VOLUME 36 · NUMBER 32 · NOVEMBER 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cancer-Related Cognitive Outcomes Among Older Breast Cancer Survivors in the Thinking and Living With Cancer Study

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Published at jco.org on October 3, 2018.

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Clinical trial information: NCT03451383.

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0732-183X/18/3632w-3211w/$20.00

A B S T R A C T

Purpose

To determine treatment and aging-related effects on longitudinal cognitive function in older breast cancer survivors.

Methods

Newly diagnosed nonmetastatic breast cancer survivors (n = 344) and matched controls without cancer (n = 347) 60 years of age and older without dementia or neurologic disease were recruited between August 2010 and December 2015. Data collection occurred during presystemic treatment/control enrollment and at 12 and 24 months through biospecimens; surveys; self-reported Functional Assessment of Cancer Therapy-Cognitive Function; and neuropsychological tests that measured attention, processing speed, and executive function (APE) and learning and memory (LM). Linear mixed-effects models tested two-way interactions of treatment group (control, chemotherapy with or without hormonal therapy, and hormonal therapy) and time and explored three-way interactions of *ApoE* (ε4+ *v* not) by group by time; covariates included baseline age, frailty, race, and cognitive reserve.

Results

Survivors and controls were 60 to 98 years of age, were well educated, and had similar baseline cognitive scores. Treatment was related to longitudinal cognition scores, with survivors who received chemotherapy having increasingly worse APE scores ($P = .05$) and those initiating hormonal therapy having lower LM scores at 12 months ($P = .03$) than other groups. These group-by-time differences varied by *ApoE* genotype, where only ε4+ survivors receiving hormone therapy had short-term decreases in adjusted LM scores (three-way interaction $P = .03$). For APE, the three-way interaction was not significant ($P = .14$), but scores were significantly lower for ε4+ survivors exposed to chemotherapy (−0.40; 95% CI, −0.79 to −0.01) at 24 months than ε4+ controls (0.01; 95% CI, 0.16 to 0.18; $P < .05$). Increasing age was associated with lower baseline scores on all cognitive measures ($P < .001$); frailty was associated with baseline APE and self-reported decline ($P < .001$).

Conclusion

Breast cancer systemic treatment and aging-related phenotypes and genotypes are associated with longitudinal decreases in cognitive function scores in older survivors. These data could inform treatment decision making and survivorship care planning.

J Clin Oncol 36:3211-3222. © 2018 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.18.00140

Data Supplement
DOI: https://doi.org/10.1200/JCO.18.00140

DOI: https://doi.org/10.1200/JCO.18.00140

INTRODUCTION

Cognitive problems commonly have been reported among breast cancer survivors before and after systemic therapy.[1-12] However, these declines are not universal,[8,13,14] can be subtle, can vary by treatment regimen, and may only affect certain subgroups.[15] Older survivors have not been well studied, but should be at risk for cancer-related cognitive decline[1,2,6,15,16] because aging is associated with an increasing incidence of neurodegenerative

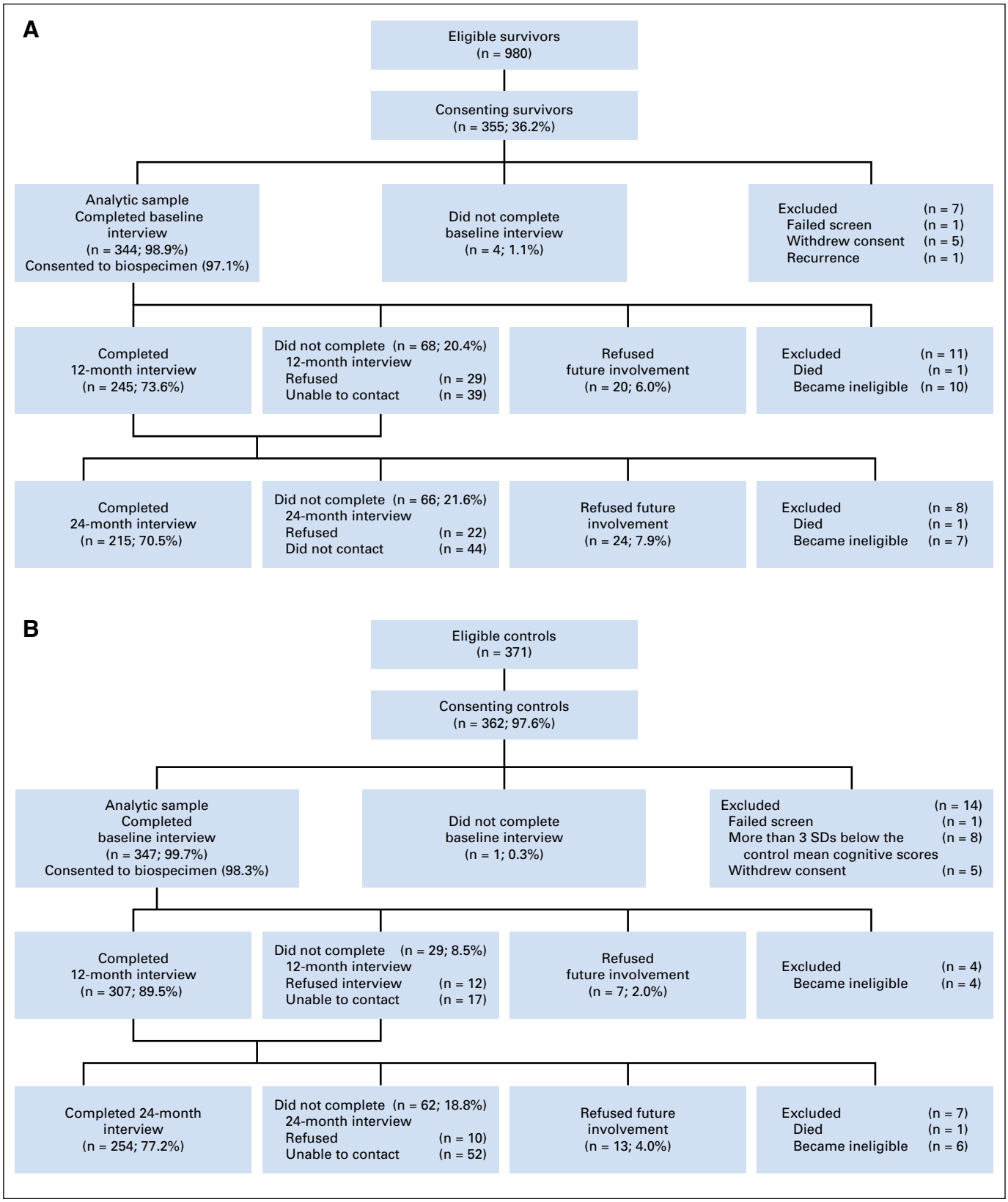

Fig 1. (A) Sample for evaluation of cognition in older breast cancer survivors and (B) matched controls without cancer. Participants were excluded if they failed the cognitive screen (at baseline). The percentage who consented and refused was calculated among those alive and eligible to continue the study at each time point. Eligibility for continuing in the study was the same as enrollment eligibility and included development of a neurologic disease (eg, stroke, Parkinson's disease) and a diagnosis of cancer. Survivors who were diagnosed with breast cancer recurrence were excluded from assessment for the 6 months before diagnosis of recurrence. Participants may have refused an interview at one time point but then completed later interviews. Most participants completed two or three assessments (continued on next page)

disease and shares many common biologic pathways with putative mechanisms of cancer-related cognitive decline.[15] Furthermore, chemotherapy produces changes in biomarkers[17] and brain structure that mimic aging.[18-21] Chronologic age and aging phenotypes, such as frailty[22] and/or high comorbidity burden, may be markers for risk of cognitive decline.[3] Genotypes associated with neurodegenerative disease, including polymorphisms in the apolipoprotein E (*ApoE*) gene, a risk factor for Alzheimer's disease, also have been reported to be associated with cancer-related cognitive decline.[2,23,24]

Identification of specific risk factors for cancer-related cognitive decline in older populations has important implications for oncology care[1] because 75% of breast cancer survivors in the United States are 60 years of age and older[25] and because detection of subtle cognitive problems can be challenging in practice.[2,26,27] Among the few prospective studies that have examined risk of cognitive decline in older survivors,[3,26] few included a contemporaneous noncancer control group to assess the effect of aging[28] or examine whether risk factors vary in their effects by treatment regimen.[2,26]

Thinking and Living With Cancer (TLC) is a multisite prospective study designed to fill this clinical gap. We used data from older breast cancer survivors and matched controls without cancer followed for 24 months to evaluate cognition after breast cancer and its therapies relative to that seen with aging alone. We focused on two cognitive domains related to aging and commonly affected in cancer-related cognitive decline: attention, processing, and executive function (APE) and learning and memory (LM).[1,2] We tested the hypothesis that older survivors exposed to chemotherapy (with or without hormonal therapy) would have lower neuropsychological domain and self-reported cognitive scores over time than survivors who received hormonal therapy only or controls. We also examined whether age, frailty, or comorbidity was independently related to cognitive scores and explored whether *ApoE* gene polymorphisms affected the differences in cognitive domain scores among treatment groups over time. The results are intended to inform clinical practice.

METHODS

This study was conducted at Georgetown University and affiliated practices in the Washington, DC, area; Memorial Sloan Kettering Cancer Center; Moffitt Cancer Center; City of Hope Comprehensive Cancer Center; Hackensack University Medical Center; Indiana University (IU) School of Medicine; and University of California, Los Angeles. IU and University of California, Los Angeles, joined the study for laboratory support and IU for participant recruitment in 2016, so data in this report are from the five other sites. All institutional review boards approved the protocol.

Setting and Population

We included participants recruited between August 1, 2010, and December 31, 2015; the study is ongoing. Eligible survivors were 60 years of age or older, newly diagnosed with primary nonmetastatic breast cancer, and English speaking. Those with stroke, head injury, major axis I psychiatric disorders, and neurodegenerative disorders were ineligible. Survivors with a history of other cancers were excluded if active treatment was for less than 5 years or they had systemic therapy. Among eligible survivors, 355 consented (36.5%; consent rate across sites, 17.2% to 72.7%; median, 62.5%; Fig 1). Consenting survivors were similar in age to nonparticipants.

