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Longitudinal relationship between frailty and cognition in patients age 50 years with breast cancer

Allison Magnuson, DO^{a,*}, Lianlian Lei^a, Nikesha Gilmore, PhD^a, Amber S. Kleckner, PhD^a, Feng V. Lin, PhD, RN^a, Robert Ferguson, PhD^b, Arti Hurria, MD^c, Marsha N. Wittink, MD^a, Benjamin T. Esparaz, MD^d, Jeffrey K. Giguere, MD^e, Jamal Misleh, MD^f, Javier Bautista, M.S.^a, Supriya G. Mohile, MD^a, and Michelle C. Janelins, PhD, MPH^{a,*}

^aUniversity of Rochester, Rochester, NY

^bUniversity of Pittsburgh, Pittsburgh, PA

^cCity of Hope, Duarte, CA

^dCancer Care Specialists of Illinois, Decatur, IL

^eGreenville Health System, Greenville, SC

^fChristiana Health Care System, Newark, DE

Abstract

Objective: To evaluate relationships between frailty and cognition longitudinally in adults aged 50 with breast cancer receiving chemotherapy.

Design: Secondary analysis of a prospective, longitudinal observational study.

Participants: Patients with breast cancer aged 50 receiving adjuvant/neoadjuvant chemotherapy (n=376) and age-matched controls without cancer (n=234).

Setting: University of Rochester NCI Community Oncology Research Program community oncology clinics.

Measures: Frailty was assessed using a modified frailty score from self-reported assessments (weakness, exhaustion, physical activity, gait speed). Cognition was assessed by patient-report (Functional Assessment of Cancer Therapy-Cognition [FACT-Cog]) and objective measures. Frailty and cognition were measured at three time-points (pre-chemotherapy [A1], post-chemotherapy [A2], 6-months post-chemotherapy [A3]; similar time interval for controls). Linear regression models evaluated associations between frailty and cognition adjusting for covariates.

*Allison Magnuson, D.O. Department of Medicine, Division of Hematology/Oncology, University of Rochester Medical Center, Wilmot Cancer Institute, 601 Elmwood Ave, Box 704, Rochester, NY 14642, USA, Allison_magnuson@urmc.rochester.edu, P: (585) 276-7155. Michelle C. Janelins, Ph.D., M.P.H. Departments of Surgery, Radiation Oncology and Neuroscience, University of Rochester Medical Center, Wilmot Cancer Institute, 601 Elmwood Ave, Box CU420658, Rochester, NY 14642, USA, michelle_janelins@urmc.rochester.edu, P: (585) 276-4656.

Author contributions

A.M., L.L., N.G., S.G.M., and M.C.J. conceived and designed the study. B.T.E, J.K.G., J.M., and M.C.J. participated in data acquisition. A.M., L.L., N.G., J.B., S.G.M., and M.C.J. analyzed data. A.M., L.L., N.G., A.S.K., F.V.L., R.F., A.H., M.N.W., J.B., S.G.M., and M.C.J. interpreted the data. A.M., L.L., A.S.K., and M.C.J. wrote the manuscript. All authors revised for intellectual content and approved the final version of the manuscript.

Conflict of interest

Results: The average age was 59 years (SD 6.4 years). At baseline patients with cancer had higher mean frailty score (1.21 vs 0.73, $p<0.001$), and lower mean FACT-Cog score (158.4 vs 167.3, $p<0.001$) compared to controls, objective cognitive measures were not statistically different. Longitudinal decline in FACT-Cog between A1 and A2 ($p<0.05$) and between A1 and A3 ($p<0.01$) was associated with increased frailty score in patients compared to controls. Longitudinal worsening in Controlled Oral Word Association ($p<0.05$) and Trail Making Test ($p<0.01$) were associated with increase in frailty between A1 and A2 in patients compared to controls; longitudinal decline in Delayed Match Sample was associated with increase in frailty between A1 and A3 ($p<0.05$) in patients compared to controls. This finding remained significant for a subset analysis of those aged ≥ 65 .

Conclusions: In patients with breast cancer aged ≥ 50 , longitudinal decline in FACT-Cog and objective measures of attention and memory were associated with increased frailty during treatment and up to 6 months post-treatment. Overall, our study suggests cognition and frailty are both important factors to assess in breast cancer patients.

Keywords

frailty; cognition; cognitive impairment; breast cancer; chemotherapy

INTRODUCTION

Frailty is a clinically recognizable syndrome of increased vulnerability associated with adverse clinical outcomes in older adults.¹⁻³ The frailty phenotype is characterized by weakness, low physical activity, exhaustion, slow gait speed, and unintentional weight loss. In patients with cancer, the presence of frailty at the time of cancer diagnosis is predictive of all-cause mortality.^{4,5} Older adults with cancer that are frail or pre-frail are more likely to experience chemotherapy toxicity, to be hospitalized or discontinue chemotherapy treatment.⁶

Although frailty is typically considered in the older adult population, studies in oncology have examined the presence of frailty characteristics in younger cancer survivors due to the physiologic stress that cancer treatment induces.^{7,8} In fact, the prevalence of pre-frailty and frailty has been shown to be similar between younger cancer survivors and adults aged >65 years old who have not had cancer, despite the average age of survivors included in these studies being much younger.^{7,8} Additionally, frail adult survivors of childhood cancer had an increased risk of death and chronic condition onset, as compared to those that were not frail.⁷ Therefore the construct of frailty in cancer survivors who receive chemotherapy is important, even at ages younger than the typical geriatric population.

