Functional Capacity of Patients with Advanced Gastrointestinal and Breast Cancer Pre-treatment - a Cross-Sectional Comparison to Healthy Age-matched Women

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Research Article

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Abstract

Purpose: The aim of the study was to compare the functional status of patients with advanced gastrointestinal and breast cancer prior treatment to healthy age-matched volunteers.

Methods: In this 3-arm cross-sectional study female patients with advanced cancer (UICC ≥ III) (gastrointestinal: n=17; 68.4±5.6years; BMI: 24±5.1kg/m^2; breast: n=17; 64.1±7.8years; BMI: 23.6±3.7kg/m^2) before first-line chemotherapy and 17 healthy age-matched women (68.6±5.8years; BMI 24.6±3.2kg/m^2) were included. The functional status was assessed using the short physical performance battery (SPPB). A capacitive force platform was used for gait speed recordings during free level walking. Maximal isometric voluntary contraction force (MIVF) of the quadriceps muscle was assessed by a strain gauge force system. Body composition was obtained from bioelectrical-impedance-analysis. Physical activity was assessed via accelerometry.

Results: Compared to the healthy controls and to patients with breast cancer, gastrointestinal cancer patients have lower values in the SPPB (10.4±1.3vs.8.9±2.0 vs.6.8±2.6; p<.01), phase angle (5.4±0.5°vs.5.2±0.5°vs.4.5±0.8°; p<.01), MIVF (8.8±1.9vs.9.2±3.5vs.6.0±2.1N/kg; p<.01), and gait speed (5.0±0.6vs.4.6±0.5vs. 3.6±1.1km/h; p<.01). The daily steps were significantly lower in gastrointestinal cancer patients compared to healthy women (3407±2408;8774±3975, p<.01).

Conclusions: Already prior treatment patients with advanced gastrointestinal cancer have a reduced functional status compared to breast cancer patients and healthy controls. Gait speed, phase angle and MIVF are below cut-off values for a low prognosis of survival. This physical deconditioning prior treatment might influence the toxicity of the therapy. Thus, supportive interventions to improve the functional status and to support the treatment in patients with advanced gastrointestinal cancer seems to be of high concern.

Trial Registration: Registered study at ClinicalTrials.gov (NCT02677129).

Background

Many factors influence the clinical outcome of cancer patients under oncological treatment. Besides to chemotherapy the functional and body status become increasingly more relevant. Many studies already report that frailty, cachexia and decreased physical function during chemotherapy of cancer patients predict a higher mortality risk, most likely due to a worse tolerance of chemotherapy and more side effect of chemotherapy. Especially advanced cancer patients are a collective with many disease-related side effects while chemotherapy.

Brown, Harhay and Harhay [1] report that an increase of 0.1 m/s in walking speed and an increase in the short physical performance battery (SPPB) predicted a 12 % reduction in mortality. Other studies show that the strength correlates with the survival. The handgrip strength is independently associated with survival and important biological, functional and quality of life characteristics in advanced cancer

patients [2]. Hui et al. [3] monitored hospitalized advanced cancer patients until their death. This workgroup found the phase angle of the bioelectrical impedance analysis as a novel predictor of survival, which is independent of established prognostic factors in the advanced cancer setting.

Many studies confirm the above described negative factors for patients undergoing chemotherapy. However, to the best of our knowledge the functional and body status of patients with different types of advanced cancer before first-line chemotherapy has not been systematically evaluated.

Gastrointestinal cancer patients have a prevalence to develop a cachectic state in up to 80% [4] and they represent a population with many disease-related side effects while undergoing chemotherapy.

The aim of the study was to compare the functional status of patients with advanced gastrointestinal (GI) and advanced breast cancer prior to chemotherapy treatment to healthy age-matched volunteers to check for potential pre-therapeutic differences in patients with a high and low prevalence to obtain a cachectic state.

Participants And Methods

Study Design

The following study is a 3-armed cross-sectional comparative trial. The study protocol was approved by the independent ethics committee of the local medical faculty and registered at ClinicalTrials.gov (NCT02677129).

Participants and Setting

Chemotherapy-naïve patients with histologically confirmed locally or systemically advanced breast or gastrointestinal cancer (UICC stage III - IV) and scheduled for first-line chemotherapy (neoadjuvant, adjuvant or palliative) were considered eligible. Potential participants were recruited in a local clinic and received oral and written information about the study by their treating oncologists. After receiving written informed consent patients were checked for study eligibility and contraindications for physical function assessments via a standardized clinical examination. Inclusion and exclusion criteria are presented in supplementary table 1.

