −21%), indicating an insufficient physical activity. Furthermore, low PWB at T1 is associated with processing pain, lack of energy, illness, and being forced to spend time in bed. According to the perceived FWB, women could not work or accept the illness and struggled to sleep well or enjoy daily activities. Breast cancer-specific concerns at T1 are accompanied by unsatisfied sexual attractiveness, body weight change, the inability to feel like a woman, increased pain in certain parts of their body, hair loss, and swollen arms.

Women who received chemotherapy reported reduced satisfaction with sex life, communication about the illness, and experiences of less support from family and friends (SWB; −5.4 points, −26%).

Intense worries about dying, losing hope in the fight against the illness, not knowing how to cope with the disease, and feelings of sadness led to a disruption in emotional well-being (EWB 15.8) at T0. Slight improvements in the patients' emotional well-being (EWB 17.0) could be detected after breast cancer treatment (T1). In consideration of normative data from the general US population (n = 1.075) with EWB 19.9 aged 45.9 years[61] and population-based reference EWB 19.0 of women aged 49.3 ± 16.8 (n = 447) drawn from an Austrian population,[62] a more substantial alignment to patient-orientated indicators of those affected is recommended. Supportive forms such as pain therapy, nutritional medicine, psycho-oncology, physiotherapy, and exercise therapy represent sensible measures that should be implemented.[63] The promotion of social support, in particular emotional support from family, may have a positive effect on psychological stress and psychiatric morbidities.[64]

The valid HADS questionnaire appeared to help track mental impairment. According to the HADS score classification,[32] values imply that patients felt restlessness, frightened, and tense with moderate to severe expression, especially at T0. It is difficult to distinguish whether there is a timely fearful reaction to the diagnosis of cancer or whether there is an anxiety symptom that requires intervention. Therapy appears to be necessary if the

behavior and experience of the patients' everyday lives are impaired. All too often, anxiety disorders or depression is not recognized or dismissed as an understandable reaction to a life-threatening illness.[65] For more transparency, routine assessments of psychiatric morbidities need to achieve widespread implementation in oncologic care.[66] Several authors propose a different classification for the HADS; cut-off scores of $\geq$11 indicate the probable presence of a mood disorder, and a score of 8 to 10 suggests the possible presence of the respective state.[67] Different valuation bases may result in the underreporting of psychiatric morbidity in chronic diseases.[68,69]

German general population-based FACIT-F norm of women aged 40 to 49 years with a mean score of 42.7 indicates the presence of fatigue in our study population.[70] Severe fatigue was experienced by most of the women after treatment (FACIT-F mean score of 28.5). Several potential mechanisms showed why women might develop CRF post-treatment.[71] As a multifactorial symptom, severity is influenced by more significant pain, sleep disruption, distress, lower activity, and lower physical and social health status.[72] For the FACIT-F, age effects have to be taken into account when interpreting the score. The time of receiving cancer treatment may be long-lasting, increasing lifestyle stresses, such as lack of ability to work, child care, or elderly care. Moreover, young women who experience limitations of their social activity due to tiredness may neglect regular physical activity habits, contributing to fatigue. Support for balancing stressors may be considered by pointing out a lack of energy or the inability to eat due to tiredness.

The strength of this investigation was the ability to collect a wide range of data of young women with breast cancer for prospective capturing and guidance of patients' needs. Moreover, establishing the general use of patient-orientated indicators may lead to a beneficial approach in subsequent oncological rehabilitation treatment.

After all, further work is required to determine a genuinely representative biopsychosocial profile. Additionally, suitable modalities and timing for implementation for each individual are needed.

Limitations

We could not include an additional follow-up analysis. Since the number of patients was small (n = 19), our findings can only be regarded as preliminary, and future investigations are necessary for the generalizability of our findings. Our results can only give an early picture of treatment-related BIVA pattern and body composition status. Data regarding the body composition were not clinically quantified and therefore could not be correlated for a multivariable risk-stratified approach. Assessing oxygen consumption as the "gold standard" using the 6MWT[73] could provide more accurate data and be considered in future studies. Studies with larger sample sizes are necessary for a treatment-specific consideration and to confirm the present data.

