Protective Effects of *APOE* ε2 Genotype on Cognition in Older Breast Cancer Survivors: The Thinking and Living with Cancer Study

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Abstract

**Background:** Cancer-related cognitive decline (CRCD) has been linked to apolipoprotein E (APOE) gene ε4 polymorphisms. APOE ε4 polymorphisms are also the strongest genetic risk for late-onset Alzheimer’s disease (AD), while ε2 polymorphisms protect against AD. However, the effects of ε2 polymorphisms on CRCD have not been evaluated.

**Methods:** We evaluated non-metastatic breast cancer survivors (n=427) and matched non-cancer controls (n=407) ages 60-98 assessed pre-systemic therapy/enrollment from August 2010-December 2017 with annual follow-up to 24 months. Neuropsychological assessment measured attention, processing speed, and executive function, and learning and memory. Linear mixed-effects models tested the effects of having an ε2 allele (vs. none) on longitudinal cognitive domain z-scores by treatment group (chemotherapy +/- hormonal therapy, hormonal therapy, and control) controlling for covariates; participants with ε2/ε4 genotype were excluded. Sensitivity analyses examined effects of other covariates and any ε4 positivity.

**Results:** There was an interaction with genotype for attention, processing speed, and executive functioning domain scores (Beta=0.32 (95% CI:0.00, 0.65)): the chemotherapy group with an ε2 allele had higher scores at baseline and maintained higher scores over time compared to those without an ε2 allele, and this protective effect was not seen for other groups. There was no effect of ε2 on learning and memory domain scores.

**Conclusions:** APOE ε2 polymorphisms may protect against CRCD in older breast cancer survivors receiving chemotherapy. With replication, this information could be useful for survivorship care and informing future studies of possible links to AD and defining mechanisms of protection.
Keywords: Breast cancer, cancer-related cognitive decline, genotype, cognition, apolipoprotein E (APOE) gene, aging, older patients
Cancer-related cognitive decline (CRCD) is increasingly recognized among some breast cancer survivors, and even subtle declines can adversely affect functioning and quality of life.\textsuperscript{1-4} Efforts to identify risk factors suggest the etiology is multifactorial and may include direct effects of cancer, treatment toxicity, age, and genetic vulnerability.\textsuperscript{5-11} The apolipoprotein E (\textit{APOE}) gene is the most commonly studied gene in CRCD.\textsuperscript{11,12} The \(\varepsilon4\) allele is seen in roughly 25\% of the population, is the strongest genetic risk factor for late-onset Alzheimer’s disease (AD) and has been associated with risk of CRCD in most studies,\textsuperscript{11-14} particularly after chemotherapy.\textsuperscript{15} The \(\varepsilon2\) allele, seen in about 8\% of the population,\textsuperscript{16} is considered to be protective against developing AD.\textsuperscript{17-19} However, there are no data on the potential protective effects of the \(\varepsilon2\) allele on CRCD.\textsuperscript{11}

To fill this clinical gap, we conducted an evaluation of the role of \textit{APOE} \(\varepsilon2\) in longitudinal cognitive function among older breast cancer survivors and a matched non-cancer control group in the Thinking and Living with Cancer (TLC) study.\textsuperscript{15,20} We hypothesized that having an \(\varepsilon2\) allele would have the greatest protective effects in women who received chemotherapy +/- hormonal therapy compared to those taking hormonal therapy only or controls. The results are intended to guide future research, to inform practice,\textsuperscript{21} extend our results, and study possible links between CRCD and AD.

\textbf{Methods}

\textit{Design, Population, and Data Collection}

We conducted a secondary analysis using data from the TLC multi-site prospective study (ClinicalTrials.gov Identifier: NCT03451383) of older breast cancer survivors and frequency-
matched non-cancer controls. All Institutional Review Boards approved the protocol (NCT03451383).

We included participants recruited between August 1, 2010 and December 31, 2017 and followed until January 29, 2020; the study is ongoing. Eligible breast cancer survivors were 60 years of age or older, newly diagnosed with primary nonmetastatic breast cancer, and able to complete assessments in English; women with a history of stroke, head injury, major axis I psychiatric disorders, and neurodegenerative disorders were excluded. We also excluded women with a prior history of cancer if active treatment occurred in the five years prior to enrollment or included systemic therapy. Controls included friend and community controls frequency-matched to survivors by age, race, education, and recruitment site; controls had the same exclusion criteria as survivors. To be included in this analysis, participants were also required to have APOE genotype data (available for 98.3% of survivors and 96.6% of controls).

Participants were screened using the Mini-Mental State Examination (MMSE) and the Wide Range Achievement Test, 4th edition (WRAT-4) Word Reading subtest. Those with scores of <24 or <3rd grade-equivalent reading level, respectively, were ineligible (1 survivor, 1 control). Controls who scored >3 standard deviations (SD) below the control mean baseline neuropsychological scores for their age- and education-group were ineligible post-hoc (n=8) per protocol. Patients were ineligible for follow-up if they developed any of the initial exclusions and prior data were excluded if the change in eligibility occurred within six months of the prior follow-up visit. The final analytic sample included 427 survivors and 407 controls (Figure 1).
Assessments were conducted by trained staff at enrollment (post-surgery, pre-systemic therapy for survivors) and annually through 24-months and included a structured survey, neuropsychological testing, and provision of lab specimens.

Measures

Our primary outcomes were longitudinal scores on neurocognitive testing of two domains relevant to CRCD and supported by previous factor analysis: attention, processing speed, and executive functioning (6 tests); and verbal learning and memory (5 tests) (Supplementary Table 1). Scores were transformed into Z-scores based on age- and education-group matched non-cancer control baseline means and standard deviations. In sensitivity analyses we included self-reported cognition as measured on the Functional Assessment of Cancer Therapy-Cognition (FACT-Cog).