In the non-cancer setting, the relationship between frailty and cognition has been explored in multiple studies.^{2,9,10} In cross-sectional studies of older adults, higher odds of cognitive impairment have been observed in frail patients as compared to those that are not frail.^{9,10} In a longitudinal study, patients with a greater degree of frailty at baseline had a higher risk of subsequent development of mild cognitive impairment.¹¹ Additionally, greater annual rate of change in frailty is associated with subsequent development of Alzheimer's disease.¹² Physical function and cognitive impairment have been shown to be independent predictors

of incident disability and death in older adults without cancer, and when cognitive measures are added to frailty assessment, the combination was better at identifying vulnerable older adults at risk of future activities of daily living dependence.¹³

Given our aging population, the prevalence of cancer, and the association of cognitive impairment with frailty in older adults, improved understanding of the relationships between frailty and cognition in cancer is critical for managing these risk factors.^{14–17} This analysis evaluates frailty and its relation to cognition longitudinally over the course of adjuvant chemotherapy and up to 6-months post-chemotherapy, in patients with breast cancer aged 50 years old, including both subjective and objective assessments of cognition.¹⁸

METHODS

2.2 Study design and participants

This study is a secondary analysis of data from a nationwide, multicenter, prospective longitudinal study that examined whether chemotherapy is associated with worse cognition in female patients with non-metastatic breast cancer undergoing treatment at community oncology clinics associated with the University of Rochester Cancer Center (URCC) National Cancer Institute Community Oncology Research Program (NCORP).^{19,20} Eligible subjects had a diagnosis of invasive breast cancer, stage I to stage IIIC disease, were chemotherapy naïve, and were scheduled to begin adjuvant or neoadjuvant chemotherapy. Subjects were excluded if they had metastatic disease, a prior diagnosis of neurodegenerative disease, currently pregnant, hospitalized within the past year for psychiatric illness, or were receiving concurrent radiation therapy. Age-matched non-cancer control participants were also recruited from the same geographic location as patients.¹⁹ The current study evaluated participants from the parent study that were aged 50 years old with complete data for cognitive assessment and frailty characteristics. We focused our analysis on subjects aged 50 years and over to include mainly post-menopausal subjects who may be more vulnerable to frailty. Institutional review boards at the URCC NCORP Research Base and each of the NCORP Community Affiliates approved the study. All subjects provided informed consent before entering the study.

2.2 Measures

Clinical and demographic information was collected by research coordinators. Measures at three time points were assessed: 1) within seven days before chemotherapy (pre-chemotherapy baseline; assessment 1 [A1]); 2) within 4 weeks of completion of chemotherapy (post-chemotherapy; assessment 2 [A2]); and 3) six-months after A2 (six month follow-up; assessment 3 [A3]). Controls completed study assessments within the same time windows as the patients with breast cancer.

Frailty Assessment—The frailty assessment was based upon the Fried frailty phenotype, which has previously been described as a clinical syndrome involving self-reported exhaustion, weakness, slow walking speed, low physical activity, and/or unintentional weight loss.² We approximated frailty by creating a modified Fried frailty score based on four of five self-report measures: 1) exhaustion and 2) weakness, were measured using the

symptom inventory questionnaire (impaired defined as score ≥ 4 on scale 1–10); 3) walk speed and 4) physical activity were measured using the Aerobics Center Longitudinal Study (ACLS) questionnaire with impaired gait speed defined as “casual or strolling” (2 mph) and impaired physical activity defined as <150 minutes per week of physical activity. The frailty score was the sum of the 4 scales yielding (range 0–4), with higher scores reflecting a greater number of frailty characteristics. Prior studies investigating frailty have demonstrated the ability to assess frailty using self-report measures^{21,22} or modification of the traditional frailty assessment components.^{23,24} Unintentional weight loss was not consistently assessed at follow-up time points and could not be evaluated longitudinally; thus it was not included in the modified frailty score. Prior studies have demonstrated that patients with breast cancer receiving adjuvant chemotherapy do not experience significant change in weight over the course of treatment,²⁵ thus it was felt that omitting weight from the frailty approximation would not influence the longitudinal change in frailty significantly.

Cognitive Assessment—Perceived cognition was assessed using the Functional Assessment of Cancer Therapy (FACT-Cog) version 2, a validated measure to evaluate cognitive complaints related to cancer therapy.²⁶ The FACT-Cog consists of four subscales that assess different facets of self-reported cognitive function. An overall cognitive function score (total FACT-Cog) was calculated as the sum of the four subscales, with smaller values implying greater cognitive difficulties. For our analysis, we compared patients with a lower than median value (“worse” subjective cognitive assessment) versus greater than median value (“better” subjective cognitive assessment).

