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Cognitive Impairment in Older Patients With Breast Cancer Before Systemic Therapy: Is There an Interaction Between Cancer and Comorbidity?

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ABSTRACT

Purpose
To determine if older patients with breast cancer have cognitive impairment before systemic therapy.

Patients and Methods
Participants were patients with newly diagnosed nonmetastatic breast cancer and matched friend or community controls age > 60 years without prior systemic treatment, dementia, or neurologic disease. Participants completed surveys and a 55-minute battery of 17 neuropsychological tests. Biospecimens were obtained for *APOE* genotyping, and clinical data were abstracted. Neuropsychological test scores were standardized using control means and standard deviations (SDs) and grouped into five domain z scores. Cognitive impairment was defined as any domain z score two SDs below or ≥ two z scores 1.5 SDs below the control mean. Multivariable analyses evaluated pretreatment differences considering age, race, education, and site; comparisons between patient cases also controlled for surgery.

Results
The 164 patient cases and 182 controls had similar neuropsychological domain scores. However, among patient cases, those with stage II to III cancers had lower executive function compared with those with stage 0 to I disease, after adjustment ($P = .05$). The odds of impairment were significantly higher among older, nonwhite, less educated women and those with greater comorbidity, after adjustment. Patient case or control status, anxiety, depression, fatigue, and surgery were not associated with impairment. However, there was an interaction between comorbidity and patient case or control status; comorbidity was strongly associated with impairment among patient cases (adjusted odds ratio, 8.77; 95% CI, 2.06 to 37.4; $P = .003$) but not among controls ($P = .97$). Only diabetes and cardiovascular disease were associated with impairment among patient cases.

Conclusion
There were no overall differences between patients with breast cancer and controls before systemic treatment, but there may be pretreatment cognitive impairment within subgroups of patient cases with greater tumor or comorbidity burden.

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INTRODUCTION

Many of the 290,000 women diagnosed each year in the United States with breast cancer[1] will be candidates for systemic treatment.[2,3] Despite survival benefits,[4] short-[5-7] and long-term[8-10] cognitive deficits have been reported after these systemic therapies.[11-19] However, the effects are not universal[20-22] and may only affect certain subgroups of patients.[12,23] There are emerging neuropsychological[24] and neuroimaging[25-27] data suggesting that some patients with cancer may have cognitive impairment before systemic treatment, independent of anxiety, depression, or fatigue,[8,28] type of anesthesia or surgery,[29,30] or nutritional status.[31] There are several hypothesized biologic mechanisms whereby cancer might exert an influence on cognition function before systemic therapy,[32] including inflammation,[6,33] oxidative stress,[34] DNA damage and compromised DNA repair,[35] genetic susceptibility,[36,37] decreased telomere length,[38,39] and/or cell senescence.[40,41]
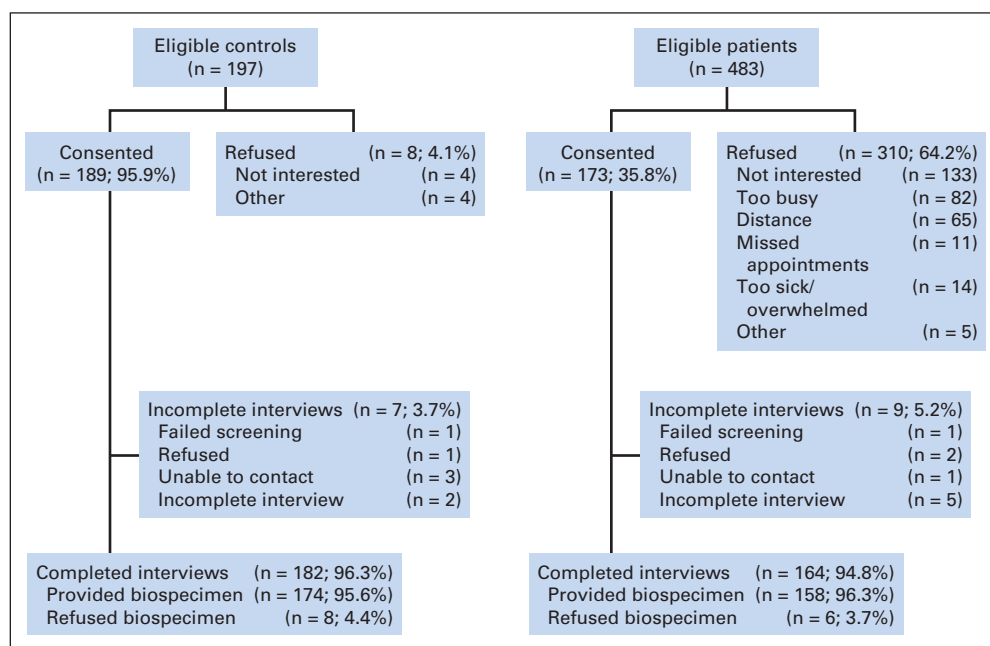
Fig 1. Sample for evaluation of cognition in older patients with breast cancer and noncancer controls.

One common feature of these putative mechanisms is the aging process, leading to the speculation that older patients may be vulnerable to pre- and post-treatment cancer-related cognitive deficits.[42,43] Unfortunately, there have been few studies examining outcomes for older patients,[11,44-46] and the mean age in the most recent meta-analysis of cognition in patients with cancer was 53 years.[13]

The TLC (Thinking and Living With Cancer) study was a national, multisite prospective study designed to identify the impact of cancer and systemic cancer treatments on cognition among older women with breast cancer. We used presystemic therapy data to test the hypothesis that compared with older controls, older patients have lower baseline cognition as measured by neuropsychological testing. We also tested whether cognitive reserve, physiological reserve (defined by comorbidity level), age, or presence of *APOE* e4 alleles affects baseline pretreatment cognitive differences between patient cases and controls. Finally, we explored whether disease stage distinguishes patient cases with more versus less cognitive impairment.

