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Higher Symptom Burden is Associated with Lower Function in Women Taking Adjuvant Endocrine Therapy for Breast Cancer

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Abstract

Objective: To explore the impact of symptoms on physical function in women on adjuvant endocrine therapy for breast cancer.

Methods: Eligible women were postmenopausal, had hormone receptor positive, stage I-IIIA breast cancer, completed surgery, chemotherapy, radiation, and on adjuvant endocrine therapy. At a routine follow-up visit, women (N=107) completed standardized symptom measures: Brief Fatigue Inventory, Brief Pain Inventory, Menopause Specific Quality of Life Questionnaire, Functional Assessment of Cancer Therapy Neurotoxicity scales. Two performance measures assessed function: grip strength (Jamar dynamometer; n=71) and timed get-up-and-go (TUG;

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n=103). Analyses were performed with an overall symptom composite score. Correlations and multiple linear regression analyses were performed to test adverse effects on physical function.

Results: The mean age was 64 years (range 45–84), 81% white, 84% on an aromatase inhibitor, and on endocrine therapy for mean 35 months (range 1–130 months). Dominant hand grip strength was inversely correlated with symptom composite scores (r=−.29, p=.02). Slower TUG was positively correlated with higher Charlson comorbidity level (r=.36, p<.001) and higher symptom composite scores (r=.24, p=.01). In multivariate analyses, weaker dominant and non-dominant hand grip strength were significantly associated with greater symptom composite scores (β=−.27, t=2.43, p=.02 and β=−.36, t=3.15, p=.003, respectively) and slower TUG was associated with higher symptom composite scores (β=.18, t=1.97, p=.05).

Conclusions: Higher symptom burden is associated with worse physical function, as measured by hand grip strength and TUG. Further study to determine the impact of endocrine therapy and its side effects on function is warranted.

Keywords

Breast cancer; endocrine therapy; side effects; function; grip strength; Timed-Up-And-Go

INTRODUCTION

Breast cancer is the leading cancer affecting women in the U.S., with an estimated 266,120 new cases of invasive breast cancer diagnosed in 2018.[1] More than half of breast cancers are hormone- receptor positive, and in older women over three-quarters are hormone-receptor positive.[2–4] Endocrine therapy is a crucial component of adjuvant therapy for breast cancer in patients with hormone receptor positive disease, reducing breast cancer mortality and preventing recurrence, with the benefit of therapy being directly proportional to the risk of disease recurrence.[5] Side effects, however, are often implicated as a cause for early discontinuation of endocrine therapy. Several studies, for instance, have found that arthralgia is significantly associated with endocrine therapy discontinuation.[6–8] In one retrospective cohort study among 437 patients, discontinuation of aromatase inhibitors was associated with reported joint pain score of 4 or greater on the Brief Pain Inventory (BPI) (Hazard Ratio [HR] 2.09, 95% Confidence Interval [CI] 1.14–3.80, P = 0.016) and prior use of tamoxifen (HR 2.01, 95% CI 1.09–3.70, P = 0.026).[6] Further, a review of the literature estimates that up to 20% of patients will be non-adherent with the endocrine therapy because of the joint pain.[7]

In older women, who may already suffer from arthritis and other age-related comorbidities[9], the added side effects from endocrine therapy may increase overall symptom burden and have an impact on function and independence. In fact, we observed in the clinic that proximal muscle weakness occurs in patients taking aromatase inhibitors.[10] We, therefore, hypothesize that symptom burden in women taking adjuvant endocrine therapies may be associated with a decline in physical function, as measured by two physical performance measures, timed get-up-and-go (TUG) and grip strength. Understanding potential physical impairment secondary to symptoms in women taking endocrine therapy for breast cancer is not only important in its potential relation to adverse effects and poor

adherence to treatment, but physical impairment, in and of itself, has been linked to disability and poorer health care quality of life in older adults.[11–15] Further, a decline in physical function may even be associated with mortality as a recent longitudinal population study demonstrated that grip strength was inversely related to all-cause mortality and to cardiovascular death and disease.[16] If adjuvant endocrine therapy use causes symptoms that are related to physical function decline, this relationship could have potential broad health implications. Therefore, in this pilot study we examined the association of symptoms experienced by patients with breast cancer on adjuvant endocrine therapy and physical function, as measured by: 1) grip strength and 2) TUG.