There were 362 consenting controls without cancer, including 88 friends. When no friend was available, we recruited age-, race-, education-, and site-frequency–matched controls. All controls met the same eligibility criteria as survivors.

Participants were screened using the Mini-Mental State Examination and the Wide Range Achievement Test 4 (WRAT4) Word Reading subtest; those with scores less than 24 or less than third-grade–equivalent reading level were ineligible (one control and one survivor, respectively). Controls who scored more than 3 standard deviations (SDs) below the control mean baseline neuropsychological scores for their age- and education group were ineligible post hoc (n = 8). Data for survivors who experienced a recurrence (n = 1) were excluded for the 6 months before recurrence. Nine consenting survivors and six controls did not complete baseline assessments. The final sample included 344 survivors and 347 controls. Among participants remaining alive and eligible, 73.6% and 70.5% of survivors and 89.5% and 77.2% of controls completed 12- and 24-month assessments, respectively (Fig 1).

Data Collection

Assessments included neuropsychological testing, a structured survey, and biospecimens for *ApoE* genotyping. Staff members were certified bi-annually on neuropsychological test administration. *ApoE* genotype was batch tested using TaqMan assays (rs429358 assay identifier: C_3084793_20; rs7412 assay identifier: C_904973_10; Life Technologies, Carlsbad, CA) on a 7900HT Fast Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA); analyses were blinded to group and used TaqMan Genotyper Software version 1.3 (Thermo Fisher Scientific).

Measures

Outcomes. The primary cognitive outcome was the domain-specific scores on neuropsychological tests of APE (six tests)[2,6,23]; verbal LM (five tests) was the other outcome of interest. Visuospatial ability (two tests) was a secondary domain. We used recommended tests with established reliability and validity in older populations[29-31] and included instruments with equivalent forms[31] where possible to minimize practice effects.

Factor analysis confirmed that domain structure and reliability were consistent for survivors and controls at all time points (Appendix Table A1, online only). A language domain included in earlier reports[3] was dropped because it was not a separate factor and had limited variation. The visuospatial domain was not reported because of poor reliability. Secondary outcomes included cognitive subdomain scores and self-reported cognition on the basis of the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog[32,33]; Cronbach's $\alpha = 0.96$); declines of 5% to 7%, or 7 to 10 points, were considered clinically meaningful.[34]

Variables. The primary predictor was treatment group (chemotherapy [with or without hormonal therapy], hormonal therapy only, or noncancer control). We explored whether *ApoE* genotype (ε4+ *v* not) affected treatment group differences in cognitive scores over time and examined whether baseline age, frailty, comorbidity burden (two or fewer *v* more than two illnesses), or diabetes were independently related to cognition.[3] Frailty was measured using the Searle's deficits accumulation index.[35-41] Our 40-item adapted index excluded cognition but included baseline comorbidity; prediagnosis/pre-enrollment physical, social, role, and emotional function using the 12-Item Short-Form Health Survey

(Continued). (64% completed three, 21% completed two, and 15% completed baseline only). No significant differences existed in age, frailty, apolipoprotein E ε4 status, or self-reported cognition by number of completed assessments. Those completing baseline only tended to have slightly lower baseline attention, processing speed, and executive function and learning and memory scores than those completing two or more assessments and to be a survivor versus a control, which potentially underestimated declines in mean post-treatment 12- and 24-month scores. SD, standard deviation.

Table 1. Baseline Characteristics of Older Breast Cancer Survivor Versus Controls Without Cancer

Characteristic	Participants, No. (%)					
	Controls (n = 347)	Survivors (n = 344)	P^a	Survivors Who Received Chemotherapy ± Hormonal Therapy (n = 94)	Survivors Who Received Hormonal Therapy Only (n = 237)	P^b
Sociodemographic						
Age, years			.49			< .01
Mean (SD)	67.8 (7.0)	68.1 (6.1)		66.1 (4.8)	68.8 (6.4)	
Range	60-91	60-98		60-84	60-98	
Race			.97			.67
White, non-Hispanic	273 (78.9)	271 (78.8)		73 (77.7)	189 (79.7)	
Nonwhite[c]	73 (21.1)	73 (21.2)		21 (22.3)	48 (20.3)	
Marital status			< .01			.44
Married	163 (47.8)	197 (59.9)		53 (57.0)	138 (61.6)	
Widowed, divorced, single	178 (52.2)	132 (40.1)		40 (43.0)	86 (38.4)	
Mean education, years (SD)	15.4 (2.3)	15.1 (2.2)	.08	15.3 (2.3)	15.1 (2.1)	.56
Mean WRAT4 score (SD)	111.8 (16.1)	110.9 (15.4)	.49	110.9 (15.3)	111.2 (15.8)	.87
Family history of dementia			.21			.34
Yes	121 (37.9)	101 (33.1)		31 (36.9)	65 (31.1)	
No	198 (62.1)	204 (66.9)		53 (63.1)	144 (68.9)	
Standardized, unadjusted baseline cognition scores						
Neuropsychological testing[d]						
Mean APE (SD)	−0.05 (0.04)	−0.11 (0.04)	.30	−0.12 (0.07)	−0.10 (0.05)	.98
Mean LM (SD)	−0.03 (0.04)	−0.05 (0.05)	.86	−0.05 (0.09)	0.00 (0.06)	.63
Mean self-report[e] (SD)	129.1 (16.1)	128.2 (18.5)	.51	128.9 (17.6)	127.7 (18.9)	.62
Lifestyle factors						
Smoking status			.97			.75
Current/former smoker	152 (45.1)	147 (45.2)		43 (46.7)	99 (44.8)	
Never smoked	185 (54.9)	178 (54.8)		49 (53.3)	122 (55.2)	
Current alcohol use			.18			.24
Unknown/refused	39 (11.2)	52 (15.1)		14 (14.9)	36 (15.2)	
Nondrinker	45 (13.0)	57 (16.6)		17 (18.1)	38 (16.0)	
≤ 1 drink/d	197 (56.8)	173 (50.3)		52 (55.3)	113 (47.7)	
> 1 drink/d	66 (19.0)	62 (18.0)		11 (11.7)	50 (21.1)	
Mean age at menopause (SD)	49.5 (6.0)	48.8 (6.9)	.15	50.0 (5.8)	48.4 (7.2)	.06
Hormonal replacement therapy (any type, excluding oral contraceptives)			.21			.64
Never/unsure	177 (51.0)	172 (50.0)		50 (53.2)	48.4 (7.2)	
< 1 year	19 (5.5)	23 (6.7)		6 (6.4)	115 (48.5)	
1 to < 5 years	60 (17.3)	47 (13.7)		12 (12.8)	17 (7.2)	
5 to < 10 years	38 (11.0)	30 (8.7)		5 (5.3)	32 (13.5)	
≥ 10 years	53 (15.3)	72 (20.9)		21 (22.3)	25 (10.5)	
Current use of hormonal therapy			< .01			.41
Yes	37 (21.8)	2 (1.2)		0 (0.0)	2 (1.6)	
No	133 (78.2)	171 (98.8)		42 (100.0)	121 (98.4)	
Clinical factors						
Frailty[f]			.02			.69
Prefrail/frail	60 (18.1)	81 (25.6)		22 (25.0)	59 (27.2)	
Robust	272 (81.9)	236 (74.4)		66 (75.0)	158 (72.8)	
Comorbidities						
Mean No. (SD)	2.4 (1.8)	2.6 (1.9)	.17	2.4 (2.1)	2.7 (1.9)	.24
≤ 2 (median)	196 (58.2)	168 (52.7)	.16	57 (63.3)	104 (47.9)	.01
> 2	141 (41.8)	151 (47.3)		33 (36.7)	113 (52.1)	
ApoE genotype[g]			.12			.19
ApoE ε4−	252 (75.0)	250 (79.9)		73 (84.9)	168 (78.1)	
ApoE ε4+	85 (25.0)	63 (20.1)		13 (15.1)	47 (21.9)	
AJCC stage			—			< .01
0	—	41 (12.0)		1 (1.1)	32 (13.5)	
I	—	190 (55.4)		36 (38.7)	152 (64.1)	
II	—	94 (27.4)		41 (44.1)	50 (21.1)	
III	—	18 (5.2)		15 (16.1)	3 (1.3)	
Surgery type			—			.08
BCS ± RT	—	189 (55.4)		46 (48.9)	139 (59.4)	
Mastectomy	—	152 (44.6)		48 (51.1)	95 (40.6)	

(continued on following page)

Table 1. Baseline Characteristics of Older Breast Cancer Survivor Versus Controls Without Cancer (continued)

Characteristic	Participants, No. (%)					
	Controls (n = 347)	Survivors (n = 344)	P^a	Survivors Who Received Chemotherapy ± Hormonal Therapy (n = 94)	Survivors Who Received Hormonal Therapy Only (n = 237)	P^b
Mean time since surgery to baseline, days (SD)[h]	—	49.9 (54.9)	—	29.4 (46.7)	55.8 (52.4)	< .01
ER status			—			< .01
Positive	—	301 (87.5)		65 (69.1)	236 (99.6)	
Negative	—	43 (12.5)		29 (30.9)	1 (0.4)	
HER2 status			—			< .01
Positive	—	39 (13.4)		25 (26.9)	14 (7.3)	
Negative	—	251 (86.6)		68 (73.1)	179 (92.7)	
Mean physical function score before diagnosis[i] (SD)	52.0 (7.1)	52.0 (7.0)	.91	51.4 (7.9)	52.0 (6.8)	.56
Mean emotional function score before diagnosis[i] (SD)	56.3 (5.0)	57.1 (4.7)	.04	57.9 (3.8)	56.8 (5.1)	.06
Depression[j] (≥ 16 on CES-D)	18 (5.4)	43 (13.9)	< .01	20 (23.0)	23 (10.9)	< .01
Mean anxiety score[k] (SD)	26.7 (5.7)	29.5 (8.4)	< .01	31.5 (11.0)	28.7 (7.1)	< .01
Mean fatigue score[l] (SD)	46.4 (5.8)	43.1 (8.5)	< .01	43.4 (8.0)	42.7 (8.8)	.56
Mean baseline physical function score[m] (SD)	21.9 (2.4)	19.9 (3.9)	< .01	19.8 (3.8)	19.9 (3.9)	.97
Mean baseline emotional function score[n] (SD)	14.5 (1.6)	13.1 (2.8)	< .01	11.9 (3.2)	13.5 (2.5)	< .01

