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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

Objective: 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.
Materials and 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 years) versus age-matched controls who had not ($n = 29$; age 70.0 ± 4.3 years). 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, $p = 0.52$) and long-distance walking speed (1.2 ± 0.21 vs. 1.3 ± 0.41 m/s, $p = 0.17$) 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 AU, $p = 0.24$). 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.

1. 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), and 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-

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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.

2. Methods

2.1. 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.

2.2. 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.

2.2.1. 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 [16,44] 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 [45]. The data were summarized as steps per day, time spent being sedentary (<1.5 METs) and time spent in moderate to vigorous activity (>3METs).

2.2.2. 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 [46,47]. Fatigue was assessed with the 7-item Fatigue Disruptiveness Index of the Fatigue Symptom Inventory (FSI) [48,49]. 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

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