METHODS

Design and Setting

The study was approved by the Duke University Institutional Review Board. Women were recruited from the Duke University Medical Center (DUMC) Breast Oncology Clinic. Recruitment procedures have been previously described.[17]

Study Population/Eligibility

Inclusion criteria were: 1) stage I to stage IIIA breast cancer, 2) hormone receptor positive tumor defined as any positivity of estrogen or progesterone receptor, 3) completed definitive treatment (i.e., surgical treatment, chemotherapy and/or radiation therapy), 4) post-menopausal defined as having no ovaries, age > 60, or no menstrual period for one year in the absence of any endocrine or anti-endocrine therapy, and 5) taking tamoxifen or an aromatase inhibitor (i.e., anastrozole, letrozole, exemestane) for at least one month. Exclusion criteria were 1) women <21 years of age and 2) unable to provide consent (e.g. Women with severe cognitive impairment such that the research descriptions were not clearly understood).

Of the 143 women approached for the study, 125 agreed to participate. One patient was excluded because she had not completed surgery. Twelve participants were excluded because they did not complete the study measures. During the study, there was a malfunction of the dynamometer to measure grip strength, requiring repair and calibration, resulting in 28 patients with unusable data. Five patients were excluded for lack of both grip strength and TUG measures. There were, therefore, four women with grip strength with no TUG, 36 with TUG with no grip strength, and 67 women with grip strength and TUG.

Measures

After completing informed consent, participants completed self-reported questionnaires.

Physical symptoms—Four measures were used to assess symptom domains of pain, fatigue, vasomotor symptoms, and neuralgia / arthralgia. Pain was assessed using the Brief Pain Inventory Short Form(BPI-SF)[18] which has been validated among patients with cancer. This measure assesses levels of pain and the degree to which pain interfered with daily activities in the past week. In the present study, this scale had high internal consistency (Cronbach’s alpha = 0.92).

Fatigue was assessed using the Brief Fatigue Inventory[19] that measures present level of fatigue, worst fatigue in the past week, and usual level of fatigue in the past week using a zero to ten point scale. This measure has been validated for patients with cancer. The three items were averaged to create a total score ranging from 0 to 10, with higher scores indicating greater fatigue. This scale had high internal consistency in the present sample (Cronbach's alpha= 0.93).

Vasomotor symptoms were measured using the vasomotor subscale of the menopause specific quality of life questionnaire (MENQOL). This is a 32-item self-report questionnaire that assesses the occurrence and severity of menopausal symptoms including physical, vasomotor, psychosocial, and sexual. The internal consistency was high (Cronbach's alpha was 0.90).

Neuralgia and arthralgia were assessed using the FACT-Taxane questionnaire. While this questionnaire was designed to capture Taxane-related adverse effects, it also assesses adverse effects that may be associated with AI treatment.[20] Taxane chemotherapy was received by 41 participants in this study as well. This scale also had high internal consistency (Cronbach's alpha = 0.88).

To assess the overall symptom burden, an overall symptom composite score was then calculated from these measures (BPI-SF, brief fatigue inventory, MENQOL, and FACT-T) as has been done in previous studies.[17] Intercorrelations among the four measures ranged from r=.37 to r=.70. The symptom composite score was calculated in three steps. First, total scores for each measure were computed. Next, standardized scores (Z scores) with a mean of zero and a standard deviation of one were computed for each measure. Finally, standard scores of the four measures were averaged. Composite scores ranged from −1.33 to 3.03. Cronbach's alpha for the composite scale was 0.81. Correlations were then calculated between the function tests (grip strength and TUG) and each of the above symptom measures as well as the overall symptom composite score.

Measures of function included grip strength and the get-up-and-go test (TUG). Grip strength was assessed using a latex free JAMAR hydraulic hand dynamometer specially designed for this purpose and has been extensively validated.[21] To assess grip strength, the individual sat with their forearm in a neutral position, and wrist between 0º and 30º dorsiflexion and between 0º and 15º ulnar deviation. After the individual was positioned properly, they were asked to squeeze the handle of the dynamometer as hard as they can and then relax. Data were recorded in pounds. One trial with each hand was conducted and a note was made of the dominant hand.