Healthy age-matched women served as the comparison group and were recruited via flyers. Following informed consent they were screened for study eligibility and contraindications via a physician-based examination.

Enrolled participants were invited for a preliminary meeting to explain and initiate the accelerometry, which was scheduled around 10–14 days prior first chemotherapy for the included cancer patients. At the second appointment 8–10 days later (for patients approximately one to five days before first chemotherapy) the study assessments took place

Outcomes Measures

Sociodemographic and clinical data

Sociodemographic data (age, gender, height, body weight) and clinical characteristics (tumor characteristics, date of diagnosis, treatment schedule, comorbidities, further medication etc.) were documented with a standardized questionnaire based on medical records and an interview. Body weight and height in light clothing was measured using standard techniques.

Primary endpoint was the functional status, assessed via the short physical performance battery (SPPB). Secondary endpoints comprised objective measured physical activity, walking speed, strength and body composition.

Primary outcome

The SPPB includes measures of usual gait speed, balance, and ADL-related muscle endurance of the lower extremity [5]. For each of the aforementioned tests, patients were scored on a Likert scale from 0 to 4 points using established cut point criteria [5] with a summary SPPB score ranging from 0 to 12 points. This ordinal scale has been demonstrated to have predictive validity in analyses showing a gradient of risk for mortality, nursing home admission, and incident disability. The internal consistency of the summary scale as assessed by Cronbach's alpha was 0.76 [5]. For interval-scaled analysis and comparisons with other studies the objective measured physical function was applied. For gait speed testing participants were asked to walk at their normal comfortable pace over a capacitive force-measuring platform (WinFDM v0.0.41®; Zebris© GmbH, Isny, Germany). Gait was monitored in the middle of a 10 m walkway when participants were required to walk across the sensor platform in a self-determined (usual) free walking speed (100Hz) [6]. For SPPB, the average velocity of three trials was calculated. For balance testing, the participants had to hold three different static standing positions: feet side by side, semitandem and full tandem (heel of 1 foot in front of and touching the toes of the other foot) for at least 10 seconds. The muscular endurance of the lower extremity was tested via chair rise test. Participants were asked to stand up from a chair and sit down five times in a row as quickly as possible. Data from gait speed, balance and chair rise were classified according to the cut points and rated from 0 to 4, finally resulting in an overall SPPB rating from 0 to 12 points.

Secondary outcomes

Physical activity was objectively measured with the Actigraph GT1M accelerometer (ActiGraph LLC, Pensacola, FL, USA). Patients were asked to wear the accelerometer on the right side of the hip for seven consecutive days during waking hours except bathing and water activities. Data were collected as activity counts in 30 Hz intervals. Raw data were downloaded and analysed via the ActiLife software (ActiGraph, Pensacola, FL, version 6.6.3). Measurements were considered valid if the accelerometer was worn for at least four days with a minimum of ten hours wear time each day[7]. Non-wear time was defined as at least 60 minutes of consecutive zero counts and will be subtracted from 24h to calculate the wear time per day[8]. Activity counts, step counts, time spent in activities with low, moderate and vigorous intensity as well as time spent sedentary per day will be calculated[7] [9] to characterize physical activity

behaviour. Thresholds for inactivity and classification of the intensity of physical activity will be defined according to to existing guidelines and large population-based studies[7–9]. Maximal isometric voluntary force of the randomly chosen knee extensor side was measured with a strain gauge force transducer (ASYS®; SPOREG; 100 Hz) in a standardised seating position (predefined knee and hip angle = 90°). After warm-up (two submaximal practice trials), three tests with contractions lasting 5 s, separated by 2 min rest intervals, were performed. The highest value of the three trials relative to body weight [N] was considered to characterise maximal strength of the knee extensors. Sufficent test-retest reliability and construct validity has been shown [10]. Body composition was assessed via bioelectrical impedance analysis (BIA) with a phase-sensitive multi-frequency Nutriguard MS (Data Input GmbH,Darmstadt, Germany) following a standardised procedure [11]. This non-invasive method determines the electrical impedance, or opposition to the flow of an electric current through body tissues to calculate total body water, fat-free body mass and body fat as well as extracellular and intracellular water [11]. BIA results are reliable measurements with minimal intra- and inter-observer variability [12]. The phase angle is an indicator of membrane integrity and water distribution between the intra-and extracellular spaces [13] and used as a nutritional indicator in adults and children [14] [15].

