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Brief Communication

Interaction of endocrine therapy for breast cancer with APOE4 status on cognition over 5-year follow-up

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Abstract

Cognitive effects of breast cancer antiestrogen endocrine therapy are a salient concern for survivors, given the growing evidence that estrogen plays a role in late-life dementia risk. The APOE4 genotype has been linked with risk for cognitive difficulties, studied mainly in younger cancer survivors. We found that women aged 60+ with nonmetastatic breast cancer enrolled in the prospective Thinking and Living with Cancer study who underwent endocrine therapy had lower subjective ($P = .06$) and objective ($P = .08$) cognitive function than frequency-matched controls across time. At 5 years, however, women with breast cancer exposed to endocrine therapy and APOE4 carriers in particular exhibited lower learning and memory scores than other groups ($P < .05$). Our results suggest endocrine therapy may have long-term effects on cognitive function in women with breast cancer, particularly APOE4 carriers. Further characterization of genetic risk for long-term cognitive decline will be useful to inform survivorship care of older women.

Antiestrogen endocrine therapy is prescribed to treat and prevent recurrence of hormone-receptor positive breast cancers, which comprise the majority of breast cancers. Recommended treatment duration is typically 5 to 10 years.[1] Some, but not all, women on endocrine therapy experience disruptive symptoms from the disruption of estrogen function in the body and brain, including adverse cognitive effects.[2-4] However, the evidence linking endocrine therapy to cognitive decline has been inconsistent, potentially due to the timing of assessments before the full course of therapy is completed and a focus mainly on younger women.[3,5]

Efforts to understand risk for cognitive problems among cancer survivors have identified some increased risk with carriers of the APOE4 allele, the best known genetic risk for Alzheimer's disease.[6-8] Women are at higher risk of developing Alzheimer's disease than men, and APOE4 status in particular may have differential effects in women,[9] leading researchers to suspect APOE4 status interacts with estrogen function.[10] However, examining the interaction of APOE4 status and antiestrogen endocrine therapy for breast cancer is surprisingly understudied. One study investigated the interaction of APOE4 status and endocrine therapy exposure among breast cancer survivors and found that survivors with an APOE4 allele tended to have worse cognitive performance, but this difference was only detectable 3 to 5 years from treatment initiation.[11] Although that study was the first to highlight the possibility that the interactive effects of APOE4 status and endocrine therapy on cognition may not manifest until

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Table 1. Enrollment characteristics of older breast cancer survivors treated with antiestrogen endocrine therapy and frequency-matched noncancer controls.[a]

Variable	Control $n = 522$	Survivors on endocrine therapy $n = 465$	P
	Mean (SD) or Percent (No.)[b]		
Age	67.7 (6.6)	67.7 (SD 5.7)	.98
Race (Other/White)			
Other (Black, Asian, other)	17.9% (93)	18.9% (88)	.66
White (Non-Hispanic)	82.1% (428)	81.1% (377)	
Hispanic			
No	93.5% (488)	94.2% (438)	.65
Yes	6.5% (34)	5.8% (27)	
Education (years)	15.6 (SD 2.3)	15.4 (SD 2.1)	.39
WRAT4 Word Reading Standard Score[c]	111.4 (SD 16.0)	110.1 (SD 15.3)	.21
Obese (based on BMI ≤30 kg/m2)			
Not obese	72.4% (373)	62.3% (287)	<.01
Obese	27.6% (142)	37.7% (174)	
Family history of dementia or cognitive decline			
No	60.4% (291)	61.7% (264)	.69
Yes	39.6% (191)	38.3% (164)	
Comorbidities (number)	2.4 (SD 1.9)	2.8 (SD 2.0)	<.01
Age at menopause	49.4 (SD 6.1)	49.1 (SD 6.5)	.55
APOE E4 positivity[d]			
APOE E4 Negative	74.3% (388)	78.9% (367)	.09
APOE E4 Positive	25.7% (134)	21.1% (98)	
AJCC stage			
Stage 0		11.4% (53)	
Stage 1		61.4% (285)	
Stage 2		23.7% (110)	
Stage 3		3.4% (16)	
Chemotherapy			
No		81.5% (379)	
Yes		18.5% (86)	
Radiation			
No		33.5% (156)	
Yes		66.5% (309)	
Surgery (BCS vs mMastectomy)			
Lumpectomy		68.8% (318)	
Mastectomy		31.2% (144)	

[a] Enrollment was before systemic therapy, but postoperative (except women undergoing neoadjuvant chemotherapy) for survivors; enrollment is the first assessment time point for all participants.
[b] Some numbers may not total 100% of the sample due to missing data.
[c] WRAT4 = Wide Range Achievement Test-4.
[d] APOE = Apolipoprotein E

years after initiating treatment, the study lacked a control group and had a relatively small sample size.

