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ORIGINAL ARTICLE

Cognitive effects of adjuvant endocrine therapy in older women treated for early-stage breast cancer: a 1-year longitudinal study

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Abstract

Purpose Evidence suggests endocrine therapy (ET) for breast cancer (BC) has adverse cognitive effects, but its specific effects on older women are unknown. This is despite the fact that older women are at increased risk of both breast cancer (BC) and cognitive decline relative to younger women. This study prospectively examined the cognitive effects of ET in a cohort of older BC patients. Our primary outcome measure was change in verbal memory, the cognitive domain most consistently affected by estrogen deprivation.

Methods Forty-two chemotherapy-naïve women age 60+, without dementia and recently diagnosed with hormone receptor-positive BC, completed neuropsychological tests at the time of ET initiation and after 1 year of treatment. Change in age-standardized verbal memory performance was examined using paired *t* tests. To assess a broader range of potential cognitive effects, we also examined changes in visual memory, processing speed, frontal executive function, and perceptual reasoning.

Results Participants exhibited significant decline from baseline to 1 year in verbal memory ($p = 0.01$). This decline was small to moderate in effect size ($d = -0.40$). Performance on other domains did not change significantly over the year (all $p > 0.05$).

Conclusions Our findings suggest potentially detrimental effects of ET on verbal memory in older women after just 1 year of treatment. Given that ET is prescribed for courses of 5 to 10 years, additional studies examining longer-term effects of treatment in older women are critical.

Keywords Breast cancer · Cognition · Endocrine therapy · Verbal memory · Aged

Background

Breast cancer (BC) is the most commonly diagnosed cancer in women, and approximately 75% of cases are hormone receptor positive (HR+) [1, 2]. Prevalence estimates are even higher among older women, as the risk of HR+ BC increases with age [3]. Since HR+ BC proliferation is driven by estrogen signaling, anti-estrogen endocrine therapies (ETs)

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represent important treatments for the disease [1]. Tamoxifen (TAM; a selective estrogen receptor modulator which blocks the effects of estrogens in the breast) and aromatase inhibitors (AIs; agents which inhibit estrogen biosynthesis) are the most widely prescribed treatments for HR+ BC and are typically prescribed for 5 to 10 years [1].

In light of estrogen's established roles in neuroprotection and cognitive functioning [4], concerns have been raised that treatment with ET may lead to adverse effects on cognition. While findings regarding the cognitive effects of ET have been somewhat mixed, a growing number of studies report an association between ET use and impaired cognitive performance. In fact, the cumulative pooled evidence provided in our recent meta-analysis demonstrated adverse cognitive effects of ET on verbal memory in cross-sectional comparisons of BC patients treated with ET and untreated control groups [5]. While cross-sectional studies are informative, evidence that 20–30% of women with BC experience cognitive dysfunction prior to initiating treatment [6] highlights the importance of prospective study designs that include pre-treatment assessment of cognitive functioning. Only five prospective studies were available for inclusion in our meta-analysis, and quantitative pooling of data from these studies suggested no significant effects of ET on cognitive performance over time. All but one of these studies, however, were limited by short follow-up periods of less than 1 year, which may be insufficient to allow detection of cognitive decline [5]. An additional limitation of existing studies examining the cognitive effects of ET is an underrepresentation of older women. The BC patients examined in our meta-analysis had an average age of 56 years, and none of the included studies focused specifically on older women. This is despite the fact that older women are at increased risk of both HR+ BC and cognitive impairment [3] and may be particularly vulnerable to treatment-related cognitive decline [7–10].

The present study focused on the neuropsychological effects of adjuvant ET in women age 60+ who were recently diagnosed with early-stage HR+ BC. Our purpose was to examine changes from pre-treatment cognitive performance over the course of 1 year on ET using a prospective repeated-measures design. Change in verbal memory was examined as the primary outcome because of its known sensitivity to estrogen deprivation [11–13].

Methods

Participant recruitment

Patients were recruited from medical and radiation oncology clinics at two BC centers in large university-affiliated teaching hospitals in Toronto, Canada, from July 2015 to March 2016. The study was approved by the research ethics boards at both hospitals (Sunnybrook Health Sciences Centre Research Ethics Board ID 130-2015; Mount Sinai Hospital Research Ethics Board ID 15-0249-E). Written informed consent was obtained from all individual participants included in the study.