APOE genotype for rs7412 and rs429358 was determined using a combination of TaqMan assays (Life Technologies, Carlsbad, CA) and Fluidigm genotyping using a custom-designed 96-SNP fingerprinting chip (Fluidigm, San Francisco, CA).

We examined several potential covariates of the relationship between cognition and genotype, including socio-demographics (age, race, marital status), psychological factors (depression, anxiety), sleep (disturbed sleep yes/no based on a two-item measure), smoking history (ever vs. never), and cognitive and physical reserve. Clinical depression was defined as >16 on The Center for Epidemiologic Studies Depression Scale, and the State-Trait Anxiety Inventory State total score measured anxiety. We used the Wide Range Achievement Test-4 (WRAT4) to measure cognitive reserve. A 42-item deficit accumulation index was used
to capture comorbidities, polypharmacy, functional ability, psychosocial factors (e.g., marital status, social support, anxiety, depression, fatigue), and self-reported family history of dementia (first-degree relative) but excluded cognition. We also explored baseline cardiovascular disease (any angina, arrhythmia, myocardial infarction, and other cardiovascular diseases) as a potential confounder of the effects of APOE on cognition.

**Statistical Analysis**

Univariable statistics summarized the relationship between baseline characteristics and APOE ε2 genotype (any ε2 allele vs. not) and survivors/controls. The non-Finnish European population frequency for APOE alleles\(^\text{16}\) was used to compare genotype distributions in our sample to those expected in the general population, and assessed for statistically significant differences using Hardy-Weinberg equilibrium testing.\(^\text{36,37}\)

For multivariable analyses, we excluded participants with the ε2/ε4 genotype because any protective effect of ε2 might be attenuated by the ε4 allele.\(^\text{13}\) We used separate linear mixed models to test the effect of APOE ε2 genotype (any vs. no ε2 allele) and treatment group (chemotherapy +/- hormonal therapy, hormonal therapy alone, or non-cancer control) on longitudinal standardized z-scores for the attention, processing speed, and executive functioning and learning and memory cognitive domains. We examined two- and three-way interactions of genotype, treatment group, and time. We also evaluated deficit accumulation index (which includes family history of dementia), an anxiety, depression, smoking history, time since surgery, and sleep disturbance as potential covariates. Variables were retained in the final models if they had p values <.20, face validity, and improved the model goodness of fit based
on Bayesian Information Criterion. All models included baseline age, race (white vs. non-white), WRAT-4 score, recruitment site, and baseline deficit accumulation scores to capture variability related to factors that might affect genotype-cognition relationships. We also tested whether there were statistically significant interactions between baseline deficit accumulation scores, treatment group, and genotype. We considered $p<.05$ to be statistically significant, all tests were two-sided.

We also conducted several sensitivity analyses. First, we examined models that excluded participants with $\varepsilon3/\varepsilon4$ and $\varepsilon4/\varepsilon4$ genotypes to confirm that the presence of any $\varepsilon4$ allele did not confound results. Next, since cognitive declines can be subtle, we modeled the effects of $\varepsilon2$ on individual neuropsychological test scores and self-reported cognition. The $APOE \varepsilon2$ genotype has been associated with type III hyperlipoproteinemia, which may increase risk for heart disease and adversely affect cognition, so we tested the effects of cardiovascular-related comorbidities in lieu of baseline deficit accumulation. Finally, we evaluated model results with inverse probability weighting to address the effects of participants that dropped out or died during the course of the study. There was no statistically significant association between genotype, baseline cognition, or baseline deficits accumulation index score and subsequent dropout or death, and model results were not sensitive to missing data based on inverse probability weighting, so we report unweighted results. Analyses were conducted between October 19, 2019 and August 21, 2020 using SAS 9.4.b statistical software (SAS Institute, Cary, NC).

**Results**
Study Sample

The analytic sample remaining alive and eligible for follow-up after baseline comprised 77.0% and 70.3% of survivors and 89.2% and 78.0% of controls completed 12- and 24-month assessments, respectively. There were no statistically significant differences in baseline variables related to cognition by number of assessments completed. The majority of the sample (94%) provided specimens for genotyping, and did not differ in terms of age, race, WRAT, education, or baseline cognition scores from those who did not; the control group had a smaller proportion of women with no specimens than that of either of the other two treatment groups (chemotherapy vs. control p=.04, hormonal only vs. control p=.06). The survivors and non-cancer controls were demographically comparable (Table 1). Among survivors, women who received chemotherapy (+/- hormonal treatment) had more advanced stage (p<.001), were younger (p<.001), and had fewer cardiovascular comorbidities (p=.02) than women treated with hormonal therapy alone. Survivors selected for chemotherapy also had the highest levels of baseline anxiety and depression across the group; survivors also had higher levels of baseline sleep disturbance than controls. Participants had an overall frequency of any ε2 allele of 15.2%, similar to the expected frequency (13.5%) in white non-Hispanic populations, with no statistically significant differences among treatment groups in ε2 status (Table 2).

Effect of APOE ε2 allele on Cognitive Outcomes

We found an interaction between genotype and chemotherapy (vs. control) on adjusted cognition scores for the attention, processing speed, and executive function domain (p=.05), however, an overall interaction (df=2) between genotype and treatment group was not
statistically significant (p=.13). In the chemotherapy group, those with an ε2 allele had higher attention, processing speed, and executive function domain scores across all time points compared to those without an ε2 allele and this effect was not seen in the other groups (Table 3 and Figure 2). Post-hoc comparisons showed non-statistically significant 0.16 of a standard deviation difference in baseline attention, processing speed, and executive functioning scores between ε2 carriers versus non-carriers in the chemotherapy group (p=.26, see Supplementary Table 2).

