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Impact of chemotherapy on medium-term physical function and activity of older breast cancer survivors, and associated biomarkers

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Abstract

Background—Chemotherapy is less often prescribed in older individuals due to concerns about post-treatment morbidity and quality of life. We evaluated the physical performance of breast cancer survivors treated with and without adjuvant chemotherapy.

Methods—We conducted a case-control study in 56 estrogen receptor positive breast cancer survivors (BCS) on adjuvant aromatase inhibitors 1-2 years after definitive surgery. Cases had received adjuvant chemotherapy (n = 27; age 70.5±3.6 yrs) versus age-matched controls who had not (n = 29; age 70.0±4.3 yrs). Measures of grip strength, physical activity and performance, walking speed, fatigue, and self-reported physical function were collected. Biological correlates of inflammation, frailty and markers of DNA and RNA oxidation were compared.

Results—Grip strength (Controls: 21±7.4 vs. Cases: 29.7±5.0 kg, p=0.20), physical activity (5403±3204 vs. 6801±9320 steps/day, p=0.45), physical performance (Short Physical Performance Battery score: 10.1±1.8 vs. 10.4±1.1, p=0.52), long-distance walking speed (1.2±0.21 vs. 1.3±0.41

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m/sec, p=0.17) were similar between the two groups. Self-reported physical function was marginally lower in cases than controls (Controls: 72±24 vs. Cases: 57±34 AU, p=0.07). Fatigue disruptiveness was not different between groups (Controls: 11.1±13.0 vs. Cases: 15.7±16.2 AUs, p=0.24). Similarly, the inflammation, oxidation, and frailty markers did not present a significant difference between groups, except for vitamin D levels (p=0.04).

Conclusion—Older women who received chemotherapy reported having slightly lower physical function, but a similar physical performance compared to women who did not. These data suggest that older BCS treated with chemotherapy recover to an extent similar to survivors who only received hormonal therapy.

Keywords

Chemotherapy; elderly; function; physical performance; breast cancer; survivorship; functional status; inflammation; TNF-alpha; IL-6; d-dimers; IGF-1; IGFBP-3; DNA oxidation; RNA oxidation; vitamin D; albumin

Introduction

The majority of cancer survivors are over 65 years of age. In the case of breast cancer, that proportion is about 60% [1]. However, most survivorship studies have focused on childhood cancer or cancer in young adults. Evidence from multiple randomized studies and meta-analyses points to a survival advantage of adjuvant chemotherapy beyond the age of 70 [2, 3]. This must be weighed however against the potential short- and long-term side-effects of fatigue, losses in physical function, reduced quality of life (QOL), secondary malignancies from chemotherapy, especially in patients with estrogen-receptor positive breast cancer where a substantial risk reduction can be obtained with hormonal therapy alone. The short-term side effects of chemotherapy have been studied[4]. They are frequent but resolve rapidly after the end of treatment. The short-term functional impact is mild to moderate, at least when measured by questionnaires such as Lawton's Instrumental Activities of Daily Living (IADL)[5]. Preliminary data from our group show that severe muscle weakness is as frequent as febrile neutropenia or severe diarrhea among older adults undergoing chemotherapy[6], and more importantly, is independent of fatigue symptoms. Little is known however on the impact of chemotherapy on muscle function and general activity levels on a long-term basis, even among younger survivor cohorts. Studies have focused on fatigue and QOL— questionnaire-based assessments— with heterogeneous results [7-11] but few have assessed standardized and objective measures of physical function that are highly associated with increased risk of disability, nursing home admission and mortality[12].

In a non-cancer setting, the association between muscle weakness and physical impairment in elders has been well understood to be a major risk factor for disability and mortality in older men and women[13-15]. Muscle weakness is considered an independent predictor of incident mobility limitation, which is connected to subsequent hospitalization, nursing home placement, increased healthcare costs, and death[16-20]. In patients with cancer undergoing chemotherapy and patients without cancer, muscle weakness is independently associated with falls, which further supports these objective measures of physical function [21, 22].