Potential participants were identified according to a consecutive sampling procedure. Daily clinic lists were reviewed to identify newly diagnosed patients at each site, and patient eligibility was assessed by review of medical records and discussion with treating oncologists. Women were eligible if they were postmenopausal, age 60+, chemotherapy-naïve, and prescribed TAM or an AI for the adjuvant treatment of early-stage HR+ BC. HR positivity was defined as > 1% positive cell staining for estrogen and/or progesterone receptors, and "early-stage" disease was defined as T1-2, N0-1, M0 using the TNM staging system [14]. Patients were proficient in English with at least a grade five education, capable of reading large print and hearing normal conversation (with or without corrective aids), and able to provide informed consent.

To prevent potential confounding effects on cognitive performance, patients were excluded if they met any of the following criteria: (1) treatment with chemotherapy (for previous or current disease); (2) previous history of BC or other cancers, except non-melanoma skin cancers or cancers treated for cure over 5 years ago; (3) previous history of ET; (4) ET initiation > 14 days prior to baseline study assessment; (5) use of estrogen or hormone replacement therapy (ERT/HRT) within 4 weeks of baseline assessment; (6) diagnosis of major psychiatric disorder other than depression within the last 10 years; (7) acute illness or delirium; (8) history of neurologic disorder (including dementia, stroke, Parkinson's disease, etc.); or (9) signs of dementia on the Memory Impairment Screen (i.e., scores < 4) [15].

Study design

A prospective repeated-measures design was used to control for pre-treatment cognitive performance. Participants completed a 2-hour baseline assessment of neuropsychological function and mood after surgery but within 14 days of starting ET (T1), and again after 1 year of treatment (T2). The battery of valid and reliable tests was individually administered in a private room at each assessment. Tests were administered by a trained psychometrist (EAU) with the oversight of a neuropsychologist (MCT). ET adherence was monitored monthly throughout the follow-up period. A full description of the measures used is provided below.

Measures

Neuropsychological battery

The neuropsychological battery included tests of verbal memory performance, our primary outcome. The battery also

included tests of four additional cognitive domains (described below) which were examined as secondary outcomes. Neuropsychological test scores were converted to age-adjusted *z*-scores based on published normative data to control for the effects of age on cognition and to permit the calculation of summary scores for each domain, which were computed by averaging the *z*-scores of the tests or subtests within each domain. The neuropsychological tests used to assess each domain were as follows:

Verbal memory Change in our primary outcome of verbal memory performance was measured using the Rey Auditory Verbal Learning Test (RAVLT) [16]. Administration of the RAVLT consists of immediate recall of a 15-item word list presented five times. These five immediate recall trials are followed by an intervening task consisting of a new 15-item word list. After this, participants are asked to recall the original 15-item word list (delayed recall). Scores from the final immediate recall trial and the delayed recall trial were averaged to yield a verbal memory summary score. An alternate word list was used at T2 to minimize practice effects [17].

Visual memory Scores on the final immediate recall test (i.e., trial 3) and the delayed recall test of the Brief Visual Memory Test-Revised [18] were used to compute a visual memory summary score. An alternate figure display was used at T2 to minimize practice effects.

Processing speed A processing speed summary score was computed by averaging across three tests scores: (1) time in seconds to complete Trail Making Test part A [19], (2) Weschler Adult Intelligence Scale (WAIS-IV) Digit-Symbol Coding [20], and (3) WAIS-IV Symbol Search [20].

Frontal executive function A frontal executive function summary score was computed by averaging across two test scores: (1) time in seconds to complete Trail Making Test part B [19] and (2) total number of correct responses on a phonemic fluency test (FAS at T1 and PRW at T2) [21].

Perceptual reasoning A perceptual reasoning summary score was computed by averaging across three test scores: (1) WAIS-IV Matrix Reasoning [20], (2) WAIS-IV Block Design [20], and (3) WAIS-IV Visual Puzzles [20].