NOTE. Some percentages may not add to 100 because of missing data; 13 survivors were missing systemic therapy data. *P* values are based on χ^2 or *t* tests.
Abbreviations: AJCC, American Joint Committee on Cancer; APE, attention, processing speed, and executive function; *ApoE*, apolipoprotein E; BCS, breast-conserving surgery; CES-D, Center for Epidemiologic Studies Depression Scale; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LM, learning and memory; RT, radiotherapy; SD, standard deviation; WRAT4, Wide Range Achievement Test 4 Word Reading subtest.
[a]Survivors versus controls.
[b]Survivors chemotherapy versus hormonal therapy.
[c]Nonwhite includes black, Hispanic, and Asian American/Pacific Islander; one participant without cancer was missing race data.
[d]Neuropsychological test scores by domain. Cognitive scores were standardized using the sample mean and SD of age- and education group–matched baseline controls. Hence, a score of 0 indicates a score at the mean of the control group; scores < 0 indicate lower scores than the mean of the control group, and positive scores indicate scores higher than the mean of the control group.
[e]On the basis of the Functional Assessment of Cancer Therapy (FACT)-Cognitive Function. Scores range from 0 to 148, with higher scores indicating better cognition; declines of 5% to 7%, or 7 to 10 points, on this 148-point scale are considered clinically meaningful.[34]
[f]On the basis of scores for baseline frailty adapted from Searle's deficits accumulation index.[35,36] Excludes cognitive function.
[g]Consent for *ApoE* biospecimens was provided by 97.1% and 98.3% of survivors and controls in the final analytic sample, respectively; 21 consenting survivors and four controls were unable to provide a specimen, had a specimen with insufficient DNA, or were lost, so percentages do not add to 100. Twenty-four percent provided blood, and 76% gave saliva using an Oragene kit (DNA Genotek, Ottawa, Ontario, Canada). Samples were tested while blinded to group status. Among those with an ε4 allele, only seven survivors and seven controls were homozygous.
[h]Time since surgery was not calculated for participants who underwent neoadjuvant therapy (six with lumpectomy and two with mastectomy).
[i]On the basis of the 12-Item Short-Form Health Survey for the period 2 months before cancer diagnosis; higher scores indicate better function.
[j]Depression defined by score above the cut point of 16 on the CES-D.
[k]On the basis of the State-Trait Anxiety Inventory. Scores range from 20 to 80, with higher scores reflecting more anxiety.
[l]On the basis of the FACT-Fatigue. Scores range from 0 to 52; higher scores reflect less fatigue.
[m]On the basis of the FACT-General Physical Well-Being subscale. Scores range from 0 to 24; higher scores reflect better function.
[n]On the basis of the FACT-General Emotional Well-Being subscale. Scores range from 0 to 16; higher scores reflect better function.

(Cronbach's α = 0.85)[42]; prediagnosis/pre-enrollment activities of daily living and instrumental activities of daily living[43]; and baseline Timed Up and Go score.[44] Scores were categorized using established cut points (robust, 0 to less than 0.2; prefrail, 0.2 to less than 0.35; frail, 0.35 or greater).[40]

Several covariates were examined as possible confounders of the effects of group on cognition. Sociodemographic measures included race (white *v* nonwhite), cognitive reserve (WRAT4 score), self-reported family history of dementia (first-degree relative, yes *v* no), married versus not married, and years of education. Lifestyle habits included self-reported ever use of any type of hormonal replacement therapy (excluding oral contraceptives), cigarette smoking (ever/current *v* never), and current alcohol use. Baseline function was assessed using the FACT-General (Cronbach's α = 0.71).[45,46]

Scores of 16 or greater on the Center for Epidemiologic Studies Depression Scale defined clinical depression.[47] The State-Trait Anxiety Inventory was used to measure state anxiety (Cronbach's α = 0.86).[48] Fatigue was assessed using the FACT-Fatigue scale (Cronbach's α = 0.90).[49] Clinical variables included surgery type, breast irradiation, biomarkers, and stage.

Statistical Analysis

Raw neuropsychological test results (Appendix Table A2, online only) were standardized to *z* scores using the baseline means and SDs of age- and education group–matched controls without cancer.[50] Standardized *z* scores were calculated for domains (Appendix Table A3, online only). Univariable tests compared characteristics by group and evaluated potential confounders. All participants with complete baseline data were included in the analyses, and the characteristics of those with two to three assessments (*v* one) were evaluated for relationships to key variables.

Linear mixed-effects models tested the protocol-specified analyses: the presence of group-by-time and group-by-time-by-*ApoE* interactions for cognitive domain, subdomain, and self-reported scores (and 95% CIs). These models included a participant-specific random effect. Age, race, WRAT4 score, and site were included as fixed effects to adjust for potential confounding effects. Given strong correlations, frailty, comorbidity, or diabetes was included in the models one at a time. We estimated that there was 80% power to detect a group-by-time effect size equivalent to a Cohen's *d* of 0.3 when 30% to 40% of 342 survivors received chemotherapy.

In sensitivity analyses, we evaluated effects of group on specific tests or subdomain scores and whether fatigue, anxiety, depression, or smoking changed conclusions about interactions. Finally, we explored two- and three-way interactions of age with group and time. Analyses were conducted using SAS 9.4.b statistical software (SAS Institute, Cary, NC).

RESULTS

Participants ranged in age from 60 to 98 years and had an average of 15 years of education. There were no baseline differences in sociodemographic factors, cognitive scores, or *ApoE* genotypes between survivors and controls, except survivors were more often married and had a higher proportion who were frail (Table 1). Twenty-seven percent of survivors received chemotherapy (with or without hormonal therapy); the majority of chemotherapy regimens were anthracycline based, and most hormonal treatment was initiated with aromatase inhibitors (Table 1).

APE Domain

Cognitive scores tended to improve over time, consistent with expected practice effects. However, there was a significant group-by-time interaction (P = .05) where survivors exposed to chemotherapy did not show practice effects and actually had declines in adjusted mean APE scores, whereas the other groups increased over time (Fig 2). Baseline frailty was an independent predictor of baseline APE scores ($P < .001$; Table 2). In models that included comorbidity or diabetes instead of frailty, those with more than two comorbid conditions (v two or fewer; $P < .01$) had significantly lower baseline mean APE scores independent of other effects (Appendix Table A4, online only), and diabetes (v no diabetes) was borderline significantly associated with lower scores (P = .09; Appendix Table A5, online only).

The three-way group-by-time-by-*ApoE* interaction was not statistically significant for APE scores (P = .14; Table 2; Fig 3A). Despite this, an inspection of the means indicated that the small number of survivors who were *ApoE* ε4+ and exposed to chemotherapy had lower adjusted APE mean scores at 24 months (−0.40; 95% CI, −0.79 to −0.01) than the *ApoE* ε4+ controls (0.01; 95% CI, 0.16 to 0.18; $P < .05$).

Depression, anxiety, fatigue, or smoking and other lifestyle factors did not affect the mean scores for the various group-by-time or group-by-time-by-*ApoE* combinations (data not shown). Results for the APE subdomain and individual test scores followed a similar pattern as the overall domain results (data not shown). Older age was significantly associated with lower baseline cognitive scores, but the effects of treatment over time did not vary by age (data not shown).

LM Domain

A significant group-by-time interaction was found where survivors taking hormonal therapy alone had less improvement in cognitive scores at 12 months than other groups but improved by 24 months (P = .03 for two-way interaction; Fig 2). There was also a statistically significant group-by-time-by-*ApoE* interaction (P = .03), where differences in LM scores between treatment groups over time were largely confined to those who were *ApoE* ε4+ and initiated hormonal therapy. This group had a small LM decline at 12 months but subsequent improvement at 24 months, whereas other genotypes and groups showed early improvements (Table 2; Fig 3B). Frailty, comorbidity, diabetes, and other covariates did not change the conclusions with regard to interaction effects. LM

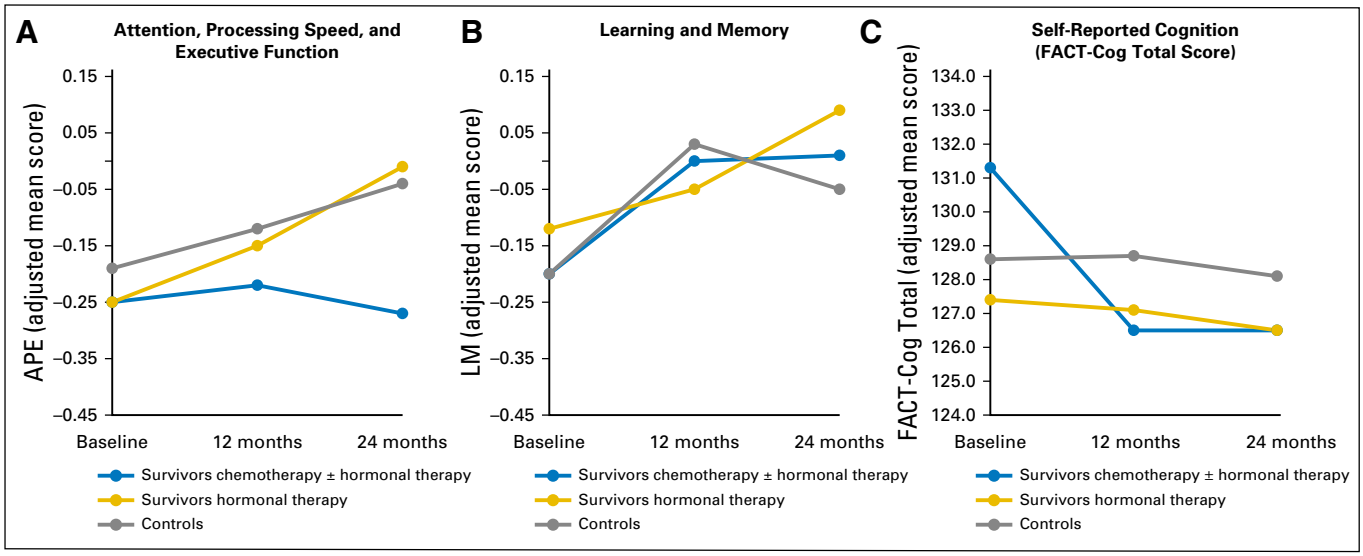

Fig 2. Adjusted mean cognitive scores over time for older breast cancer survivors and controls without cancer. Adjusted mean cognitive domain scores on the basis of least squares means from linear mixed-effects models show scores at baseline, 12 months, and 24 months for three treatment groups, including survivors who received chemotherapy with or without hormonal therapy, survivors who received only hormonal therapy, and controls. The models included as fixed effects time; group; apolipoprotein E genotype; all two- and three-way interactions for group, apolipoprotein E, and time; baseline age; frailty; standardized Wide Range Achievement Test 4 score; race; and recruitment site. Adjusted mean scores are shown by treatment group and time for the (A) attention, processing speed, and executive function (APE) domain (P = .05 for group-by-time interaction) and (B) learning and memory (LM) domain (P = .03 for group-by-time interaction) for the genotypes combined. (C) Self-reported cognition scores on the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog), with higher scores indicating better cognitive function. Declines of 5% to 7%, or 7 to 10 points, on this 148-point scale are considered clinically meaningful.[34] Tables 2 and 3 include the 95% CIs for each mean score at each time point and for each outcome.