There are several mechanisms linked to age- and cancer-related muscle impairments and related losses in physical function. Chronic inflammation and DNA damage are clearly involved in both processes. Common risk factors include smoking history and obesity, especially visceral adiposity, and age itself which is a strong predictor of elevated inflammation[23-25]. Studies of the aging process suggest that senescent cells secrete Interleukin-6 (IL-6), initiated by Interleukin-1 alpha (IL-1 alpha) and regulated by tumor growth factor-beta (TGF-beta)[26]. Persistent, chronic and even mild elevations of C-reactive protein (CRP), IL-6, TNF-alpha and other inflammatory markers are associated with low physical function, physical disability, mobility limitations[27, 28] and mortality[29-31] independently of other risk factors. Cancer and chemotherapy treatment are associated with inflammatory reactions that can have a clinically significant impact[32, 33]. Chemotherapy treatment has potential to increase senescent cells leading to an increase in inflammatory and DNA damage burden[34], which could interfere with muscle function [35, 36]. Elevated pro-inflammatory cytokines are correlated with fatigue in breast cancer survivors[37], patients with cancer in general [38] and frailty in breast cancer survivors [39].

This pilot study sought to build a preliminary understanding about functional and biological residual effects of chemotherapy during the second year after initial treatment in older patients with estrogen-receptor positive breast cancer. Our first aim was to evaluate muscle weakness, physical function and quality of life among survivors treated with and without chemotherapy. Our working hypothesis was that survivors treated with chemotherapy have poorer muscle strength, physical activity, physical performance, and QOL compared to survivors not treated with chemotherapy. We next aimed at building a biological connection between cancer, aging and physical function by examining a variety of markers related to systemic inflammation (plasma IL-6, TNF alpha), DNA/RNA oxidation in circulating white blood cells and urine, and plasma frailty biomarkers (low albumin, IGF-1, IGF-BP3, vitamin D, d-dimers) as a possible explanation for the potential effect that chemotherapy has on self-assessed measures of function, fatigue and objective measures of physical performance.

Methods

Participants

Women were identified through the Moffitt cancer registry, for the Moffitt site, and through the Shands records and the Florida Cancer Registry for the University of Florida (UF) site. English-speaking women aged 65 and older with a history of estrogen-receptor positive stage I-III breast cancer were eligible. They were enrolled between 1 and 2 years after definitive surgery and had to have ongoing hormonal therapy with an aromatase inhibitor. Women having had chemotherapy were identified first and then controls were frequency matched by age (within 3 years), type of surgery and use of adjuvant radiation. Women had to have completed all adjuvant chemotherapy, HER-2 directed therapy, and radiation therapy, and be disease-free. No history of other cancer was allowed, except for non-melanoma skin cancers. Other exclusion criteria included: cognitive impairment, as assessed by a Telephone Interview for Cognitive Status (TICS) score < 30; inability to complete the questionnaires (insufficient understanding of the questions, visual or auditory impairments interfering with study data collection); inability to walk without help; and chronic

corticosteroid or anti-TNF-alpha treatment. The protocol and consent form were approved by the Institutional Review Boards of the University of South Florida, The University of Florida and The Florida Department of Health. All participants provided written informed consent prior to their enrollment in the study.

Study design

This study was designed as a cross-sectional frequency-matched case control study. It was conducted at two sites: H. Lee Moffitt Cancer Center and the UF Shands Hospital at Gainesville and Jacksonville locations. Physical performance testing and questionnaires were administered during a single 2-hour visit. Blood draw and urine sample were taken following an overnight fast (water permitted). At the end of testing, participants were fitted with a Sensewear arm band and asked to wear it for one week to record physical activity levels.