Contrary to expectation, controls with an ε2 allele had lower attention, processing speed, and executive functioning scores than those without an ε2 allele (p-value=.047) across timepoints. There was no effect of ε2 genotype on learning and memory (Figure 3). Results were unchanged if anxiety, depression, or sleep disturbance was considered (Supplementary tables 3-5). Smoking history, family history of dementia, and time since surgery were not statistically significant contributors to the models, did not change the genotype-cognition results, and were not included in final models.

**Sensitivity Analysis**

When we excluded participants with ε3/ε4 and ε4/ε4 genotypes, similar results were obtained (Supplementary tables 6-8). We also examined models of each constituent neuropsychological test comprising the attention, processing speed, and executive functioning domain. The effect of the ε2 genotype on cognition by treatment group tended to be driven by two of the six tests (COWAT, p=.02; Trail Making B, p=.09; Supplementary table 9). Additionally, we found no relationships between ε2 and self-reported cognition (Table 3 and Supplementary
If we considered the effect of mean baseline cardiovascular comorbidities instead of deficit accumulation score, we saw a similar pattern to the primary analyses, and the model fit indices were not improved compared to initial models (Supplementary table 10).

Discussion

To our knowledge, this is the first study to examine the effect of the apolipoprotein E (APOE) ε2 allele on cognitive outcomes of cancer survivors. We found that older breast cancer survivors that were ε2 allele carriers that received chemotherapy had better cognitive performance on tests of attention, processing speed, and executive functioning before systemic therapy, and; this stronger performance was maintained over 24-months. The observed protective effect was not seen among survivors on hormonal therapy or non-cancer controls. While the observed effect was of small magnitude, it may nonetheless be clinically meaningful given the subtle neurocognitive changes associated with CRCD. Genotype was not related to tests of learning and memory in any group. Results were very similar when we excluded all participants with an APOE ε4 allele. Neither mood, history of smoking, family history of dementia, nor time since surgery affected results. The lack of an ε2 protective effect in the non-cancer control group was not explained by deficit accumulation, number of comorbidities, cardiovascular comorbidities, or other variables.

Most prior genetic studies of CRCD in breast cancer survivors have focused on APOE ε4. Compared to non-carriers, we expected that survivors and non-cancer controls with an ε2 allele would have better cognition over time, with more pronounced protective effects for survivors due to cancer-related toxicities. However, we found that having an ε2 allele was only protective
for survivors selected for chemotherapy, and the source of this effect was higher cognitive function prior to systemic therapy that then persisted over time after treatment exposure. These effects were not explained by younger age or lower comorbidities or deficits in survivors selected for chemotherapy compared to hormonal therapy alone. These findings may suggest that having an ε2 allele promoted cognitive reserve and buffered against cognitive decline in the face of challenges of high tumor burden and/or exposure to chemotherapy-related toxicities.\textsuperscript{9,40}

The \textit{APOE} gene has pleotropic effects, although the exact mechanisms by which \textit{APOE} genotypes affect CRCD (and AD) are largely undetermined. However, \textit{APOE} ε2 promotes anti-inflammatory and anti-oxidant processes, supports synaptic plasticity, and protects against aging-related cognitive decline, while ε4 confers risk for cognitive decline.\textsuperscript{18,41–44} Thus, it is reasonable that survivors who were ε2 carriers and were exposed to chemotherapy were the most protected from cognitive loss since cancer and chemotherapy are associated with DNA damage and inflammation. An alternative explanation for our result could be that oncologists are selecting older patients for treatment based on their clinical assessment of ability to survive long enough to benefit from chemotherapy,\textsuperscript{45,46} and our results may reflect unmeasured factors related to this selection bias.

Similar to prior reports from our group and others,\textsuperscript{5,9,12,15} we found that \textit{APOE} genotype was statistically significantly associated with differences in the domain of attention, processing speed, and executive functioning, but not learning and memory. However, the impact of \textit{APOE} genotype on cognitive performance is small therefore it is possible that despite our relatively large sample size, we were unable to detect small effects of the ε2 genotype on learning and
memory. Indeed, only two of the six tests of attention, processing speed, and executive function were related to the genotype-cognition interaction observed in the aggregate domain score. These two tests are arguably more demanding on executive processes than the others, and thus may provide better sensitivity to subtle effects. There is a growing consensus that refining cognitive measurement sensitivity will increase the likelihood of signal detection for clinically meaningful effects in cancer populations.47

Interestingly, we did not observe any genotype effects on self-reported cognitive function. Since the benefit of ε2 was observed at study entry and prior to chemotherapy treatment, differences in cognitive function may be more longstanding than those typically captured by the FACT-Cog (i.e., acute, noticeable changes related to cancer treatment). Prior work in this cohort has similarly detected effects of the ε4 genotype only on neuropsychological testing and not on self-report.15 CRCD is likely multifactorial and measured using both objective and subjective means, and the association of self-reported cognition to genetic factors requires further study.

A strength of our study is having a control group, allowing comparison of longitudinal findings among breast cancer survivors to those in a normative sample without cancer. We were surprised by the finding of a relative disadvantage of ε2 positivity in our non-cancer control group across timepoints. It is unclear how to interpret this finding, since survivors and non-cancer controls were well-matched at enrollment, and accounting for covariates that differed between the treatment groups such as anxiety and depression did not affect results. Since the APOE ε2 genotype has been associated with type III hyperlipoproteinemia39 and is linked to cardiovascular health,48,49 we also evaluated cardiovascular comorbidities, and these
did not markedly change the results. It is possible that the exclusion of participants with neurodegenerative disease had a differential effect on results for survivors and controls. It will be important to understand the broader effects of ε2 on health and cognition in cancer populations and integrate evidence from non-cancer studies. Furthermore, these unexpected findings in our control group could signal the need to attend to specific genotype in study design or analysis of comparison samples. Overall, the effects of ε2 may dynamically influence risks and benefits across multiple outcomes, yet to be fully appreciated.