Psychological distress

To control for the potential effect of psychological distress on neuropsychological performance, the 37-item Profile of Mood States-short form (POMS-sf) was administered at each assessment. The POMS-sf assesses mood across six subscales: depression, anxiety, fatigue, anger, confusion, and vigor. The POMS-sf Total Mood Disturbance (TMD) score [22], which provides an overall measure of psychological distress, was calculated for each participant by summing scores for the five unfavorable mood subscales (depression, anxiety, fatigue, anger, and confusion) and subtracting this total from the score for the favorable mood subscale (vigor). TMD scores could range from − 24 to + 184, with higher scores indicating higher levels of psychological distress. Scores were left as continuous due to the absence of established cut-offs for psychological distress on the POMS-sf.

Demographic and clinical information

Information pertaining to participant demographic (education, marital status, employment status, ethnicity) and medical (age at menopause, medical comorbidities, use of prescription medications) characteristics was collected at baseline using self-report questionnaires. Education was measured as the total number of years spent in school, including primary school (maximum 8 years), high school (maximum 13 years), and any post-secondary education (e.g., technical school, community college, university). Information regarding BC stage, primary surgery type (lumpectomy or mastectomy), and radiotherapy exposure were extracted from electronic medical records. An additional questionnaire was administered at follow-up to capture any changes in comorbidity and prescription medication use.

ET adherence

On a monthly basis, participants were telephoned and asked to confirm which ET they were currently taking. They were also asked to estimate the percentage of their prescribed doses they had taken in the past month (with 0% being none and 100% being all of the prescribed doses). Participants were considered to be adherent if they reported taking ≥ 80% of their prescribed doses of ET [23].

Statistical analysis

The Shapiro-Wilk test was used to assess whether verbal memory change scores were normally distributed, and a paired *t* test (or Wilcoxin signed-rank tests when data were not normally distributed) was used to assess our primary outcome measure of change in verbal memory *z*-score from T1 to T2. An effect size (Cohen's d) was calculated to describe the magnitude of change in this domain. If significant change was observed from T1 to T2, multivariable regression analyses were conducted to explore the extent to which change in performance (i.e., T2 z-score – T1 z-score) was associated with relevant independent variables. Based on our sample size, a maximum of four independent variables could be included in the regression models without overfitting [24]. Age at T1, years of education, duration of retest interval, and change in

measures of mood/psychological distress were selected a priori based on their potential to influence change in neuropsychological performance. Multicollinearity between independent variables was examined based on inspection of variance inflation factors, and residual plots were examined to assess departure from the normality assumption. To minimize bias, these independent variables were entered simultaneously into the regression model and kept in the model regardless of whether or not they were found to be significantly associated with the dependent variable [24]. Because various aspects of mood/psychological distress were measured using the POMS-sf, which may differ in their effects on cognition, we ran three separate regression models which differed only in the POMS-sf change score that was entered as the measure of mood/psychological distress: one that used the POMS-sf TMD score (an aggregate measure of global psychological distress which encompasses depression, anxiety, fatigue, and confusion), one that used the depression subscale score, and one that used the anxiety subscale score. Secondary exploratory analyses examined change from T1 to T2 in the other four cognitive domain z-scores, using the same analyses described above for the verbal memory domain. Analyses were conducted using SAS version 9.2, and a two-sided alpha level of 0.05 was used to assess statistical significance.

Results

Participant characteristics

Details of participant recruitment and attrition are shown in Fig. 1. Of the 626 patients aged 60+ that were screened, 82 (13%) met study criteria and were eligible to participate. Forty-six (56%) of these patients consented to the study and completed T1 assessments. There was no significant age difference between eligible patients who declined participation in the study (mean age = 70.81 years) and those who consented (mean age = 68.07) ($t = 1.66$, $p = 0.11$). No further demographic or medical information was collected for patients who declined study participation. Despite attempts to arrange T1 assessments prior to ET initiation, 25 (54%) participants had initiated ET prior to T1. Among these participants, the average number of days on ET at T1 was 7.84 (SD = 3.95, range: 1–14). T1 summary z-scores on our primary outcome measure of verbal memory did not differ significantly between participants who had (mean = 0.07, SD = 0.94) and had not (mean = 0.32, SD = 0.86) initiated ET at T1 ($t = 0.95$, $p = 0.34$). Forty-two (91%) participants returned to complete T2 assessments, which took place an average of 382.64 days after T1 assessments (SD = 36.10; range 318–475). Reasons for declining retest were not related to cognitive functioning or risk factors for cognitive decline (Fig. 1). Due to the small number of participants who declined retest ($n = 4$), no statistical comparisons were made between those who did and did not return for follow-up.

