Original Article

Pretreatment Psychoneurological Symptoms and Their Association With Longitudinal Cognitive Function and Quality of Life in Older Breast Cancer Survivors

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Abstract

Context. Symptoms affect quality of life (QOL), functional status, and cognitive function in cancer survivors, but older survivors are understudied.

Objectives. The objectives of this study were to identify prototypical presystemic therapy psychoneurological symptom clusters among older breast cancer survivors and determine whether these symptom clusters predicted cognition and QOL over time.

Methods. Women with newly diagnosed nonmetastatic breast cancer ($n = 319$) and matched noncancer controls ($n = 347$) aged 60+ years completed questionnaires and neuropsychological tests before systemic therapy and 12 and 24 months later. Latent class analysis identified clusters of survivors based on their pretherapy depression, anxiety, fatigue, sleep disturbance, and pain. Linear mixed-effects models examined changes in objective cognition, perceived cognition, and functional status (Instrumental Activities of Daily Living disability, functional well-being, and breast cancer–specific QOL) by group, controlling for covariates.

Results. Nearly one-fifth of older survivors were classified as having high pretherapy symptoms ($n = 51$; 16%); the remainder had low symptoms ($n = 268$; 84%); both groups improved over time on all outcomes. However, compared to the low symptom group and controls, survivors with high symptoms had lower baseline objective cognition and lower perceived cognition at baseline and 24 months, lower functional well-being at baseline and 12 months, greater Instrumental Activities of Daily Living disability at baseline, and lower breast cancer–specific QOL at all time points (all $P < 0.05$).

Conclusion. Nearly one-fifth of older breast cancer survivors had high psychoneurological symptoms at diagnosis, which predicted clinically meaningful decrements in perceived cognition and function in the first 24 months after diagnosis. Pretreatment psychoneurological symptom clusters could identify survivors for monitoring or intervention. J Pain Symptom Manage 2019;57:596–606. © *2018 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

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Key Words
Symptoms, symptom cluster, geriatric assessment, cognition, quality of life

Introduction

Anxiety, depression, fatigue, sleep disturbance, and pain are prevalent and distressing psychoneurological symptoms[1–4] that have individually been associated with cognitive problems such as difficulties with concentration, decision making, and memory in cancer survivors.[5-7] Older survivors may be at particularly high risk for these symptoms, as well as adverse cognitive function and quality of life (QOL) outcomes due to concurrent forces of aging, comorbid conditions, and risk for neurodegeneration.[7,8] Psychoneurological symptoms often co-occur, or cluster, and their combined effects on QOL can be greater than the sum of their individual effects.[9–17] Psychoneurological symptom clusters and cognitive problems appear to share some common underlying mechanisms such as proinflammatory cytokines, hormone dysregulation, and genetic vulnerabilities.[10–12,14,18–20] These observations lead some to suggest that cognitive problems are part of the psychoneurological symptom cluster[10,14]; however, psychoneurological symptoms before systemic treatment may be a risk factor for subsequent cognitive dysfunction as well as poor QOL.[6,7] Cancer survivors, especially older cancer survivors (ages 60+ years), are particularly concerned about cognitive problems as an outcome of their health conditions.[2,21,22]

Despite the fact that 74% of the 15.5 million U.S. cancer survivors are aged 60 years and older,[23] there is a paucity of symptom research focused on older survivors. An early study in this area found that older breast cancer survivors have significantly greater anxiety, depression, and fatigue before systemic cancer treatment than matched cancer-free controls at the same time point.[24] Although these symptoms were not associated with baseline objective cognitive function,[24] the longitudinal relationships between pretreatment psychoneurological symptom clusters and subsequent cognitive functioning, functional status, and QOL have yet to be examined. This evidence would be important for identifying subgroups of older breast cancer survivors who may be at risk for poor functional outcomes, to inform potential intervention targets and survivorship care planning for older survivors as they age.

We used data from the longitudinal Thinking and Living with Cancer study of older breast cancer survivors and matched cancer-free controls to address these knowledge gaps.[24] In this report, we evaluate whether presystemic treatment symptom clusters are associated with cognition and QOL outcomes over time. We hypothesized that older survivors with high pretreatment symptoms would have worse objective and perceived cognitive function, greater functional disability, and poorer breast cancer-specific QOL relative to those with low symptoms and matched noncancer controls.

Methods

This is a secondary analysis of data from the longitudinal multisite Thinking and Living with Cancer study, which was established to examine cognitive function in older breast cancer survivors.[24] Participants included in the current analyses were recruited from five sites from August 2010 to December 2015; recruitment and follow-up are ongoing. The research protocol was registered at ClinicalTrials.gov (#NCT03451383), met Health Insurance Portability and Accountability standards, and was approved by all institutional review boards.

Participants

Participants were aged ≥60 years and fluent in English. Survivors were newly diagnosed with primary nonmetastatic breast cancer (Stages 0–III). Controls were frequency-matched to survivors based on age (in five-year groups), race (i.e., white, black/African American, Hispanic, and Asian American/Pacific Islander), education (i.e., ≤high school, some college+), and site. Participants were excluded if they had a stroke, head injury, major psychiatric disorder or neurodegenerative disorder, prior chemotherapy or hormonal therapy, or treatment for another cancer within the past five years. Those taking psychoactive medications were eligible if the dose was stable for at least two months before enrollment.