Other clinically relevant findings include the fact that similar to past studies of CRCD and current models of dementia risk, we found that APOE genotypes do not correspond to a family history of dementia. Further, baseline mood symptoms and smoking history failed to explain the relationship between ε2 status and neuropsychological outcomes, suggesting these are distinct clinical outcomes, consistent with current multifactorial theories of CRCD.

There are several limitations to this study that should be considered in evaluating our results. First, this was a secondary unplanned analysis, and while a protective effect of ε2 on cognitive function in cancer survivors is biologically plausible and consistent with the AD literature, it will be important to replicate our findings in diverse settings and populations. Second, our power to detect small effects was limited because the ε2 allele is infrequent. Very few women who received chemotherapy had the ε2/ε2 or ε2/ε3 genotype, and an even lower percentage of women receiving only hormonal therapy had either genotype, underscoring the need for further study across treatment exposures. We were also not able to examine dose-response effects of the number of ε2 alleles or examine effects among different chemotherapy regimens. Third, follow-up of more than 24-months may be needed to evaluate
the role of genotype on later risk of cognitive decline. Finally, ε2 may protect aspects of
cognition not captured in our neuropsychological battery.

Our result that the APOE ε2 allele may confer protection against cognitive decline for
cancer survivors selected to receive chemotherapy adds a new dimension to the body of
evidence supporting a role of APOE genotype broadly and strengthens evidence suggesting
parallels between CRCD and AD.9,12,15,31,53 This idea is supported by indirect evidence, including
neuroimaging studies showing that breast cancer survivors and individuals with AD have
abnormalities in similar brain regions,54,55 and overlap in the cognitive domains affected.9,56
There is also increasing evidence showing that inflammatory pathways are likely involved in the
development of both conditions, and anti-inflammatory activity varies by APOE genotype.18,57–62
Since our results were unchanged when we excluded all ε4 carriers, our ε2 findings are not
merely the inverse of the ε4 findings previously reported,15 and are consistent with the unique
effects of each variant described in the AD literature.18 Overall, this study is the first to
demonstrate a potential protective effect of the ε2 allele on CRCD in breast cancer survivors,
and the need for replication is emphasized. Determining genetic protection from or risk for
CRCD remains a priority to help patients understand their risk for these symptoms and improve
prevention, assessment, and informed treatment decisions.5,21

Funding

This research was supported by the National Cancer Institute at the National Institutes of
Health grants K08CA241337 to KVD and R01CA129769 and R35CA197289 to JM. This study was
also supported in part by National Institute of Aging at the National Institutes of Health grant
R01AG068193 to JM and AJS. This research was also support in part by the National Cancer Institute at the National Institutes of Health grant P30CA51008 to Georgetown-Lombardi Comprehensive Cancer Center for support of the Biostatistics and Bioinformatics Resource and the Non-Therapeutic Shared Resource. The work of AJS and BCM was supported in part by the National Cancer Institute, National Institute of Aging, and National Library of Medicine at the National Institutes of Health grants R01CA244673, P30CA082709, P30AG10133, R01AG19771 and R01LM01136. GWR was supported in part by National Institute of Aging at the National Institutes of Health grant R01AG067258. TAA was supported in part by National Cancer Institute at the National Institutes of Health grants R01CA172119 and P30CA008748. The work of JC was supported in part by the American Cancer Society Research Scholars grant 128660-RSG-15-187-01-PCSM and the National Cancer Institute at the National Institutes of Health grant R01CA237535. HJC was supported in part by the National Institute of Aging at the National Institutes of Health grant P30AG028716 for the Duke Pepper Center. SKP was supported in part by the American Cancer Society Research Scholar grant RSG-17-023-01.

Notes

Role of the funder: The study sponsor did not play any role in the study design, data collection, analysis or interpretation, manuscript preparation or submission.

Disclosures: DG reports COTA stock ownership. HJ reports grant funding from Kite Pharmaceuticals, and consultant to RedHill BioPharma, Janssen Scientific Affairs, and Merck. KN reports salary and projects are supported by grants from the NIH (U24AG021886, U24NS095871, U01AG057195, U01AG24904), a sub-award from a collaborative clinical trial
between the ADCS and Biohaven Pharmaceuticals (UCSD sub-award, IU site, 107214854), nonprofit entities (Michael J. Fox, 10457.04, and Lilly Endowment Inc., 20091568000), U.S. Army Medical Research (W81XWH1820047), and U.S. Department of Defense (4638). AJS reports relationships with Bayer Oncology (Advisory Board unrelated to this work); Springer Nature (editorial office support unrelated to this work). All other authors report no disclosures.

Acknowledgements: We would like to thank the participants in the TLC study for their sharing of their time and experiences; without their generosity this study would not have been possible. We are also indebted to Sherri Stahl, Naomi Greenwood, Margery London, and Sue Winarsky who serve as patient advocates from the Georgetown Breast Cancer Advocates for their insights and suggestions on study design and methods to recruit and retain participants. We thank the TLC study staff who contributed by ascertaining, enrolling and interviewing participants. The work of Paul Jacobsen was done while he was at Moffitt Cancer Center.

Disclaimer: The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health or other funding agencies.