Physical tests—Hand grip strength was measured in both hands using an adjustable, hydraulic grip strength dynamometer (Jamar Hydraulic Hand Dynamometer, Model No. BK-7498, Fred Sammons, Inc. Burr Ridge, IL). Three trials with brief pauses were conducted for each hand and the highest amount of strength was used for analysis.

Physical performance was measured using the short physical performance battery (SPPB) and the 400 meter walk test. The SPPB involves timing a short distance walk at a usual pace, 10 repeated chair stands and balancing in three different positions (feet together, semi-tandem and in tandem). The times to complete each task are scored from 0 to 12 based on normative data as described by Guralnik et al[12])[40-43]. The 400-m walk was chosen because, clinically, it has been proposed as a threshold of high level of performance[44, 45] and is strongly associated with measures of functional limitations, disability and mortality, and predicts future loss of ability to complete the walk[45]. Participants were asked to walk 400 m at their usual pace, without over exerting, on a 20 m course for 10 laps (40 m per lap).

Physical activity: The SenseWear Pro armband (SWA; BodyMedia Inc., Pittsburgh, PA) is a portable multi-sensor device that estimates physical activity energy expenditure using a heat flux sensor, a galvanic skin response sensor, a skin temperature sensor, a near body temperature sensor, and a bi-axial accelerometer. The armband was worn over the right triceps muscle for one week and data were sampled in one-minute epochs from each sensor. These data were used in combination with participant characteristics including gender, age, height, weight, smoking status, and handedness to estimate physical activity energy expenditure that was expressed at metabolic equivalents (METs) with proprietary software developed by the manufacturer (InnerView Research Software, Version 5.1). Our previous work has established the validity of the SenseWear arm compared to the gold standard doubly-water technique[46]. The data were summarized as steps per day, time spent being sedentary (<1.5 METs) and time spent in moderate to vigorous activity (> 3METs).

Questionnaires—Self-reported QOL was assessed with the Acute (past week) Version of the Medical Outcomes Study 36-Item Short Form (MOS SF-36), a widely used self-report measure designed to assess perceived mental and physical functioning[47, 48]. Fatigue was

assessed with the 7-item Fatigue Disruptiveness Index of the Fatigue Symptom Inventory (FSI)[49, 50]. It is composed of 7 questions assessing the extent to which fatigue has interfered with usual activities and well-being in the past week. Previous research has demonstrated the reliability and validity of the FSI with individuals diagnosed with cancer[49, 50]. The Late Life Function instrument (LLFI)[51] assessed how much difficulty participants had on a typical day across three dimensions of function that included upper extremity (e.g. unscrewing a lid), basic lower extremity (e.g. walking in the house), and advanced lower extremity (e.g. hiking). The responses were converted into cumulative raw scores and also scaled from 0 to 100 (highest function).

Biologic tests—For plasma ELISA studies, blood was collected using standard after overnight fasting to EDTA and Citrate Vacutainer tubes. The plasma was separated with a 20 minute, 4°C, 400 × g centrifugation. Half milliliter aliquots were made and stored at -80°C until assayed. EDTA plasma was used for all ELISAs except for D-dimer which required citrate plasma. For WBC samples, EDTA tubes were placed on ice immediately after collection and were centrifuged 20 minutes at 4°C, 400 × g. Using a large orifice pipette tip the white blood cell layer was transferred into chilled 1.5 mL cryovials and immediately stored at –80°C. Urine samples were collected mid-stream in standard collection containers. One ml of urine from collection container was transferred to a chilled 1.5 mL cryovial. Five ml urine from the collection container was transferred to a 15 ml polypropylene tube. Five ml of 100mM DTPA (Diethylenetriamine Pentaacetic Acid) in 100% phenol was added and inverted to mix before aliquoting to cryovials. Argon gas was applied to all urine sample tubes before capping and storage at -80°C.