Among those eligible, 36.2% of survivors and 97.6% of controls consented (Fig. 1). Survivors' consent rates varied across sites from 17.2% to 72.7% (median 62.5%), with the lowest consent rate at a large urban cancer center that had many competing research studies. Participants were screened after informed consent to ensure ability to complete the study and were ineligible if they scored <24 on the Mini–Mental State Examination or <3rd grade on the Wide Range Achievement Test–fourth Edition (WRAT-4); one survivor and one control were excluded for these reasons. The analytic sample included 319 breast cancer survivors and 347 controls.

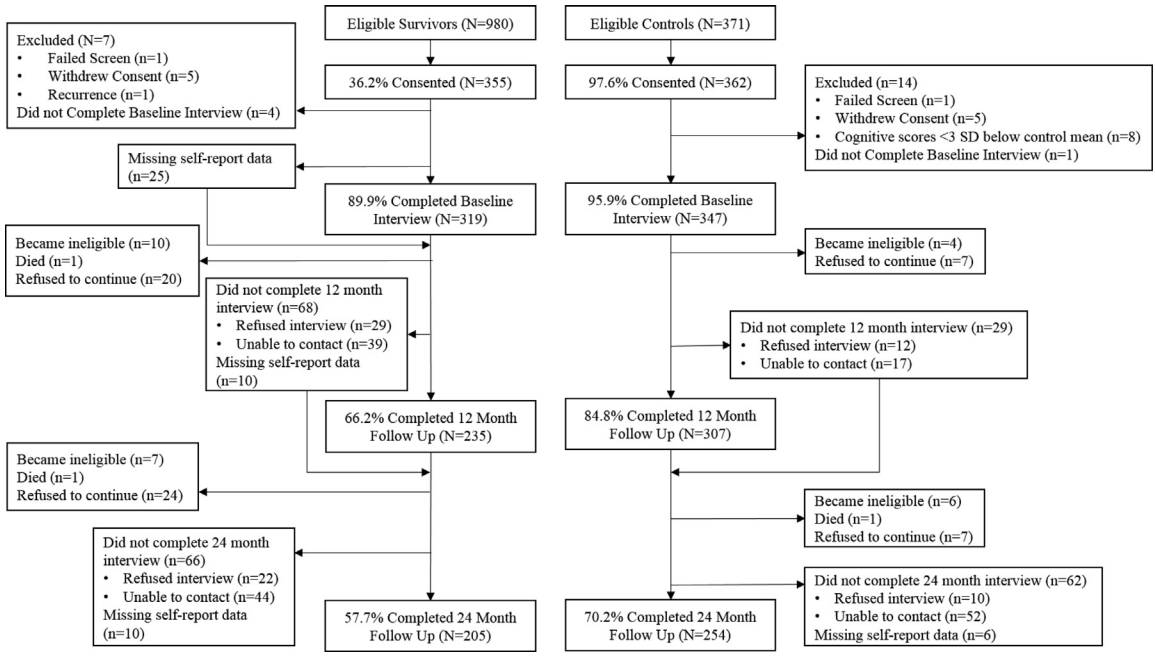

Fig. 1. Study flowchart. Those who did not complete an assessment or have missing self-report data remain eligible to complete the next assessment unless they refuse to continue study participation.

Data Collection

Data collection procedures have been described previously.[24] Survivors completed baseline assessment before radiation or systemic therapy and after surgery (except for seven treated with neoadjuvant therapy). Survivors' medical records were reviewed for clinical data, including subsequent recurrences. Biospecimens were collected for APOE genotyping.[25,26] Follow-up assessments were conducted at 12 and 24 month after enrollment. Controls were assessed contemporaneously. Assessments included in-person neuropsychological testing and an in-person or telephone interview.

Measures

Outcomes. The battery of neuropsychological assessments used in this study has been previously described.[27,28] Two cognitive domains were assessed: attention/processing speed/executive function (APE; six tests: Neuropsychological Assessment Battery [NAB] digits forward, NAB digits backward, Controlled Oral Word Association Test, Trail Making A, Trail Making B, and Digit Symbol Coding; baseline, 12- and 24-month Cronbach's $\alpha = 0.66–0.72$)[29,30] and learning/memory (LM; five tests: Logical Memory I, Logical Memory II, NAB list learning immediate recall, NAB list learning short delay, NAB list learning long delay; $\alpha = 0.85–0.90$).[27,31] These domains were selected because they are affected in cancer,[32] can change over time,[33] and are relevant to aging.[34] Raw scores from neuropsychological tests were standardized to the means and SDs for age and education strata-matched control scores at baseline.[28] Domain scores were created from the standardized *z*-scores for each test.