PATIENTS AND METHODS

This study was conducted at Georgetown University (Washington, DC), Memorial Sloan-Kettering Cancer Center (New York, NY), Moffitt Cancer Center (Tampa, FL), and City of Hope Comprehensive Cancer Center (Los Angeles, CA). Assessment training and certification were conducted at Boston University School of Medicine (Boston, MA).[47] The research protocol met Health Insurance Portability and Accountability Act standards and was approved by all institutional review boards.

Setting and Population

Women were recruited between August 1, 2010, and June 30, 2013. Eligible patient cases were age ≥ 60 years, newly diagnosed with primary nonmetastatic breast cancer (American Joint Committee on Cancer [AJCC] stages 0 to III), and English speaking; those with stroke, head injury, major Axis I psychiatric disorders, or neurodegenerative disorders were ineligible. Women with a history of other cancers were excluded if active treatment occurred < 5 years before or if they had ever received chemotherapy or hormonal therapy. Of eligible patient cases, 173 consented (median consent rate, 48.2%; range across sites, 24.7% to 67.4%; Fig 1). We recruited controls who were friends of participating patient cases; if no friend was available, we recruited an age-, race-, education-, and frequency-matched control from the same region as the patient case. Controls met the same eligibility criteria as patient cases. Consenting participants were screened for final eligibility using the Mini-Mental State Examination and the Wide Range Achievement Test (fourth edition; WRAT-4) to ensure ability to complete the study; those with a score < 24 or < third-grade level on either test were ineligible (patient case, n = 1; control, n = 1). The final sample included 164 patient cases and 182 controls.

Data Collection

Study staff identified potentially eligible patients from physician referrals and/or appointment schedules, obtained permission to contact patients, consented patients, and conducted testing. All data were collected after postoperative visits but before administration of radiation or systemic therapy. Assessment included neuropsychological testing (55 minutes), a structured survey, and a blood or saliva biospecimen (Oragene kit; DNA Genotek, Kanata, Ontario, Canada) for DNA testing to determine *APOE* genotype. All data were collected simultaneously or within 1 week of each other. Biospecimens were processed centrally and tested in batches; 100% of the specimens had sufficient DNA for analysis. We abstracted data on AJCC stage, estrogen receptor status, human epidermal growth factor receptor 2 status, and surgery for patient cases.

Measures

Outcomes. The primary outcome variable was baseline presystemic therapy cognition based on neuropsychological testing. We selected domains most likely to be affected by cancer,[48] relevant to older patients,[49,50] and related to cognitive impairment and aging (eg, prefrontal or hippocampal involvement on functional magnetic resonance imaging),[51,52] including attention, working memory, and psychomotor speed; executive functioning and language; learning and memory; and visual-spatial ability. The secondary outcome was impairment based on domain score.

Tests with established reliability and validity in diverse older populations were used to measure the domains, including some of those recommended by the International Task Force on Cancer and Cognition[53] and/or part of the Unified Data Set of the National Alzheimer's Coordinating Center.[54,55] The administration length (55 minutes) was deemed feasible for older patients.[56]

Table 1. Neuropsychological Tests and Domains Used to Assess Cognition in Older Patients With Breast Cancer and Noncancer Controls

Test	Approximate Time to Administer (minutes)	Source
Attention, working memory, and processing speed domain		
NAB digits forward	4:00	Stern and White[55]
NAB digits backward	4:00	Stern and White[55]
Trail making A	2:00	Reitan and Wolfson[57]
Digit symbol test	2:00	Wechsler[58]
NAB driving scenes	12:00	Stern and White[55]
Language domain		
Boston naming test	4:00	Kaplan et al[59]
Category fluency	1:30	Morris et al[60]
Executive Functioning		
Trail making B	3:00	Reitan and Wolfson[57]
Controlled oral word association test	4:00	Benton[61]
NAB figure drawing	3:00	Stern and White[55]
Learning and memory domain		
Logical memory I	3:00	Wechsler[58]
Logical memory II	2:00	Wechsler[58]
NAB list A immediate recall	4:00	Stern and White[55]
NAB list B immediate recall	1:30	Stern and White[55]
NAB list A short delay recall	1:00	Stern and White[55]
NAB long delay	4:00	Stern and White[55]
Visual-spatial domain		
NAB figure drawing copy	Variable	Stern and White[55]

Abbreviation: NAB, Neuropychological Assessment Battery.

The test battery is summarized in Table 1, and raw scores are included on Appendix Table A1 (online only); Appendix Table A2 (online only) includes scores stratified by stage for patient cases.

Variables. The primary variable related to cognition was patient case versus control status. We also present self-reported cognition based on the Functional Assessment of Cancer Therapy (FACT) –Cognition[62] subscale for perceived cognitive impairment. This scale assesses difficulty in memory, concentration, and intellectual activities ($\alpha = 0.93$). On the basis of prior research in cancer[42,63] and other diseases,[64] we expected that the effects of cancer on cognition might be moderated by stage, reserve, age, or presence of *APOE* e4 allele (ie, e2/e4, e3/e4, or e4/4). Stage was grouped as early (AJCC 0 to I) versus more advanced (AJCC II to III) based on tumor burden. Cognitive reserve was defined as high versus low based on median WRAT-4 score in controls and by education. Physiologic reserve was estimated based on self-reported number of comorbid illnesses; we also dichotomized the number of illnesses at the median for ease of describing interactions. We further examined specific comorbidities, such as diabetes and cardiovascular disease. Age was considered as a continuous variable; we also dichotomized to examine subgroups (age 60 to 74 and ≥ 75 years).