Objective cognitive function was assessed using computerized cognitive assessments as well as paper-based neuropsychological assessments. The Cambridge Neuropsychological Test Battery (CANTAB) software was used for computerized assessment in specific cognitive domains; tests included delayed match to sample test (DMS) at the 12-second delay, a measure of visual memory, and the Rapid Visual Processing (RVP), an evaluation of sustained attention.²⁷ Paper-based assessments included the Controlled Oral Word Association test (COWA), a test assessing verbal fluency,²⁸ the Trail Making Test (TMT), an assessment of attention (the CTMT trail 1 was used),^{29,30} and Hopkins Verbal Learning and Memory Test-Revised (HVLT-R), a measure of verbal memory.^{31,32}

2.3 Statistical Analysis

The aim of this study was to assess longitudinal change in frailty in patients with breast cancer receiving curative intent chemotherapy, and whether baseline cognition, as well as longitudinal change in cognition, were associated with change in frailty post-treatment in patients with breast cancer receiving chemotherapy compared to controls.

Descriptive analyses—For comparison of baseline characteristics of patients with breast cancer and controls, t-tests were used for continuous variables and Chi square tests were used for categorical variables. Characteristics included age (50–64 versus ≥ 65 years), race (Caucasian versus other), marital status (married versus other), education (some college versus high school), Karnofsky performance status (≥ 70 versus <70), frailty score (0–4, continuous), total FACT-Cog score (continuous), anxiety (State Trait Anxiety Inventory

[STAI] continuous), depression (Multidimensional Fatigue Symptom Inventory [MFSI] question #21 “I feel depressed”, continuous with 0–4 indicating “not at all” to “very much”), and objective cognitive assessment measure scores (CANTAB DMS and RVP, COWA, TMT, HVLT-R; all continuous). Means and standard deviations were calculated for all continuous variables. Differences between cancer and control groups in dichotomous characteristics were compared using a Chi-square test; differences in continuous characteristics were compared using a t-test. Change in scores over time was assessed by unadjusted mean change analysis of the change in frailty and cognitive measures from A1 to A2 and A1 to A3 (similar time interval for controls) to show overall trajectories of the population in frailty and cognitive outcomes. Differences in the change over time between cancer and control groups were compared using a t-test.

Regression analysis—Linear regression models were used to evaluate the association between frailty and cognition, controlling for age, race, marital status, education, performance status, anxiety, depression and baseline frailty score. Separate models were utilized to assess each of the cognitive measures to evaluate the independent association with change in frailty. We explored the association of baseline cognition with change in frailty between A1 to A2 and A1 to A3. We also tested the association of change in cognition with change in frailty score between A1 to A2 and A1 to A3.

Computations were performed using SAS, version 9.4 (SAS Institute, Cary, NC). $P < 0.05$ was used to assess statistical significance.

RESULTS

Baseline Characteristics

The parent study enrolled 964 subjects, of which 945 were evaluable. For this sub-study, we excluded subjects age < 50 years, leaving 610 patients in our analysis (376 patients with breast cancer, 234 age-matched controls; Supplemental Figure 1)

The mean age of the study population was 59.36 (SD 6.42), and mean age was similar between cancer and control groups. There were more subjects in the control group with higher education (some college or above). The population included 7.9% non-Caucasian subjects, with more in the breast cancer group than in the control group (Table 1).

Prior to chemotherapy, patients with breast cancer had a higher mean frailty score than controls (mean \pm SD: 1.21 \pm 1.10 versus 0.73 \pm 0.85, $p < 0.001$). Also at baseline, FACT-Cog scores were lower in patients with breast cancer compared to controls (mean \pm SD: 158.4 \pm 26.3 versus 167.3 \pm 20.1, $p < 0.001$), although there was no significant difference in objective neuropsychological measures (Table 1).

Unadjusted Longitudinal Analyses in Frailty and Cognition

In an unadjusted change score analysis to assess overall trends of the data in our sub-study of patients and controls 50, patients with breast cancer had an increase in mean frailty score between A1 to A2, whereas controls did not experience a change in frailty score across a similar time frame ($p < 0.001$; Figure 1a). Mean frailty score for breast cancer patients

improved at A3, although remained greater than control patients (1.34 in breast cancer patients versus 0.74 in controls, $p=0.099$ [Figure 1a]). Patients with breast cancer also reported worsening of perceived cognition between A1 and A2 as well as from A1 to A3, whereas controls did not experience a decline over the same timeframes ($p<0.001$ for both; Figure 1b). Patients with worse perceived cognition (e.g., those with FACT-Cog below the median) had higher frailty scores as compared to patients reporting better perceived cognition at A1, A2, and A3 ($p<0.001$ for all time points; Figure 2).

In an unadjusted change score analysis to assess overall trends of the data in our cognitive sub-study of patients and controls $n=50$, patients with cancer experienced a decline in COWA score as compared to controls at A2 ($p<0.001$); however at A3, scores were similar between the two groups ($p=0.929$; Figure 1c). On computerized neuropsychological testing, both the DMS and RVP were similar between patients with cancer at A2 ($p=0.802$ for DMS and $p=0.191$ for RVP), however began to diverge by A3, with patients having worse scores compared to controls compared to A1 ($p=0.05$ for DMS [Figure 1e] and $p=0.01$ for RVP [Figure 1f]). Overall, in unadjusted analyses, TMT and HVLTL mean score changes from A1 to A2 and A1 to A3 did not differ between the two groups (Figure 1d).