Self-reported outcomes included the following: 1) perceived cognitive function assessed with the Functional Assessment of Cancer Therapy–Cognitive Function[35] (FACT-Cog; $\alpha = 0.95–0.96$; scores range from 0 to 148; minimal clinically important difference (MCID) = 7–10 points[36]); 2) Instrumental Activities of Daily Living (IADL) disability assessed using the Older Americans Resource Scale[37] (OARS; scores range from 1 to 7; MCID = 3 points[38]); 3) The Functional Well-being (FWB) subscale of the FACT-B (or FACT-G for controls)[39] assessed ability to function, do work, and enjoy activities ($\alpha = 0.79–0.87$; scores range from 6 to 24; MCID = 2–3 points[40]; one item addressing sleep was excluded to limit overlap with sleep measure); 4) The Breast Cancer Subscale of the FACT-B assessed QOL attributable to breast cancer concerns ($\alpha = 0.42–0.75$; scores range from 9 to 45; MCID = 2–3 points[40]; one item addressing pain was excluded to limit overlap with symptom measures).

Predictors. Symptoms of anxiety, depression, fatigue, sleep disturbance, and pain were selected a priori based on prior research.[9] Anxiety was assessed with the State-Trait Anxiety Inventory ($\alpha = 0.86$). Depression was assessed with the Center for Epidemiological Studies–Depression scale, excluding the item on sleep problems ($\alpha = 0.86$). Fatigue was assessed with the FACIT-F ($\alpha = 0.90$). Assessments of sleep

Table 1
Participant Characteristics

Characteristic	All Survivors ($N = 319$)	High Symptom ($N = 51$)	Low Symptom ($N = 268$)	Controls ($N = 347$)
Completed 12-month follow-up, *n* (%)	235 (73.7)	33 (64.7)	202 (75.4)	307 (88.5)
Completed 24-month follow-up, *n* (%)	205 (64.3)	29 (56.9)	176 (65.7)	254 (73.2)
Age, mean (SD)	68.2 (6.1)	67.5 (5.1)	68.4 (6.3)	67.8 (7.0)
Race, *n* (%)				
Other[a]	66 (20.7)	13 (25.5)	53 (19.8)	73 (21.0)
Non-Hispanic white	253 (79.3)	38 (74.5)	215 (80.2)	273 (78.7)
Years of education, mean (SD)	15.2 (2.2)	14.9 (2.1)	15.2 (2.2)	15.4 (2.3)
WRAT-4 standardized score, mean (SD)	111.2 (15.4)	107.0 (15.1)[b]	112.0 (15.4)	111.8 (16.1)
Total number of comorbidities, mean (SD)	2.6 (1.9)	3.2 (2.4)[b]	2.4 (1.8)	2.4 (1.8)
APOE ε4 carrier, *n* (%)	57 (17.9)	9 (17.6)	48 (17.9)	84 (24.2)
AJCC stage, *n* (%)				
0–1	213 (66.8)	26 (51.0)[b]	187 (69.8)	n/a
2–3	105 (32.9)	24 (47.1)[b]	81 (30.2)	
Surgery, *n* (%)				
Lumpectomy	177 (55.5)	28 (54.9)	149 (55.6)	
Mastectomy	140 (43.9)	23 (45.1)	117 (43.7)	
Cancer treatment received, *n* (%)				
Hormonal only	90 (28.2)	21 (41.2)[b]	69 (25.7)	
Chemotherapy ± hormonal therapy	217 (68.0)	30 (58.8)[b]	187 (69.8)	
Radiation treatment, *n* (%)	171 (53.6)	27 (52.9)	144 (53.7)	
Pretreatment symptom T-score, mean (SD)				
Anxiety	51.9 (11.6)	70.4 (14.9)[b]	48.5 (6.5)	48.2 (7.8)
Depression	51.8 (11.6)	73.7 (10.7)[b]	47.9 (6.0)	48.3 (7.9)
Fatigue	52.3 (12.2)	70.7 (18.2)[b]	48.8 (6.1)	47.8 (6.6)
Sleep disturbance	51.6 (10.5)	61.8 (9.5)[b]	49.7 (9.5)	48.5 (9.3)
Pain	50.7 (10.4)	60.4 (12.2)[b]	48.9 (8.9)	49.2 (9.6)

WRAT-4 = Wide Range Achievement Test, fourth edition.
[a]Other race includes black, Hispanic, and American Indian/Alaska Native. Numbers may not add to 100% due to missing data.
[b]Significantly different from low symptom group at $P < 0.05$.

problems and pain were adapted from the FACT-B and Center for Epidemiological Studies–Depression. Sleep problems were assessed by participants' five-point Likert-scale ratings on two questions: "I have been sleeping well in the past week" and "My sleep was restless in the past week" ($\alpha = 0.78$). Pain was assessed on a five-point Likert-scale with two questions: "I have had pain in the past week" and "I have had certain parts of my body where I experience pain" ($\alpha = 0.77$). Higher scores on each symptom measure indicated higher symptom levels, and scores were scaled to *T*-scores based on control means and SDs.

Covariates. Covariates were determined a priori. Cancer stage and treatments were collected from medical records. Cancer stage was coded Stage 0–1 versus 2-3. There was little variability in treatment type, dosage, or duration; therefore, treatment was coded as chemotherapy with or without hormone therapy and versus hormone therapy alone. Demographics included age, education, and race. Self-reported comorbidities were assessed using the OARS comorbidity scale.[24] *APOE* genotype[26] was determined by standard single nucleotide polymorphism genotyping. *APOE* genotype status was categorized as carrier (presence of any ε4 allele) versus noncarrier (no ε4 alleles). The WRAT-4 was used to measure cognitive reserve.[41] Study site was also included as a covariate due to the variability in survivors' consent rates across sites.