We sought to follow-up these initial analyses in the larger prospective Thinking and Living with Cancer (TLC) study that followed older breast cancer survivors and a control group for up to 5 years. Prior TLC reports have found an interaction between APOE4 status and chemotherapy, but no interaction with endocrine therapy was found during the first 2 years of treatment.[8] For the current report, we examined cognitive function over time among older breast cancer survivors on endocrine therapy and frequency-matched controls and the interaction with APOE4 allele status. This report extends our prior findings in 2 important ways: first, we report on cognitive outcomes for breast cancer survivors and a control group up to 60 months post-treatment initiation; and, second, we are now reporting on a larger sample of women on endocrine therapy, more than twice that previously reported.

The TLC study has been described in detail elsewhere.[8] Briefly, postmenopausal women aged 60+ diagnosed with non-metastatic breast cancer from across multiple sites and non-cancer controls were matched on age, race, education, and study site. Participants underwent cognitive and psychosocial assessments beginning pre-systemic therapy/enrollment and then on a yearly basis. The analytic sample of women with breast cancer included only those who began an endocrine therapy ($n = 465$), with most (~90%) starting an aromatase inhibitor. Factor analysis was used to identify cognitive domains from the extensive neuropsychological battery: Attention, Processing Speed, and Executive Function (APE) and Learning and Memory (LM).[8,12] The Functional Assessment of Cancer Therapy—Cognitive Function Perceived Cognitive Impairments (FACT-Cog PCI)[13] was used to assess subjective cognitive function. We examined the main effects plus the interaction between group (women with breast cancer on endocrine therapy vs noncancer controls) and APOE4 status (carrier of 1 or 2 alleles vs not a carrier) and time using 2 separate linear mixed-effects models. We included a planned cross-sectional comparison at 60 months given the prior evidence suggesting delayed effects. A priori covariates included in the models included age, race, an estimate of premorbid verbal IQ (Wide Range Achievement Test [WRAT][14] performance), and site. The endocrine therapy and noncancer control groups were generally comparable (Table 1); however, we found group differences in body mass index (BMI) and the number of comorbidities, so both were consequently included as covariates in models.

Figure 1 portrays cognitive outcomes over time by group and APOE4 status. Model estimates are available in Tables S1-S3, and