DNA/RNA oxidation: The urinary RNA and DNA oxidative damage products 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua), 8-oxo-7,8-dihydroguanine (8-oxoGua), 8-oxo-7,8-dihydroguanosine (8-oxoGuo), and 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxodGuo) was simultaneously measured for participants employing electrospray tandem mass spectrometry detection (MS/MS) in multiple reaction monitoring (MRM) mode on a Finnigan TSQ 7000 triple quadrupole mass spectrometer (Thermo Electron Corporation, San Jose, CA). The urinary biomarkers were normalized to the concentration of creatinine, which was assessed using a creatinine kit (Cayman Chemical, Ann Arbor, MI).

RNA and DNA oxidative damage levels to peripheral blood WBC was measured in lysed cells in 4.5 mL of 3 M GTC buffer (0.2 wt.% *N*-L-Sarcosine, 20 mM tris [pH 7.5]) containing 10 mM of the freshly dissolved metal chelator deferoxamine meylate (DFOM) during homogenization using a Potter-Elvehjem homogenizer. RNA/DNA hydrolysis was performed using Nuclease P1 and alkaline phosphatase, and 8- oxoGuo/ guanosine (Guo) and 8-oxodGuo/2-deoxyguanosine (dGuo) ratios were determined using HPLC-ECD with a Coulochem III electrochemical detector (ESA Inc., Chbelmsford, MA), as described previously[52].

Aging and frailty biomarker: Biomarkers typically modified with age and frailty may also be altered by cancer and chemotherapy[53, 54]. Therefore, we evaluated the following

biomarkers that have been associated with functional decline in the elderly: IL-6[28, 39, 55], D-dimers[56], albumin[57], IGF-1 & IGFBP3[58, 59], TNF-alpha[60] in plasma samples.

We also evaluated plasma 25- hydroxyvitamin D levels, as they have been associated with muscle strength [61]

Circulating levels of D-dimers, IGF-1, IGFBP-3, IL-6, TNF-1α, vitamin D, and albumin were determined using commercially available chemiluminescent or HRP based ELISA kits. Plasma samples were stored at -80°C before being batch assayed. The ELISA kits were purchased from Sekisui Diagnostics (Stamford, CT; D-dimer), Beckman Coulter (Brea, CA; IGF-1), R&D Systems (Minneapolis, MN; IGFBP-3, IL-6, TNF-alpha), Immunediagnostik AG (Bensheim,Germany; 25(OH)-vitamin D), Innovative Research (Novi, MI; albumin). ELISAs were performed as described in the manufacturer's instructions. Briefly, on each plate plasma samples and standards will be assayed in triplicate and read for luminescence absorbance (450nm/690nm correction) with a Synergy 4 microplate reader (BioTek, Inc., Winooski, VT). Using Gen5 software (Biotek, Inc), a 4-parameter fit was applied to the titrated standards to produce a standard curve and for determination of unknowns. Plasma samples resulting in absorbance values above the highest concentration used in the standard curve were further diluted in assay buffer and re-assayed.

Statistics: This study was considered a pilot and was designed to gain an understanding of the variability and effect size differences. Thus, a sample of 20-25 subjects per group would provide a confident measure of variability in the many assessments for developing power estimates to conduct a larger study. The two groups were compared using analysis of variance for continuous variables and chi-square tests for categorical variables. Statistical significance was set at an alpha level of 0.05. Pearson correlations were calculated for the associations between biological markers and clinical function tests. Values after '+/-' indicate standard deviation unless otherwise indicated.

Results

Fifty-six women were enrolled. Twenty-six did receive chemotherapy, 30 did not. Patient characteristics were balanced between groups (Table 1). Patients were on average 18.6 (SD 3.3) months after their final operation when assessed. For those receiving chemotherapy, full details were available for 17 patients, whereas the 9 patients identified through the Florida Cancer Registry had limited information. Three out of 17 had neo-adjuvant chemotherapy, the others had adjuvant chemotherapy. Patients were on average 15.3 (SD 3.2) months after the end of their chemotherapy. The regimens used were: docetaxel/cyclophosphamide (7 patients); carboplatin/docetaxel/trastuzumab (2); docetaxel/cyclophosphamide/trastuzumab (2); 5-FU/epirubicin/cyclophosphamide(FEC100) followed by docetaxel (2); doxorubicin/ cyclophosphamide followed by paclitaxel (2); doxorubicin/cyclophosphamide (1); FEC100 (1)