Statistical Analyses

Demographic and clinical characteristics of survivors and controls were compared with t and χ^2 tests. Latent class analysis was performed in Mplus (Version 7; Muthen & Muthen, Los Angeles, CA)[42] and used to identify groups of survivors with high versus low symptoms. Models were run iteratively and the Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test[43] was used to determine the number of symptom cluster groups among survivors. Model entropy is also reported, with values above 0.80 indicating a good fitting solution.

Linear mixed-effects models predicting objective cognition, perceived cognition, and functional scores over time (APE, LM, FACT-Cog, FACT-FWB, and IADLs) examined differences between symptom and control groups on outcomes and the group-by-time interaction, adjusting for age, race, cognitive reserve, site, comorbidity, and *APOE* status (any + vs. no ε4). Among survivors, linear mixed-effects models also examined concurrent and longitudinal associations of symptom group with FACT–Breast Cancer Subscale score and group-by-time interactions, adjusting for covariates plus stage and treatment. Maximum

likelihood estimation was employed to use all available data.

Results

Participants ranged in age from 60 to 98 (Table 1). Survivors and controls were similar in baseline demographics, cognitive reserve, comorbidities, APOE genotype, and objective and perceived cognitive function.

Symptom Clusters in Survivors

The results of the latent class analysis indicated that a two-group solution fit the data better than a one-group model (VLMR $P < 0.001$, entropy = 0.946). Although the entropy was good for the three-group solution (0.911), the VLMR indicated that it did not provide a statistically better fit to the data ($P = 0.504$). Therefore, the two-group solution was considered as final. The high symptom group included 16% ($n = 51$) and the low symptom group 84% ($n = 268$) of survivors. The symptom groups among survivors were significantly different on all five individual symptoms ($P < 0.05$); the low symptom group had similar symptom T-scores to controls (Fig. 2). Compared to the low symptom group, the high symptom group had lower average WRAT-4 scores, had greater total comorbidities, was more likely to have later stage disease, and was less likely to receive chemotherapy with or without hormone therapy (Table 1) (all $P < 0.05$).

Cognition Outcomes

The high symptom group had statistically lower baseline APE ($P = 0.025$) and LM ($P = 0.018$) scores than the control group (Table 2). All groups showed improvement in neuropsychological scores over time (APE $P < 0.0001$; LM $P < 0.0001$; Fig. 3a and 3b). There were no significant symptom cluster group-by-time interactions.

Perceived cognition (FACT-Cog) was similar at baseline between the low symptom and control groups, but the high symptom group had statistically and clinically meaningful worse baseline perceived cognitive scores than controls (high: 116.91, controls: 132.19, $P < 0.0001$; Fig. 3c). There was also a significant group-by-time interaction ($P = 0.007$), with perceived cognition scores worsening from baseline to 12 months for the low symptom group ($P = 0.049$), and improving in the high symptom group ($P = 0.007$). Despite improvement for the high symptom group, 95% CIs of adjusted means (Table 3) showed that the high symptom group reported statistically and clinically worse perceived cognition than the control group at 12 months (high: 124.60, controls: 132.14, $P < 0.05$) and both groups at 24 months (high: 119.66, low: 130.70, controls: 131.83, $P < 0.05$).

Functional Outcomes

For Functional Well-being QOL (FACT-FWB; Fig. 4a), controls exhibited significantly better scores at baseline than the low ($P = 0.005$) and high symptom groups ($P < 0.0001$). All groups showed improvement over time ($P < 0.0001$). The group-by-time interaction was statistically significant ($P < 0.0001$); controls maintained Functional Well-being QOL over time, and there was improvement from baseline to 12 and 24 months for the low (12 months:

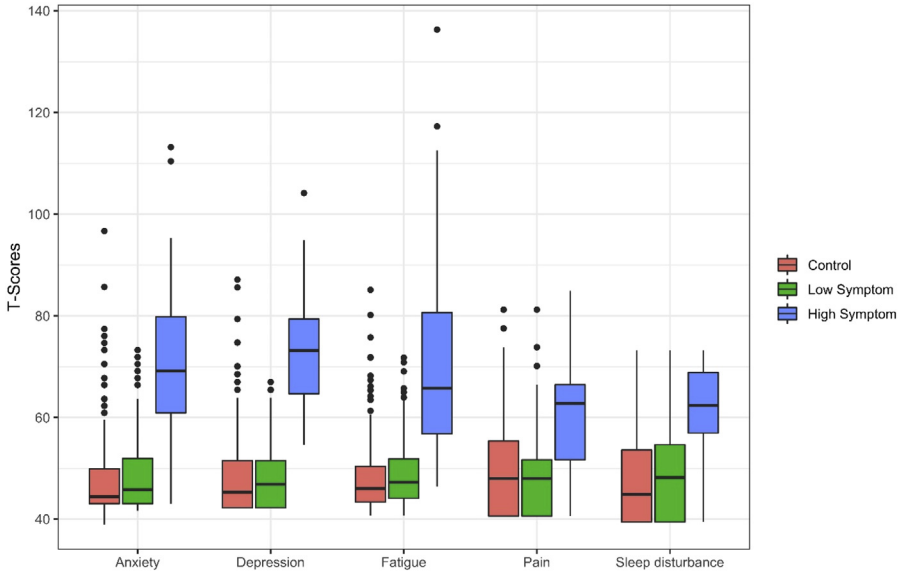

Fig. 2. Distributions of T-scores for symptoms by symptom group or control.