Statistical power and sample size

Regarding the effects of advanced cancer disease on functional capacity or any of the secondary outcomes no prior studies and effect sizes are available for patients with advanced gastrointestinal and breast cancer. Thus, we chose to use a medium effect size of 0.4 and a statistical power of 80% (1-ß=0.8) to detect a difference between the three study groups considering physical function (SPPB) for the sample size calculation (G-power). 51 participants (17 per group) had to be enrolled in the study to achieve an adequate power in multifactorial analysis of variance with post-hoc test and Bonferroni correction. The a priori propability is 1 %.

Results

In total 51 patients included in the study. Participants’ characteristics are presented in supplementary table 2. No significant group differences were observed for age or body mass index.

Primary outcome SPPB

ANOVA with post-hoc test Bonferroni correction show significant differences between the GIT patients and the two other groups. The SPPB values are displayed in Table 1. Group differences are presented in Fig. 1.

Table 1
Results of the primary and secondary endpoints; mean ± standard deviation (SD)

		Control	GIT	breast
SPPB [points]	mean + SD	10.4 ± 1.3	6.8 ± 2.6	8.9 ± 2.0
Phase angle [°]	mean + SD	5.4 ± 0.5	4.5 ± 0.8	5.2 ± 0.5
Gait speed [km/h]	mean + SD	5.0 ± 0.6	3.6 ± 1.1	4.6 ± 0.5
MIVF [N/kg/BW]	mean + SD	8.8 ± 1.9	6.0 ± 2.1	9.2 ± 3.5
Steps	mean + SD	8774 ± 3975	3407 ± 2408	5926 ± 2987

Secondary outcomes

The ANOVA with post-hoc test and Bonferroni correction of the secondary outcomes phase angle, gait speed and MIVF present the same differences as shown in the primary outcome. The results of the GIT patients are significant. decreased compared to the control and breast cancer group (Table 1; Fig. 2; Fig. 3; Fig. 4). By measuring the daily steps, the GIT cancer patients have significant less steps compared to the healthy control (Table 1; Fig. 5).

Discussion

The present study shows significant differences of the body and functional status prior to chemotherapy for patients with advanced GI cancer compared to breast cancer patients and healthy women. Gait speed, phase angle and force are below the cut-off values for worse prognosis of survival and may reflect a diminished tolerance of chemotherapy. To the best of our knowledge, this is the first report that evaluates the status of advanced GI cancer patients prior to treatment.

The Short physical performance battery

The results of the SPPB reflect the impaired functional capacity. This impairment result in a decreased activity of daily living (ADL), reduced quality of life and a higher risk of mortality has to be assumed [16]. Functional status is a more reasonable indicator of cancer treatment tolerance[17], therefore the obtained results reflect a possible reason for the known variety of side effects in advanced GI cancer patients.

Phase angle

The mean phase angle of advanced GI cancer patients was 4.5° ± 0.75. According to Hui et al. [3] the survival time correlated with the phase angle in advanced cancer patients. In the study of Hui et al. [3] the mean survival with a phase angle of 4.0-4.9 were 112 days. Low phase angle values are strongly predictive of low muscle strength, impaired quality of life, symptom severity and impaired ADL and survival time [18–20]. Another study reports an increased toxicity with reduced lean body mass [21]. In his study, Ali defined a dose-limiting toxicity. Oxaliplatin doses less than 3.1 mg/kg lean body mass were

associated with low risk of dose-limiting toxicity. There was negligible toxicity in the patients below the cut point. Chemotherapy-induced toxicity in patients treated with paclitaxel and cisplatin was associated with malnutrition and hypoalbuminemia [22]. Malnutrition of colorectal cancer patients measured with poor scores for MNA was independently associated with increased hazard ratios for mortality and poor MNA-scores were predictive for a less than planned number of chemotherapy cycles in palliative treated patients. The physical aspects showed a clear decline after at least four cycles of chemotherapy [23].