Associations between baseline cognitive measures and longitudinal change in frailty:

Adjusted Analyses

In linear regression models evaluating the association between baseline cognitive measures with the change in frailty score controlling for baseline covariates, lower baseline FACT-Cog was associated with increase in frailty score between A1 to A2 and A1 to A3 ($p<0.05$ for A1 to A2 and $p<0.01$ for A1 to A3, Supplemental Table 1 and Supplemental Table 2). For objective cognitive assessment measures using a linear regression model controlling for baseline covariates, there was no association between any of the baseline objective cognitive measures and change in frailty score between A1 to A2. Lower baseline CANTAB RVP score was significantly associated with increase in frailty score between A1 to A3 ($p<0.01$, Supplemental Table 1 and Supplemental Table 2).

Associations between longitudinal change in cognitive measures and longitudinal change in frailty: Adjusted Analyses

In a separate model, evaluating the association between longitudinal change in cognitive measures with longitudinal change in frailty score, also controlling for baseline covariates, change in FACT-Cog, change in COWA, and change in TMT were significantly associated with change in frailty score between A1 and A2 ($p<0.05$ for FACT-Cog, $p<0.05$ for COWA and $p<0.01$ for TMT) where greater perceived cognitive impairment and worse cognitive function on objective tests were observed with increasing frailty. Between A1 and A3, change in FACT-Cog and change in CANTAB DMS were significantly associated with change in frailty score ($p<0.01$ for FACT-Cog and $p\leq 0.05$ for DMS), where the association between change in frailty and change in COWA remained a trend ($p=0.104$). (Tables 2 and 3)

Additionally, we performed a subset analysis of patients aged ≥ 65 to evaluate the associations between longitudinal change in cognitive measures and frailty in this population

specifically (N= 133). Between baseline and post-chemotherapy in patients aged ≥ 65 , change in frailty was not associated with change in FACT-Cog score, however in this smaller group of patients association with multiple objective measures was observed at the $p < 0.1$ level (COWA, CANTAB DMS, CANTAB RVP and TMT; data not shown). Between baseline and 6-months post-chemotherapy, the association between change in frailty and change in CANTAB DMS score remained ($p < 0.05$).

DISCUSSION

Using a modified Fried frailty index, we found that frailty characteristics are common among patients with breast cancer aged ≥ 50 years even before receiving adjuvant chemotherapy, and mean frailty scores in this population were higher than age-matched controls. We also observed that frailty characteristics increased from pre- to post-chemotherapy in breast cancer patients, as compared to non-cancer controls. Although frailty scores in breast cancer patients improved at A3, mean frailty remained greater than age-matched non-cancer controls even six months after completion of chemotherapy compared to the control time-equivalent assessment. Within this cohort, subjects with worse perceived cognition at baseline had higher frailty scores at baseline and both follow-up time points when compared to patients with better subjective cognitive function at baseline. Baseline score on the CANTAB RVP was associated with change in frailty at 6-months post-treatment. Additionally, patients who experienced decline in FACT-Cog, as well as decline in COWA and TMT between A1 and A2 were more likely to develop increased frailty over the course of treatment. The association between change in FACT-Cog with change in frailty persisted even to 6-month post-chemotherapy completion, and decline in CANTAB DMS was also associated change frailty at 6-months post-chemotherapy completion. Although there was a more dramatic difference between patients with cancer and controls in perceived cognition as compared to objective measures, this is consistent with several prior studies^{33–36} and is likely because perceived cognition captures perceptions of global cognitive functioning whereas objective measures target functioning in specific cognitive domains. A subset analysis of patients aged ≥ 65 demonstrated that although perceived cognition was not associated with change in frailty in this group, there was a trend towards association between change in several objective cognitive measures and change in frailty. We have previously observed that younger age was predictive of problems with perceived cognition.¹⁹ This may be that patients < 65 are more aware or more likely to report cognitive problems. Alternatively, the FACT-Cog was developed based upon qualitative work in a younger population of patients³⁷ and thus may not fully capture cognitive complaints of older adults. This finding also emphasizes the potential importance of using objective cognitive assessments in this population, as opposed to relying on self-report measures alone. It should also be noted that the smaller number of patients aged ≥ 65 may limit the interpretation of this finding as well.

The relationship between frailty and cognition has been evaluated in breast cancer survivors in two prior studies.^{38,39} In the first, investigators used group-based trajectory modeling to identify the trajectories of cognitive and physical function and determined that patients who were frail were more likely to be in the accelerated cognitive decline or the phase shift group (declines that are shifted below but parallel to mild decline). Additionally, patients receiving

chemotherapy were more likely to be in the accelerated cognitive decline group compared to survivors who did not receive chemotherapy.³⁸ Investigators also observed that oncology patients who were frail at baseline were more likely to report subjective cognitive decline with longitudinal follow-up. Comparing this to our results, we identified that patients who had worse perceived cognition at baseline had greater frailty scores, further strengthening the connection between cognition and frailty in this population of patients. In the second study, also by Mandelblatt and colleagues,³⁹ breast cancer patients aged 60 were compared to matched controls without cancer and assessment included perceived and objective cognitive measures at baseline and 12 and 24 months. Frailty was also assessed in this study at baseline using an adapted Searle's deficits accumulation index. Investigators determined that, at baseline, frailty was associated with impairment on neuropsychological tests measuring attention, processing speed, and executive function as well as self-reported decline in cognition. In our study, we also observed an association between frailty and perceived cognition as well as an association between change in frailty and change in objective measures in TMT which assesses attention, and CANTAB RVP which assesses sustained attention. Taken together, this suggests that interventions focusing in the area of attention and memory may be potential considerations to mitigate the development of cognitive and frailty problems with cancer treatment.