Table 2
Associations With Cognitive and Functional Outcomes in Models With Survivors and Controls

	APE		LM		FACT-Cog		FACT-FWB		OARS-IADLs	
Effect	*B*	SE	*β*	SE	*β*	SE	*β*	SE	*β*	SE
Intercept	0.14	0.27	0.11	0.35	126.62[a]	7.93	15.71[a]	1.48	−1.34[a]	0.35
Group—high symptom	−0.20[b]	0.09	−0.27[b]	0.11	−15.28[a]	2.69	−6.66[a]	0.55	0.95[a]	0.14
Group—low symptom	0.00	0.05	0.03	0.06	1.01	1.42	−0.82[c]	0.29	0.11	0.07
Time—12 months	0.07[a]	0.02	0.18[a]	0.03	−0.05	0.88	−0.21	0.23	0.04	0.04
Time—24 months	0.13[a]	0.02	0.14[a]	0.04	−0.36	0.91	−0.18	0.25	0.10	0.05
Group × time—high symptom, 12 months	0.09	0.07	0.19	0.10	7.75[c]	2.84	4.13[a]	0.74	−0.57[a]	0.14
Group × time—high symptom, 24 months	0.06	0.08	0.21	0.11	3.11	2.87	5.25[a]	0.79	−0.79[a]	0.16
Group × time—low symptom, 12 months	0.03	0.03	−0.03	0.05	−2.74[b]	1.39	0.92[b]	0.36	−0.10	0.07
Group × time—low symptom, 24 months	0.00	0.04	0.07	0.06	−2.13	1.43	0.98[b]	0.39	−0.13	0.08
Age	−0.02[a]	0.00	−0.03[a]	0.00	−0.03	0.10	0.01	0.02	0.02[a]	0.00
Race—other race	−0.35[a]	0.06	−0.25[a]	0.07	0.79	1.63	0.35	0.30	0.02	0.07
Cognitive reserve	0.01[a]	0.00	0.02[a]	0.00	0.08	0.04	0.01	0.01	0.00	0.00
Comorbidity	−0.03[c]	0.01	0.01	0.02	−1.57[a]	0.35	−0.36[a]	0.06	0.10[a]	0.01

APE = attention, processing speed, and executive function; LM = learning and memory; FACT-Cog = Functional Assessment of Cancer Therapy–Cognitive Function; FACT-FWB = Functional Assessment of Cancer Therapy–Functional Well-being; OARS = Older Americans Resource Scale; IADLs = Instrumental Activities of Daily Living.
Reference groups: control for group, baseline for time, white for race, ε4 negative for APOE. The models also controlled for study site. Estimates for each group by time interaction represent the average difference in rate of change for the respective symptom groups relative to the control group after adjusting for covariates.
[a]$P < 0.001$.
[b]$P < 0.05$.
[c]$P < 0.01$.

$P = 0.012$; 24 months: $P = 0.012$) and high (12 months: $P < 0.0001$; 24 months: $P < 0.0001$) symptom groups. Despite this improvement, scores remained statistically and clinically worse for the high compared to the low symptom group and controls at 12 months (high: 14.59, low: 17.22, controls: 17.12, $P < 0.05$), but the statistically significant difference was not clinically significant at 24 months (high: 15.75, low: 17.33, controls: 17.16, $P < 0.05$).

At baseline, controls and the low symptom group had similar IADL disability scores to each other, but the high symptom group had greater IADL disability ($P < 0.0001$; Fig. 4b). All groups showed improvement over time ($P < 0.001$). The group-by-time interaction was statistically significant ($P < 0.0001$), with the high symptom group showing greater improvement in IADL disability from baseline to 12 ($P < 0.0001$) and 24 months ($P < 0.0001$) than the low symptom