Sociodemographic measures included age, race (white *v* nonwhite), family history of dementia (first- or second-degree relatives; yes *v* no), marital status, education (total years), usual occupation (clerical, administrative, management, and so on), insurance, and setting of care (health maintenance organization *v* non–health maintenance organization). Health habits included prior years of use of hormonal replacement therapy, age at menopause, self-reported cigarette (ever or current *v* never) and alcohol use (< two *v* ≥ two drinks per day), and level of physical activity.[65]

The Center for Epidemiologic Studies Depression Scale (20 items) measured depressive symptoms, with a cut point of 16 defining clinical depression.[66,67] To measure anxiety, the state version of the 20-item State Trait Anxiety Inventory was used.[68] Fatigue was assessed using the 13-item FACT-Fatigue subscale.[69] The Medical Outcomes Study Short Form 12 measured physical and mental function in the 2 months before diagnosis or interview,[70] and the FACT-General (for patient case–control comparisons) and FACT–Breast Cancer (for comparisons between patient cases) subscales captured current quality of life, including physical and emotional function.[71,72] Current function was also adjusted for prior function. Clinical variables considered in case-case comparisons included surgery (mastectomy *v* lumpectomy, as proxy for anesthesia exposure, postoperative pain, and effects on function), estrogen receptor status, and human epidermal growth factor receptor 2 status.

Statistical Analysis

We used *t* and χ^2 tests to compare characteristics of patient cases and controls. Raw neuropsychological test scores were calculated and converted to *z* scores by standardizing to control means and standard deviations (SDs). Standardized *z* scores were then averaged across each predefined domain. *t* tests compared patient case and control raw and standardized scores; two-way analysis of variance was employed to compare patient case and control domain *z* scores, adjusting for age, race, education, and site. Other factors were not related to patient case or control status or cognitive outcomes and so were not used in adjustment. Comparisons between patient cases included additional adjustment for surgery type to capture possible unmeasured postoperative effects. Differences between patient case and control groups were also examined within subgroups based on age (60 to 74 *v* ≥ 75 years), WRAT score (higher or lower than control median), comorbidity (< two *v* ≥ two illnesses based on overall median), *APOE* status (e4 allele *v* other), and stage (0 to I *v* II to III).

Because there is no universally accepted definition of lower-than-expected cognitive performance (ie, cognitive impairment),[73] we used a common convention whereby relative cognitive impairment is defined as having any one domain *z* score that is two SDs below or two domain *z* scores that are 1.5 SDs below the control mean.[42,53] In addition, we conducted sensitivity analyses using an alternative definition based on having ≥ two domains with *z* scores below one SD of the control mean. We did not consider definitions based on individual test scores, because these may overestimate impairment, given correlations of responses to tests within domains.[74]

We examined bivariate associations between cognitive impairment and covariates, overall and among the subgroups. We included any variable in logistic regression models that was related to impairment at a 0.05 level in bivariate analyses; site was retained to capture any unmeasured factors in comparisons between patient cases and controls and between patient cases; surgery type was also retained in comparisons between patient cases. There was a significant interaction between comorbidity and patient case or control status; thus, we also present separate models by patient case or control group.

We had 80% power ($\alpha = 0.05$) to detect an effect size of 0.3 SDs (small to medium effect size) between groups for any cognitive domain score. We also had 80% power ($\alpha = 0.05$) to detect an odds ratio of 2.1 for the association between patient case or control group and impairment, assuming 15% impairment among controls. All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Among eligible patient cases, those consenting were similar in age to nonparticipants. Participants were well educated and ranged in age from 60 to 98 years. There were no sociodemographic differences between patient cases and controls, except that controls had a minimally higher average education level than patient cases (15.7 [SD, 2.2] *v* 15.1 years [SD, 2.2]; $P = .012$; Table 2). Approximately one third of patient cases and controls reported a family history of dementia. Among patient cases, 65% had early-stage disease (stages 0 to I), and 88% were estrogen receptor positive. Patient cases reported significantly higher levels of anxiety, depression, and fatigue and quality of life than controls ($P \leq .005$), but there were no self-reported differences in cognition between patient cases and controls.