Although frailty is typically studied in older adult populations, we elected to use a lower age cutoff for inclusion onto our study. Prior studies have demonstrated greater than expected rates of frailty in populations of adult survivors of childhood cancers⁷ and breast cancer survivors several years after treatment,⁴⁰ thus we suspected that frailty may be a relevant issue in breast cancer patients younger than 65 years old. Indeed, we observed that despite including a "younger" population on average, frailty characteristics were prevalent and mean frailty scores were higher in cancer patients compared to controls, even prior to treatment. This finding reinforces that these issues of cognition and frailty, which are typically considered aging-related, can be reported by patients and identified objectively earlier in the lifespan for individuals receiving chemotherapy. This finding is relevant for geriatricians and other providers caring for patients with a prior history of cancer, particularly those who received chemotherapy, as they may exhibit accelerated aging phenotypes in the areas of frailty and cognition if these issues are manifesting earlier in their lifespan.

There are several strengths of this study. First, we included validated cognitive measures to provide a comprehensive assessment of cognition. Also, we utilized a large primary dataset that enrolled patients nationwide from community oncology practices, so our results are generalizable to other community oncology practices across the United States. Additionally, our study included a larger number of patients receiving chemotherapy compared to prior studies on frailty and cognition in the oncology setting, further adding to the evidence base on this issue. We also included assessments at multiple time points. Cognitive assessments may have practice effects with repeated administration^{20,41} and therefore comparing longitudinal change between patients and controls accounted for this effect.

There are limitations to this work. We developed a modified Fried frailty index which is not a validated measure of frailty and did not account for weight change as this information was not available in our dataset. Ideally, frailty evaluation would include this information,

although we observed a significant degree of frailty characteristics in our population even without this metric. Additionally, we did not include an objective measure of frailty such as grip-strength, and reliance on self-report measures of frailty is a limitation of this study. The objective cognitive measures used in our study are not tools that are typically used by oncologists or geriatricians (such as the Montreal Cognitive Assessment or Mini-Mental Status Exam). However, perceived cognition could be assessed in a clinical setting and given that perceived cognition was more strongly associated with frailty in our study and others, assessing perceived cognition in clinical practice should be considered. Additionally, this study suggests that cognitive measures based in cognitive neuroscience and neuropsychological assessment may be useful for geriatricians and geriatric oncologists to consider.

In conclusion, in this secondary analysis of a large nationwide study of cognition in breast cancer patients, we determined that breast cancer patients age 50 years old had higher mean frailty scores compared to age-matched non-cancer controls both prior to and following adjuvant chemotherapy and up to six months post-chemotherapy. Within this cohort, patients with worse subjective cognition at baseline had a higher degree of frailty at pre- and both post-treatment time points. Additionally, longitudinal increase in frailty characteristics was associated with longitudinal decline in self-reported cognition, COWA, TMT and DMS tests over the same time frame. Given that frailty is a known risk factor for older patients, and our results showing that cognitive problems are associated with frailty, consideration of this phenotype developing earlier needs to be considered for all clinicians treating patients with breast cancer. Interventions are needed to minimize the progression of frailty and cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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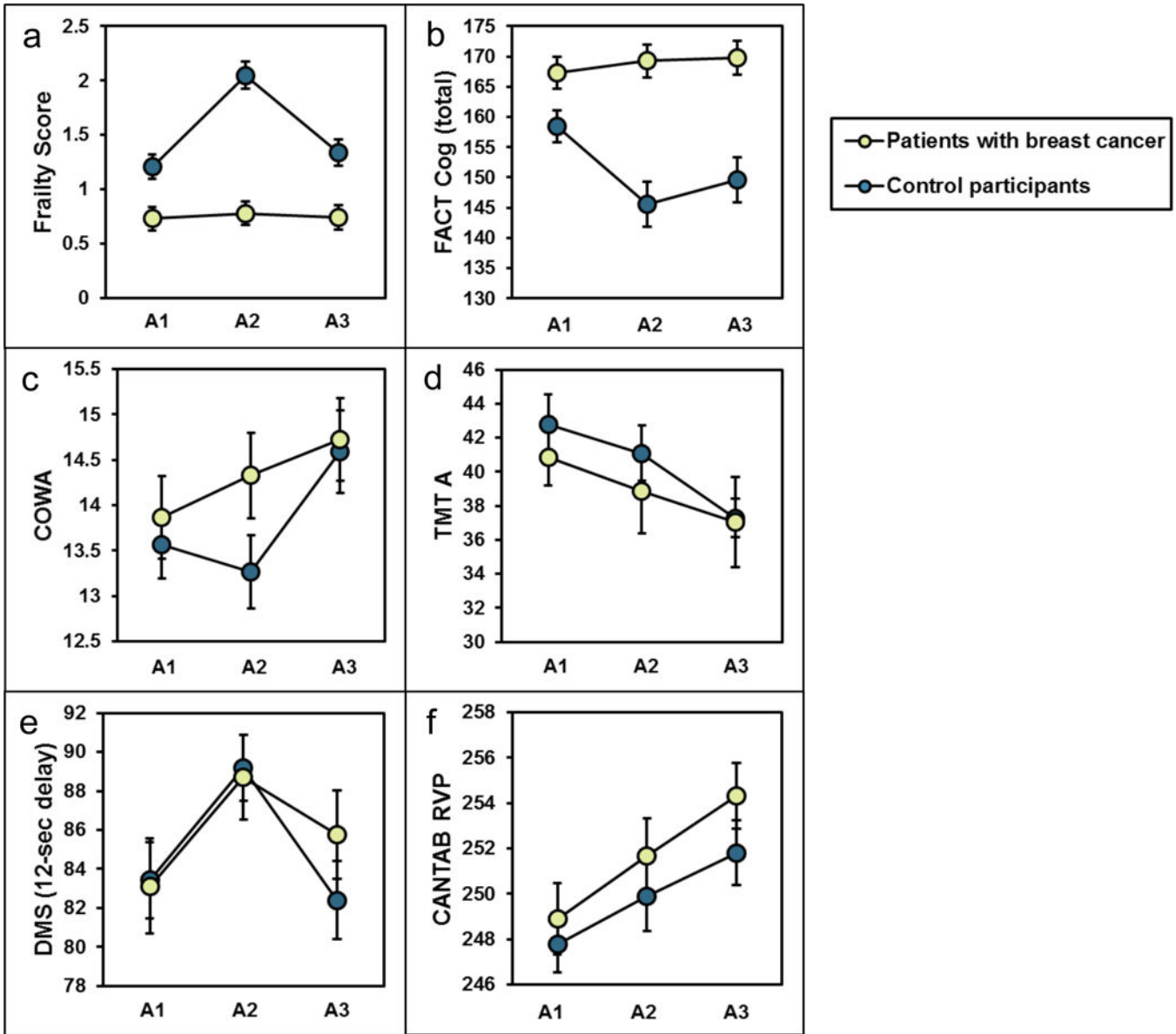