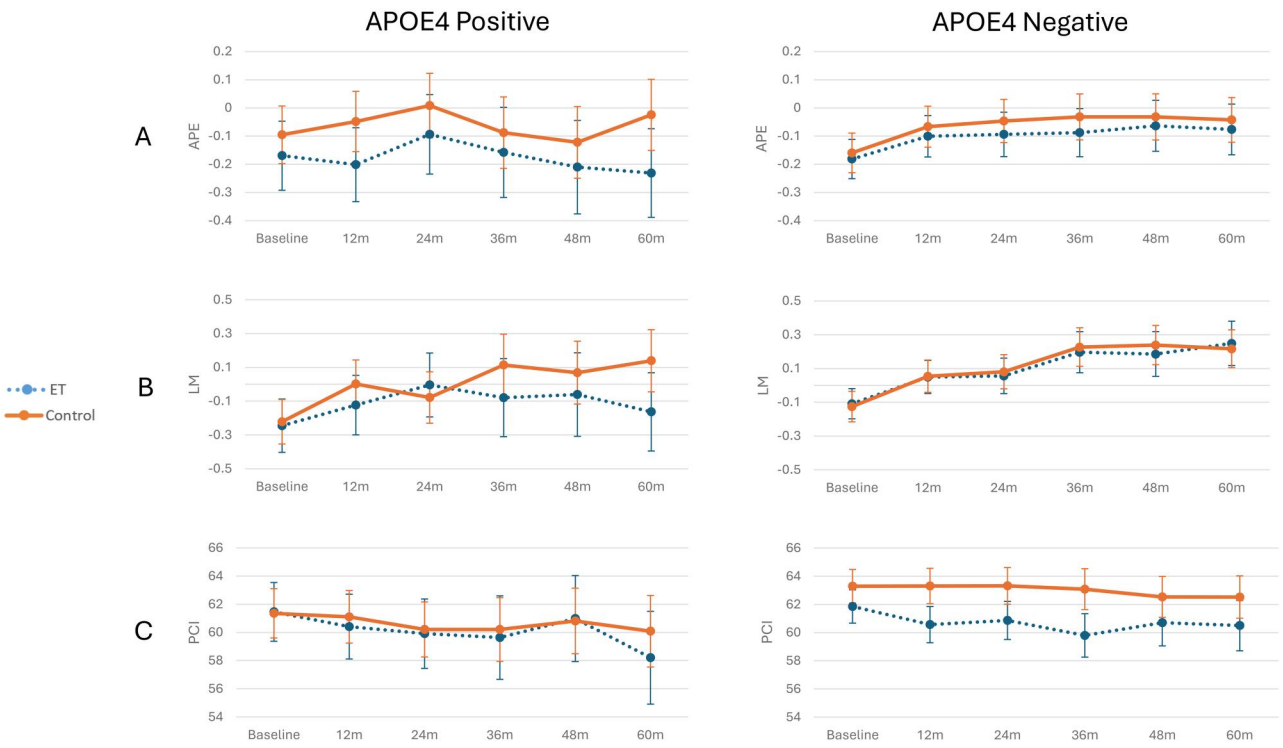

Figure 1. Cognitive function among older breast cancer survivors treated with antiestrogen endocrine therapy and noncancer controls over time by APOE4 status.

Linear mixed model results for cognition over time by APOE4 (any vs none) show a pattern of lower cognition/failure to show practice effects among survivors with APOE4 alleles vs other groups over time, and pairwise comparisons at the 60-month timepoint confirmed significantly worse performance in Learning and Memory in the APOE4+ endocrine therapy group compared with the APOE4+ control group ($P = .03$), the APOE4-endocrine therapy group ($P < .01$), and the APOE4– control group ($P < .01$), controlling for covariates.

Paneled by APOE4 status (ie, 1+ allele vs none): **A)** Attention, Processing Speed, and Executive Functioning (APE) Neuropsychological Test Performance; **B)** Learning and Memory (LM) Neuropsychological Test Performance; **C)** FACT-Cog Perceived Cognitive Impairment (PCI) score

Bars represent 95% standard error.

Abbreviation: ET = endocrine therapy.

Numbers for each group at each timepoint

		Baseline	12 m	24 m	36 m	48 m	60 m
APOE+	ET	97	75	61	32	31	29
	Control	134	114	95	50	59	46
APOE–	ET	366	278	217	119	107	84
	Control	385	332	270	155	185	169

the models' tests of fixed effects are available in Tables S4-S6. In terms of main effects, we found that survivors on endocrine therapy trended toward lower APE scores than controls across time ($P = .08$), but this was not found for LM scores ($P = .27$). We also found a trend main effect of group in models of the FACT-Cog PCI, with lower scores (ie, worse reported cognitive function) among survivors on endocrine therapy vs controls over time ($P = .06$).

Examining interactions of group by APOE4 status by time, we found a trend interaction on LM scores ($P = .09$) but not APE ($P = .66$) or FACT-Cog ($P = .88$); see Figure 1. The pattern of LM performance observed suggested that APOE4 carriers treated with endocrine therapy exhibited a unique decline at later timepoints compared with controls and survivors without an APOE4 allele, whereas these other groups demonstrated generally improved functioning over time with expected practice effects. This supported our planned pairwise comparisons at the 60-month timepoint; this analysis confirmed significantly worse LM scores in the APOE4+ endocrine therapy group compared with the APOE4+ control group (difference = 0.31, $P = .03$) and APOE4– control group (difference = 0.38, $P = .03$), and a trend toward worse scores compared with the APOE4– endocrine therapy group (difference = 0.41, $P = .08$).