	Controls (n = 182)[a]		All (n = 164)[a]		Stages 0 to I (n = 106)		Stages II to III (n = 58)		Patient Case v Control	Patient Case Stages 0 to I v II to III	Patient Case Stages 0 to I v Control	Patient Case Stages II to III v Control
Characteristic	No.	%	No.	%	No.	%	No.	%				
Age, years									.27	.75	.41	.30
Mean	67.3		68.1		68.0		68.4					
SD	6.5		6.7		6.7		6.8					
Range	60-90		60-98		60-98		60-91					
Race									.92	.85	.86	.95
White, non-Hispanic	146	80.7	130	80.2	83	79.8	47	81.0				
Nonwhite (black, Hispanic, AAPI)	35	19.3	32	19.8	21	20.2	11	19.0				
Marital status									.08	.31	.04	.58
Married	96	52.7	102	62.2	69	65.1	33	56.9				
Widowed, divorced, or single	86	47.3	62	37.8	37	34.9	25	43.1				
Education, years									.01	.15	.12	.006
Mean	15.7		15.1		15.3		14.8					
SD	2.2		2.2		2.1		2.2					
WRAT-4 score									.62	.93	.64	.77
Mean	111.2		112.0		112.1		111.9					
SD	16.0		15.4		16.0		14.5					
Insurance coverage									.27	.32	.09	.99
Private	147	80.8	144	87.8	96	90.6	48	82.8				
Medicaid	4	2.2	4	2.4	3	2.8	1	1.7				
	14	7.7	7	4.3	3	2.8	4	6.9				
None	17	9.3	9	5.5	4	3.8	5	8.6				
Usual adult occupation									.65	.95	.72	.71
Managerial or professional	124	68.1	108	65.9	70	66.0	38	65.5				
Other	58	31.9	56	34.1	36	34.0	20	34.5				
Smoking status									.35	.72	.33	.68
Current or former	96	53.0	94	58.0	62	59.0	32	56.1				
Never	85	47.0	68	42.0	43	41.0	25	43.9				
Alcohol use, drinks per day									.56	.92	.64	.64
< 2	173	95.1	158	96.3	102	96.2	56	96.6				
≥ 2	9	4.9	6	3.7	4	3.8	2	3.4				
Age at menopause, years									.97	.21	.50	.35
Mean	49.5		49.4		48.9		50.4					
SD	6.1		6.7		7.1		6.0					
Hormone replacement therapy duration, years									.37	.21	.77	.09
< 1	6	5.9	8	8.9	3	5.4	5	14.7				
1 to < 5	39	38.6	25	27.8	19	33.9	6	17.6				
5 to < 10	23	22.8	20	22.2	11	19.6	9	26.5				
≥ 10	33	32.7	37	41.1	23	41.1	14	41.2				
Family history of dementia									.57	.10	.80	.12
Yes	62	37.3	50	34.2	37	38.9	13	25.5				
No	104	62.7	96	65.8	58	61.1	38	74.5				
No. of comorbidities									.34	.62	.53	.31
Mean	2.4		2.5		2.5		2.7					
SD	1.8		2.0		1.8		2.4					
Physical activity									.15	.92	.21	.41
Low or none	42	23.3	41	27.7	26	26.8	15	29.4				
Moderate	75	41.7	70	47.3	47	48.5	23	45.1				
High	63	35.0	37	25.0	24	24.7	13	25.5				
APOE genotype[b]									.21	.85	.31	.32
e4 negative	131	75.3	128	81.0	83	80.6	45	81.8				
e4 positive	43	24.7	30	19.0	20	19.4	10	18.2				
AJCC stage									—	—	—	—
0		—	3	1.8	3	2.8		—				
I		—	103	62.8	103	97.2		—				
II		—	51	31.1		—	51	87.9				
III		—	7	4.3		—	7	12.1				

Table 2. Demographic and Clinical Characteristics of Older Participants

(continued on following page)

Characteristic	Controls (n = 182)[a] No.	%	Patient Cases All (n = 164)[a] No.	%	Stages 0 to I (n = 106) No.	%	Stages II to III (n = 58) No.	%	Patient Case v Control	Patient Case Stages 0 to I v II to III	Patient Case Stages 0 to I v Control	Patient Case Stages II to III v Control
Surgery type									—	.001	—	—
Lumpectomy	—		93	57.8	71	67.6	22	39.3				
Mastectomy	—		68	42.2	34	32.4	34	60.7				
Time from surgery, days[c]									—	.640	—	—
Mean	—		50.6		51.1		49.5					
SD	—		20.4		19.9		21.5					
ER status									—	.53	—	—
Positive	—		144	88.3	94	89.5	50	86.2				
Negative	—		19	11.7	11	10.5	8	13.8				
HER2 status									—	.18	—	—
Positive	—		18	12.4	9	9.7	9	17.3				
Negative	—		127	87.6	84	90.3	43	82.7				
Past physical function[d]									.18	.36	.45	.10
Mean	52.0		50.8		51.3		50.0					
SD	7.5		8.7		8.0		9.9					
Past emotional function[d]									.55	.35	.31	.77
Mean	47.7		48.1		48.4		47.5					
SD	4.8		5.6		5.6		5.8					
Depression[e]									.004	.17	.05	< .001
> 16 on CES-D	8	4.5	21	13.1	11	10.5	10	18.2				
Anxiety[f]									< .001	.16	.004	< .001
Mean	26.7		29.7		29.0		31.0					
SD	5.5		8.5		8.1		9.0					
Fatigue[g]									< .001	.67	< .001	< .001
Mean	46.9		43.8		44.0		43.4					
SD	5.7		8.7		8.7		8.7					
Current physical function[h]									< .001	.24	< .001	< .001
Mean	22.0		20.3		20.6		19.8					
SD	2.5		3.8		3.5		4.3					
Current emotional function[i]									< .001	.13	< .001	< .001
Mean	14.7		12.9		13.1		12.4					
SD	1.5		2.9		2.9		3.0					
Overall QOL[j]									< .001	.15	.004	< .001
Mean	72.4		68.3		69.2		66.7					
SD	8.2		10.7		10.3		11.2					
Self-reported cognition[k]									.38	.67	.32	.75
Mean	62.1		61.1		60.9		61.6					
SD	8.6		10.8		11.4		9.6					

Abbreviations: AAPI, Asian American or Pacific Islander; AJCC, American Joint Committee on Cancer; CES-D, Center for Epidemiologic Studies Depression Scale; ER, estrogen receptor; FACT, Functional Assessment of Cancer Therapy; HER2, human epidermal growth factor receptor 2; QOL, quality of life; SD, standard deviation; WRAT-4, Wide Range Achievement Test (fourth edition).
[a]Some numbers may not add to 100% because of missing data; three patients refused surgery.
[b]Biospecimens provided by 95% of patient cases and 96.5% of controls; thus, results do not total 100%.
[c]Time since surgery was not calculated for participants undergoing neoadjuvant therapy (lumpectomy, n = 6; mastectomy, n = 2).
[d]Based on Short Form 12 assessed for period 2 months before cancer diagnosis; higher scores indicate better function.
[e]Depression defined by score above cut point of 16 on CES-D.
[f]Based on state version of State Trait Anxiety Inventory A scale; scores range from 20 to 80, with higher scores reflecting more anxiety.
[g]Based on Functional Assessment of Chronic Illness Therapy–Fatigue subscale; scores range from 0 to 52, with higher scores reflecting less fatigue.
[h]Based on FACT–General Population Physical Well-Being subscale; scores range from 0 to 24, with higher scores reflecting better functioning.
[i]Based in FACT–General Population Emotional Well-Being subscale; scores range from 0 to 16, with higher scores reflecting better functioning.
[j]Based on FACT-General total score; scores range from 0 to 84, with higher scores reflecting better functioning.
[k]Based on FACT–Cognitive Function Perceived Cognitive Impairment score; scores range from 0 to 72, with higher scores reflecting better perceived cognition.