There were no significant differences in the physical function tests or physical activity (Table 2). There was no difference in self-reported fatigue disruptiveness or physical function per LLFI or SF-36 questionnaire (Table 3), although there was a trend toward a

better SF-36 physical composite score in controls (40.50 +/-10.67 in post-chemotherapy subjects vs 45.61 +/- 8.30 for controls (p=0.054)). This difference was mostly driven by the physical functioning scale. Markers of DNA or RNA WBC oxidation were not different between groups. Among frailty markers (Table 4), plasma vitamin D levels were significantly higher among the controls: 42.4 +/- 21.9 nmol/L for cases vs 55.8 +/-23.6 nmol/L for controls (p=0.041). The rate of deficiency (< 50 nmol/L) was 66.7% in the chemotherapy group vs 46.7% in controls.

Correlations

In the absence of significant group difference in function and markers, we combined the groups for an analysis of the correlation between the individual level of physical functioning and the correlative markers (Table 5). The marker with the most clinical associations was plasma TNF-alpha. A higher TNF-alpha was associated with a slower walking speed (r=-0.30, p=0.038); a lower SPPB score (r=-0.34, p=0.018); a worse handgrip strength (r=-0.32, p=0.027), and a higher number of sedentary hours (r=0.41, p=0.004). A higher vitamin D level was associated with a longer time in moderate or vigorous activity (r=0.39, p=0.006). A lower IL-6 level was associated with a higher LLFI score (r=0.29, p=0.042) and a better FSI disruption index (r=0.39, p=0.006). A higher albumin was associated with a better SF-36 composite physical score (r=0.41, p=0.005), and a borderline lower FSI disruption index (r=0.28, p=0.057). D-dimers, IGF-1, IGFBP-3, and the oxidation markers showed no significant association with the clinical function parameters.

Discussion

Whereas questionnaire studies assessing the impact of chemotherapy on QOL and fatigue in breast cancer survivors are relatively abundant, astonishingly few studies have measured the actual physical function impact of prior adjuvant treatment. To our knowledge, this is the most detailed study of the medium term impact of chemotherapy on the function of older breast cancer patients. It combines physical performance tests, biological testing, and activity measurement by both recording and questionnaires, allowing a detailed picture of the functioning of these patients. Another recent study combined functional (and CGA) questionnaires with a cytokines and telomere length evaluation but did not assess physical function[62].

One to two years after initial surgery, older patients with breast cancer in our study did not appear to have a lasting impact on physical activity from their adjuvant chemotherapy. This might seem counterintuitive. The survivors in both groups accumulated daily steps slightly above the national average of 2,565–4,250 steps per day for their gender and age class[63]. They also spent 50 minutes per day in moderate to vigorous physical activity, which is significantly greater than the normative population of women 60+ years who spent 12 minutes per day[64], although it should be noted that the SenseWear armband used in this study overestimates moderate to vigorous physical activity, so direct comparisons to normative data are tenuous[65]. In patients with cancer, a cohort from the TEAM trial, which randomized postmenopausal patients to exemestane vs tamoxifen followed by exemestane[66], showed that women (median age 63.6 years) spent 6.3 hours/week in

moderate to vigorous activity –an amount similar to our patient group-- but noted a declining trend with age. A smaller trial in younger (mean age 48) post-chemotherapy breast cancer survivors showed no differences in body composition, insulin resistance, CRP, physical activity by accelerometry, and questionnaires between cases and controls at baseline, 8 weeks, and 3 months following an exercise intervention[67]. Our results are also compatible with those found in a study of exercise intervention during adjuvant treatment for younger women (median age 51 years)[68]. In that study, SF-36 scores and aerobic fitness did not fundamentally differ before or after 16 weeks between patients who did and did not receive chemotherapy. Therefore studies testing objective physical function in the adjuvant treatment setting appear to show overall a good tolerance on that aspect to chemotherapy. In their recent study, Brouwers et al. did notice a decrease in global QOL measured by EORTC QLQ-30 and IADL (but not ADL) 3 months after surgery in the chemotherapy group but these all corrected to baseline 1 year after surgery[62].