Author contributions: Kathleen Van Dyk: Conceptualization, writing–original draft, and writing–review and editing. Xingtao Zhou: Data curation, formal analysis, and writing–original draft, writing-review and editing, visualization. Brent J. Small: Writing–original draft, data curation, formal analysis, and writing–review and editing. Jaeil Ahn: Data curation, formal analysis, writing–original draft, and writing–review and editing. Wanting Zhai: Data curation, formal analysis, writing–original draft, and writing–review and editing. Tim A. Ahles: Funding acquisition, investigation, methodology, project administration, resources, supervision, or validation and writing–review and editing. Deena Graham: Funding acquisition, investigation, methodology, project administration, resources, supervision, or validation and writing–review
and editing. Paul B. Jacobsen: Funding acquisition and writing–review and editing. Heather S. Jim: Funding acquisition, investigation, methodology, project administration, resources, supervision, or validation and writing–review and editing. Brenna C. McDonald: Funding acquisition, investigation, methodology, project administration, resources, supervision, or validation and writing–review and editing. Kelly N. H. Nudelman: Data curation, formal analysis, writing–review and editing. Sunita Patel: Funding acquisition, investigation, methodology, project administration, resources, supervision, or validation and writing–review and editing. William Rebeck: Conceptualization, writing–review and editing. James Root: Funding acquisition, investigation, methodology, project administration, resources, supervision, or validation and writing–review and editing. Andrew J. Saykin: Funding acquisition, investigation, methodology, project administration, resources, supervision, or validation and writing–review and editing. Harvey J. Cohen: Conceptualization and writing–review and editing. Jeanne S. Mandelblatt: Conceptualization; writing–original draft; funding acquisition, investigation, methodology, project administration, resources, supervision, or validation; and writing–review and editing. Judith E. Carroll: Conceptualization, writing–original draft, and writing– review and editing.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author using the Thinking nad Living with Cancer data use/data sharing protocols.

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Table 1. Demographics and clinical information in the analytic sample with APOE genotypes excluding ε2/ε4

| Variable                        | All survivors<sup>a</sup> | ε2- survivors | ε2- survivors<sup>c</sup> | All controls<sup>b</sup> | ε2- controls<sup>c</sup> | ε2+ controls | P Case vs. Control | P Overall difference across case control by ε2+/ε2- |
|---------------------------------|---------------------------|---------------|---------------------------|---------------------------|---------------------------|---------------|--------------------|-----------------------------------------------|
| Total No.                       | 427                       | 367           | 60                        | 407                       | 359                       | 48            | .66                | .99                                           |
| Mean age, years (SD)            | 67.9 (5.8)                | 68.0 (5.8)    | 67.4 (6.0)                | 67.7 (6.8)                | 67.8 (6.9)                | 67.2 (6.5)    |                    |                                               |
| Race, % (No.)                   |                           |               |                           |                           |                           |               |                    |                                               |
| White                           | 78.4 (334)                | 80.3 (294)    | 66.7 (40)                 | 82.5 (335)                | 83.0 (297)                | 79.2 (38)     | .14                | .34                                           |
| Nonwhite                        | 21.6 (92)                 | 19.7 (72)*    | 33.3 (20)*                | 17.5 (71)                 | 17.0 (61)                 | 20.8 (10)     |                    |                                               |
| Marital status, % (n)           |                           |               |                           |                           |                           |               |                    |                                               |
| Married                         | 62.9 (259)                | 63.0 (223)    | 62.1 (36)                 | 50.1 (200)                | 49.9 (175)                | 52.1 (25)     | <.001              | .76                                           |
| Widowed, divorced, single       | 37.1 (153)                | 37.0 (131)    | 37.9 (22)                 | 49.9 (199)                | 50.1 (176)                | 47.9 (23)     |                    |                                               |
| Mean education, years (SD)      | 15.3 (2.2)                | 15.3 (2.1)    | 15.2 (2.3)                | 15.5 (2.3)                | 15.4 (2.3)                | 15.8 (2.1)    | .18                | .45                                           |
| Mean WRAT-4 Score (SD)          | 110.4 (15.4)              | 110.4 (15.5)  | 110.5 (15.2)              | 111.6 (15.9)              | 111.3 (15.8)              | 113.6 (16.7)  | .28                | .50                                           |
| Mean attention, processing speed, and executive functioning z-score<sup>d</sup> (SD) | -0.13 (0.67)              | -0.12 (0.67)  | -0.18 (0.66)              | -0.02 (0.66)              | 0.00 (0.66)               | -0.15 (0.63)  | .02                | .55                                           |
| Mean learning and memory z-score<sup>e</sup> (SD) | -0.05 (0.85)              | -0.05 (0.85)  | -0.08 (0.82)              | 0.01 (0.80)               | -0.00 (0.80)              | 0.10 (0.81)   | .25                | .45                                           |
| Mean FACT-Cog Perceived Cognitive Impairments<sup>e</sup> (SD) | 61.7 (10.6)               | 61.6 (10.4)   | 61.9 (12.1)               | 62.3 (8.7)                | 62.3 (8.7)                | 62.2 (8.7)    | .36                | .86                                           |
| Chemotherapy regimen, % (No.)   |                           |               |                           |                           |                           |               |                    |                                               |
| Anthracycline-cyclophosphamide without taxane | 6.9 (7)                  | 7.2 (6)       | 5.6 (1)                   | 0.0 (0)                   | --                        | --            | --                 | --                                             |

<sup>a</sup> Includes 427 participants. 
<sup>b</sup> Includes 407 controls. 
<sup>c</sup> Includes 60 participants with ε2+ genotype and 48 controls with ε2+ genotype. 