This study is unique in evaluating the interaction of APOE4 status and endocrine therapy exposure over years on cognitive function among older breast cancer survivors compared with frequency-matched noncancer controls. We found that survivors taking endocrine therapy who had an APOE4 allele, but not controls or survivors without an APOE4 allele, had a pattern of a lower long-term cognitive function in the learning and memory domain; the effect was statistically significant at 60 months. This result is consistent with and extends past work with younger breast cancer survivors by including older women with longer-term follow-up and comparing outcomes of survivors and noncancer controls.[11]

Breast cancer survivors who took endocrine therapy tended to perform worse on the APE and report worse cognitive abilities from baseline on, which is the domain typically sensitive to

cancer-related cognitive changes after chemotherapy.[8] However, effects were small and we were unable to detect a significant interaction of endocrine therapy with the APOE genotype. In addition to emerging late in the course of treatment, effects of the interaction of APOE4 and endocrine therapy may be more evident on learning and memory processes, whereas the APE domain and associated brain regions may be more sensitive to chemotherapy effects.

There are several caveats of the study that should be considered. First, the Thinking and Living with Cancer cohort is well educated with high baseline cognitive abilities. Our findings cannot be generalized to less educated or more diverse populations, and it is important to replicate our study to determine the effects of hormonal therapy on cognition in more diverse samples. Second, women with more cognitive problems may have dropped out or discontinued treatment over time, limiting representation of the effects of endocrine therapy on long-term cognitive outcomes. Finally, despite the relatively large sample size, since APOE4 was present in only 21% to 25% of participants, power was limited for 3-way interactions.

Overall, this study suggests that further examination of genetic risk and cancer-related cognitive impairment in the context of the hormonal milieu will be important for informing survivorship care practices, especially in the context of the growing appreciation of estrogen's dynamic influence on women's cognitive health, especially in middle and older ages.

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Author contributions

Kathleen Van Dyk (Conceptualization, Investigation, Writing—original draft, Writing—review & editing), Wanting Zhai (Data curation, Formal analysis, Writing—original draft), Tim A. Ahles (Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Writing—original draft, Writing—review & editing), James C. Root (Investigation, Supervision, Writing—original draft, Writing—review & editing), Jaeil Ahn (Data curation, Formal analysis, Methodology, Supervision, Writing—original draft, Writing—review & editing), Ashley L. Artese (Investigation, Writing—review & editing), Traci N. Bethea (Investigation, Writing—review & editing), Harvey J. Cohen (Conceptualization, Writing—review & editing), Martine Extermann (Investigation, Writing—review & editing), Deena Graham (Investigation, Resources, Writing—review & editing), Claudine Isaacs (Investigation, Resources, Writing—review & editing), Heather S.L. Jim (Funding acquisition, Investigation, Project administration, Resources, Writing—review & editing), Brenna C. McDonald (Funding acquisition, Investigation, Project administration, Resources, Writing—original draft, Writing—review & editing), Zev M. Nakamura (Conceptualization, Investigation, Writing—review & editing), Sunita K. Patel (Investigation, Project administration, Resources, Writing—review & editing), Kelly E. Rentscher (Investigation, Writing—review & editing), Andrew J. Saykin (Funding acquisition, Investigation, Project administration, Resources, Writing—original draft, Writing—review & editing), Brent J. Small (Data curation, Formal analysis, Methodology, Supervision, Writing—original draft, Writing—review & editing), Danielle B. Tometich (Investigation, Writing—review & editing), Xingtao Zhou (Data curation, Formal analysis, Writing—review & editing), Judith E. Carroll (Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing—original draft, Writing—review & editing), and Jeanne S. Mandelblatt (Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing—original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *JNCI Cancer Spectrum* online.

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Conflicts of interest

Jeanne Mandelblatt is a co-inventor on a pending invention patent application (PCT/US2022/028741) filed by Georgetown University titled "Use of RAGE inhibitors to Treat Cancer-Related Cognitive Decline" and licensed to Cantex Pharmaceuticals. Dr Mandelblatt has waived her rights and will not receive any renumeration, consideration, or revenue generated from this license or the patents and patent applications licensed thereunder. This declaration has no effect on this article. Martine Extermann has been a consultant for Aileron and Alnylam and has received honoraria from OncLive. Claudine Isaacs has been a consultant for Genentech, AstraZeneca, Gilead Sciences, Novartis, Puma Biotechnology, Seagen, and Pfizer and received royalties from McGraw-Hill Companies and Wolter Kluwer; other disclosures are available at https://coi-asco-org.libproxy.lib.unc.edu/share/KZZ-5URC/Claudine%20Isaacs. Heather S. L. Jim has received funding from Kite Pharma and has been a consultant for SBR Bioscience. Andrew J. Saykin has received support from Avid

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Data availability

Thinking and Living with Cancer data are available to share via contact with the investigators.

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