It is interesting to note that while there were no apparent differences in objective physical performance testing, self-reported physical function was slightly lower on the SF-36. Poorer self-reported physical function in older breast cancer survivors relative to controls has been reported [69], although some investigators found that this difference tended to correct over time[70]. In contrast, a study of breast cancer survivors found no differences in SF-36 scores between patient who did or did not receive adjuvant chemotherapy, although chemotherapy treatment was associated with more musculoskeletal pain[7]. Overall, our findings suggest that aspects of physical functioning assessed by MOS SF-36 (stair climbing, bending, kneeling, stooping and walking several blocks) might be impacted in free-living conditions. As such, functional challenges might be occurring in the environment that are not adequately captured during objective physical performance testing in a clinic setting.

Our finding of a higher vitamin D level in controls is intriguing. Data have reported a worse outcome of breast cancer patients with low levels of vitamin D[71]. Our data lend support to testing and if necessary correcting vitamin D levels and encouraging more physical activity in older breast cancer survivors, especially those who received adjuvant chemotherapy. The data from Lim et al. suggest that such a correction is associated with improved survival in breast cancer survivors[71].

Our findings of a general lack of difference in cytokines levels 1-2 years after surgery are in accord with those of Brouwers et al[62]. Similarly to us, they did not find differences in IL-6, IGF-1, and TNF-alpha. In addition, they did not find differences in IL-10, Monocyte Chemotactic protein 1, and Regulated on Activation, Normal T cell Express and Secreted (RANTES). Telemere length decreased significantly but similarly in both of their treatment groups. In our study, higher levels of TNF alpha were moderately associated with worse performance in physical testing. The literature is heterogeneous. In the VITAL study, investigators assessed the correlation of 8 chronic inflammation markers [such as CRP, interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α), and soluble TNF receptors (sTNFR) in plasma; and prostaglandin E2 -metabolite (PGE-M) in urine] in 217 adults aged 50-76 years with multiple exposures and function, including a history of cancer[24]. In that study, CRP had the largest number of associations. TNF-α was associated with age, intake of saturated fat, and of EPA+DHA, but not with physical activity (moderate/

vigorous: yes/no) (p=0.15). sTNFR-II was associated with physical activity (p=0.04). TNF-alpha was not associated with a history of cancer (p=0.44), but sTNFR-II was (p=0.02) and sTNFR-I were borderline (p=0.05). Although our study had smaller numbers, our assessment of physical performance and activity was much more detailed than in the VITAL study. In a small recent study of resistance training in younger breast cancer survivors, levels of CRP, IL-6, IL-10, and TNF-alpha did not differ between the intervention group and the control group[72]. Geriatric studies have also explored the issue. For example, in the InChianti study, sTNFR-I levels were associated with greater decline in 400m walk impairment at 6 years[55]. In the Health, Aging and Body Composition Study, the relative risk (RR) of incident mobility limitation over 30 months was 1.19 per standard deviation (SD) increase (95% confidence interval (CI) = 1.10-1.28) for IL-6, 1.20 (95% CI = 1.12-1.29) for TNFa, 1.40 (95% CI = 1.18-1.68) for CRP, 1.23 (95% CI = 1.04-1.46) for IL2sR and 1.28 (95% CI = 1.04-1.57) for sTNFR-1[28]. In a combined analysis of 4 studies of patients with chronic conditions, CRP and IL-6, but not TNF-alpha were associated with worse handgrip strength, SPPB scores, repeat chair stands, and 400m walk speed[73]. It is also interesting to note that in vitro, TNF-alpha stimulates the aromatase gene expression in adipose cells[74], and that all of our patients were on aromatase inhibitors. More study is needed to understand how inflammation relates to physical performance in older breast cancer survivors.