Table 2. Adjusted Mean APE and LM Domain Cognitive Scores Among Older Breast Cancer Survivors and Controls Without Cancer by Time, Treatment, and Genotype

Domain	Sample Size (N = 603)	Adjusted Mean Cognitive *z* Score (95% CI)*			Overall *P*†
		Baseline	12 Months	24 Months	
APE					
Group-by-time interaction					.05
Chemotherapy	80	−0.25 (−0.44 to −0.06)	−0.22 (−0.42 to −0.02)	−0.27 (−0.50 to −0.04)	
Hormonal therapy	201	−0.25 (−0.38 to −0.12)	−0.15 (−0.28 to −0.01)	−0.01 (−0.15 to 0.14)	
Control	322	−0.19 (−0.31 to −0.07)	−0.12 (−0.24 to 0.00)	−0.04 (−0.16 to 0.09)	
Group-by-time by *ApoE* interaction					.14
Survivor					
Chemotherapy ± hormonal therapy, *ApoE* ε4+	12	−0.29 (−0.61 to 0.03)	−0.33 (−0.67 to 0.01)	−0.40 (−0.79 to −0.01)	
Chemotherapy ± hormonal therapy, *ApoE* ε4−	68	−0.21 (−0.37 to −0.05)	−0.10 (−0.27 to 0.07)	−0.14 (−0.33 to 0.04)	
Hormonal therapy, *ApoE* ε4+	41	−0.31 (−0.49 to −0.12)	−0.26 (−0.46 to −0.07)	0.02 (−0.20 to 0.24)	
Hormonal therapy, *ApoE* ε4−	160	−0.19 (−0.32 to −0.06)	−0.03 (−0.16 to 0.10)	−0.03 (−0.17 to 0.11)	
Control					
ApoE ε4+	81	−0.19 (−0.34 to −0.04)	−0.12 (−0.27 to 0.04)	0.01 (−0.16 to 0.18)	
ApoE ε4−	241	−0.19 (−0.31 to −0.07)	−0.12 (−0.24 to 0.00)	−0.08 (−0.21 to 0.04)	
Age					< .01
WRAT4 score					< .01
Race, nonwhite‡ (*v* white non-Hispanic)					< .01
Frailty (frail/prefrail *v* robust)					< .01
LM					
Group-by-time interaction					.03
Chemotherapy	80	−0.20 (−0.45 to 0.05)	0.00 (−0.27 to 0.27)	0.01 (−0.28 to 0.31)	
Hormonal therapy	201	−0.12 (−0.29 to 0.05)	−0.05 (−0.22 to 0.13)	0.09 (−0.09 to 0.28)	
Control	322	−0.20 (−0.35 to −0.05)	0.03 (−0.13 to 0.18)	−0.05 (−0.21 to 0.11)	
Group-by-time-by-*ApoE* interaction					.03
Survivor					
Chemotherapy ± hormonal therapy, *ApoE* ε4+	12	−0.23 (−0.65 to 0.19)	−0.06 (−0.52 to 0.39)	−0.02 (−0.53 to 0.49)	
Chemotherapy ± hormonal therapy, *ApoE* ε4−	68	−0.17 (−0.38 to 0.04)	0.06 (−0.17 to 0.28)	0.04 (−0.20 to 0.28)	
Hormonal therapy, *ApoE* ε4+	41	−0.14 (−0.38 to 0.10)	−0.18 (−0.44 to 0.09)	0.08 (−0.20 to 0.37)	
Hormonal therapy, *ApoE* ε4−	160	−0.10 (−0.27 to 0.06)	0.08 (−0.09 to 0.26)	0.11 (−0.08 to 0.29)	
Control					
ApoE ε4+	81	−0.30 (−0.49 to −0.10)	0.01 (−0.19 to 0.21)	−0.13 (−0.34 to 0.08)	
ApoE ε4−	241	−0.10 (−0.26 to 0.05)	0.05 (−0.11 to 0.21)	0.02 (−0.14 to 0.19)	
Age					< .01
WRAT4 score					< .01
Race, nonwhite‡ (*v* white non-Hispanic)					< .01
Frailty (frail/prefrail *v* robust)					.20

NOTE. Mean score from linear mixed-effects models; separate model for each domain. Among the 603 included in the models, 79, 119, and 405 contributed one, two, or three data points, respectively. All mean scores are from a model that includes the covariates shown plus time; group; *ApoE* genotype; all two- and three-way interactions for group, *ApoE*, and time; and recruitment site. Twenty-five controls and 63 survivors are not included in the model because of missing data on covariates.

Abbreviations: APE, attention, processing speed, and executive function; *ApoE*, apolipoprotein E; LM, learning and memory; WRAT4, Wide Range Achievement Test 4.

*All cognitive scores are standardized using the sample mean and standard deviation of matched age- and education group–specific controls at baseline. A *z* score of 0 indicates that the result is equal to the control mean. A negative *z* score indicates that the result is lower than the control mean, and a positive *z* score indicates that the result is higher than the control mean. The 95% CI is based on the adjusted mean and SE. Scores are expected to improve over time (ie, go from negative to positive, from a lower to higher positive score) as a result of expected practice effects. Decline is considered when there is not the expected practice effect.

†The *P* values are shown for the interactions of interest and selected covariates.

‡Nonwhite race includes black, Hispanic, and Asian American/Pacific Islander.

subdomain and individual test scores followed a similar pattern as the overall domain results, and there was no interaction of age with longitudinal treatment effects (data not shown).

Self-Reported Cognition

Self-reported cognition was moderately but significantly correlated with APE and LM (Pearson's $r = 0.40$ to 0.41 at baseline, 12, and 24 months; all $P < .001$). Adjusted mean self-reported cognitive scores for survivors exposed to chemotherapy decreased nonsignificantly, whereas the other groups did not change over time (Fig 2). Baseline frailty was independently related to baseline self-reported cognitive scores. *ApoE* ε4+ survivors who received chemotherapy showed a clinically meaningful decrease in adjusted mean self-reported score (from 133.1 [95% CI, 123.1 to 143.0] at baseline to 126.0 [95% CI, 114.0 to 138.0] at 24 months, a 7-point mean decrease), but the group-by-time-by-*ApoE* interaction was not statistically significant (Table 3; Fig 3C).

DISCUSSION

The TLC is one of the largest prospective, controlled studies of cognitive function among older breast cancer survivors. Our results for the first 2 years after diagnosis indicate that systemic treatment and aging-related genotype and phenotypes are associated with cognitive decline. Older survivors exposed to chemotherapy had significantly lower longitudinal cognitive function scores on the APE domain than other groups, and this effect was largely confined to those with the *ApoE* ε4 allele. This genotype also was associated with having lower LM scores after hormonal