Gait speed and strength

Skeletal muscle is the largest organ in the human body, constituting 40–50% of total body mass in healthy nonobese humans [24]. Skeletal muscle function is classically defined as the ability to perform muscular contractions, generating external mechanical force, which enables physical activities of daily living and exercise. In addition, skeletal muscle plays a vital role in primary and secondary disease prevention as an essential regulator of metabolic and inflammatory homeostasis [25]. For example, Burden et al. [26] found that 54% of newly diagnosed early-stage colorectal patients had a handgrip strength, which was below 85% of the age-matched reference range. In accordance, patients with locally advanced prostate cancer undergoing androgen deprivation therapy (ADT) had 29% lower handgrip strength compared with healthy controls [27]. Furthermore, breast cancer survivors evaluated after completion of primary therapy displayed consistently lower muscle strength (20–30%) in seven different upper body exercises compared with healthy individuals [28]. Finally, evidence of late effects on muscle strength has been shown in adult survivors of childhood cancers. For example Ness et al. [29] found that 18% survivors of extracranial solid tumors, assessed a median of 25 years after diagnosis, displayed muscle weakness, defined as the dorsiflexion torque within the lowest 10th percentile compared with healthy age-matched reference subjects. Muscle loss is the key role of the development of frailty, ADL, disability and impaired quality of life in cancer patients [30]. Also, reduced ankle power generation has been proposed as a major mechanism for reduced walking speed [31] [32]. Judge et al [33] reported that walking ankle joint power generation was the strongest predictor of short step length. The reason for the reduced ankle power generation could be plantarflexor muscle weakness. It has been shown that ankle power generation developed during the push-off phase is associated with ankle plantarflexor strength [33]. Usual gait speed at 3.6 km/h respectively 1 m/s will be considered a high risk of functional declines, adverse health outcomes, hospitalization and mortalitiy [34]. The strength of the knee extensors and the usual gait speed of advanced GI cancer patients in the present study were significant reduced compaired to advanced breast cancer patients and healthy volunteers with the same age. In the knowledge that while cancer treatment the strength and muscle function decrease the findings of the present study, another decrease has to prohibit or counteract with resistance training, other physical activities or anabolic steroide.

Physical activity

The daily physical activity of the healthy control with averaged 8774 steps per day reflect a norm collective. In Baumann et al. [35] same aged healthy women show similar results, a little bit below the recommendations of 10.000 steps per day of the World health organisation. The averaged 3407 steps per

day of advanced GI cancer patients could be the result of the decreased body and functional status. This result is beyond other study results of cancer patients with different entities. The consequence of diminished physical activity are long periods of sedentary time. Sedentary time were strongly associated with higher triglycerides and markers of insulin resistance [36]. There is evidence that cancers at different sites (particularly breast, colon, pancreas and prostate) are associated with mechanisms that include hyperinsulinemia, peripheral resistance to insulin and increased production of insulin-like growth factor-1 [37, 38].

The decreased steps of advanced breast cancer patients are not the consequences of an impaired functional or body status. Therefore, possibly the mental situation resulting from cancer diagnosis are the reason of this diminished activity.

Accurate survival prediction is essential for decision-making in cancer therapies and care planning. Also, the probability of many side effects and thereby a decreased quality of life influence the strategy of the therapy. Many studies with physical activity interventions showed positive effects of the body composition, muscle, quality of life, and functional status. Therefore, possibly with some exercise before or while cancer therapy, the therapy tolerance can enhanced, the side effects diminished and indeed the prognosis of survival improved[39–43].

Conclusion

The study reveal a significant decreased body and functional status of advanced GI cancer patients for a high prognosis of a negative process of chemotherapy and side effects. The measured functional and body composition parameter predict a higher toxicity of cancer chemotherapy and mortality risk. Following studies have to prove the ability to enhance the initial functional and body statues of advanced GI cancer patients. A physical activity program, muscle-growing medications at the time of first diagnosis should be tested.

Declarations

Funding: The research was not supported

Conflicts of interest/Competing interests: The authors have declared no conflicts of interest

Availability of data and material: All data are collected and available in an anonymized form.

Code availability: N/A

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Katrin Stücher, Claus Bolling and Lutz Vogt. The Conceptualization and methodology were made by Katrin Stücher, Lutz Vogt and Winfried Banzer. The

first draft of the manuscript was written by Katrin Stücher and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval:The study protocol was approved by the independent ethics committee of the local medical faculty and registered at ClinicalTrials.gov (NCT02677129).

Consent to participate: Potential participants were recruited in a local clinic and received oral and written information about the study by their treating oncologists. After receiving written informed consent patients were checked for study eligibility and contraindications for physical function assessments via a standardized clinical examination. The declaration of participation of each participant is available.