The get-up-and-go test (TUG), a measure of function and mobility, involved participants standing up from a chair, walk ten feet, turn, walk back to the chair, and then sitting down. This intervention was timed in seconds with the following scale (seconds): <10 Freely mobile, <20 Mostly independent, 20–29 Variable mobility, >20 Impaired mobility.[22] Timed get-up-and-go has been validated in several populations including the geriatrics population[23] and in patients with knee osteoarthritis.[24]

Control variables.—All participants completed a questionnaire assessing demographic characteristics, including age, race, education, and marital status. Medical records were abstracted to determine current and past use of endocrine therapies, breast surgery type and date, and receipt of chemotherapy and radiation. Comorbidity level was determined from chart review using the Adult Comorbidity Evaluation Scale (ACE-27).[25]

Statistical Analysis

Descriptive statistics were calculated for all variables. Correlational analysis (Pearson and point- biserial correlations were computed as appropriate) were conducted to examine the relationship between demographic, medical, symptom composite and function variables. Correlations were calculated separately for grip strength in the dominant and the non-dominant hand. Variables associated ($p<10$) with grip strength or TUG in correlational analyses were included in multiple linear regression analyses examining variables associated with grip strength and TUG. Three separate multiple linear regression models were examined: dominant hand grip strength, non-dominant hand grip strength, and TUG. Each regression model for grip strength included age, education, time on endocrine therapy, type of endocrine therapy (tamoxifen versus an aromatase inhibitor), and symptom composite scores. The multiple linear regression model for TUG included variables with DV at <0.10 from the bivariate analysis: age, marital status, education, race, comorbidity level, and symptom composite score.

RESULTS

The study population included 107 women. Participants' characteristics are shown in Table 1. Mean age was 64 years (range 45–84) with 81% white, and 84% on an aromatase inhibitor. Patients had been on endocrine therapy for a mean of 35 months (range 1–130 months).

In bivariate analyses, weaker grip strength and slower TUG was correlated with greater symptom burden (Table 2). Dominant and non-dominant hand grip strength was inversely correlated with symptom composite scores ($r=-.29$, $p=.02$ for dominant and $r=-.34$, $p<.01$ for non-dominant). Slower TUG was positively correlated with symptom composite scores ($r=0.24$, $p=.01$). Dominant hand grip strength was also inversely related to pain intensity ($r=-.30$, $p=.01$) and neurotoxicity score ($r=-.25$, $p=.04$) (see Table 2). Non-dominant hand grip strength was inversely correlated with pain intensity ($r=-.31$, $p=.01$) and fatigue ($r=-.26$, $p=.03$). However, non-dominant hand grip strength was not significantly related to neurotoxicity ($-.23$, $p>0.05$). TUG was positively correlated with age ($r=.21$, $p=.03$) and race ($r=.29$, $p<0.01$). Slower TUG was inversely correlated with marriage (r-.28, $p=.01$) and education (r-.23, $p=.02$). Slower TUG was also positively correlated with comorbidity burden ($r=.36$, $p<.001$), higher pain intensity ($r=.38$, $p<.001$) and fatigue ($r=.21$, $p=.04$) levels.

Significant associations between function and symptom composite scores were also noted in multiple linear regression analyses. Controlling for age, education, months on endocrine therapy, and endocrine therapy type, weaker dominant and non-dominant hand grip strength were significantly associated with greater symptom composite scores ($\beta=-.27$, $t=2.43$, $p=.02$ for dominant hand and $\beta=-.36$, $t=3.15$, $p=.003$ for non-dominant hand). Controlling for age,

marital status, education, race, and comorbidity level, slower TUG was associated with symptom burden (β=.18, t=1.97, p=.05).

DISCUSSION

As hypothesized, this study indicated that weaker dominant and non-dominant hand grip strength and slower TUG were significantly associated with greater pain and overall symptoms. Decreased dominant hand grip strength also was significantly associated with worse neurotoxicity (arthralgia score). TUG was observed to worsen with age and with increasing comorbidities. These are important objective findings indicating that commonly reported symptoms from endocrine therapy might have a profound impact on function.