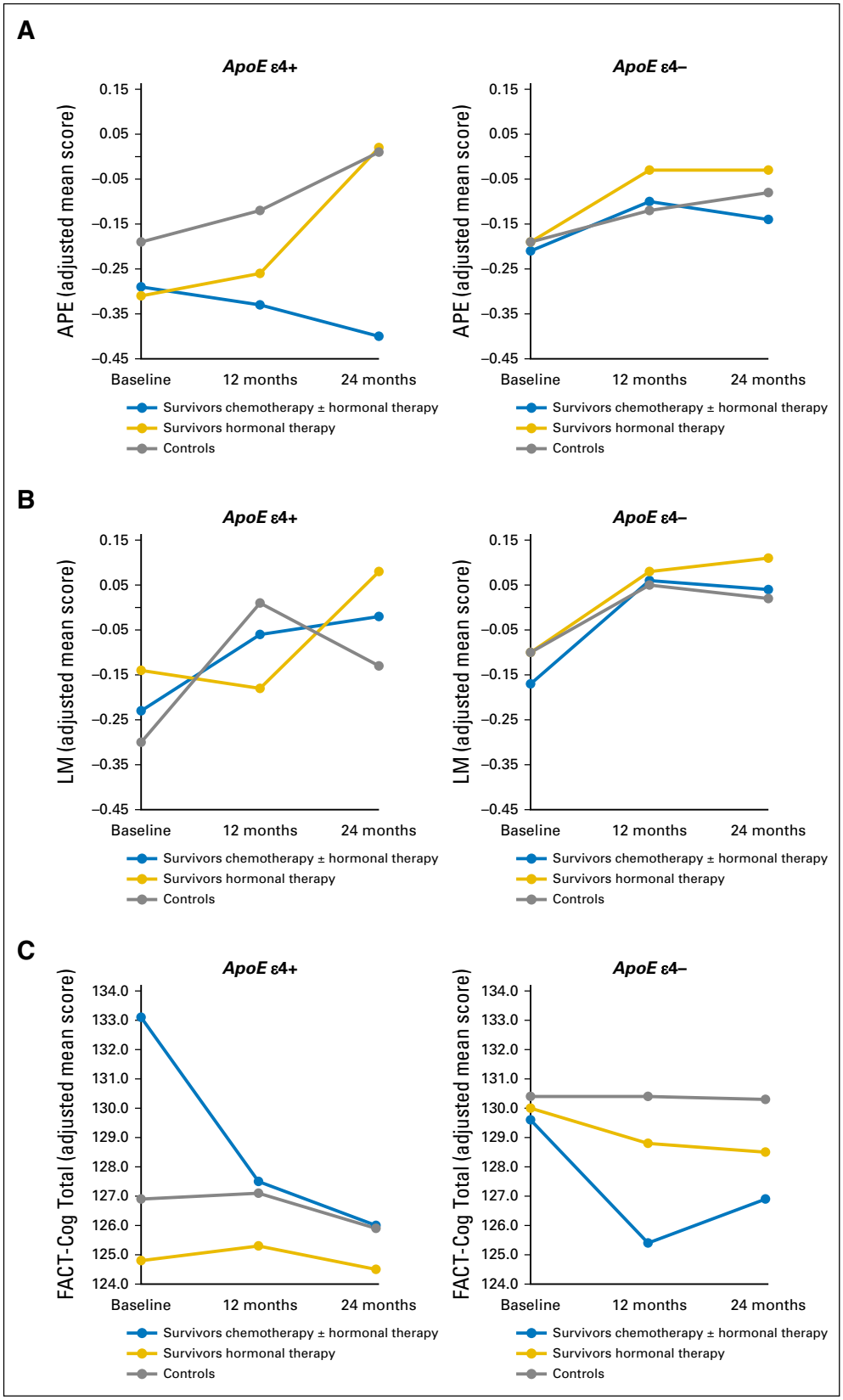

Fig 3. Adjusted mean cognitive scores over time for older breast cancer survivors and controls without cancer by apolipoprotein E (*ApoE*) status. Adjusted mean cognitive domain scores on the basis of least squares means from linear mixed-effects models show scores at baseline, 12 months, and 24 months for three treatment groups, including survivors who received chemotherapy with or without hormonal therapy, survivors who received only hormonal therapy, and controls. The models included as fixed effects time; group; *ApoE* genotype; all two- and three-way interactions for group, *ApoE*, and time; baseline age; frailty; standardized Wide Range Achievement Test 4 score; race; and recruitment site. (A) Results for the attention, processing speed, and executive function (APE) domain for group-by-time-by-*ApoE* ε4 positivity, where adjusted means are plotted for participants who are *ApoE* ε4+ and *ApoE* ε4− ($P = .14$ for three-way interaction). (B) Results for the learning and memory (LM) domain for group-by-time-by-*ApoE* ε4 positivity, where adjusted means are plotted for participants who are *ApoE* ε4+ and ApoE ε4− ($P = .03$ for three-way interaction). (C) Results for self-reported cognition on the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) scale for group-by-time-by-*ApoE* ε4 positivity, where adjusted means are plotted for participants who are *ApoE* ε4+ and *ApoE* ε4− (*P* not significant for three-way interaction). Declines of 5% to 7%, or 7 to 10 points, on this 148-point scale are considered clinically meaningful.[34] Tables 2 and 3 include the 95% CIs for each mean score at each time point for each outcome.

Table 3. Adjusted Mean Self-Reported Cognitive Function Scores Among Older Breast Cancer Survivors and Matched Controls by Time, Treatment, and Genotype

Domain	Sample Size (N = 603)	Adjusted Mean Score (95% CI)*			*P*†
		Baseline	12 Months	24 Months	
Group-by-time interaction					.50
Chemotherapy	80	131.3 (125.4 to 137.3)	126.5 (120.1 to 132.8)	126.5 (119.6 to 133.4)	
Hormonal therapy	201	127.4 (123.5 to 131.4)	127.1 (122.9 to 131.2)	126.5 (122.0 to 130.9)	
Control	322	128.6 (125.0 to 132.2)	128.7 (125.1 to 132.3)	128.1 (124.4 to 131.9)	
Group-by-time-by-*ApoE* interaction					.94
Survivor					
Chemotherapy ± hormonal therapy, *ApoE* ε4+	12	133.1 (123.1 to 143.0)	127.5 (116.7 to 138.3)	126.0 (114.0 to 138.0)	
Chemotherapy ± hormonal therapy, *ApoE* ε4−	68	129.6 (124.7 to 134.6)	125.4 (120.1 to 130.7)	126.9 (121.3 to 132.5)	
Hormonal therapy, *ApoE* ε4+	41	124.8 (119.0 to 130.5)	125.3 (119.1 to 131.4)	124.5 (117.5 to 131.4)	
Hormonal therapy, *ApoE* ε4−	160	130.0 (126.1 to 133.9)	128.8 (124.7 to 132.9)	128.5 (124.2 to 132.8)	
Control					
ApoE ε4+	81	126.9 (122.2 to 131.5)	127.1 (122.4 to 131.8)	125.9 (120.9 to 130.9)	
ApoE ε4−	241	130.4 (126.7 to 134.1)	130.4 (126.7 to 134.1)	130.3 (126.5 to 134.2)	
Age					.50
WRAT4 score					.05
Race, nonwhite‡ (*v* white non-Hispanic)					.60
Frailty (frail/prefrail *v* robust)					< .01

NOTE. Adjusted mean score and 95% CI from a linear mixed-effects model. Among the 603 included in the model, 79, 119, and 405 contributed one, two, or three data points, respectively. All mean scores are from a model that included the covariates shown plus time; group; *ApoE*; all two- and three-way interactions for group, *ApoE*, and time; and recruitment site. Twenty-five controls and 63 survivors are not included in the model because of missing data on covariates.

Abbreviations: *ApoE*, apolipoprotein E; Wide Range Achievement Test 4.

*From the Functional Assessment of Cancer Therapy-Cognitive Function. The score is 0 to 148; higher scores reflect better cognitive function. Scores are expected to improve over time (ie, go from negative to positive, from a lower to higher positive score) as a result of expected practice effects.[74] Decline is considered when there is not the expected practice effect.

†The *P* values are shown for the interactions of interest and selected covariates.

‡Nonwhite race includes black, Hispanic, and Asian American/Pacific Islander.

therapy initiation. Older age and frailty were independently related to lower baseline cognitive scores.

Most[2,5,6,8,9,26,51] but not all[13,14,52] studies of breast cancer–related cognitive decline have reported cognitive problems after chemotherapy among predominately younger survivors. The current findings confirm an adverse effect of chemotherapy on APE scores in older survivors on the basis of not only failure to show the expected practice effects[74] but also declining scores. In other studies, the *ApoE* ε4 genotype was linked to post-chemotherapy decline in similar domains and with reductions in gray matter in younger breast cancer[23,53] and testicular cancer survivors.[54-57] The current data suggest a similar selective deficit in APE among *ApoE* ε4 carriers exposed to chemotherapy, but the overall interaction effect was not statistically significant.

In our cohort, the *ApoE* ε4 genotype also was associated with small, nonpersistent decreases in LM scores after hormonal therapy initiation. Some reports have noted decrements in LM after hormonal therapy,[58] but others have shown inconsistent results.[10-12,59] Because even short-term cognitive deficits are meaningful to survivors, confirmation of our results and extension of follow-up will be important. Additional knowledge about genotype-treatment interactions could suggest mechanistic pathways, be used in decisions to recommend extended hormonal therapy duration,[60] and could potentially affect the use of direct-to-consumer *ApoE* testing.[61]

Chronologic age and aging phenotypes also were associated with lower baseline APE and self-reported cognitive function scores. Baseline cognitive scores have been shown to be a predictor of cognitive trajectories in other older cancer cohorts.[39] These results, together with the growing body of evidence from other studies,[1,2,15,28,62] support the idea that chemotherapy (and possibly hormonal therapy) can lead to cancer-related cognitive declines through acceleration of aging processes. Aging processes, *ApoE* ε4 genotype, and insulin resistance (seen with diabetes, a common comorbidity and component of frailty) each has been related to inflammation, which in turn is one of the putative risks for cancer-related cognitive decline and Alzheimer's disease.[63,64] Aging and the *ApoE* ε4 genotype also reduce brain plasticity and repair, another possible mechanism of cancer-related cognitive decline.[65] Biomarker and imaging studies may provide additional insights into the role of aging processes in cancer-related cognitive decline. For instance, Sanoff et al[17] reported that chemotherapy exposure in younger breast cancer survivors was associated with increased expression of $p16^{INK4a}$, a marker of cellular senescence, at levels equivalent to 10 to 15 years of chronologic aging. Neuroimaging studies of younger survivors have shown postchemotherapy decreases in frontal gray matter volume, abnormalities in brain network structure, and lower hippocampal volume consistent with aging.[18-21] We suggest that future research on mechanistic pathways focus on areas of overlap among aging processes, Alzheimer's disease, and risks for cancer-related cognitive decline.

Despite the strength of the evidence and rigor of our design, several limitations should be considered in interpreting the findings. First, the functional effect of the observed cognitive declines is uncertain, and we do not know whether survivors will develop dementia-related diagnoses. Prior research with older survivors found that accelerated self-reported cognitive decline is associated with lower physical and emotional function over 7 years postdiagnosis.[39] Second, the study population was well educated, cognitively intact at baseline, and recruited primarily from academic centers and affiliated community hospitals, which potentially underestimates cognitive declines in general populations.

Third, despite the large sample, statistical power was low to detect a significant three-way interaction of group-by-time-by-genotype effects because relatively few underwent chemotherapy, and rates of *ApoE* ε4+ were low. Furthermore, too few participants had two copies of the ε4 allele to test dose-response relationships. Other genotypes, such as *COMT* and *BDNF*, also may be important in cancer-related cognitive decline.[24,66] Pooling of samples from other studies of older survivors using similar eligibility and assessments could be used to confirm results and increase statistical power for detecting significant gene-treatment effects on cognition over time. Fourth, although we used recommended tests,[29] drawing conclusions about whether specific subdomains were affected differentially by treatment was difficult because many tests capture multiple cognitive constructs, and some tests did not have alternative forms and might show greater improvement with practice than tests with alternative forms. Fifth, there was limited treatment variability, so the evaluation of specific agents was not possible.[9] Hormonal therapy effects were based on treatment initiation and assumed adherence for the first 24 months. Early discontinuation as a result of cognitive problems could underestimate the effects of this modality on outcomes. Finally, too few survivors had human epidermal growth factor receptor 2–positive or hormone receptor–negative tumors to assess the respective effects of trastuzumab or chemotherapy alone. Future clinical studies and preclinical experiments[67,68] will be necessary to examine the separate and combined effects and mechanisms of specific agents.