There were no differences between patient cases and controls with respect to unadjusted and adjusted means of standardized neuropsychological test domain scores (Table 3). There were also no differences between patient cases and controls in scores when stratified by age group, WRAT score, or APOE genotype results (data not shown). There was a trend among patient cases with more advanced disease stage toward lower executive function than controls after adjustment (P = .13; data not shown). There were differences among patient cases by stage group; those with more advanced disease stage had lower executive function than patient

1913

Table 3. Baseline Pretreatment Neuropsychological Test Results for Older Patients With Breast Cancer Versus Noncancer Controls

| | Unadjusted Standardized z Score* | | | | | Adjusted Standardized z Score† | | | | |
| | Controls | | Patient Cases | | | Controls | | Patient Cases | | |
Test	Mean	SE	Mean	SE	P	Mean	SE	Mean	SE	P
Attention, working memory, and processing speed domain	0.00	0.05	−0.03	0.05	.699	−0.17	0.05	−0.12	0.05	.464
NAB digits forward	0.00	0.07	−0.04	0.08	.682	−0.19	0.08	−0.20	0.09	.913
NAB digits backward	0.00	0.07	−0.01	0.08	.890	−0.19	0.08	−0.16	0.08	.838
Trail making A	0.00	0.07	−0.04	0.08	.738	−0.18	0.08	−0.13	0.08	.620
Digit symbol test	0.00	0.08	−0.05	0.08	.640	−0.16	0.08	−0.12	0.08	.679
NAB driving scenes	0.00	0.07	0.02	0.08	.888	−0.12	0.08	−0.00	0.08	.228
Language domain	0.00	0.06	−0.07	0.07	.410	−0.24	0.06	−0.23	0.06	.840
Boston naming test	0.00	0.07	−0.07	0.07	.528	−0.32	0.07	−0.29	0.07	.747
Category fluency	0.00	0.07	−0.08	0.08	.438	−0.17	0.08	−0.16	0.08	.982
Executive function domain	0.00	0.05	−0.12	0.05	.091	−0.12	0.05	−0.17	0.05	.498
Trail making B	0.00	0.08	−0.13	0.08	.229	−0.22	0.08	−0.23	0.08	.883
Controlled oral word association test	0.00	0.07	−0.26	0.07	.013	−0.10	0.08	−0.30	0.08	.042
NAB figure drawing	0.00	0.07	0.03	0.08	.796	−0.05	0.08	0.03	0.09	.441
Learning and memory domain	0.00	0.06	−0.04	0.06	.620	−0.13	0.06	−0.08	0.06	.480
Logical memory I	0.00	0.08	−0.04	0.08	.743	−0.09	0.08	−0.06	0.09	.757
Logical memory II	0.00	0.08	0.04	0.08	.686	−0.09	0.08	0.04	0.09	.219
NAB list A immediate recall	0.00	0.08	−0.11	0.08	.305	−0.19	0.07	−0.20	0.08	.915
NAB list B immediate recall	0.00	0.07	−0.01	0.07	.912	−0.15	0.07	−0.08	0.07	.421
NAB list A short delay recall	0.00	0.08	−0.05	0.08	.650	−0.14	0.08	−0.08	0.08	.540
NAB long delay	0.00	0.07	−0.09	0.08	.425	−0.14	0.08	−0.12	0.08	.877
Visual-spatial domain	0.00	0.07	0.09	0.08	.419	−0.06	0.08	0.08	0.09	.173
NAB figure drawing copy	0.00	0.07	0.09	0.08	.419	−0.06	0.08	0.08	0.09	.173

Abbreviation: NAB, Neuropychological Assessment Battery.
*Patient case scores standardized using control mean and standard deviation as referent standard; therefore, by definition, unadjusted control mean scores are zero.
†Adjusted for age, race (white v nonwhite), education (in years), and recruitment site.

cases with earlier disease stage after adjustment (P = .05; Appendix Table A2, online only).

There were no differences in unadjusted rates of cognitive impairment between patient cases and controls (14% v 15%; P = .81). However, as shown in Figure 2, patient cases with high comorbidity levels had higher rates of impairment than patient cases with low comorbidity levels (25.7% v 4.4%); this relationship was also seen for patient cases by surgery type, but controls had similar rates of impairment in the high versus low comorbidity groups (17.5% v 12.8%; P < .001 for overall comparison). Surgery, anxiety, depression, fatigue, health habits and physical activity, and current physical or emotional function were not associated with impairment in any group (Table 4).

The adjusted odds of having impairment were not related to patient case or control status, but they were significantly higher in women who were older, of nonwhite race, and with lower educational levels (P ≤ .001; Table 4). There was also an interaction between comorbidity and patient case or control status; comorbidity was associated with impairment among patient cases (adjusted odds ratio, 8.77; 95% CI, 2.06 to 37.4; P = .003) but not among controls (P = .97). The result was similar using the alternative definition of impairment (data not shown).

In exploratory analyses, there were no differences between patient cases and controls in rate of diabetes (10.4% v 7.7%; P = .39) or cardiovascular disease (52.4% v 47.3%; P = .34). However, the impairment rate was significantly higher in patient cases with diabetes (v no diabetes; 41% v 11%; P = .003) or cardiovascular disease (22% v 5%; P = .002), whereas impairment was not associated with these conditions in controls (data not shown).