Previous studies have demonstrated that endocrine therapy is associated with arthralgia and musculoskeletal symptoms in up to 60% of patients[26] and up to 50% of patient discontinuing endocrine therapy treatment early. [27–33] Yet few studies have examined objective methods of evaluating strength and function in association with these symptoms which this study shows is feasible. Thus, TUG and hand grip strength could serve as tools in the clinic to assess patients' prior to starting therapy and as a longitudinal tool to evaluate the impact of adverse effects associated with these medications.

Fundamentally understanding how endocrine therapy impacts function in patients with breast cancer is crucial given that studies show physical function, as measured by hand grip strength and/or TUG, is associated with multiple outcomes relevant for an older population (e.g. functional decline, ADL difficulties, health related quality of life, and even mortality in the generalpopulation).[34–36] For instance, Cooper et al performed a meta-analysis of objective physical function measures (including grip strength) and found that a decrease in grip strength was associated with increased mortality. When comparing the weakest 25th percentile to the strongest 25th percentile in grip strength and accounting for age, sex and body size, the summary hazard ratio for mortality was 1.67 (95% CI 1.45–1.93).[37] If endocrine therapy causes symptoms that lead to decline in physical function, the effect on subsequent mortality should be studied.

Several previous studies have found similar correlations between grip strength and TUG in patients with cancer. Owusu et al assessed 123 patients with breast cancer (stages I – III) for functional decline (defined as a 1 point or greater decrease in the activities of daily living scales) over twelve months.[13] Results indicated that 15% of patient developed functional decline, which was associated with measures of physical performance, including grip strength. In another study by Soubeyran et al, slower TUG was associated with higher risk of death in older patients with cancer (defined as older than 70 years old) receiving first line chemotherapy.[38] In a review of performance measures and cancer outcomes by Verweji et al, they reported that severalperformance tests, including TUG and gait speed, were associated with functional decline and decreased survival.[39] Thus, given the evidence that objective measures of functional decline may have significant impact on patient outcomes, including mortality, our pilot study is an important initial step in understanding how aromatase inhibitors impact patient function.

By measuring adverse effects and physical performance through objective measures such as TUG and grip strength, interventions could be designed to target these effects with the goal of improving patient quality of life, medication adherence, and thus survival [6, 27, 32, 40]. One study has demonstrated that an exercise program may help reduce arthralgia in patients on aromatase inhibitors[41]; a decrease in pain severity and life interference was observed. This study did not examine, however, if the intervention led to better aromatase inhibitor adherence or assess quality of life. A future step suggested from this pilot data is to examine longitudinally if TUG and dominant hand strength can serve as an objective test for predicting function and clinical outcomes such as health care related quality of life and survival outcomes.

This study had severalstrengths. The quantitative objectivity of grip strength and TUG as measures of function are strengths. Further, the TUG and dominant hand grip strength are brief and easy to administer in a clinic setting. Other strengths include that it is prospective study that utilizes a variety of well-validated tools to measure symptoms in comparison to TUG and dominant hand strength.

Limitations should be acknowledged. Symptom measures were obtained at a single time point. We do not have reference point of patients' symptoms prior to starting endocrine therapy and acknowledge that some reported symptoms may have simply been age-related and not due to endocrine therapy. Thus, we cannot assume causality. We do not know if the medication and/or adverse effects caused the decline in the strength or if patients with weakness prior to starting endocrine therapy had more significant adverse effects. Finally, patients had to be on endocrine therapy for at least a month, but some patients had been on endocrine therapy for years. Since this was a single point, we do not have data measuring whether TUG or hand strength changed with duration of use. These are certainly important questions for future longitudinal studies.

In conclusion, we find that higher symptom burden is associated with slower TUG and weaker grip strength in women who are taking adjuvant endocrine therapy for breast cancer. Although we acknowledge that not all of the symptoms could be directly attributed to endocrine therapy, these symptoms were negatively associated with function and should be further studied. Older women with breast cancer, in particular, are at risk for functional decline due to the combined effect of baseline age- related symptoms, and side effects of endocrine therapy. Future studies are needed to (1) examine how grip strength and TUG change with time and how this correlates with endocrine therapy adverse effects, functional status, and clinical outcomes and (2) to evaluate how grip strength and TUG can be used to test strategies for adverse effect management and improvement in clinical outcomes. Ultimately, a better understanding of these issues will help us identify the best ways help older women manage symptom burden and optimize function.