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| Therapy Combination                                    | % (No.)     | % (No.)     | % (No.)     | % (No.)     | % (No.)     | % (No.)     |
|-------------------------------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Anthracycline-cyclophosphamide and taxane             | 46.5 (47)   | 49.4 (41)   | 33.3 (6)    | 0.0 (0)     | --          | --          |
| Cyclophosphamide, methotrexate, fluorouracil          | 11.9 (12)   | 8.4 (7)     | 27.8 (5)    | 0.0 (0)     | --          | --          |
| Taxane only                                           | 34.7 (35)   | 34.9 (29)   | 33.3 (6)    | 0.0 (0)     | --          | --          |
| AJCC v. 6 Stage, % (No.)                              | --          | --          | --          | --          | --          | --          |
| 0                                                     | 12.0 (50)   | 13.1 (47)   | 5.3 (3)     | 0.0 (0)     | --          | --          |
| I                                                     | 56.3 (234)  | 56.3 (202)  | 56.1 (32)   | 0.0 (0)     | --          | --          |
| II                                                    | 26.4 (110)  | 25.1 (90)   | 35.1 (20)   | 0.0 (0)     | --          | --          |
| III                                                   | 5.3 (22)    | 5.6 (20)    | 3.5 (2)     | 0.0 (0)     | --          | --          |
| Surgery type, % (No.)                                 | --          | --          | --          | --          | --          | --          |
| BCS with/without RT                                   | 62.0 (263)  | 62.5 (228)  | 59.3 (35)   | 0.0 (0)     | --          | --          |
| Mastectomy                                            | 38.0 (161)  | 37.5 (137)  | 40.7 (24)   | 0.0 (0)     | --          | --          |
| Mean time since surgery to baseline, days (SD)        | 44.3 (52.1) | 43.6 (51.4) | 48.5 (56.4) | --          | --          | --          |
| ER status, % (No.)                                    | --          | --          | --          | --          | --          | --          |
| Positive                                              | 88.3 (377)  | 87.7 (322)  | 91.7 (55)   | 0.0 (0)     | --          | --          |
| Negative                                              | 11.7 (50)   | 12.3 (45)   | 8.3 (5)     | 0.0 (0)     | --          | --          |
| HER2 status, % (No.)                                  | --          | --          | --          | --          | --          | --          |
| Positive                                              | 9.8 (38)    | 10.6 (35)   | 5.3 (3)     | 0.0 (0)     | --          | --          |
| Negative                                              | 90.2 (349)  | 89.4 (295)  | 94.7 (54)   | 0.0 (0)     | --          | --          |
| Family history of dementia, % (No.)                   | .22         | .43         | --          | --          | --          | --          |
| Yes                                                   | 30.9 (132)  | 31.1 (114)  | 30.0 (18)   | 34.9 (142)  | 35.9 (129)  | 27.1 (13)   |
| No                                                    | 69.1 (295)  | 68.9 (253)  | 70.0 (42)   | 65.1 (265)  | 64.1 (230)  | 72.9 (35)   |
| Smoking status, % (No.)                               | .91         | .30         | --          | --          | --          | --          |
| Current/former smoker                                 | 41.8 (170)  | 42.7 (149)  | 36.2 (21)   | 42.2 (167)  | 41.7 (145)  | 45.8 (22)   |
| Never smoked                                          | 58.2 (237)  | 57.3 (200)  | 63.8 (37)   | 57.8 (229)  | 58.3 (203)  | 54.2 (26)   |
| Mean comorbidities (SD)                               | 2.6 (1.9)   | 2.6 (1.9)   | 2.7 (2.0)   | 2.3 (1.8)   | 2.4 (1.8)   | 2.0 (1.9)   | .02         | .27         |
### Mean cardiovascular comorbidities including hypertension (SD)

|                      | 0.6 (0.7) | 0.7 (0.7) | 0.5 (0.6) | 0.5 (0.7) | 0.6 (0.7) | 0.5 (0.6) | .07   | .70   |
|----------------------|-----------|-----------|-----------|-----------|-----------|-----------|-------|-------|

Mean Deficits Accumulation Index\(^a\) (SD)

|                      | 0.15 (0.08) | 0.15 (0.08) | 0.15 (0.09) | 0.13 (0.07) | 0.13 (0.07) | 0.12 (0.07) | .001  | .47   |

Depression\(^b\) (≥ 16 on CES-D), % (No.)

|                      | 12.1 (47) | 12.6 (42) | 9.4 (5) | 5.1 (20) | 4.9 (17) | 6.3 (3) | <.001 | .48   |

Mean anxiety score\(^c\) (SD)

|                      | 28.9 (7.8) | 29.0 (7.8) | 28.3 (8.0) | 26.5 (5.4) | 26.6 (5.4) | 26.4 (5.6) | <.001 | .72   |

Sleep disturbances (yes), % (No.)

|                      | 35.1 (139) | 36.3 (123) | 28.1 (16) | 24.7 (97) | 25.5 (88) | 18.8 (9) | .001  | .97   |

Attrition % (drop-out or death), % (No.)

|                      | 16.6 (71) | 16.1 (59) | 20.0 (12) | 9.3 (38) | 10.0 (36) | 4.2 (2) | .002  | .14   |

\(\varepsilon2\) positive = APOE \(\varepsilon2/\varepsilon2\) or \(\varepsilon2/\varepsilon3\); \(\varepsilon2\) negative = APOE \(\varepsilon3/\varepsilon3\), \(\varepsilon3/\varepsilon4\), \(\varepsilon4/\varepsilon4\); WRAT-4 = Wide Range Achievement Test, 4th edition, Word Reading Test Standard Score; AJCC, American Joint Committee on Cancer; BCS = breast conserving surgery; RT = radiotherapy; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2.

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**a.** Some numbers may not add to 100% due to missing data for item; 15 survivors were missing systemic therapy data. Non-white includes Black, Hispanic, and AAPI; one survivor and one control are missing race data. P-values based on chi-square or t-tests.