CONCLUSION

In summary, the biopsychosocial profile of young women with breast cancer showed impaired functional status, abnormal physiologic findings according to BIVA, decreased HRQoL, and CRF after a breast cancer diagnosis, with significant deterioration following cancer treatment. This was accompanied by a marked increase in the prevalence of critical prognostic values of mortality predictive biomarkers PhA and HGS. In addition, there was evidence of anxiety and depression. Routine assessment of biomarkers of physical function, mental health, HRQoL, and CRF may lead to individual risk stratification and multidisciplinary intervention in young patients with breast cancer, which could help to personalize and optimize survivorship care plans.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview [published online ahead of print April 5, 2021]. *Int J Cancer*. doi:10.1002/ijc.33588.
2. Randi G, Ben E, Carvalho R, et al. European Cancer Information System web-application: analysing and visualising European cancer data. *Eur J Public Health*. 2018;28(suppl 4):cky214.189.
3. Barnes B, Kraywinkel K, Nowossadeck E, et al. *Bericht Zum Krebsgeschehen in Deutschland 2016*. Berlin, Germany: Robert Koch-Institut; 2016.
4. Katalinic A, Eisemann N, Kraywinkel K, Noftz MR, Hübner J. Breast cancer incidence and mortality before and after implementation of the German mammography screening program. *Int J Cancer*. 2020;47(3):709-718.
5. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. *PLoS One*. 2009;4(11):e7695.
6. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. *J Am Coll Surg*. 2009;208(3):341-347.
7. Fabiano V, Mandó P, Rizzo M, et al. Breast cancer in young women presents with more aggressive pathologic characteristics: retrospective analysis from an Argentine national database. *JCO Glob Oncol*. 2020;6:639-646.
8. Braithwaite D, Satariano WA, Sternfeld B, et al. Long-term prognostic role of functional limitations among women with breast cancer. *J Natl Cancer Inst*. 2010;102(19):1468-1477.
9. Ten Tusscher M, Groen W, Geleijn E, et al. Physical problems, functional limitations, and preferences for physical therapist-guided exercise programs among Dutch patients with metastatic breast cancer: a mixed methods study. *Support Care Cancer*. 2019;27(8):3061-3070.
10. Gatti G, Simsek S, Kurne A, et al. Paraneoplastic neurological disorders in breast cancer. *Breast*. 2003;12(3):203-207.
11. Kubo Y, Naito T, Mori K, Osawa G, Aruga E. Skeletal muscle loss and prognosis of breast cancer patients. *Support Care Cancer*. 2017;25(7):2221-2227.
12. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368(11):987-998.
13. Kilgour R, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais J. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care Cancer*. 2013;21(12):3261-3270.
14. Enright PL. The six-minute walk test. *Respir Care*. 2003;48(8):783-785.
15. Piccoli A, Rossi B, Pillon L, Bucciante G. A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. *Kidney Int*. 1994;46(2):534-539.