Figure 1: Pre- and post- treatment data for (a) frailty, (b) Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) total score, (c) the Controlled Oral Word Association (COWA) test, (d) the Trail Making Test (TMT) A scores, and (e) Delayed Match to Sample (DMS) at the 12-second delay and (f) Rapid Visual Processing (RVP) in breast cancer patients (dark gray) age 50 years versus age-matched non-cancer controls (light gray).

The data points show the unadjusted mean and the 95% confidence interval. A1: pre-chemotherapy, A2: post-chemotherapy, A3: six months post-chemotherapy. Lower scores indicate lower performance on FACT-Cog, COWA, DMS, and RVP. Higher scores indicate lower performance on the Frailty Score and TMT.

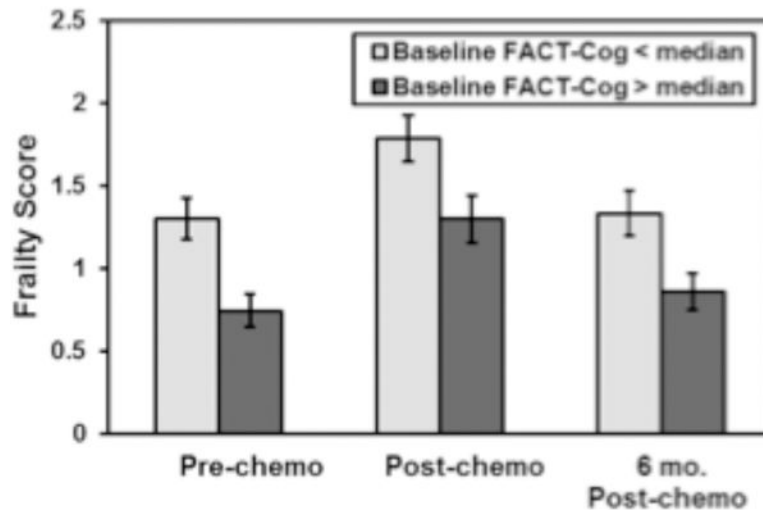


Figure 2: Follow-up frailty scores in subjects with greater than versus less than median baseline FACT-Cog score.

The values show the mean frailty score based on FACT-Cog above or below the median at each timepoint. Please note that a lower score on the FACT-Cog indicates worse perceived cognitive abilities.