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Table 1.

Participant Characteristics (n=107)

Characteristic	Mean (SD)	Range	N (%)
Age	63.9 (9.0)	45.0–84.0	
Married			71 (66.4)
Education			
Some high school			6 (5.6)
Finished high school			18 (16.8)
Vocational Training / Some college			22 (20.6)
College degree			33 (30.8)
Graduate degree			25 (23.3)
Missing			3 (2.8)
Race			
White			87 (81.3)
African American			17 (15.9)
Other			2 (1.8)
Missing			1 (1)
Ethnicity			
Hispanic			2 (1.9)
Non Hispanic			83 (77.6)
Missing			22 (20.5)
Stage			
Stage I			42 (39.3)
Stage II			53 (49.5)
Stage III			12 (11.2)
Surgery Type			
Lumpectomy			58 (54.2)
Mastectomy			49 (45.8)
Time from Surgery (Months)	41.19 (30.1)	2.8–134.4	
Chemotherapy (% yes)			56 (52.3)
Radiation (% yes)			81 (75.7)
Type of Endocrine Therapy			
Tamoxifen			17 (15.9)
AI			90 (84.1)
Months on current endocrine therapy (Months)	25.1 (21.9)	0.00–97.8	
Months on any endocrine therapy (Months)	37.4 (30.3)	1.15–130.3	
ACE Comorbidity index			
0			36 (33.6)
1			50 (46.7)
2			15 (14.0)
3			6 (5.6)

Characteristic	Mean (SD)	Range	N (%)
Grip strength (mmHg)			
Dominant hand	47.7 (14.4)	10.0–80.0	
Non-dominant hand	45.7 (12.0)	12.0–75.0	
Timed Up and Go (seconds)	10.3 (3.3)	6.0–30.0	

Note: the ACE Comorbidity Index is a tool used to predict survival among various types of patients with cancer based on co-morbidity score.[i]

Table 2:

Correlational Analyses

	Dominant hand grip strength (n=71)	Non-dominant hand grip strength (n=71)	Timed get up and go (n=102)
Age	−.12	−.24*	.21*
Marriage	.12	.19	−.28*
Education	.23	.12	−.23*
Race	.08	.10	.29*
Time since surgery	.12	.11	−.07
Time on current meds	.07	−.01	.02
Time on any meds	.20	.13	−.08
Tamoxifen vs Aromatase inhibitors	−.21	−.05	.09
Surgery Type	−.04	.06	−.19
TNM Stage	−.09	−.06	−.06
Comorbidity (ACE scale)	−.06	−.12	.36*
Fatigue (BFI)	−.21	−.26*	.21*
Pain Intensity (BPI)	−.30*	−.31*	.38*
Vasomotor symptoms (MENQOL)	−.14	−.23	.03
Neurotoxicity (FACT-T)	−.25*	−.23	.11
Symptom Composite (Z score)	−.29*	−.34*	.24*

Note: The following dummy codes were used in analyses: Marriage: 0=Unmarried, 1=Married; Race: 0=White, 1=Non-White; Surgery type: 0=Lumpectomy, 1=Mastectomy; Tam vs. AI: 0=Tamoxifen, 1=AI.

* $p < 0.05$

Table 3:

Regression

Variable	*β*	*t*	*p*
Outcome: Dominant hand grip strength			
Age	−.13	−1.17	.25
Education	.22	1.91	.06
Time on any endocrine therapy (months)	.17	1.46	.15
Tamoxifen vs. Aromatase inhibitors	−.18	−1.62	.11
Symptom Composite	−.27	−2.42	.02
Outcome: Non-dominant hand grip strength			
Age	−.27	−2.40	.02
Education	.11	0.95	.35
Time on any endocrine therapy (months)	.11	0.93	.36
Tamoxifen vs. Aromatase inhibitors	−.01	−0.07	.94
Symptom Composite	−.36	−3.15	.003
Outcome: TUG			
Age	.05	0.52	.60
Married	−.15	−1.56	.12
Education	−.23	−2.55	.01
Race (white=0; non-white=1)	.16	1.65	.10
ACE comorbidity scale	.23	2.26	.03
Symptom Composite	.18	1.97	.05