Participants underwent menopause at an average age of 51.02 years (SD = 4.19). There was no change in medical comorbidities or in the use of psychotropic medications (antidepressants, benzodiazepines, or non-benzodiazepine sedatives, anxiolytics, or hypnotics) within the study sample from T1 to T2. At T1, 37 (88%) participants had been prescribed an AI (23 letrozole and 14 anastrozole) and five (12%) had been prescribed TAM. Three participants underwent a switch in their prescribed ET agent over the course of the year (one from letrozole to TAM, one from letrozole to exemestane, and one from anastrozole to letrozole). In each case, the reason for the switch was musculoskeletal side effects. With the threshold for ET adherence set as an intake of ≥ 80% of prescribed doses, all 42 participants who returned for their T2 assessments were adherent throughout the study period. Additional demographic and clinical characteristics of the study sample are presented in Table 1.

Psychological distress

Mean TMD, depression, and anxiety scores are presented in Table 1. There was no statistically significant change in these scores from T1 to T2 (Table 1).

Change in verbal memory

A significant change in the verbal memory domain, t(41), $p < 0.01$ was observed, with participants performing more poorly at T2 than at T1 (Table 2). The effect size of this difference was small to moderate in magnitude (Cohen's $d = -0.40$). Regression analyses revealed that change in verbal memory was not significantly associated with age, education, length of retest interval, or change in psychological distress, regardless of whether POMS-sf TMD score, depression subscale score, or anxiety subscale score was entered into the model (Supplementary Table 1). There was no evidence of multicollinearity between independent variables in any of the regression analyses (all variance inflation factor values < 1.5), and based on the residual analysis, we observed no departure from the normality assumption.

Secondary analyses examining change in other cognitive domains

There were no significant changes from T1 to T2 found in our secondary analyses of the other four domain z-scores (Table 2).