Consent for publication: The consent for publication is available.

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Figures

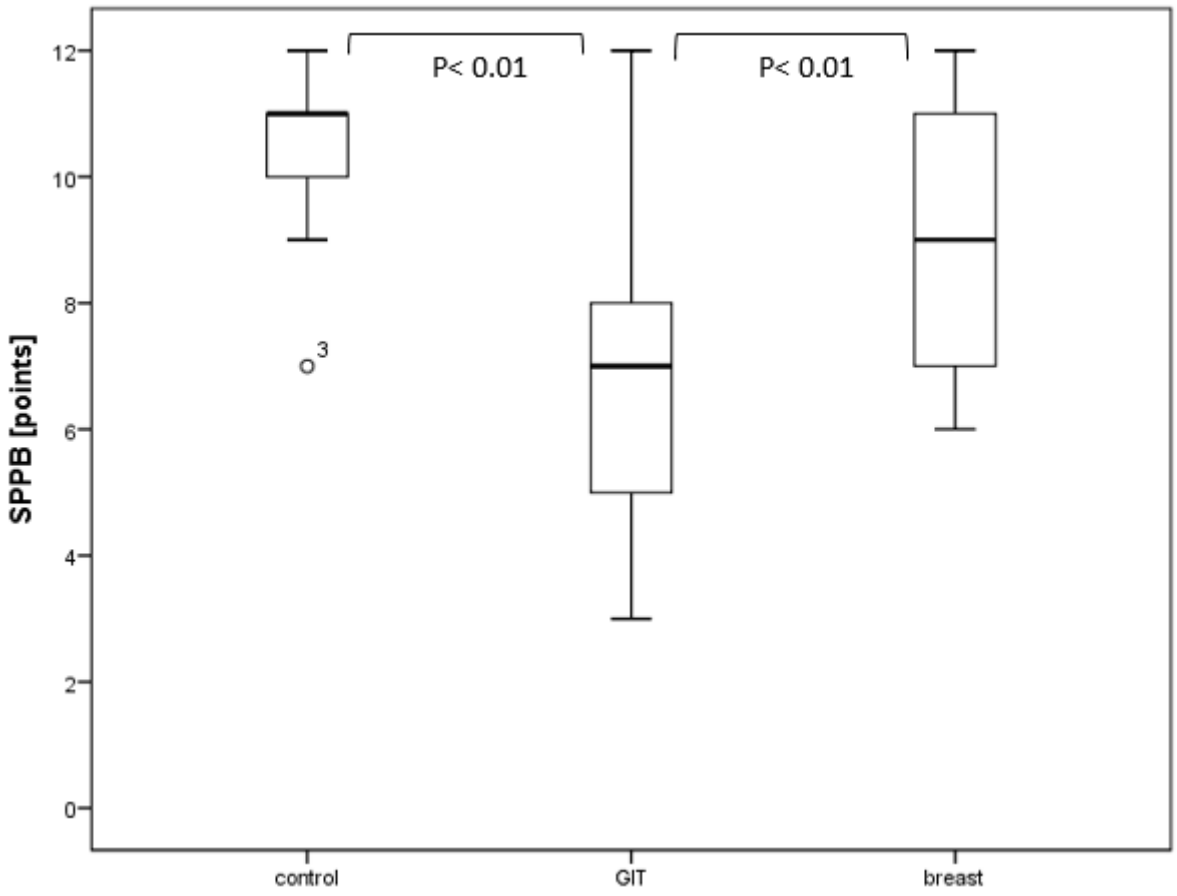

Figure 1