Table 1:

Baseline characteristics

Characteristic	Statistic	All patients	Breast Cancer	Non-Cancer Control	P-value*
Age (range 50-81)	Mean (SD)	59.36 (6.42)	59.70 (6.48)	58.82 (6.30)	0.100
50-64	N (%)	471 (77.21)	284 (75.53)	187 (79.91)	0.210
65	N (%)	139 (22.79)	92 (24.47)	47 (20.09)	
Race					0.009
White	N (%)	562 (92.13)	338 (89.89)	224 (95.73)	
Other	N (%)	48 (7.87)	38 (10.11)	10 (4.27)	
Marital status					0.113
Married	N (%)	431 (70.66)	257 (68.35)	174 (74.36)	
Other	N (%)	179 (29.34)	119 (31.65)	60 (25.64)	
Education					0.001
Some college	N (%)	474 (77.70)	276 (73.40)	198 (84.62)	
High school	N (%)	136 (22.30)	100 (26.60)	36 (15.38)	
Karnofsky Performance Status					0.526
70	N (%)	606 (99.67)	372 (99.47)	234 (100)	
<70	N (%)	2 (0.33)	2 (0.53)	0 (0)	
Menopausal status					
Post-menopausal or medically induced menopause	N (%)	527 (86.39)	326 (86.70)	201 (85.90)	0.778
Pre-menopausal or peri-menopausal	N (%)	83 (13.61)	50 (13.30)	33 (14.10)	
Anxiety (STAI)	Mean (SD)	32.02 (11.51)	34.80 (12.10)	27.59 (8.87)	<0.001
Depression (single item from MFSI)	Mean (SD)	0.56 (0.85)	0.67 (0.89)	0.37 (0.73)	<0.001
Frailty score (range 0-4)	Mean (SD)	1.02 (1.04)	1.21 (1.10)	0.73 (0.85)	<0.001
Total FACT-Cog score	Mean (SD)	161.8 (24.50)	158.4 (26.32)	167.3 (20.10)	<0.001
COWA	Mean (SD)	13.68 (3.61)	13.56 (3.65)	13.86 (3.56)	0.319
CANTAB DMS	Mean (SD)	83.31 (19.00)	83.42 (19.12)	83.12 (18.85)	0.848
CANTAB RVP	Mean (SD)	248.2 (12.08)	247.8 (12.07)	248.9 (12.08)	0.273
TMT (CTMT 1)	Mean (SD)	42.03 (16.06)	42.76 (17.71)	40.87 (12.92)	0.129
HVLT-R immediate recall	Mean (SD)	8.85 (1.60)	8.77 (1.72)	8.98 (1.37)	0.088
HVLT-R delayed recall	Mean (SD)	9.80 (2.27)	9.69 (2.39)	9.97 (2.06)	0.132

Footnote:

* The Chi-square test was used to compare the differences in age, race, marital status, education and menopausal status between cancer and control groups. Fisher's Exact test was used to compare the differences in performance status between the cancer and control groups. A t-test was used to compare the differences in anxiety, depression, frailty score, total FACT-Cog score, COWA, CANTAB DMS, CANTAB RVP, TMT A, HVLTR average, and HVLTR delayed recall between cancer and control groups.

STAI, State Trait Anxiety Inventory; MFSI, Multidimensional Fatigue Symptom Inventory; FACT-Cog, Functional Assessment of Cancer Therapy; COWA, Controlled Oral Word Association test; CANTAB, Cambridge Neuropsychological Test Battery; DMS delayed match to sample test; RVP, Rapid Visual Processing; TMT, Trail Making Test; HVLTR, Hopkins Verbal Learning and Memory Test-Revised.

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Table 2:

Association of Cognition and Frailty among Breast Cancer Patients and Controls: Change in Cognition and Change in Frailty Score between Baseline and Post-chemotherapy

Variables	Change in Frailty Score between Baseline and Post-chemotherapy						
Change in total FACT-Cog score	-0.003** (0.002)						
Change in COWA	-0.037** (0.017)						
Change in CANTAB DMS	-0.000 (0.002)						
Baseline CANTAB RVP	0.001 (0.004)						
Baseline TMT	0.008*** (0.003)						
Baseline HVLTR immediate	-0.009 (0.034)						
Baseline HVLTR delayed recall	-0.000 (0.025)						
Baseline Frailty Score	-0.635*** (0.044)	-0.647*** (0.044)	-0.641*** (0.044)	-0.649*** (0.045)	-0.643*** (0.044)	-0.643*** (0.044)	-0.641*** (0.044)
Cancer Patient (Yes=1)	1.034*** (0.097)	1.077*** (0.092)	1.095*** (0.093)	1.102*** (0.094)	1.089*** (0.091)	1.103*** (0.092)	1.112*** (0.093)
Age (>=65)	0.125 (0.104)	0.080 (0.103)	0.096 (0.104)	0.086 (0.104)	0.068 (0.102)	0.089 (0.103)	0.070 (0.104)
Race (White=1)	0.031 (0.168)	0.059 (0.165)	0.055 (0.166)	0.057 (0.167)	0.051 (0.164)	0.057 (0.165)	0.073 (0.166)
Marital Status (Married=1)	-0.198** (0.096)	-0.212** (0.095)	-0.227** (0.096)	-0.244** (0.098)	-0.237** (0.095)	-0.219** (0.095)	-0.218** (0.096)
Education (Some College or Above=1)	0.123 (0.106)	0.160 (0.104)	0.162 (0.106)	0.177* (0.107)	0.139 (0.104)	0.159 (0.105)	0.126 (0.105)
KPS (>=70)	-0.700 (0.719)	-0.564 (0.718)	-0.655 (0.725)	-0.657 (0.726)	-0.620 (0.715)	-0.650 (0.720)	-0.674 (0.716)
Baseline anxiety (STAI)	-0.003 (0.005)	-0.002 (0.005)	-0.003 (0.005)	-0.003 (0.005)	-0.001 (0.005)	-0.002 (0.005)	-0.003 (0.005)
Baseline depression (MFSI)	0.125* (0.065)	0.116* (0.065)	0.123* (0.067)	0.126* (0.067)	0.123* (0.066)	0.116* (0.065)	0.109* (0.066)
Constant	1.243 (0.774)	1.070 (0.772)	1.171 (0.780)	1.190 (0.782)	1.143 (0.770)	1.144 (0.776)	1.190 (0.770)
Obs	568	570	565	560	568	570	555
R-squared	0.370	0.374	0.364	0.367	0.376	0.369	0.373