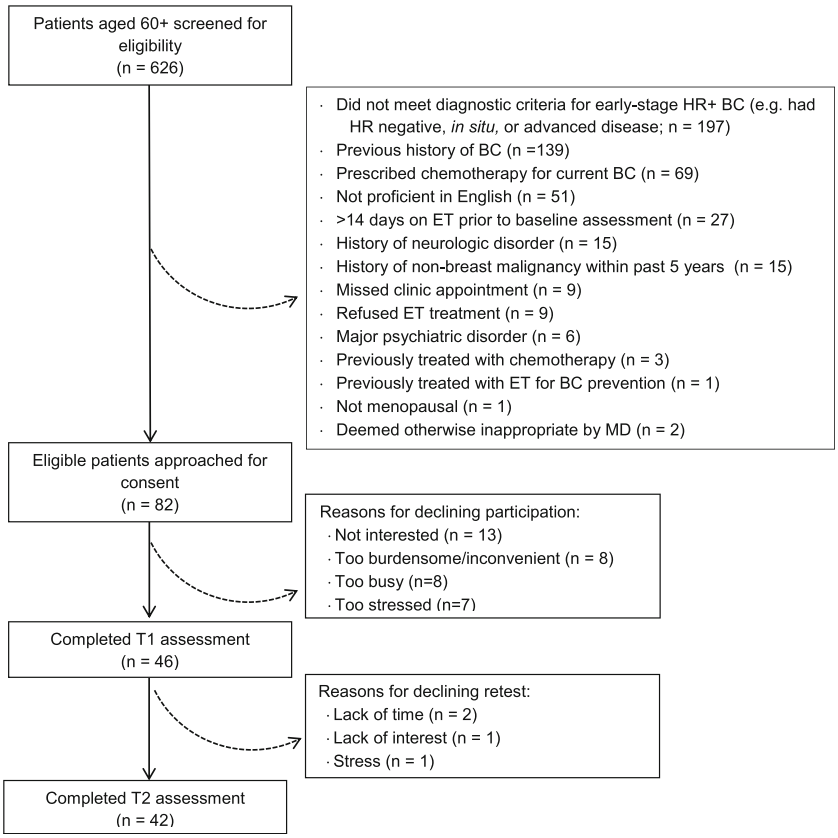

Fig. 1 Flow of participants through the study

Discussion

Our findings indicate a potentially detrimental effect of ET on verbal memory in women age 60+ after 1 year of treatment. Previous prospective studies have yielded mixed results, with some studies demonstrating adverse effects of ET on neuropsychological test performance [10, 25, 26] while others have reported no significant treatment effects [27–29]. In our recent meta-analysis, which pooled data across five of these prospective studies [10, 25–27, 29], we found an overall null effect of ET on cognition over time [5]. This null finding may have been due to the fact that all but one of the prospective studies included in this meta-analysis had short follow-up periods of less than 1 year, as well as the fact that participants were relatively young compared to the women aged 60+ in the present study. To date, only one other prospective study [28] (which did not provide the raw data needed for inclusion in our meta-analysis) has focused on the effects of ET in women aged 60+ with BC. This study also had a short follow-up period of just 6 months, which may explain why no significant effects of ET on cognitive performance were observed despite the fact that participants were older and therefore likely to be at greater baseline risk of cognitive decline. When comparing the results of our current study with these previous findings, it would appear as though older women may indeed be more vulnerable to ET-related cognitive decline than younger women, but that follow-up periods of sufficient duration are required to reveal this decline.

The finding of a potentially detrimental effect of ET on verbal memory is consistent with studies examining the cognitive effects of estrogen deprivation in postmenopausal women, where verbal memory has been found to be the domain most consistently impaired [11–13]. In line with these findings are studies indicating that verbal memory is the domain most consistently enhanced by treatment with ERT/HRT [30, 31]. Further, multiple studies have found circulating estrogen levels to be positively correlated with verbal memory performance in older women [32–34]. Results of cross-sectional comparisons of BC patients treated with ET and untreated controls in our recent meta-analysis provide additional evidence that the adverse cognitive effects of ET are specific to performance within the domain of verbal memory [5].

The statistically significant decline in verbal memory observed in this study was small to moderate in effect size. We did not expect to observe conversion to mild cognitive impairment or dementia over a 1-year period in our sample of women, who were in relatively good health (apart from their cancer diagnosis) and free of dementia at baseline. However, the fact that these women

Table 1 Participant characteristics ($n = 42$)

Characteristic	
Age at T1, years, mean (SD)	68.38 (4.86)
Years of education, mean (SD)	14.26 (4.27)
Married, *n* (%)	26 (61.90)
Employed, *n* (%)	11 (26.19)
Race, *n* (%)	
Caucasian	31 (73.81)
Asian	9 (21.43)
Other	2 (4.76)
Use of psychotropic medication[a], *n* (%)	8 (19)
Breast cancer stage at diagnosis, *n* (%)	
Stage I	26 (61.90)
Stage II	16 (38.10)
Received radiotherapy, *n* (%)	31 (73.81)
Primary surgery, *n* (%)	
Lumpectomy	30 (71.43)
Mastectomy	12 (28.57)
Days since surgery at T1, mean (SD)	74.69 (24.97)
ET prescribed at T1, *n* (%)	
Letrozole	23 (54.76)
Anastrozole	14 (33.33)
Tamoxifen	5 (11.90)
Days on ET at T2, mean (SD)	373.79 (20.91)
Days from T1 to T2 interval, mean (SD)	382.64 (36.10)
POMS-sf Total Mood Disturbance score at T1, mean (SD)	2.95 (19.82)
POMS-sf Total Mood Disturbance score at T2, mean (SD)	6.62 (24.10)
POMS-sf Depression score at T1, mean (SD)	2.10 (3.96)
POMS-sf Depression score at T2, mean (SD)	3.10 (5.86)
POMS-sf Anxiety score at T1, mean (SD)	4.38 (4.62)
POMS-sf Anxiety score at T2, mean (SD)	4.31 (4.95)