boxplots of the Short Physical Performance Battery points of each group.p<0.01

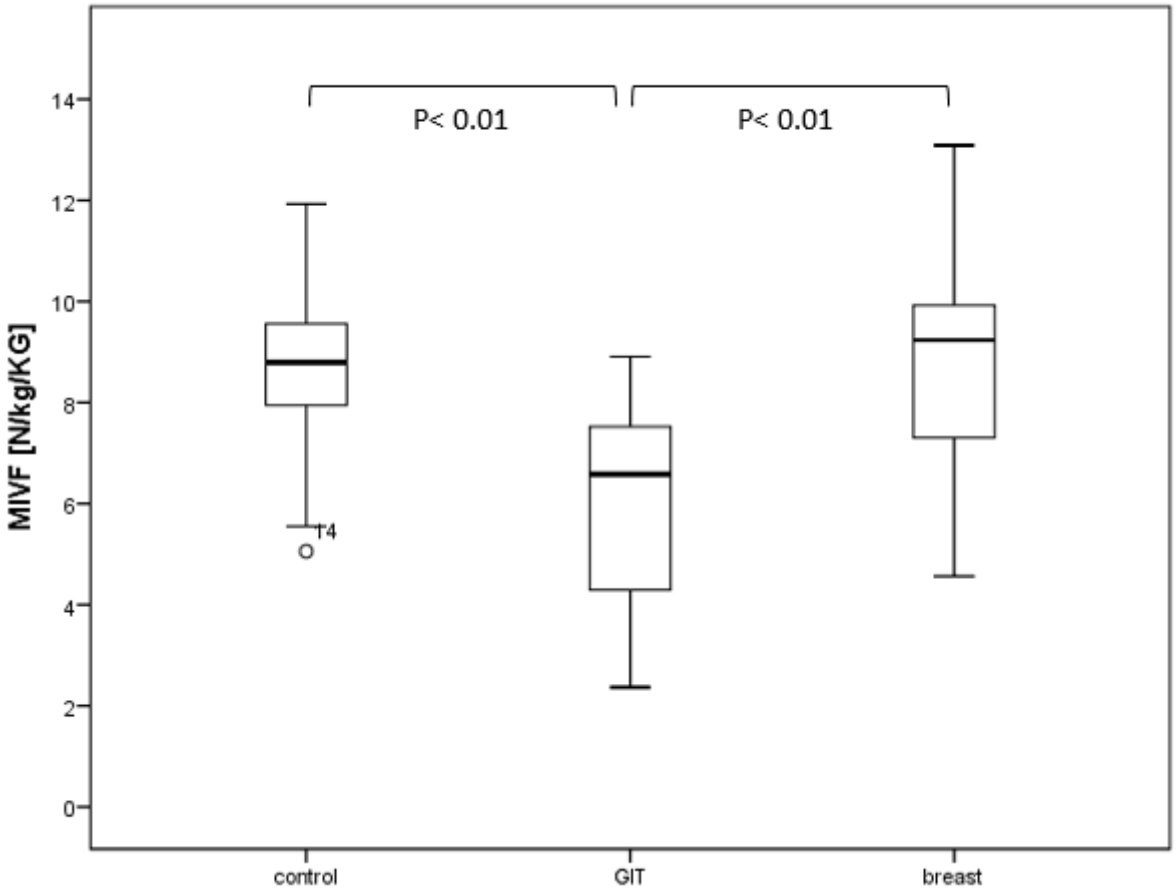

Figure 2

boxplots of the Maximal isometric voluntary force of each group; p<0.01.