**b.** Excluding 8 cases and 14 controls who are \(\varepsilon2/\varepsilon4\).

**c.** Statistical significance between \(\varepsilon2\) and \(\varepsilon2+\) participants in cases and in controls has been highlighted by a pair of single asterisks if \(p \leq .05\).

**d.** Neuropsychological test scores by domain. Cognitive scores were standardized using the sample mean and standard deviation of age- and education-group matched baseline controls. Hence, a score of zero indicates a score at the mean of the control group; scores less than zero indicate lower scores than the mean of the control group, and positive scores indicate scores higher than the control mean.

**e.** Based on the FACT-Cog Perceived Cognitive Impairments subscale. Scores range from 0-72, with higher scores indicating better quality of life.

**f.** All refusal, unknown, or missing answers to family history have been treated as “No”.

**g.** Based on scores for baseline deficits accumulation scores. Excludes cognitive function. Scores could not be calculated if >10% of items were missing. Marital status, BMI, anxiety, depression, fatigue, comorbidities, including diabetes, etc., were included in the deficit accumulation scores.

**h.** Based on the CES-D, Center for Epidemiologic Studies Depression Scale. Depression defined by score above the cut point of 16 on the CES-D.

**i.** Based on the State-Trait Anxiety Inventory. Scores range from 20 to 80, with higher scores reflecting more anxiety.
Table 2. Genotype distribution

| APOE Genotype | Overall Sample with known APOE results, % (No.) (N=856) | Non-cancer Controls, % (No.) (n=421) | Survivors receiving chemotherapy +/- hormonal treatment, % (No.) (n=119) | Survivors receiving hormonal treatment alone, % (No.) (n=301) |
|---------------|--------------------------------------------------------|---------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| ε2/2          | 0.5 (4)                                                | 0.5 (2)                               | 0.0 (0)                                                       | 0.3 (1)                                                       |
| ε2/3          | 12.1 (104)                                             | 10.9 (46)                             | 17.6 (21)                                                    | 11.6 (35)                                                    |
| ε2/4          | 2.6 (22)                                               | 3.3 (14)                              | 0.8 (1)                                                      | 2.3 (7)                                                       |
| ε3/3          | 64.3 (550)                                             | 63.9 (269)                            | 64.7 (77)                                                    | 65.1 (196)                                                    |
| ε3/4          | 18.3 (157)                                             | 19.5 (82)                             | 14.3 (17)                                                    | 18.3 (55)                                                    |
| ε4/4          | 2.2 (19)                                               | 1.9 (8)                               | 2.5 (3)                                                      | 2.3 (7)                                                       |
Table 3. Impact of APOE ε2 Genotype on Adjusted Longitudinal Scores on Objective Cognition Test Domains and FACT-Cog Perceived Cognitive Impairment Scores Among Older Breast Cancer Survivors (N=412) and Non-Cancer Controls (N=407) Excluding ε2/4 Genotype

| Term                        | Final models with baseline deficits accumulation                                                                 |
|-----------------------------|---------------------------------------------------------------------------------------------------------------|
|                             | Attention, Processing Speed and Executive Function z-score | Learning and Memory z-score | FACT-Cog 18-item Perceived Cognitive Impairment Score |
| APOE Genotype               | .83                                                                 | .64                                                                 | .91                                                                 |
| Any ε2 vs. no ε2 allele, Beta (95% CI) | -0.16 (-0.33, -0.00)* | 0.05 (-0.16, 0.25) | 0.63 (-1.87, 3.14) |
| Group                       | .75                                                                 | .69                                                                 | .20                                                                 |
| Chemotherapy +/- HT vs. control, Beta (95% CI) | -0.11 (-0.24, 0.02) | -0.05 (-0.22, 0.11) | -1.21 (-3.22, 0.81) |
| Hormonal vs. control, Beta (95% CI) | -0.03 (-0.12, 0.06) | 0.01 (-0.11, 0.12) | -1.01 (-2.43, 0.40) |
| Time                        | <.001                                                             | <.001                                                             | .07                                                                 |
| 12 months vs. baseline, Beta (95% CI) | 0.09 (0.06, 0.12)** | 0.20 (0.15, 0.24)** | -0.60 (-1.26, 0.06) |
| 24 months vs. baseline, Beta (95% CI) | 0.12 (0.09, 0.16)** | 0.19 (0.14, 0.24)** | -0.76 (-1.47, -0.05)** |
| Interaction of group and genotype | .13                                                             | .95                                                             | .78                                                                 |
| Any ε2 allele and chemotherapy vs. no ε2 allele, control, Beta (95% CI) | 0.32 (0.00, 0.65)* | -0.05 (-0.46, 0.36) | -1.78 (-6.80, 3.24) |
| Any ε2 allele and hormonal therapy vs. no ε2 allele, control, Beta (95% CI) | 0.13 (-0.12, 0.38) | 0.02 (-0.30, 0.34) | -0.47 (-4.41, 3.47) |
| Baseline deficits accumulation per 0.01 points, Beta (95% CI) | -0.01 (-0.02, -0.01)** | 0.00 (-0.00, 0.01) | -0.29 (-0.37, -0.21)** |
| Model Fit - BIC             | 2501.5                                                            | 3742.6                                                            | 13374.7                                                        |

*aResults from mixed linear models; model fit was assessed using the Bayesian Information Criteria (BIC) score; lower scores indicate better fit. This primary analysis includes women with APOE ε2/2, ε2/3, ε3/3, ε3/4, or ε4/4 genotypes, grouped as having any vs. no ε2 allele; women with ε2/4 genotype are excluded (n=8 survivors and 14 controls). Each covariate adjusted for the effects of the other variables, time, interactions, and age, race, WRAT score and recruitment site. Comparable models further excluding genotypes ε3/4 and ε4/4 are included in secondary analyses in Supplementary Table 3.*