In summary, older breast cancer survivors with aging-related phenotypes and genotypes may be at risk for cognitive decline, especially after chemotherapy. These results could be useful in several ways to clinicians who care for older adults. First, information about risks for cognitive decline could help clinicians to discuss treatment options when chemotherapy is discretionary because many older cancer survivors are concerned about cognitive problems related to their cancer and its treatment.[69-72] The low percentage of older survivors with cognitive decline also could provide some reassurance if chemotherapy is clinically indicated. Second, knowledge of the cognitive effects of systemic therapy could prompt plans for monitoring during survivorship care to facilitate adherence to long-term cancer and other medical therapies.[73] Cognitive function monitoring also could be useful to flag survivors at risk for impaired daily functioning as a consequence of cognitive decline.[39,51] Finally, geriatric assessments that measure cognitive function before treatment and during the survivorship phase of cancer care could provide data for risk prediction tools and assist clinicians in identifying older adults for preventive or other interventions to maximize function and healthy lifespans.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Mandelblatt JS, Jacobsen PB, Ahles T: Cognitive effects of cancer systemic therapy: Implications for the care of older patients and survivors. J Clin Oncol 32:2617-2626, 2014
2. Vega JN, Dumas J, Newhouse PA: Cognitive effects of chemotherapy and cancer-related treatments in older adults. Am J Geriatr Psychiatry 25: 1415-1426, 2017
3. Mandelblatt JS, Stern RA, Luta G, et al: Cognitive impairment in older patients with breast cancer before systemic therapy: Is there an interaction between cancer and comorbidity? J Clin Oncol 32:1909-1918, 2014
4. Ahles TA, Saykin AJ, McDonald BC, et al: Cognitive function in breast cancer patients prior to adjuvant treatment. Breast Cancer Res Treat 110: 143-152, 2008
5. Janelsins MC, Heckler CE, Peppone LJ, et al: Cognitive complaints in survivors of breast cancer after chemotherapy compared with age-matched controls: An analysis from a nationwide, multicenter, prospective longitudinal study. J Clin Oncol 35: 506-514, 2017
6. Ahles TA, Saykin AJ, McDonald BC, et al: Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: Impact of age and cognitive reserve. J Clin Oncol 28: 4434-4440, 2010
7. Kesler S, Janelsins M, Koovakkattu D, et al: Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. Brain Behav Immun 30: S109-S116, 2013 (suppl)
8. Jim HS, Phillips KM, Chait S, et al: Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol 30:3578-3587, 2012
9. Lange M, Heutte N, Rigal O, et al: Decline in cognitive function in older adults with early-stage breast cancer after adjuvant treatment. Oncologist 21:1337-1348, 2016
10. Schilder CM, Eggens PC, Seynaeve C, et al: Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: Cross-sectional findings from the neuropsychological TEAM-side study. Acta Oncol 48:76-85, 2009
11. Bender CM, Sereika SM, Brufsky AM, et al: Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer. Menopause 14:995-998, 2007
12. Mitsiades N, Correa D, Gross CP, et al: Cognitive effects of hormonal therapy in older adults. Semin Oncol 35:569-581, 2008
13. Du XL, Xia R, Hardy D: Relationship between chemotherapy use and cognitive impairments in older women with breast cancer: Findings from a large population-based cohort. Am J Clin Oncol 33: 533-543, 2010
14. Freedman RA, Pitcher B, Keating NL, et al: Cognitive function in older women with breast cancer

treated with standard chemotherapy and capecitabine on Cancer and Leukemia Group B 49907. Breast Cancer Res Treat 139:607-616, 2013

15. Ahles TA, Root JC, Ryan EL: Cancer- and cancer treatment-associated cognitive change: An update on the state of the science. J Clin Oncol 30: 3675-3686, 2012

16. Huang Z, Zheng Y, Bao P, et al: Aging, obesity, and post-therapy cognitive recovery in breast cancer survivors. Oncotarget 8:12364-12373, 2017

17. Sanoff HK, Deal AM, Krishnamurthy J, et al: Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. J Natl Cancer Inst 106:dju057, 2014

18. Menning S, de Ruiter MB, Veltman DJ, et al: Changes in brain white matter integrity after systemic treatment for breast cancer: A prospective longitudinal study. Brain Imaging Behav 12:324-334, 2018

19. Koppelmans V, de Groot M, de Ruiter MB, et al: Global and focal white matter integrity in breast cancer survivors 20 years after adjuvant chemotherapy. Hum Brain Mapp 35:889-899, 2014

20. Kesler SR, Rao V, Ray WJ, et al: Probability of Alzheimer's disease in breast cancer survivors based on gray-matter structural network efficiency. Alzheimers Dement (Amst) 9:67-75, 2017

21. Schuitema I, Deprez S, Van Hecke W, et al: Accelerated aging, decreased white matter integrity, and associated neuropsychological dysfunction 25 years after pediatric lymphoid malignancies. J Clin Oncol 31:3378-3388, 2013

22. Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146-M157, 2001

23. Ahles TA, Saykin AJ, Noll WW, et al: The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology 12:612-619, 2003

24. Small BJ, Rawson KS, Walsh E, et al: Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. Cancer 117:1369-1376, 2011

25. Bluethmann SM, Mariotto AB, Rowland JH: Anticipating the "Silver Tsunami": Prevalence trajectories and comorbidity burden among older cancer survivors in the United States. Cancer Epidemiol Biomarkers Prev 25:1029-1036, 2016

26. Loh KP, Janelsins MC, Mohile SG, et al: Chemotherapy-related cognitive impairment in older patients with cancer. J Geriatr Oncol 7:270-280, 2016

27. Chodosh J, Petitti DB, Elliott M, et al: Physician recognition of cognitive impairment: Evaluating the need for improvement. J Am Geriatr Soc 52: 1051-1059, 2004

28. Lange M, Rigal O, Clarisse B, et al: Cognitive dysfunctions in elderly cancer patients: A new challenge for oncologists. Cancer Treat Rev 40: 810-817, 2014

29. Wefel JS, Vardy J, Ahles T, et al: International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 12:703-708, 2011

30. Weintraub S, Salmon D, Mercaldo N, et al: The Alzheimer's Disease Centers' Uniform Data Set (UDS): The neuropsychologic test battery. Alzheimer Dis Assoc Disord 23:91-101, 2009

31. Stern RA, White T: Neuropsychological Assessment Battery (NAB). Lutz, FL, Psychological Assessment Resources, 2003

32. Wagner LI, Lai JS, Cella D, et al: Chemotherapy-related cognitive deficits: Development of the FACT-Cog instrument. Ann Behav Med 27, 2004; 27:S010

33. Wagner LI, Sweet J, Butt Z, et al: Measuring patient self-reported cognitive function: Development of the Functional Assessment of Cancer Therapy–Cognitive Function Instrument. J Support Oncol 7:W32-W39, 2009

34. Cheung YT, Foo YL, Shwe M, et al: Minimal clinically important difference (MCID) for the Functional Assessment Of Cancer Therapy: Cognitive Function (FACT-Cog) in breast cancer patients. J Clin Epidemiol 67:811-820, 2014

35. Searle SD, Mitnitski A, Gahbauer EA, et al: A standard procedure for creating a frailty index. BMC Geriatr 8:24, 2008

36. Rockwood K, Mitnitski A: Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 62:722-727, 2007

37. Sheppard VB, Faul LA, Luta G, et al: Frailty and adherence to adjuvant hormonal therapy in older women with breast cancer: CALGB protocol 369901. J Clin Oncol 32:2318-2327, 2014

38. Cohen HJ, Smith D, Sun CL, et al: Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. Cancer 122:3865-3872, 2016

39. Mandelblatt JS, Clapp JD, Luta G, et al: Long-term trajectories of self-reported cognitive function in a cohort of older survivors of breast cancer: CALGB 369901 (Alliance). Cancer 122: 3555-3563, 2016

40. Rockwood K, Mitnitski A, Song X, et al: Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc 54:975-979, 2006

41. Mandelblatt JS, Cai L, Luta G, et al: Frailty and long-term mortality of older breast cancer patients: CALGB 369901 (Alliance). Breast Cancer Res Treat 164:107-117, 2017

42. Ware J Jr, Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. Med Care 34:220-233, 1996

43. Katz S, Ford AB, Moskowitz RW, et al: Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. JAMA 185:914-919, 1963

44. Podsiadlo D, Richardson S: The timed "Up & Go": A test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 39:142-148, 1991

45. Brady MJ, Cella DF, Mo F, et al: Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol 15:974-986, 1997

46. Cella DF, Tulsky DS, Gray G, et al: The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. J Clin Oncol 11:570-579, 1993

47. Radloff LS: The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1:385-401, 1977

48. Spielberger C: Manual for the State-Trait Anxiety Inventory (STAI: Form Y). Palo Alto, CA, Consulting Psychologists, 1983

49. Yellen SB, Cella DF, Webster K, et al: Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage 13:63-74, 1997

50. Clapp JD, Luta G, Small BJ, et al: The impact of using different reference populations on measurement of breast cancer-related cognitive impairment rates. Arch Clin Neuropsychol 10.1093/arclin/acx142 [epub ahead of print on February 17, 2018]

51. Kvale EA, Clay OJ, Ross-Meadows LA, et al: Cognitive speed of processing and functional declines in older cancer survivors: An analysis of data from the ACTIVE trial. Eur J Cancer Care (Engl) 19: 110-117, 2010

52. Raji MA, Tamborello LP, Kuo Y-F, et al: Risk of subsequent dementia diagnoses does not vary by types of adjuvant chemotherapy in older women with breast cancer. Med Oncol 26:452-459, 2009

53. Caselli RJ: Does an Alzheimer's disease susceptibility gene influence the cognitive effects of cancer therapy? Pediatr Blood Cancer 61:1739-1742, 2014

54. Schagen SB, Boogerd W, Muller MJ, et al: Cognitive complaints and cognitive impairment following BEP chemotherapy in patients with testicular cancer. Acta Oncol 47:63-70, 2008

55. Wefel JS, Vidrine DJ, Veramonti TL, et al: Cognitive impairment in men with testicular cancer prior to adjuvant therapy. Cancer 117:190-196, 2011