16. Kumar S, Dutt A, Hemraj S, Bhat S, Manipadybhima B. Phase angle measurement in healthy human subjects through bio-impedance analysis. *Iran J Basic Med Sci.* 2012;15(6):1180-1184.
17. Paiva SI, Borges LR, Halpern-Silveira D, Assunção MCF, Barros AJ, Gonzalez MC. Standardized phase angle from bioelectrical impedance analysis as prognostic factor for survival in patients with cancer. *Support Care Cancer.* 2011;19(2):187-192.
18. Gupta D, Lammersfeld CA, Vashi PG, et al. Bioelectrical impedance phase angle as a prognostic indicator in breast cancer. *BMC Cancer.* 2008;8(1):249.
19. Norman K, Stobäus N, Zocher D, et al. Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. *Am J Clin Nutr.* 2010;92(3):612-619.
20. Norman K, Stobäus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis—clinical relevance and applicability of impedance parameters. *Clin Nutr.* 2012;31(6):854-861.
21. Corey B, Smania MA, Spotts H, Andersen M. Young women with breast cancer: treatment, care, and nursing implications. *Clin J Oncol Nurs.* 2020;24(2):139-147.
22. Härtl K, Engel J, Herschbach P, Reinecker H, Sommer H, Friese K. Personality traits and psychosocial stress: quality of life over 2 years following breast cancer diagnosis and psychological impact factors. *Psychooncology.* 2010;19(2):160-169.
23. Wong-Kim EC, Bloom JR. Depression experienced by young women newly diagnosed with breast cancer. *Psychooncology.* 2005;14(7):564-573.
24. Koch L, Bertram H, Eberle A, et al. Fear of recurrence in long-term breast cancer survivors—still an issue. Results on prevalence, determinants, and the association with quality of life and depression from the cancer survivorship—a multi-regional population-based study. *Psychooncology.* 2014;23(5):547-554.
25. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol.* 2014;11(10):597-609.
26. Hansen JA, Feuerstein M, Calvio LC, Olsen CH. Breast cancer survivors at work. *J Occup Environ Med.* 2008;50(7):777-784.
27. Ahn E, Cho J, Shin DW, et al. Impact of breast cancer diagnosis and treatment on work-related life and factors affecting them. *Breast Cancer Res Treat.* 2009;116(3):609-616.
28. Kuhnt S, Brähler E, Faller H, et al. Twelve-month and lifetime prevalence of mental disorders in cancer patients. *Psychother Psychosom.* 2016;85(5):289-296.
29. Eccles SA, Aboagye EO, Ali S, et al. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. *Breast Cancer Res.* 2013;15(5):1-37.
30. Richardson A, Addington-Hall J, Amir Z, et al. Knowledge, ignorance and priorities for research in key areas of cancer survivorship: findings from a scoping review. *Br J Cancer.* 2011;105(1):S82-S94.
31. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing.* 2011;40(4):423-429.
32. Stern AF. The Hospital Anxiety and Depression Scale. *Occup Med (Lond).* 2014;64(5):393-394.
33. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol.* 1997;15(3):974-986.
34. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage.* 1997;13(2):63-74.
35. Cohen J. *Statistical Power Analysis for the Behavioural Sciences.* 2nd ed. Hillsdale, NJ: L. Erlbaum Associates; 1988.
36. Piccoli A, Pillon L, Dumler F. Impedance vector distribution by sex, race, body mass index, and age in the United States: standard reference intervals as bivariate Z scores. *Nutrition.* 2002;18(2):153-167.
37. Naranjo-Hernández D, Reina-Tosina J, Min M. Fundamentals, recent advances, and future challenges in bioimpedance devices for healthcare applications [published online ahead of print July 15, 2019]. *J Sens.* doi:10.1155/2019/9210258.
38. Steiber N. Strong or weak handgrip? Normative reference values for the German population across the life course stratified by sex, age, and body height. *PLoS One.* 2016;11(10):e0163917.
39. Bosy-Westphal A, Danielzik S, Dörhöfer RP, Later W, Wiese S, Müller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. *JPEN J Parenter Enteral Nutr.* 2006;30(4):309-316.
40. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med.* 1998;158(5):1384-1387.
41. Malecka-Massalska T, Chara K, Smolen A, Kurylcio A, Polkowski W, Lupa-Zatwarnicka K. Bioimpedance vector pattern in women with breast cancer detected by bioelectric impedance vector analysis. Preliminary observations. *Ann Agric Environ Med.* 2012;19(4):697-700.
42. Norman K, Wirth R, Neubauer M, Eckardt R, Stobäus N. The bioimpedance phase angle predicts low muscle strength, impaired quality of life, and increased mortality in old patients with cancer. *J Am Med Dir Assoc.* 2015;16(2):173.e17-e22.
43. Barbosa-Silva MCG, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. *Curr Opin Clin Nutr Metab Care.* 2005;8(3):311-317.
44. Buffa R, Mereu R, Putzu P, Floris G, Marini E. Bioelectrical impedance vector analysis detects low body cell mass and dehydration in patients with Alzheimer's disease. *J Nutr Health Aging.* 2010;14(10):823-827.
45. Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer.* 2010;116(22):5138-5149.
46. Lawenda BD, Mondry TE, Johnstone PA. Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. *CA Cancer J Clin.* 2009;59(1):8-24.
47. Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A systematic review of exercise systematic reviews in the cancer literature (2005-2017). *PM R.* 2017;9(9):S347-S384.
48. Mustian KM, Katula JA, Zhao H. A pilot study to assess the influence of tai chi chuan on functional capacity among breast cancer survivors. *J Support Oncol.* 2006;4(3):139-145.
49. Riesenberg H, Lübbe AS. In-patient rehabilitation of lung cancer patients—a prospective study. *Support Care Cancer.* 2010;18(7):877-882.
50. Kehmeier ES, Sommer MH, Galonska A, Zeus T, Verde P, Kelm M. Diagnostic value of the six-minute walk test (6MWT) in grown-up congenital heart disease (GUCH): comparison with clinical status and functional exercise capacity. *Int J Cardiol.* 2016;203:90-97.
51. Hashemi SHB, Karimi S, Mahboobi H. Lifestyle changes for prevention of breast cancer. *Electron Physician.* 2014;6(3):894-905.
52. Bohannon RW. Muscle strength: clinical and prognostic value of hand-grip dynamometry. *Curr Opin Clin Nutr Metab Care.* 2015;18(5):465-470.
53. Celis-Morales CA, Welsh P, Lyall DM, et al. Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and all cause mortality: prospective cohort study of half a million UK Biobank participants. *BMJ.* 2018;361:k1651.
54. Cantarero-Villanueva I, Fernandez-Lao C, Fernández-DE-Las-Peñas C, Díaz-Rodríguez L, Sanchez-Cantalejo E, Arroyo-Morales M. Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment. *Eur J Cancer Care (Engl).* 2011;20(5):632-639.
55. Cairney J, Dudley D, Kwan M, Bulten R, Kriellaars D. Physical literacy, physical activity and health: toward an evidence-informed conceptual model. *Sports Med.* 2019;49(3):371-383.
56. Brown DM, Graham JD, Innes KI, Harris S, Flemington A, Bray SR. Effects of prior cognitive exertion on physical performance: a systematic review and meta-analysis. *Sports Med.* 2020;50(3):497-529.
57. DuMontier C, Clough-Gorr KM, Silliman RA, Stuck AE, Moser A. Health-related quality of life in a predictive model for mortality in older breast cancer survivors. *J Am Geriatr Soc.* 2018;66(6):1115-1122.
58. Müller V, Nabieva N, Häberle L, et al. Impact of disease progression on health-related quality of life in patients with metastatic breast