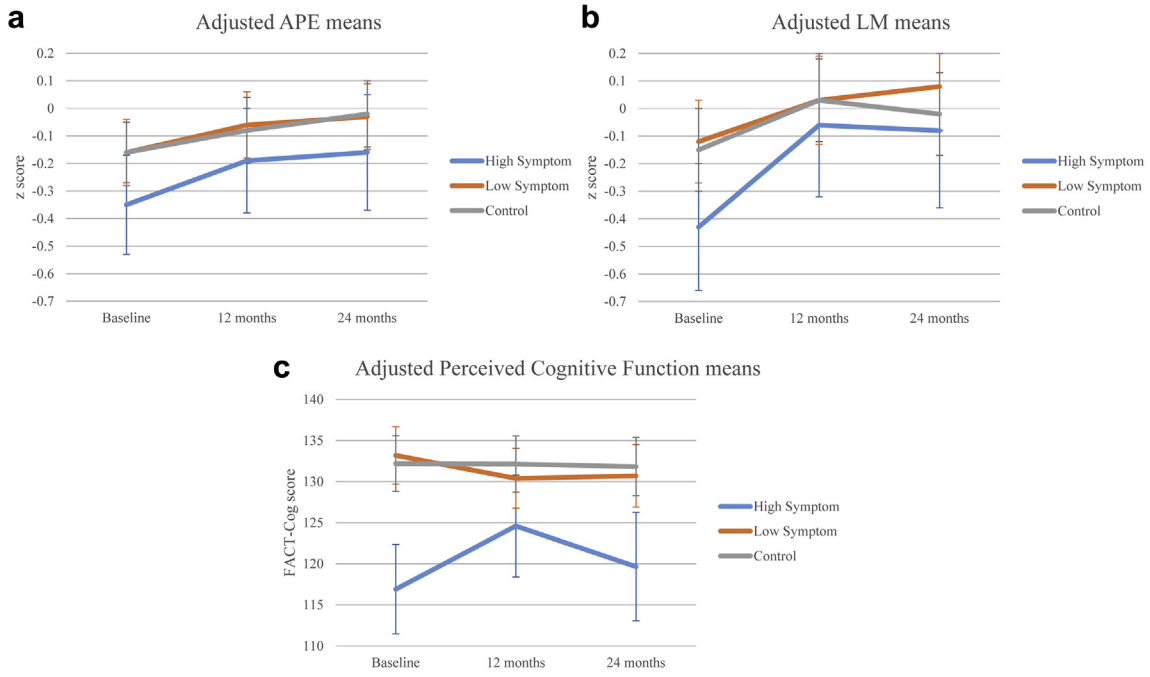

Fig. 3. a) Mean attention, processing speed, and executive function (APE) domain *z*-scores by symptom or control group, after adjusting for covariates. b) Adjusted mean learning and memory (LM) domain *z*-scores by symptom or control group. c) Adjusted mean perceived cognitive function by symptom or control group.

Table 3
Adjusted Least Squares Means for Cognitive and Quality of Life Outcomes

	High Symptom Group	Low Symptom Group	Controls
Outcome			
Time point	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
APE score[a]			
Baseline	−0.35 (−0.53, −0.18)	−0.16 (−0.28, −0.04)	−0.16 (−0.27, −0.04)
12 months	−0.19 (−0.38, 0.00)	−0.06 (−0.18, 0.07)	−0.08 (−0.20, 0.03)
24 months	−0.16 (−0.37, 0.05)	−0.03 (−0.15, 0.10)	−0.02 (−0.14, 0.10)
LM score[a]			
Baseline	−0.43 (−0.66, −0.19)	−0.12 (−0.27, 0.03)	−0.15 (−0.30, −0.01)
12 months	−0.06 (−0.32, 0.21)	0.03 (−0.13, 0.19)	0.03 (−0.12, 0.18)
24 months	−0.08 (−0.36, 0.20)	0.08 (−0.08, 0.24)	−0.02 (−0.17, 0.13)
Perceived cognitive function[b]			
Baseline	116.91 (111.47, 122.34)	133.19 (129.69, 136.70)	132.19 (128.80, 135.58)
12 months	124.60 (118.40, 130.80)	130.40 (126.76, 134.04)	132.14 (128.72, 135.55)
24 months	119.66 (113.08, 126.24)	130.70 (126.90, 134.50)	131.83 (128.29, 135.36)
Functional well-being[c]			
Baseline	10.68 (9.59, 11.76)	16.52 (15.85, 17.19)	17.34 (16.70, 17.98)
12 months	14.59 (13.23, 15.95)	17.22 (16.49, 17.95)	17.12 (16.46, 17.79)
24 months	15.75 (14.34, 17.16)	17.33 (16.58, 18.08)	17.16 (16.48, 17.85)
IADLs[d]			
Baseline	1.14 (0.87, 1.41)	0.30 (0.14, 0.46)	0.19 (0.04, 0.34)
12 months	0.61 (0.36, 0.86)	0.24 (0.09, 0.39)	0.23 (0.09, 0.37)
24 months	0.45 (0.16, 0.75)	0.27 (0.11, 0.43)	0.29 (0.14, 0.45)
QOL—breast cancer concerns[e]			
Baseline	22.87 (21.41, 24.33)	29.61 (28.58, 30.64)	n/a
12 months	26.82 (24.95, 28.69)	30.03 (28.92, 31.14)	
24 months	27.09 (25.15, 29.02)	30.68 (29.53, 31.83)	