DISCUSSION

This is one of the largest controlled studies of cognitive impairment before systemic treatment in an older population with breast cancer. Rates of impairment were low, and we did not find any overall presystemic treatment differences between patient cases and their frequency-matched noncancer controls. However, patient cases with more advanced disease stage tended to have lower executive function than patient cases with early-stage disease. Additionally, after adjustment, the odds of presystemic treatment impairment were higher in patient cases with greater (v less) comorbidity, whereas impairment was not associated with comorbidity among controls. Last, demographic factors, such as age, race, or education, were associated with impairment, whereas psychological variables like anxiety, depression, fatigue, lifestyle factors, APOE genotype, and surgery were not.

It is difficult to compare our rates of presystemic treatment cognitive impairment with those from other studies, because most prior research has been conducted among young patients,[75,76] been based on self-report,[77,78] or used different definitions of impairment.[73] In one study that examined postmenopausal patients with breast cancer, Ahles et al[42] reported a 22% rate of impairment among patient cases with stage I to III disease, similar but somewhat higher than our rate of 14% for those with stages 0 to III disease.
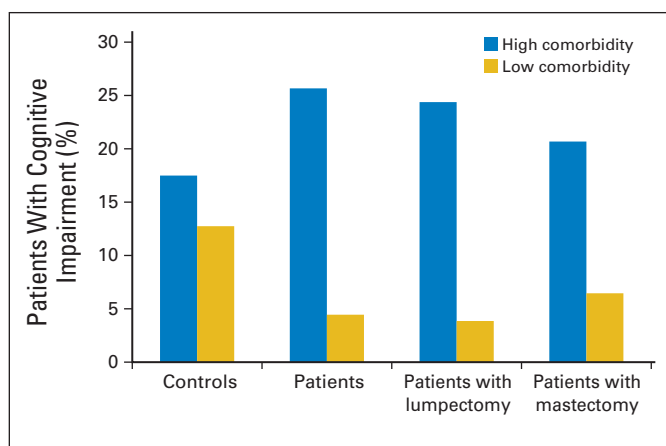
ilar to our results, this was not attributable to differences in surgery, function, anxiety, depression, or fatigue.[42] If confirmed, it would be important to understand if any executive dysfunction affects treatment decision making. A stage effect could also have biologic plausibility, with greater tumor burden exerting paraneoplastic effects or reflecting shared risk factors for cancer development and progression and cognitive impairment.[42] Another explanation for the inconsistent results for pretreatment differences is that effects are subtle. This possibility is suggested by findings showing significant differences between patient cases with breast cancer before systemic therapy and healthy controls on functional magnetic resonance imaging tasks related to visual-spatial working memory[25] or attention and working memory[26] in the absence of differences on neuropsychological tests.

The finding that independent of age, surgery, and other factors, comorbidity was associated with pretreatment cognitive impairment in patient cases but not controls is intriguing. There are several potential explanations for this result. First, comorbidity may be a marker for chronic inflammation. There have been some reports of associations between proinflammatory cytokine signaling biomarkers and cognitive impairment after systemic cancer therapy.[6,82,83] Another explanation is that comorbid illnesses such as diabetes or cardiovascular disease directly increase the risk of both cancer and cognitive impairment.[81] Comorbidity may also be a marker of common underlying processes related to aging, cancer development, or frailty or of specific diseases that may accelerate aging.[84] One such indicator may be insulin resistance, which has been suggested as a risk factor for dementia[85] and cancer.[86,87] Our study was not designed to elucidate or test these mechanisms. However, this will be an important area for further research, because older women generally have several comorbid illnesses.[88-91]

The result that older age, nonwhite race, and lower education increased the odds of having cognitive impairment was not unexpected. These demographic variables may help to identify individual older women at risk of cognitive problems, especially if considered within the context of a geriatric assessment.[92] We were surprised that presence of any *APOE* e4 allele was not associated with impairment,

Fig 2. Percent with cognitive impairment among older patients with breast cancer and noncancer controls by comorbidity level. Comorbidity categorized based on overall median. High comorbidity defined as ≥ two comorbid illnesses; low defined as < two illnesses. Impairment rates based on ≥ one domain score two standard deviations (SDs) below control mean or two domain scores 1.5 SDs below control mean. Figure shows unadjusted rates of impairment. Overall comparison between all patient cases and controls significant at $P < .001$. Among all patient cases, association between impairment and comorbidity significant at $P < .001$, whereas control difference not significant ($P = .98$).

There have been inconsistent findings regarding cognitive differences between patient cases with breast[13] or other cancers before systemic therapy[53] and controls.[7,42,79] For instance, Wefel et al[24] reported cognitive deficits before systemic treatment, whereas we and others[42,80,81] have not found these effects. There are several explanations for the conflicting results, including variability in definitions of impairment and referent standards.[73,74] Alternatively, the effects may only be experienced by subgroups that have not been clearly identified. Our observation that patient cases with more advanced disease stage had lower executive function than controls suggests one such potential subgroup. This finding is consistent with the finding in a study that noted slower reaction times among patient cases with later-stage disease compared with controls before systemic treatment. Sim-