56. Amidi A, Wu LM, Pedersen AD, et al: Cognitive impairment in testicular cancer survivors 2 to 7 years after treatment. Support Care Cancer 23: 2973-2979, 2015

57. Amidi A, Agerbæk M, Wu LM, et al: Changes in cognitive functions and cerebral grey matter and their associations with inflammatory markers, endocrine markers, and APOE genotypes in testicular cancer patients undergoing treatment. Brain Imaging Behav 11:769-783, 2017

58. Boele FW, Schilder CM, de Roode ML, et al: Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer. Menopause 22:17-25, 2015

59. Hurria A, Rosen C, Hudis C, et al: Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: A pilot prospective longitudinal study. J Am Geriatr Soc 54:925-931, 2006

60. Zwart W, Terra H, Linn SC, et al: Cognitive effects of endocrine therapy for breast cancer: Keep calm and carry on? Nat Rev Clin Oncol 12:597-606, 2015

61. Food and Drug Administration: FDA allows marketing of first direct-to-consumer tests that provide genetic risk information for certain conditions, 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm

62. Ahles TA, Hurria A: New challenges in psychooncology research IV: Cognition and cancer: Conceptual and methodological issues and future directions. Psychooncology 27:3-9, 2018

63. Farrer LA, Cupples LA, Haines JL, et al: Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. JAMA 278:1349-1356, 1997

64. Johnson LA, Torres ER, Impey S, et al: Apolipoprotein E4 and insulin resistance interact to impair cognition and alter the epigenome and metabolome. Sci Rep 7:43701, 2017

65. Ahles TA, Saykin AJ: Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 7:192-201, 2007

66. Ng T, Teo SM, Yeo HL, et al: Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer. Neuro-oncol 18:244-251, 2016

67. Fardell JE, Zhang J, De Souza R, et al: The impact of sustained and intermittent docetaxel chemotherapy regimens on cognition and neural morphology in healthy mice. Psychopharmacology (Berl) 231:841-852, 2014

68. Seigers R, Loos M, Van Tellingen O, et al: Cognitive impact of cytotoxic agents in mice. Psychopharmacology (Berl) 232:17-37, 2015

69. Fried TR, Bradley EH, Towle VR, et al: Understanding the treatment preferences of seriously ill patients. N Engl J Med 346:1061-1066, 2002

70. Hurria A, Goldfarb S, Rosen C, et al: Effect of adjuvant breast cancer chemotherapy on cognitive function from the older patient's perspective. Breast Cancer Res Treat 98:343-348, 2006

71. Castel H, Denouel A, Lange M, et al: Biomarkers associated with cognitive impairment in treated cancer patients: Potential predisposition and risk factors. Front Pharmacol 8:138, 2017

72. Chouliara Z, Miller M, Stott D, et al: Older people with cancer: Perceptions and feelings about information, decision-making and treatment–A pilot study. Eur J Oncol Nurs 8:257-261, 2004

73. Bluethmann SM, Alfano CM, Clapp JD, et al: Cognitive function and discontinuation of adjuvant hormonal therapy in older breast cancer survivors: CALGB 369901 (Alliance). Breast Cancer Res Treat 165:677-686, 2017

74. Calamia M, Markon K, Tranel D: Scoring higher the second time around: Meta-analyses of practice effects in neuropsychological assessment. Clin Neuropsychol 26:543-570, 2012

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Support

Supported by National Cancer Institute (NCI) grants R01CA129769 and R35CA197289 to J.S.M. This study was also supported in part by NCI grant P30CA51008 to Georgetown-Lombardi Comprehensive Cancer Center for a Cancer Center Support Grant Development grant and for support of the Biostatistics and Bioinformatics and Non-Therapeutic Shared Resources at Georgetown-Lombardi Comprehensive Cancer Center. The work of B.C.M. and A.J.S. was supported in part by NCI grants P30AG10133, R01AG19771, and R01LM01136. The work of D.T. was supported in part by NCI grants T32CA117865 and F31CA220964. The work of L.C.K. was supported in part by an institutional American Cancer Society grant (IRG-92-152) to Georgetown-Lombardi Comprehensive Cancer Center (Michael B. Atkins, MD, principal investigator). The work of R.A.S. was supported in part by National Institute on Aging grant P30AG13846 to the Boston University Alzheimer's Disease Center. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

Prior Presentation

Presented at the International Cognition and Cancer Task Force Meeting, Amsterdam, the Netherlands, March 14-16, 2016.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cancer-Related Cognitive Outcomes Among Older Breast Cancer Survivors in the Thinking and Living With Cancer Study

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Acknowledgment

This work was conducted while P.B.J. was affiliated with the Moffitt Cancer Center. We thank the participants in the TLC study for sharing their time and experiences; without their generosity, this study would not have been possible. We also thank Sherri Stahl, Naomi Greenwood, Margery London, and Sue Peach from Georgetown Breast Cancer Advocates for their insights and suggestions about the study design and methods to recruit and retain participants. We thank the following TLC study staff members who ascertained, enrolled, and interviewed participants: Chie Akiba, Anait Arsenyan, Jessica Bailey, Grace Butler, Savannah Carpenter, Caitlin Carr, Megan Chamberlain, Kemeberly Charles, Amy Chen, Jennifer Choi, Elana Cook, Julia Fallon, Maria Farberov, Robin Fatovic, Julie Filo, Alyssa Hoekstra, Mallory Hussin, Vani Katheria, Brittany Kennedy, Ty Lee, Abe Levi, Trina McClendon, Kat McNeal, Meghan Mihalache, Kelsey Obremski, Olivia O'Brian, Renee Ornduff, Elsa Roberts, Melissa Rose, Rupal Ramani, Ian SerVaas, Minna Song, Rebecca Wellner, Jessica Whitley, Rebecca Young, and Laura Zavala. Finally, we acknowledge the support of Irene Simpkin and the staff at the Genetics Core Lab at Boston University as well as the support of Linda Abularch and Meenakshi Chivukula in processing *ApoE* samples.

Appendix

Table A1. Neuropsychological Tests and Domains Used to Assess Cognition in Older Breast Cancer Survivors and Matched Controls Without Cancer

Domain and Test	Cronbach's α			Factor Loading			First Author
	All	Survivor	Control	All	Survivor	Control	
APE							
Baseline	0.72	0.74	0.70				
NAB Digits Forward				0.60	0.65	0.56	Stern[31]
NAB Digits Backward				0.57	0.60	0.58	Stern[31]
Trail Making A				0.66	0.61	0.68	Reitan*
Trail Making B				0.69	0.64	0.73	Reitan*
COWAT				0.55	0.60	0.48	Benton†
Digit Symbol Test				0.66	0.66	0.63	Wechsler‡
12 months	0.71	0.75	0.66				
NAB Digits Forward				0.50	0.60	0.40	
NAB Digits Backward				0.46	0.46	0.47	
Trail Making A				0.72	0.75	0.68	
Trail Making B				0.67	0.69	0.64	
COWAT				0.62	0.66	0.59	
Digit Symbol Test				0.68	0.66	0.71	
24 months	0.74	0.77	0.71				
NAB Digits Forward				0.61	0.67	0.53	
NAB Digits Backward				0.60	0.64	0.54	
Trail Making A				0.63	0.64	0.62	
Trail Making B				0.68	0.69	0.66	
COWAT				0.61	0.61	0.58	
Digit Symbol Test				0.69	0.70	0.71	
LM							
Baseline	0.86	0.86	0.86				
Logical Memory I				0.81	0.81	0.78	Abikoff§
Logical Memory II				0.83	0.85	0.78	Abikoff§
NAB List A Immediate Recall				0.73	0.72	0.76	Stern[31]
NAB List A Short Delay Recall				0.74	0.72	0.78	Stern[31]
NAB Long Delay				0.75	0.72	0.79	Stern[31]
12 months	0.88	0.87	0.88				
Logical Memory I				0.78	0.80	0.76	
Logical Memory II				0.82	0.82	0.83	
NAB List A Immediate Recall				0.79	0.79	0.80	
NAB List A Short Delay Recall				0.79	0.76	0.80	
NAB Long Delay				0.82	0.80	0.84	
24 months	0.89	0.87	0.91				
Logical Memory I				0.84	0.81	0.85	
Logical Memory II				0.87	0.83	0.88	
NAB List A Immediate Recall				0.77	0.74	0.80	
NAB List A Short Delay Recall				0.78	0.77	0.79	
NAB Long Delay				0.76	0.77	0.76	

Abbreviations: APE, attention, processing speed, and executive function; COWAT, Controlled Oral Word Association Test; LM, learning and memory; NAB, Neuropsychological Assessment Battery.
*Reitan: Reitan Neuropsychology Laboratory, 1986.
†Benton: Annu Rev Psychol 45:1-23, 1994.
‡Wechsler: Psychological Corporation, 1997.
§Abikoff et al: J Clin Exp Neuropsychol 9:435-448, 1987.

Table A2. Raw Baseline Neuropsychological Testing Scores of Pretreatment Cognitive Performance for Older Breast Cancer Survivors and Matched Controls Without Cancer

Domain/Test	Study Group, Mean (SD)			
	Control (n = 347)	Survivor (n = 344)	Survivor Chemotherapy (n = 94)	Survivor Hormonal Therapy (n = 237)
APE				
NAB Digits Forward[a]	8.31 (2.36)	8.21 (2.31)	8.12 (2.13)	8.27 (2.39)
NAB Digits Backward[a]	4.50 (2.18)	4.42 (2.14)	4.70 (2.09)	4.35 (2.18)
Trail Making A[b]	36.90 (12.43)	37.41 (14.31)	35.25 (11.87)	38.22 (15.41)
Trail Making B[b]	85.24 (43.32)	91.68 (48.36)	83.29 (48.46)	94.32 (48.74)
COWAT[c]	43.22 (12.54)	40.78 (12.33)	41.15 (12.98)	40.76 (12.27)
Digit Symbol Test[d]	53.36 (10.46)	52.09 (11.51)	53.09 (11.12)	51.92 (11.64)
LM				
Logical Memory I[e]	13.17 (3.81)	12.79 (3.82)	12.98 (3.65)	12.79 (3.84)
Logical Memory II[f]	11.86 (4.05)	11.61 (4.07)	12.16 (3.53)	11.48 (4.24)
NAB List A Immediate Recall[g]	23.06 (4.72)	22.55 (5.03)	22.99 (4.94)	22.43 (5.15)
NAB List A Short Delay Recall[h]	7.59 (2.48)	7.38 (2.66)	7.39 (2.49)	7.45 (2.72)
NAB List Long Delay[i]	7.65 (2.61)	7.51 (2.61)	7.54 (2.61)	7.58 (2.57)

NOTE. With the exception of Trail Making A and B, higher raw scores reflect better performance.
Abbreviations: APE, attention, processing speed, and executive function; COWAT, Controlled Oral Word Association Test; LM, learning and memory; NAB, Neuropsychological Assessment Battery.
[a]Number of sequences correctly recalled.
[b]Time in seconds.
[c]Number of words given in allowed time.
[d]Number of symbols produced in allowed time.
[e]Number of pieces of a story recalled immediately.
[f]Number of pieces of a story recalled after delay.
[g]Sum of three trials of word recall.
[h]Number of words recalled after short delay.
[i]Number of words recalled after long delay.