IADLs = Instrumental Activities of Daily Living; QOL = quality of life; FACT-Cog = Functional Assessment of Cancer Therapy—Cognitive Function; FACT-FWB = Functional Assessment of Cancer Therapy—Functional Well-being; OARS = Older Americans Resource Scale; IADLs = Instrumental Activities of Daily Living; MCID = minimal clinically important difference.
All results are adjusted for age, race, WRAT score, recruitment site, comorbidity, and APOE status. Results for FACT—Breast Cancer Subscale are also adjusted for stage of disease and receipt of chemotherapy.
[a]APE = attention, processing speed, and executive function; LM = learning and memory; *z*-scores standardized to the baseline scores of age- and education-matched controls.
[b]Based on FACT-Cog; scores range from 0 to 148; higher scores indicate better cognition; MCID = 7–10 points.
[c]Based on FACT—Functional Well-Being subscale without the question on sleep; scores range from 6 to 24; higher scores indicate better QOL; MCID = 2–3 points.
[d]Based on OARS-IADLs score; scores range from 1 to 7; higher scores indicate greater IADL disability; MCID = 3 points.
[e]Based on FACT-Breast Cancer Subscale without the question on pain; scores range from 9 to 45; higher scores indicate better QOL; MCID = 2–3 points.

group and controls. Despite this improvement, the high symptom group did not differ from the low symptom group and controls at 12 (high: 0.61, low: 0.24, controls: 0.23, $P > 0.05$) or 24 months (high: 0.45, low: 0.27, controls: 0.29, $P > 0.05$).

Breast Cancer—Specific QOL

The high symptom group exhibited statistically and clinically meaningful worse baseline breast cancer QOL than the low symptom group (Table 4; Fig. 4c). Both groups significantly improved over time ($P < 0.0001$). The group-by-time interaction was significant ($P < 0.0001$). Relative to the low symptom group, the high symptom group showed significantly improved scores from baseline to 12 months ($P = 0.001$) and 24 months ($P = 0.002$). However, the high symptom group remained statistically and clinically lower than the low symptom group at baseline (high: 22.87, low: 29.61, $P < 0.05$), 12 (high: 26.82, low: 30.03, $P < 0.05$), and 24 months (high: 27.09, low: 30.68, $P < 0.05$).

Discussion

This study is among the first to examine the relationship between pretreatment symptom clusters and longitudinal cognitive and functional outcomes over two years in a large prospective study of older breast cancer survivors and matched cancer-free controls. Nearly one-fifth of older breast cancer survivors reported high symptoms before systemic therapy. Despite some improvement over time, high pretreatment symptoms were significantly associated with persistently worse perceived cognition and breast cancer—specific QOL scores. In addition, the high symptom group had lower objective cognition at baseline than noncancer controls. By contrast, the low symptom group appeared similar to matched noncancer controls on all outcomes across time.

Our findings for older breast cancer survivors converge with prior research showing that a subgroup of survivors report initial high levels of anxiety, depression, fatigue, sleep disturbance, and pain.[9] Prior data also support a relationship between high

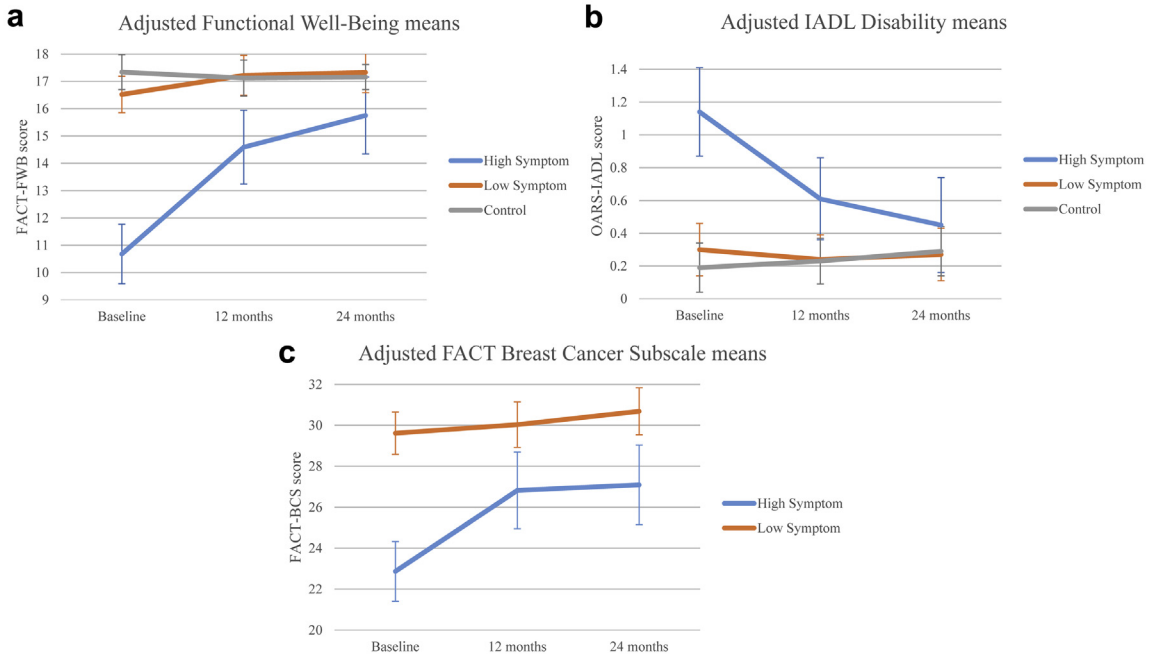

Fig. 4. a) Adjusted mean functional well-being by symptom or control group. b) Adjusted mean Instrumental Activities of Daily Living (IADL) disability by symptom or control group. c) Adjusted mean breast cancer quality of life by symptom group.