Table 4. ORs for Associations With Pre–Systemic Treatment Cognitive Impairment* in Older Patients With Breast Cancer and Noncancer Controls

| | All Participants | | | | | | Patient Cases (n = 159)† | | | Controls (n = 181)† | | |
| | Unadjusted (N = 346) | | | Adjusted (n = 343)‡§ | | | | | | | | |
Variable	OR	95% CI	P	OR	95% CI	P	Adjusted OR	95% CI	P	Adjusted OR	95% CI	P
Patient case (v control)	0.93	0.51 to 1.71	.83	0.74	0.37 to 1.47	.39	—			—		
Age, per 1-year increase	1.12	1.07 to 1.17	< .001	1.10	1.05 to 1.15	< .001	1.09	1.02 to 1.18	.02	1.10	1.03 to 1.18	.003
Education, per 1-year increase	0.77	0.67 to 0.88	< .001	0.81	0.69 to 0.95	.008	0.83	0.64 to 1.08	.17	0.80	0.65 to 1.00	.050
Nonwhite race (v white, non-Hispanic)‖	2.90	1.51 to 5.60	.002	3.38	1.57 to 7.28	.002	5.45	1.57 to 18.9	.008	2.91	0.98 to 8.63	.054
≥ 2 comorbidities (v < 2)	2.81	1.50 to 5.27	.001	2.31	1.14 to 4.69	.020	8.77	2.06 to 37.4	.003	0.98	0.39 to 2.49	.97
Mastectomy (v lumpectomy)¶	—			—			0.59	0.16 to 2.25	.44	—		

NOTE. ORs are from logistic regression models. Variables not considered in models because they were not significantly related to impairment: current physical ($P = .22$) or emotional function ($P = .31$), depression ($P = .99$), anxiety ($P = .20$), fatigue ($P = .34$), smoking ($P = .93$), physical activity ($P = .33$), and presence of *APOE* e4 allele ($P = .21$).
Abbreviation: OR, odds ratio.
*Cognitive impairment defined as any one domain z score two SDs or two domain z scores 1.5 SDs below control mean.
†Models stratified by patient case or control status included because of interaction between patient case or control status and comorbidity.
‡All adjusted ORs adjusted for covariates shown plus recruitment site.
§Three patient cases were missing surgery or refused surgery and are not included.
‖Nonwhite race includes black, Hispanic, Asian American, and Pacific Islander.
¶Results for unadjusted association between surgery and impairment in patient case group: OR, 1.03; 95% CI, 0.41 to 2.60; $P = .951$.

because these genotypes have been previously related to cancer,[93,94] cognitive impairment, and dementia.[95,96] One explanation for our null result was the exclusion of those with pre-existing cognitive impairment. It is still possible that *APOE* e4 represents a marker for vulnerability to adverse cognitive effects of cancer systemic therapies among those meeting study entrance criteria. We will test this in longitudinal follow-up.

Despite the rigor of our design, there are several limitations that should be considered in interpreting the findings. First, patient cases were recruited primarily from academic centers and are not representative of all patients. However, the comparison of patient cases to well-matched noncancer controls and standardization of neuropsychological test scores to the control group enhance the internal validity of comparisons between patient cases and controls. Next, we cannot draw causal inferences about the association between comorbidity and impairment in patient cases, given the cross-sectional analysis. Also, despite the large sample, we were only powered to detect ≥ two-fold increase in the odds of impairment associated with patient case versus control status, so we cannot rule out smaller associations. However, we did have sufficient power to detect small to moderate effects of patient case versus control status for individual neuropsychological domains. Given the number of tests performed, some significant observations may have resulted from chance. The low overall impairment rate observed may reflect eligibility screening and the high education level in our sample. To the extent that education protects against cognitive decline, our estimates of impairment are likely to be conservative and lower than in the general population of older women. It would have also been interesting to look at our results by stage 0 versus invasive cancer, but the small number of patient cases with stage 0 disease precluded this analysis.

In summary, our results do not support an effect of cancer on pretreatment cognition among older patients with breast cancer. However, the findings do suggest that subgroups of older patients with breast cancer defined by greater tumor or comorbidity burden may be more susceptible to impairment before systemic therapy. It will be important to confirm these results, examine the biologic underpinnings of these observations, and observe the cohort longitudinally to fully understand how aging, cancer, and cancer treatments affect cognitive outcomes. Understanding at-risk groups could ultimately suggest avenues for intervention research to avoid adverse cognitive effects of breast cancer systemic treatments.

AUTHOR CONTRIBUTIONS

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Appendix

Table A1. Raw Baseline Pretreatment Cognitive Performance *z* Scores for Older Patients With Breast Cancer and Noncancer Controls Based on Neuropsychological Testing

| | | | Patient Cases | | | | | | *P* | | | |
| | Controls (n = 182) | | All (n = 164) | | Stages 0 to I (n = 106) | | Stages II to III (n = 58) | | Control *v* Patient Case | Control *v* Patient Case Stages 0 to I | Control *v* Patient Case Stages II to III | Patient Case Stages 0 to I *v* II to III |
Test	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Attention, working memory, and processing speed domain	0.00	0.66	−0.03	0.65	0.02	0.61	−0.11	0.72	.699	.815	.276	.227
NAB digits forward[a]	8.34	2.34	8.23	2.34	8.41	2.33	7.91	2.35	.682	.805	.235	.199
NAB digits backward[a]	4.49	2.17	4.46	2.10	4.52	2.20	4.34	1.90	.890	.911	.651	.613
Trail making A, time in seconds	36.79	14.30	37.30	14.26	36.90	11.99	38.04	17.76	.738	.947	.584	.624
Digit symbol test[b]	52.73	11.18	52.15	12.02	53.62	11.33	49.45	12.85	.640	.517	.062	.033
NAB driving scenes[c]	46.55	6.78	46.65	6.74	46.44	7.05	47.05	6.15	.888	.895	.620	.583
Language domain	0.00	0.85	−0.07	0.82	−0.06	0.76	−0.09	0.91	.410	.531	.469	.813
Boston naming test[d]	26.60	3.30	26.38	3.00	26.39	2.76	26.38	3.43	.528	.577	.662	.988
Category fluency[e]	21.27	5.02	20.85	4.91	20.96	4.88	20.66	4.99	.438	.614	.418	.703
Executive functioning domain	0.00	0.67	−0.12	0.64	−0.05	0.56	−0.25	0.77	.091	.507	.020	.065
Trail making B, time in seconds	85.77	50.62	92.51	53.39	86.83	47.21	102.90	62.27	.229	.861	.035	.065
Controlled oral word association test[f]	43.83	13.87	40.28	12.46	40.97	12.40	39.02	12.58	.013	.081	.019	.338
NAB figure drawing organization[g]	7.96	1.82	8.01	1.81	8.09	1.79	7.86	1.84	.796	.549	.719	.433
Learning and memory domain	0.00	0.78	−0.04	0.79	−0.06	0.79	−0.00	0.78	.620	.502	.996	.620
Logical memory I[h]	13.33	3.74	13.20	3.89	13.18	3.97	13.22	3.77	.743	.748	.852	.944
Logical memory II[i]	11.92	4.04	12.10	4.23	11.86	4.24	12.55	4.23	.686	.895	.309	.317
NAB list A immediate recall[j]	23.43	4.91	22.88	5.16	22.57	4.99	23.45	5.45	.305	.151	.985	.296
NAB list B immediate recall[k]	4.58	1.96	4.55	1.74	4.57	1.60	4.53	1.98	.912	.961	.886	.912
NAB list A short delay recall[l]	7.58	2.52	7.46	2.59	7.44	2.69	7.48	2.42	.650	.660	.792	.926
NAB long delay[m]	7.86	2.54	7.64	2.50	7.62	2.54	7.67	2.45	.425	.451	.627	.903
Visual-spatial domain	0.00	1.00	0.09	0.97	0.04	1.04	0.17	0.84	.419	.754	.237	.403
NAB figure drawing copy[n]	25.95	4.19	26.31	4.08	26.11	4.35	26.79	3.51	.419	.754	.237	.403