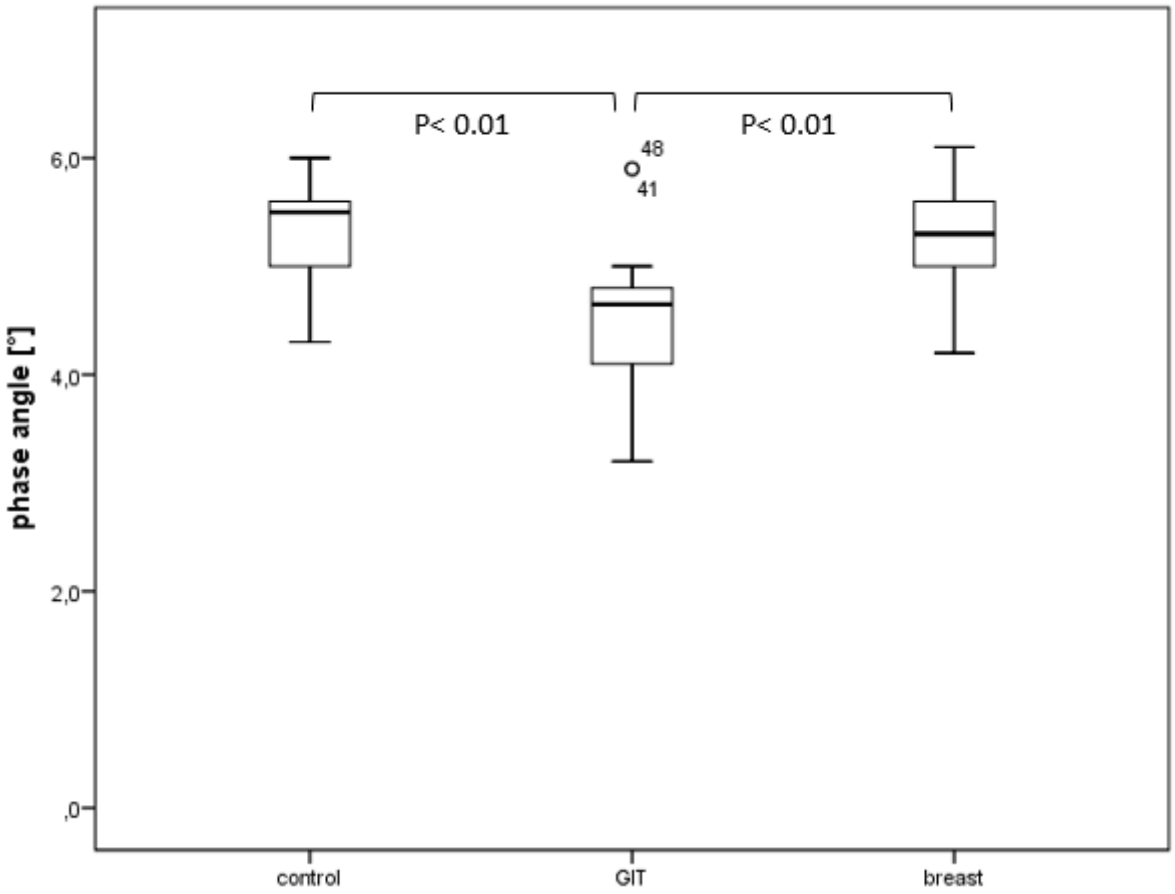

Figure 3

boxplots of the phase angle of each group; p<0.01.