This pilot study has several limitations. First of all, its size is limited and larger studies might detect more subtle associations. Second, it is a cohort of volunteer survivors and is likely to have selected a subset of survivors with a higher level of functioning who thought they could successfully complete the testing protocol. We also excluded patients who needed assistive devices for safety reasons. Similar limitations apply to the two studies mentioned above [67, 68]. Additionally, none of our testing measures addressed maximal performance capacity. A recent study by Klassen et al. found a VO_{2PEAK} that was 63% of predicted in post-chemotherapy women[75]. Given the general trend of aging to limit functional reserve rather than baseline functioning, this type of tests might be more sensitive to change in future studies. A third limitation is that we do not have the prechemotherapy functioning of these patients. Although one might argue that patients receiving chemotherapy might have been more functional at baseline, that bias – if present – is likely minimized by the above average population level of function of our cohort, as observed in our activity measurements. In the study by Brouwers et al. the baseline difference between groups was smaller than our within group variation.

The goal of our study was to build an understanding of the potential longer-term consequences of adjuvant chemotherapy on physical and biological markers related to aging and cancer. In general, there were very few physical or biological marker differences between patients treated with or without adjuvant chemotherapy. The results also suggest that adjuvant chemotherapy had little impact on functional outcomes, 1-2 years post diagnosis in non-disabled patients aged 65 years or more. This suggests that interventions to increase physical function and quality of life should target patients with a lower physical function, either pre- or post-chemotherapy, to prevent the onset of disability[76, 77]. They could aim at increasing vitamin D levels by exercise and/or oral supplementation, especially in patients having received chemotherapy. Better understanding of the relationship between

inflammatory cytokines and physical function in older breast cancer survivors on aromatase inhibitors should also be sought.

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Table 1

Breast cancer survivor characteristics treated and not treated with chemotherapy.

Characteristics	Chemotherapy (N = 26)	No Chemotherapy (N = 30)	P-value
Age in years, mean (SD)	70.0 (4.2)	70.5 (3.6)	0.628
Caucasian, N (%)	25 (92.7)	26 (92.8)	0.970
Mastectomy, N (%)	9 (34.6)	6 (20.0)	0.218
Breast-conserving surgery, N (%)	17 (63.4)	24 (80.0)	
Radiation, N (%)	13 (48.1)	22 (75.8)	0.032
Body mass index (kg/m^2), mean (SD)	27.2 (6.2)	27.5 (7.6)	0.892
Systolic blood pressure (mmHg), mean (SD)	133.7 (19.8)	133.8 (16.3)	0.974
Diastolic blood pressure (mmHg), mean (SD)	75.6 (12.7)	77.6 (9.7)	0.517

Table 2

Physical performance and physical activity measures according to chemotherapy status in breast cancer survivors

Measures	Chemotherapy	No Chemotherapy	P-value
Maximal hand grip strength	23.0 (5.00)	21.3 (7.38)	0.315
400 meter walk speed (m/sec)	1.29 (0.41)	1.17 (0.21)	0.173
Maximal Rating of perceived exertion during rapid 400 meter walk (range 1 to 10)	3.02 (2.91)	2.37 (2.40)	0.425
SPPB			
Balance score	3.92 (0.70)	3.72 (0.27)	0.167
Gait speed score	3.78 (0.51)	3.72 (0.45)	0.678
Chair stand score	2.74 (0.81)	2.65 (1.20)	0.758
Total Short physical performance battery score	10.41 (1.10)	10.14 (1.80)	0.512
Physical activity (Sensewear)			
Average hours/day spent sedentary (includes sleeping)	21.20 (2.50)	20.40 (4.20)	0.443
Average hours/day spent in moderate and vigorous intensity physical activity	0.82 (0.77)	0.72 (0.68)	0.603
Average steps per day	5099.89 (2949.43)	5596.18 (3086.89)	0.545