NOTE. Patient case domain scores standardized using control mean and SD as referent standard. With the exception of Trail making A and B, higher raw scores reflect better performance.

Abbreviations: NAB, Neuropychological Assessment Battery; SD, standard deviation.
[a]No. of sequences correctly recalled.
[b]No. of symbols produced in allowed time.
[c]No. of new or missing items correctly identified.
[d]No. of objects correctly named.
[e]No. of animals named in allowed time.
[f]No. of words given in allowed time.
[g]Sum of fragmentation and planning scores.
[h]No. of pieces of story recalled immediately.
[i]No. of pieces of story recalled after delay.
[j]Sum of three trials of word recall.
[k]No. of words recalled.
[l]No. of words recalled after short delay.
[m]No. of words recalled after long delay.
[n]Accuracy of figure copy.

Table A2. Standardized Baseline Pretreatment Neuropsychological Test Results for Older Patients With Breast Cancer

| | Unadjusted Standardized z Score* | | | | | Adjusted Standardized z Score† | | | | |
| | Stages 0 and I | | Stages II and III | | | Stages 0 and I | | Stages II and III | | |
Test	Mean	SE	Mean	SE	P	Mean	SE	Mean	SE	P
Attention, working memory, and processing speed domain	0.02	0.06	−0.11	0.09	.23	0.14	0.11	0.03	0.11	.25
NAB digits forward	0.03	0.10	−0.18	0.13	.20	0.30	0.19	0.10	0.20	.23
NAB digits backward	0.01	0.09	−0.07	0.13	.61	0.01	0.19	−0.02	0.20	.85
Trail making A	−0.01	0.10	−0.09	0.13	.62	0.14	0.18	0.05	0.19	.56
Digit symbol test	0.08	0.10	−0.29	0.14	.03	0.14	0.19	−0.14	0.19	.10
NAB driving scenes	−0.02	0.10	0.07	0.13	.58	0.11	0.18	0.16	0.19	.74
Language domain	−0.06	0.08	−0.09	0.11	.81	0.13	0.14	0.14	0.14	.80
Boston naming test	−0.06	0.09	−0.07	0.12	.99	0.16	0.15	0.20	0.16	.74
Category fluency	−0.06	0.10	−0.12	0.13	.70	0.09	0.18	0.09	0.18	.96
Executive function domain	−0.05	0.06	−0.25	0.08	.06	0.05	0.12	−0.16	0.12	.05
Trail making B	−0.02	0.10	−0.34	0.14	.07	0.14	0.19	−0.18	0.19	.054
Controlled oral word association test	−0.21	0.09	−0.35	0.12	.34	−0.12	0.17	−0.26	0.18	.34
NAB figure drawing	0.07	0.10	−0.05	0.13	.43	0.11	0.19	−0.04	0.20	.38
Learning and memory domain	−0.06	0.08	−0.00	0.10	.62	−0.08	0.14	0.06	0.14	.26
Logical memory I	−0.04	0.10	−0.03	0.14	.94	−0.12	0.20	−0.00	0.21	.50
Logical memory II	−0.02	0.10	0.16	0.14	.32	−0.17	0.20	0.11	0.20	.12
NAB list A immediate recall	−0.18	0.10	0.00	0.14	.30	−0.12	0.18	0.16	0.18	.07
NAB list B immediate recall	−0.01	0.09	−0.02	0.12	.91	0.17	0.16	0.20	0.16	.84
NAB list A short delay recall	−0.06	0.10	−0.04	0.14	.93	−0.12	0.18	−0.06	0.19	.71
NAB long delay	−0.09	0.10	−0.07	0.13	.90	−0.09	0.18	−0.04	0.18	.72
Visual-spatial domain	0.04	0.09	0.17	0.13	.40	0.05	0.19	0.24	0.20	.24
NAB figure drawing copy	0.04	0.09	0.17	0.13	.40	0.05	0.19	0.24	0.20	.24

Abbreviation: NAB, Neuropychological Assessment Battery.
*Patient case scores standardized using control mean and standard deviation as referent standard.
†Adjusted for age, race (white v nonwhite), education (in years), recruitment site, and surgery (mastectomy and lumpectomy).