(vs. low) symptoms and worse QOL and functional status, with similar effect sizes as seen in our sample.[14–17] The number of survivors in the high symptom group is also similar to prior research (14%–28%) in survivors from diverse age groups.[16,17,44,45] Although we expected older survivors to experience greater pretreatment symptoms due to aging, prior findings indicate that younger survivors are more likely than older survivors to report high symptoms.[16,45] Potentially, older survivors may generally report low levels of symptoms due to a shift in their pattern of responding as they become accustomed to age-related physical ailments.[46]

Table 4
Associations of Symptom Cluster With Survivors' Breast Cancer-Specific Quality of Life

	FACT-BCS	
Effect	β	SE
Intercept	23.90[a]	3.02
Group—high symptom (vs. low)	−6.74[a]	0.72
Time—12 months	0.43	0.36
Time—24 months	1.07[b]	0.39
Group × time—high symptom, 12 months	3.53[a]	0.97
Group × time—high symptom, 24 months	3.15[b]	1.05
Age	0.10[c]	0.04
Race—other race	−0.25	0.59
Cognitive reserve (WRAT score)	0.00	0.02
Comorbidity	−0.58[a]	0.13
APOE—ε4 positive	0.75	0.57
Stage—Stage 2–3	−0.52	0.51
Treatment—hormone only	0.07	0.55

WRAT = Wide Range Achievement Test.
Reference groups: low symptom for group, baseline for time, white for race, ε4 negative for APOE, Stage 0–1 for stage, chemotherapy with or without hormone therapy for treatment. The model also controlled for study site. Estimates for each group by time interaction represent the average difference in rate of change for the high symptom group relative to the low symptom group after adjusting for covariates.
[a]$P < 0.001$.
[b]$P < 0.01$.
[c]$P < 0.05$.

Specific symptoms of anxiety, depression, fatigue, and sleep disturbance have each been independently associated with worse perceived cognition in cancer samples.[7,47,48] Research on symptom clusters in cancer occasionally includes cognitive complaints in the cluster because they often co-occur.[10,14] However, poor performance on objective tests of cognitive function is inconsistently related to these symptoms.[49,50] Our findings confirm that these symptoms and self-reported cognition are associated. The lack of overall effect for objective cognitive function may reflect the very subtle changes in these measures over time. Perceived cognitive function, QOL, and functional status remain clinically important and should be assessed early in care processes[51] because, beyond QOL and cognition, they predict treatment toxicity and mortality.[52]

Our findings have clinical implications for geriatric assessment and survivorship interventions. Assessment of pretreatment symptomatology as part of a comprehensive geriatric assessment may help clinicians identify older cancer survivors at risk for functional impairment and worse QOL. Although our results indicate that those in the high symptom group gradually improved over time, lower perceived

cognition, and QOL persisted over two years in the high symptom group. By contrast, survivors in the low symptom group appear similar to women without cancer on all outcomes. The ability to distinguish older survivors who are at greatest risk before treatment from those similar to cancer-free older adults should help providers determine which patients are most in need of support. Symptoms at diagnosis may be a promising method to help providers identify this potentially higher risk older survivor group and make early referrals for interventions.

Initial evidence suggests that cognitive-behavioral therapy can reduce severity of symptoms such as depression, fatigue, and insomnia; cognitive-behavioral therapy and pharmacological treatment both may be effective for treating mood, adjustment, and sleep disorders, and in turn, improve cancer survivors' QOL and functional status.[53–55] Other behavioral interventions may also be effective in lowering symptoms, including yoga, meditation, and journaling.[56,57] Therefore, providers may also consider behavioral interventions to mitigate symptomatology.

Limitations of the present study should be considered. Although the sample of survivors was ethnically and racially representative of older cancer survivors in the U.S., the sample was well educated and recruited mainly from academic cancer centers and their affiliated community sites. Survivors' consent rates also differed across study sites. Therefore, results may not generalize to broadly representative survivor groups. Although the sample was large, the small subgroup of survivors with high symptoms may have limited power to detect some relationships with outcomes. Attrition may also have limited power. In addition, assessment of symptoms, perceived cognition, IADL disability, and quality of life was self-reported, and any systematic error or bias in responses could have affected the magnitude and directions of the observed relationships. However, the consistency of associations between symptoms and several diverse types of outcomes suggests that results are robust. Measures of sleep disturbance and pain were not validated measures, although they showed good internal consistency; and the other symptoms were from well-validated, reliable scales. Finally, differences in IADLs at baseline did not appear to be clinically meaningful according to current benchmarks for older adults; however, little is known regarding clinically meaningful differences in subtle IADL difficulties for older breast cancer survivors.

Overall, nearly one-fifth of older breast cancer survivors in this study experienced high symptoms before systemic cancer treatment, and being in the high symptom group predicted poor outcomes. Identifying older breast cancer survivors who are at risk for cognitive complaints and poor QOL has implications for geriatric assessment and referral for interventions to support symptom management and mental health.

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