Table A3. Unadjusted Standardized Mean *z* Scores for Older Breast Cancer Survivors and Matched Controls Without Cancer by Assessment Time and Treatment Group

Domain/Test	Control (n = 347)			Survivor Chemotherapy ± Hormonal Therapy (n = 94)			Survivor Hormonal Therapy Only (n = 237)		
	Baseline	12 Months	24 Months	Baseline	12 Months	24 Months	Baseline	12 Months	24 Months
APE	−0.05	0.02	0.08	−0.12	−0.03	−0.07	−0.10	0.03	0.09
LM	−0.03	0.16	0.10	−0.05	0.18	0.17	0.00	0.14	0.21

NOTE. Survivor cognition scores are standardized using the baseline control mean and SD from age- and education-matched control groups. By definition, the control mean *z* score is 0 with an SD of 1. Across controls, variation exists so that some controls have scores less than the control group mean (–) and others have scores higher than the control group mean. Higher positive scores indicate better cognitive function. Over time, groups are expected to have scores that improve as a result of practice effects.[74] Hence, scores that show a failure to improve may indicate cognitive deficits.
Abbreviations: APE, attention, processing speed, and executive function; LM, learning and memory.

Table A4. Adjusted Mean Domain Scores Among Older Breast Cancer Survivors and Matched Controls Without Cancer by Time and Genotype: Comorbidity Effects

Domain	Sample (N = 609)	Adjusted Mean Cognitive *z* Score (95% CI)*			*P*†
		Baseline	12 Months	24 Months	
APE					
Group-by-time interaction					.05
Group-by-time-by-*ApoE* interaction					.14
Survivor					
Chemotherapy ± hormonal therapy, *ApoE* ε4+	13	−0.26 (−0.58 to 0.06)	−0.30 (−0.64 to 0.03)	−0.37 (−0.76 to 0.02)	
Chemotherapy ± hormonal therapy, *ApoE* ε4−	69	−0.20 (−0.36 to −0.04)	−0.09 (−0.26 to 0.08)	−0.13 (−0.32 to 0.05)	
Hormonal therapy, *ApoE* ε4+	41	−0.27 (−0.45 to −0.09)	−0.23 (−0.42 to −0.03)	0.06 (−0.16 to 0.27)	
Hormonal therapy, *ApoE* ε4−	160	−0.16 (−0.29 to −0.03)	0.00 (−0.13 to 0.13)	0.00 (−0.14 to 0.14)	
Control					
ApoE ε4+	83	−0.15 (−0.30 to −0.00)	−0.08 (−0.23 to 0.07)	0.05 (−0.12 to 0.21)	
ApoE ε4−	243	−0.16 (−0.28 to −0.04)	−0.09 (−0.21 to 0.03)	−0.05 (−0.18 to 0.07)	
Age					< .01
WRAT4 score					< .01
Race, nonwhite‡ (*v* white non-Hispanic)					< .01
Comorbidities (> 2 *v* ≤ 2)					< .01
LM					
Group-by-time interaction					.03
Group-by-time-by-*ApoE* interaction					.03
Survivor					
Chemotherapy ± hormonal therapy, *ApoE* ε4+	13	−0.20 (−0.62 to 0.22)	−0.03 (−0.48 to 0.42)	0.01 (−0.50 to 0.52)	
Chemotherapy ± hormonal therapy, *ApoE* ε4−	69	−0.15 (−0.36 to 0.05)	0.08 (−0.15 to 0.30)	0.06 (−0.18 to 0.30)	
Hormonal therapy, *ApoE* ε4+	41	−0.11 (−0.35 to 0.13)	−0.15 (−0.41 to 0.11)	0.11 (−0.17 to 0.39)	
Hormonal therapy, *ApoE* ε4−	160	−0.09 (−0.25 to 0.08)	0.10 (−0.08 to 0.27)	0.12 (−0.06 to 0.30)	
Control					
ApoE ε4+	83	−0.27 (−0.46 to −0.08)	0.03 (−0.17 to 0.23)	−0.11 (−0.32 to 0.11)	
ApoE ε4−	243	−0.08 (−0.23 to 0.07)	0.07 (−0.09 to 0.23)	0.05 (−0.12 to 0.21)	
Age					< .01
WRAT4 score					< .01
Race, nonwhite‡ (*v* white non-Hispanic)					< .01
Comorbidities (> 2 *v* ≤ 2)					.79

NOTE. Mean score from a linear mixed-effects model. Among the 609 included in the model, 79, 121, and 409 contributed one, two, or three data points, respectively. All mean scores are from a model that included the covariates shown plus time; group; *ApoE*; all two- and three-way time, group, and *ApoE* interactions; and recruitment site. Twenty-one controls and 61 survivors are not included in the model because of missing data on covariates.

Abbreviations: APE, attention, processing speed, and executive function; *ApoE*, apolipoprotein E; LM, learning and memory; WRAT4, Wide Range Achievement Test 4.

*All cognitive scores are standardized to matched age- and education group–specific mean control score at baseline. A *z* score of 0 indicates that the result is equal to the control mean score. A negative *z* score indicates that the result is lower than the control mean, and a positive *z* score indicates that the result is higher than the control mean. Scores are expected to improve over time (ie, go from negative to positive, from a lower to higher positive score) as a result of expected practice effects.[74] Decline is considered when there is not the expected practice effect.

†*P* values are shown for the interactions of interest and selected covariates.

‡Nonwhite race includes black, Hispanic, and Asian American/Pacific Islander.

Table A5. Covariate-Adjusted Mean Domain Scores Among Older Breast Cancer Survivors and Matched Controls Without Cancer by Time and Genotype-Diabetes Effects

Domain	Sample (N = 607)	Adjusted Mean Cognitive *z* Score (95% CI)*			*P*†
		Baseline	12 Months	24 Months	
APE					
Group-by-time interaction					.05
Group-by-time by *ApoE* interaction					.15
Survivor					
Chemotherapy ± hormonal therapy, *ApoE* ε4+	13	−0.30 (−0.62 to 0.03)	−0.33 (−0.68 to 0.01)	−0.40 (−0.79 to −0.00)	
Chemotherapy ± hormonal therapy, *ApoE* ε4-	69	−0.22 (−0.39 to −0.05)	−0.11 (−0.29 to 0.07)	−0.15 (−0.34 to 0.04)	
Hormonal therapy, *ApoE* ε4+	41	−0.30 (−0.50 to −0.11)	−0.26 (−0.46 to −0.06)	0.02 (−0.20 to 0.25)	
Hormonal therapy, *ApoE* ε4−	159	−0.20 (−0.34 to −0.07)	−0.05 (−0.19 to 0.10)	−0.05 (−0.20 to 0.10)	
Control					
ApoE ε4+	83	−0.19 (−0.35 to −0.03)	−0.12 (−0.28 to 0.04)	0.01 (−0.16 to 0.18)	
ApoE ε4−	242	−0.19 (−0.32 to −0.06)	−0.12 (−0.25 to 0.01)	−0.09 (−0.22 to 0.05)	
Age					< .01
WRAT4 score					< .01
Race, nonwhite‡ (*v* white non-Hispanic)					< .01
Diabetes (yes *v* no)					.09
LM					
Group by time interaction					.03
Group by time by *ApoE* interaction					.03
Survivor					
Chemotherapy ± hormonal therapy, *ApoE* ε4+	13	−0.14 (−0.57 to 0.28)	0.02 (−0.44 to 0.48)	0.07 (−0.45 to 0.58)	
Chemotherapy ± hormonal therapy, *ApoE* ε4−	69	−0.11 (−0.33 to 0.10)	0.12 (−0.12 to 0.35)	0.10 (−0.14 to 0.35)	
Hormonal therapy, *ApoE* ε4+	41	−0.07 (−0.32 to 0.18)	−0.11 (−0.38 to 0.16)	0.15 (−0.14 to 0.45)	
Hormonal therapy, *ApoE* ε4−	159	−0.04 (−0.22 to 0.13)	0.14 (−0.04 to 0.33)	0.17 (−0.02 to 0.36)	
Control					
ApoE ε4+	83	−0.22 (−0.43 to −0.02)	0.08 (−0.13 to 0.29)	−0.06 (−0.28 to 0.17)	
ApoE ε4−	242	−0.03 (−0.20 to 0.14)	0.12 (−0.05 to 0.29)	0.09 (−0.08 to 0.27)	
Age					< .01
WRAT4 score					< .01
Race, nonwhite‡ (*v* white non-Hispanic)					< .01
Diabetes (yes *v* no)					.17

NOTE. Mean scores are from a linear mixed model. Among the 607 included in the model, 79, 121, and 407 contributed one, two, or three data points, respectively. All mean scores are from a model that included the covariates shown plus time, group; *ApoE*; all two- and three-way time, group, and *ApoE* interactions; and recruitment site. Twenty-two controls and 62 survivors are not included in the model because of missing data on covariates.

*All cognitive scores are standardized to matched age- and education group–specific mean control score at baseline. A *z* score of 0 indicates that the result is equal to the control mean score. A negative *z* score indicates that the result is lower than the control mean, and a positive *z* score indicates that the result is higher than the control mean. Scores are expected to improve over time (ie, go from negative to positive, from a lower to higher positive score) as a result of expected practice effects.[74] Decline is considered when there is not the expected practice effect.

†*P* values are shown for the interactions of interest and selected covariates.

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