Table 3

Self-report fatigue and physical function according to chemotherapy status in breast cancer survivors

Measures, mean (SD)	Chemotherapy	No Chemotherapy	P-value
Fatigue disruption index *	15.15 (16.23)	11.10 (13.04)	0.311
Late-life function score (raw)	62.07 (9.69)	64.64 (13.31)	0.413
Late-life function score (scaled)	55.00 (6.30)	55.60 (6.40)	0.716
Short-form-36 domains			
Physical functioning	57.96 (34.22)	72.24 (23.81)	0.074
Physical role functioning	57.41 (42.07)	73.28 (34.67)	0.128
Bodily pain	64.26 (26.53)	70.17 (26.78)	0.410
General health	54.44 (17.70)	56.72 (14.26)	0.599
Vitality	54.23 (24.15)	58.79 (24.95)	0.338
Social role functioning	75.00 (25.94)	85.34 (17.69)	0.085
Emotional role functioning	75.80 (33.20)	77.80 (33.20)	0.841
Mental health	80.00 (12.13)	81.43 (12.98)	0.678
Physical composite score	40.50 (10.67)	45.61 (8.30)	0.054
Mental composite score	52.48 (9.87)	52.67 (7.69)	0.877

* The disruption index is estimated from general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life, and mood.

Table 4
Biomarkers according to chemotherapy status in breast cancer survivors

Measures, mean (SD)	Chemotherapy (N = 23)	No Chemotherapy (N = 28)	
Oxidation and inflammation			
DNA oxidation in WBC, mean (SD)	5.8 (3.4)	5.4 (3.6)	0.713
RNA oxidation in WBC, mean (SD)	23.1 (23.9)	21.2 (17.7)	0.744
Frailty biomarkers			
D-dimers, ug/ml	0.47 (0.29)	0.74 (1.41)	0.384
IGF-1, ng/ml	145.9 (42.1)	137.6 (54.4)	0.552
IGFBP-3, ng/ml	3.05 (0.87)	2.87 (0.86)	0.457
IL-6, pg/ml	2.80 (4.30)	5.96 (9.20)	0.136
TNF alpha, pg/ml	3.78 (1.30)	4.4 (1.80)	0.195
Vitamin D, nM	42.4 (21.9)	55.8 (23.6)	**0.041**
Albumin, mg/ml	745.0 (663.8)	856.9 (1034.0)	0.658

Table 5

Correlation of plasma biomarker concentrations and clinical scores

	D-dimers	IGF-1	IGFBP-3	IL-6	TNF-alpha	Vit D	Albumin
Steps	-0.26	-0.08	0.09	-0.12	-0.19	0.18	0.26
Sedentary hours	0.05	0.27	0.17	0.13	**0.41** **	-0.22	0.20
Mod/vig. Activity hours	-0.25	0.21	0.32	-0.13	-0.01	**0.39** **	0.04
Walking speed	-0.05	-0.13	-0.25	-0.22	**-0.30** *	-0.01	0.16
SPPB	-0.05	-0.12	-0.04	-0.14	**-0.34** *	0.21	0.14
Max. hand grip strength	-0.03	-0.22	-0.22	-0.24	**-0.32** *	-0.11	0.19
Late lifefunctional index scaled	-0.10	0.06	0.17	**0.29** *	0.01	0.05	-0.07
SF-36 composite physical	0.19	0.08	0.04	-0.23	-0.14	0.21	**0.41** **
FSI disruption index	0.19	0.11	0.14	**0.39** **	0.26	-0.15	-0.28

Mod/vig.: Moderate/vigorous;

* $p<0.05$

** $p<0.01$