cancer in the PRAEGNANT breast cancer registry. *Breast*. 2018;37:154-160.
59. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes*. 2003;1(1):1-7.
60. Eton D, Cella D, Yost K, Yount S, Peterman A, Sledge G. Minimally important differences on the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale: results from ECOG study 1193. *J Clin Epidemiol*. 2003;57(9),898-910.
61. Brucker PS, Yost K, Cashy J, Webster K, Cella D. General population and cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G). *Eval Health Prof*. 2005;28(2):192-211.
62. Holzner B, Kemmler G, Cella D, et al. Normative data for Functional Assessment of Cancer Therapy general scale and its use for the interpretation of quality of life scores in cancer survivors. *Acta Oncol (Madr)*. 2004;43(2):153-160.
63. Johannsen M, Farver I, Beck N, Zachariae R. The efficacy of psychosocial intervention for pain in breast cancer patients and survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013;138(3):675-690.
64. Lueboonthavatchai P. Prevalence and psychosocial factors of anxiety and depression in breast cancer patients. *J Med Assoc Thai*. 2007;90(10):2164-2174.
65. Lehenbauer-Dehm S. Angst und Depression bei Tumorpatienten: Ergebnisse einer vergleichenden Studie über die Entwicklung eines Kurzinterviews zur schnellen Diagnose von Depression bei Tumorerkrankungen. Berlin, Germany: Charité-Universitätsmedizin Berlin; 2008.
66. Rana R, Latif S, Gururajan R, et al. Automated screening for distress: a perspective for the future. *Eur J Cancer Care (Engl)*. 2019;28(4): e13033.
67. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale—a review of validation data and clinical results. *J Psychosom Res*. 1997;42(1):17-41.
68. Love AW, Kissane DW, Bloch S, Clarke DM. Diagnostic efficiency of the Hospital Anxiety and Depression Scale in women with early stage breast cancer. *Aust N Z J Psychiatry*. 2002;36(2):246-250.
69. Esser P, Hartung TJ, Friedrich M, et al. The Generalized Anxiety Disorder Screener (GAD-7) and the anxiety module of the Hospital and Depression Scale (HADS-A) as screening tools for generalized anxiety disorder among cancer patients. *Psychooncology*. 2018;27(6):1509-1516.
70. Montan I, Löwe B, Cella D, Mehnert A, Hinz A. General population norms for the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. *Value Health*. 2018;21(11):1313-1321.
71. Bower JE. The role of neuro-immune interactions in cancer-related fatigue: biobehavioral risk factors and mechanisms. *Cancer*. 2019;125(3):353-364.
72. Berger AM, Higginbotham P. Correlates of fatigue during and following adjuvant breast cancer chemotherapy: a pilot study. *Oncol Nurs Forum*. 2000;27(9):1443-1448.
73. Marek E, Friz Y, Pohl W, et al. Effizienz als ein neuer Parameter zur Objektivierung der körperlichen Leistungsfähigkeit mittels 6-Minuten-Gehtest. *Rehabilitation (Stuttg)*. 2011;50(02):118-126.