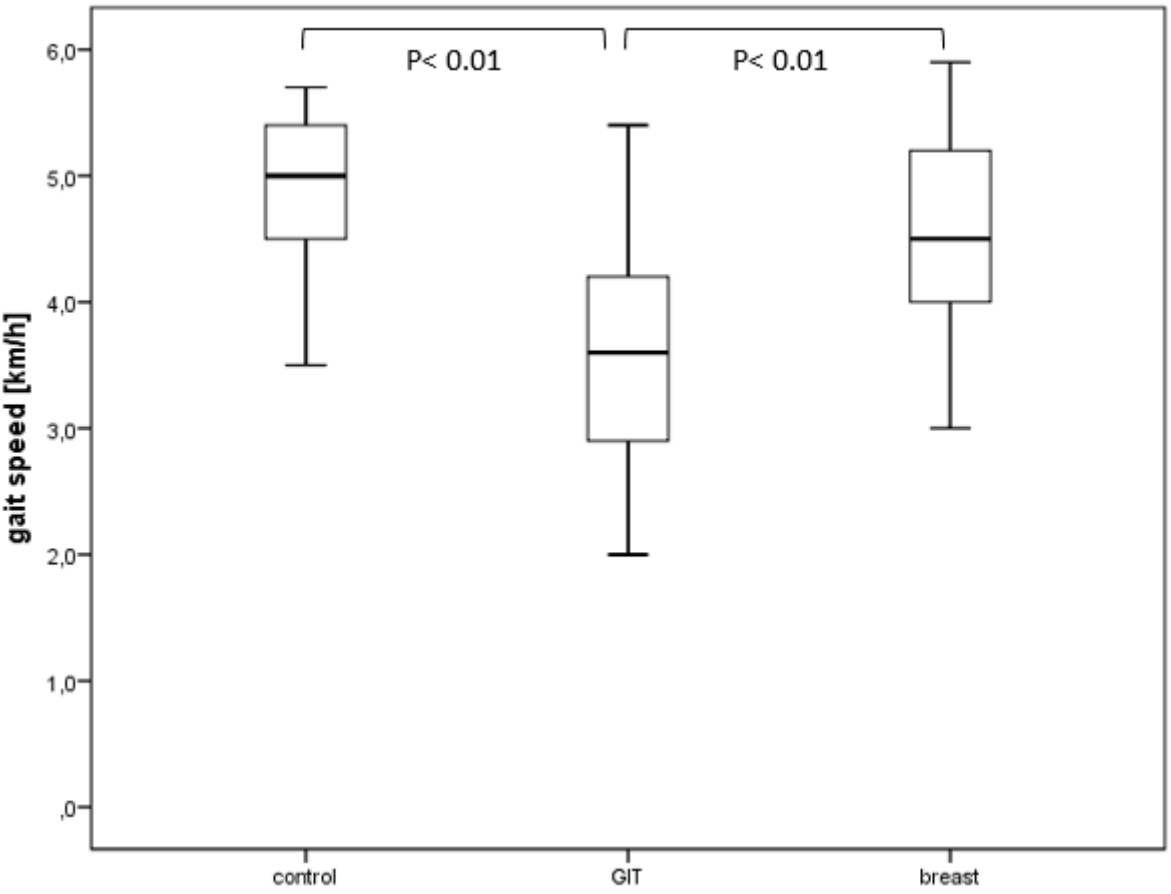

Figure 4

boxplots of the gait speed of each group; p<0.01.

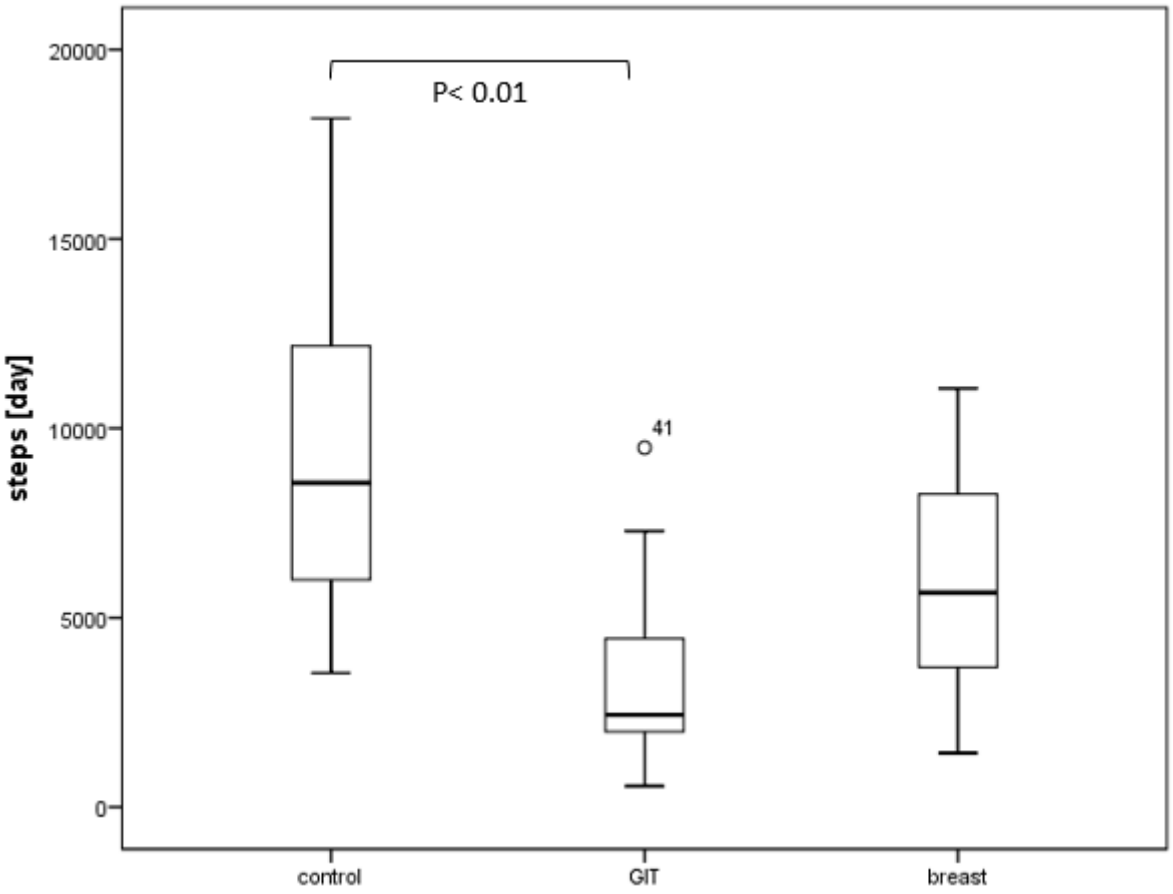

Figure 5

boxplots of the daily walked steps of each group; p<0.01.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryTable1.docx
- supplementaryTable2.docx