Footnote: Linear regression models were used to evaluate the association between frailty and cognition, controlling for age (50–64 versus 65 years), race (Caucasian versus other), marital status (married versus other), education (some college versus high school), performance status (>70 versus <70), baseline anxiety (STAI), baseline depression (MSFI) and baseline frailty score. Standard errors are reported in brackets.

* significant at 10%;

** significant at 5%;

*** significant at 1%.

[†] significant at 11%.

STAI, State Trait Anxiety Inventory; MFSI, Multidimensional Fatigue Symptom Inventory; FACT-Cog, Functional Assessment of Cancer Therapy; COWA, Controlled Oral Word Association test; CANTAB, Cambridge Neuropsychological Test Battery; DMS delayed match to sample test; RVP, Rapid Visual Processing; TMT, Trail Making Test; HVLIT-R, Hopkins Verbal Learning and Memory Test-Revised.

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Table 3:

Association of Cognition and Frailty among Breast Cancer Patients and Controls: Change in Cognition and Change in Frailty Score between Baseline and Six Months Post-chemotherapy

Variables	Change in Frailty Score between Baseline and 6 Months Post-chemotherapy						
Change in total FACT-Cog score	-0.010 ^{***} (0.002)						
Change in COWA	-0.024 [†] (0.015)						
Change in CANTAB DMS	-0.004 ^{**} (0.002)						
Baseline CANTAB RVP	0.001 (0.004)						
Baseline TMT	-0.002 (0.003)						
Baseline HVLTR immediate	-0.037 (0.032)						
Baseline HVLTR delayed recall	-0.023 (0.023)						
Baseline Frailty Score	-0.584 ^{***} (0.041)	-0.580 ^{***} (0.042)	-0.582 ^{***} (0.042)	-0.582 ^{***} (0.043)	-0.579 ^{***} (0.042)	-0.580 ^{***} (0.042)	-0.574 ^{***} (0.043)
Cancer Patient (Yes=1)	0.203 ^{**} (0.086)	0.342 ^{***} (0.086)	0.305 ^{***} (0.086)	0.327 ^{***} (0.087)	0.340 ^{***} (0.086)	0.342 ^{***} (0.086)	0.349 ^{***} (0.087)
Age (>=65)	-0.037 (0.094)	-0.100 (0.097)	-0.120 (0.098)	-0.100 (0.099)	-0.086 (0.097)	-0.098 (0.097)	-0.101 (0.099)
Race (White=1)	-0.312 [*] (0.161)	-0.179 (0.164)	-0.239 (0.164)	-0.214 (0.166)	-0.193 (0.165)	-0.212 (0.165)	-0.171 (0.168)
Marital Status (Married=1)	-0.131 (0.088)	-0.200 ^{**} (0.090)	-0.172 [*] (0.091)	-0.189 ^{**} (0.093)	-0.201 ^{**} (0.090)	-0.197 ^{**} (0.090)	-0.213 ^{**} (0.092)
Education (Some College or Above=1)	-0.159 [*] (0.096)	-0.130 (0.099)	-0.139 (0.099)	-0.115 (0.100)	-0.127 (0.099)	-0.133 (0.099)	-0.149 (0.100)
KPS (>=70)	1.134 [*] (0.638)	1.301 ^{**} (0.661)	1.203 [*] (0.657)	1.201 [*] (0.663)	1.242 [*] (0.661)	1.210 [*] (0.660)	1.218 [*] (0.662)
Baseline anxiety (STAI)	0.006 (0.005)	0.004 (0.005)	0.003 (0.005)	0.002 (0.005)	0.003 (0.005)	0.004 (0.005)	0.004 (0.005)
Baseline depression (MFSI)	0.100 [*] (0.059)	0.089 (0.062)	0.105 [*] (0.062)	0.110 [*] (0.063)	0.096 (0.062)	0.094 (0.062)	0.073 (0.062)
Constant	-0.320 (0.692)	-0.516 (0.717)	-0.350 (0.713)	-0.381 (0.720)	-0.465 (0.718)	-0.370 (0.717)	-0.437 (0.719)
Obs	542	545	538	533	544	545	530
R-squared	0.322	0.276	0.282	0.273	0.273	0.274	0.275

Footnote: Linear regression models were used to evaluate the association between frailty and cognition, controlling for age (50–64 versus 65 years), race (Caucasian versus other), marital status (married versus other), education (some college versus high school), performance status (>70 versus <70), baseline anxiety (STAI), baseline depression (MSFI) and baseline frailty score. Standard errors are reported in brackets.

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