*bThe inclusion of terms for comorbidities or cardiovascular disease or hyperlipidemia (instead of deficits accumulation scores) did not improve model fit so were not used. Since depression and anxiety only modestly altered model fit, were not statistically significant factors and did not meaningfully alter results, they were not retained in the final models. Smoking and sleep disturbance were not related to group, ε2 or cognition and were not included in the final model. Family history of dementia was included in the deficits accumulation index. Two- and three-way interactions of ε2 or treatment group, deficits accumulation, and time were not statistically
significant and were not retained in the models. Participants with missing baseline covariates or outcomes would be excluded from the model.
Figure Titles and Legends

Figure 1. Analytic Sample of Older Breast Cancer Survivors and Matched Non-Cancer Controls

Figure 2. Impact of APOE ε2 Genotype on Adjusted Longitudinal Scores on attention, processing speed, and executive functioning z-scores Among Older Breast Cancer Survivors (N=378) and Non-Cancer Controls (N=388) Excluding ε2/4 Genotype. Results for (A) chemotherapy with and without hormonal therapy, (B) hormonal therapy only, and (C) controls are shown. Supplementary Tables 11 and 2 provide adjusted mean attention, processing speed, and executive functioning z-scores over time and post-hoc group comparisons.

Figure 3: Impact of APOE ε2 Genotype on Adjusted Longitudinal Scores on learning and memory z-scores Among Older Breast Cancer Survivors (N=378) and Non-Cancer Controls (N=388) Excluding ε2/4 Genotype. Results for (A) chemotherapy with and without hormonal therapy, (B) hormonal therapy only, and (C) controls are shown. Supplementary Tables 12 and 13 provide adjusted mean learning and memory z-scores over time and post-hoc group comparisons.
Analytic sample with APOE genotype data (n=427; 89.5%)

Completed 24-month assessment (n=279; 70.3%)
Completed 12-month assessment (n=329; 77.0%)
Skipped 12-month assessment (n=68; 15.9%)
Skipped 24-month assessment (n=77; 19.4%)

Refused all future assessments (n=24; 6.0%)
Died or became ineligible (n=17; 4.3%)

Excluded (n=50)
- No APOE genotype data (n=42; 8.8%)
- APOE ε2/4 genotype (n=8; 1.7%)

Skipped 24-month assessment (n=64; 16.3%)
Refused all future assessments (n=13; 3.3%)
Died or became ineligible (n=9; 2.3%)

Refused all future assessments (n=28; 6.9%)
Died or became ineligible (n=8; 2.0%)

Enrolled Survivors (n=477)

Enrolled Controls (n=435)

Excluded (n=28)
- No APOE genotype data (n=14; 3.2%)
- APOE ε2/4 genotype (n=14; 3.2%)

Completed 24-month assessment (n=305; 78.0%)
Completed 12-month assessment (n=363; 89.2%)
Skipped 12-month assessment (n=28; 6.9%)
Skipped 24-month assessment (n=64; 16.3%)
Refused all future assessments (n=13; 3.3%)
Died or became ineligible (n=9; 2.3%)

Excluded (n=50)
- No APOE genotype data (n=42; 8.8%)
- APOE ε2/4 genotype (n=8; 1.7%)

Skipped 24-month assessment (n=64; 16.3%)
Refused all future assessments (n=13; 3.3%)
Died or became ineligible (n=9; 2.3%)

Skipped 12-month assessment (n=28; 6.9%)
Died or became ineligible (n=8; 2.0%)

Analytic sample with APOE Genotype data (n=407; 93.6%)

Skipped 24-month assessment (n=64; 16.3%)
Refused all future assessments (n=13; 3.3%)
Died or became ineligible (n=9; 2.3%)

Skipped 12-month assessment (n=28; 6.9%)
Died or became ineligible (n=8; 2.0%)

Enrolled (n=477)

Excluded (n=50)
- No APOE genotype data (n=42; 8.8%)
- APOE ε2/4 genotype (n=8; 1.7%)

Skipped 24-month assessment (n=64; 16.3%)
Refused all future assessments (n=13; 3.3%)
Died or became ineligible (n=9; 2.3%)

Enrolled Controls (n=435)

Excluded (n=28)
- No APOE genotype data (n=14; 3.2%)
- APOE ε2/4 genotype (n=14; 3.2%)

Skipped 24-month assessment (n=64; 16.3%)
Refused all future assessments (n=13; 3.3%)
Died or became ineligible (n=9; 2.3%)

Enrolled (n=435)

Excluded (n=28)
- No APOE genotype data (n=14; 3.2%)
- APOE ε2/4 genotype (n=14; 3.2%)

Skipped 24-month assessment (n=64; 16.3%)
Refused all future assessments (n=13; 3.3%)
Died or became ineligible (n=9; 2.3%)

Enrolled (n=435)
A. CHEMOTHERAPY +/- HORMONAL THERAPY

Figure 2
B. HORMONAL THERAPY ONLY

Adjusted mean attention, processing speed, and executive functioning z-score

ε2 Negative (n=240)

ε2 Positive (n=35)
C. CONTROL

Adjusted mean attention, processing speed, and executive functioning z-score

Time (months)

ε2 Negative (n=340)

ε2 Positive (n=48)
A. CHEMOTHERAPY +/- HORMONAL THERAPY

Figure 3
B. HORMONAL THERAPY ONLY

-0.30
-0.25
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15

Adjusted mean Learning and Memory z-score

Time (months)

ε2 Positive (n=35)

ε2 Negative (n=240)
C. CONTROL

Adjusted mean Learning and Memory z-score vs. Time (months).

- ε2 Positive (n=48)
- ε2 Negative (n=340)