T1 time at baseline assessment, *T2* time at retest; *POMS-sf* Profile of Mood States-short form (a higher score equals more distress)

[a] Current use of antidepressants, benzodiazepines, or non-benzodiazepine anxiolytics, sedatives, or hypnotics

experienced statistically significant decline in verbal memory performance after just 1 year of ET warrants larger-scale prospective studies examining whether longer-term treatment may be associated with clinically relevant cognitive decline. The need for such studies is heightened by the fact that current guidelines recommend at least 5 years of ET, with extended durations of up to 10 years becoming increasingly common. Further, previous studies have consistently identified verbal memory performance as an important early predictor of dementia and Alzheimer's disease [35–37].

Our secondary analyses revealed no effect of ET on visual memory, processing speed, frontal executive function, and perceptual reasoning performance. Given our relatively small sample size, it is possible that these null findings may be due to a lack of statistical power. Alternatively, it may be that these cognitive domains are less sensitive than verbal memory to the early effects of ET-induced estrogen deprivation in older women. Further analysis is warranted with larger samples.

A key strength of this study is its prospective repeated-measures design, which allowed us to take baseline cognitive performance into account. This is a critically important consideration given evidence that 20 to 30% of women with BC experience pre-treatment cognitive dysfunction [6]. Moreover, our multiple regression analyses allowed us to determine that observed changes in verbal memory performance were not attributable to change in psychological distress (including depression and anxiety) over the year. Our use of age-adjusted z-scores, rather than raw neuropsychological test scores, allows the performance of our study sample to be examined within the context of what would be expected in healthy individuals of a similar age. Other key strengths include our low rate of attrition and high rate of ET adherence over the 1-year follow-up period.

Table 2 Means (SD), ranges, and results of significance testing for age-adjusted cognitive domain summary z-scores

	T1		T2		*t(41)*	95% CI around mean difference	*p*
	Mean (SD)	Range	Mean (SD)	Range			
Primary outcome							
Verbal memory	0.15 (0.84)	− 2.19 to 1.63	− 0.10 (0.87)	− 2.24 to 1.44	− 2.60	− 0.45 to − 0.06	0.01
Secondary analyses							
Visual memory	− 0.24 (0.86)	− 2.52 to 1.65	− 0.14 (0.87)	− 2.06 to 1.55	0.91	− 0.13 to 0.35	0.37
Processing speed	0.16 (0.48)	− 0.91 to 1.14	0.23 (0.48)	− 0.94 to 1.25	1.32	− 0.04 to 0.17	0.19
Frontal executive function	0.23 (0.49)	− 0.98 to 1.49	0.22 (0.53)	− 0.51 to 2.45	− 0.14	− 0.13 to 0.16	0.89
Perceptual reasoning	0.04 (0.75)	− 1.22 to 1.89	0.02 (0.74)	− 1.33 to 1.89	− 0.43	− 0.12 to 0.08	0.67

Limitations

A limitation of the current study is its lack of a comparison group. The ideal comparison group would consist of women with HR+ BC who did not undergo ET; however, given that ET is standard of care for women with this disease, recruiting such a group is not feasible. An alternative option could have been to include a group of women without BC that underwent the same testing procedures as our ET group, which would have allowed us to control for measurement error, regression towards the mean, and practice effects using reliable change methods [38]. Given that practice-related improvements in performance are common with repeated administration of neuropsychological tests, it is possible that even greater decline might have been observed had we been able to control for normal practice effects in our analysis. Second, our sample size was relatively small and this precluded us from examining potential risk factors for ET-related changes in verbal memory (e.g., body mass index, medical comorbidities, physical activity, smoking history, alcohol consumption), or from comparing the cognitive effects of the different ETs used by participants. Given evidence that differences may exist both between (i.e., TAM vs. AI) and within (i.e., non-steroidal vs. steroidal AIs) ET classes [5, 10, 25, 39, 40], and since current treatment guidelines permit a choice between ETs, the question of whether ETs differ in their cognitive effects is clinically relevant and should be a focus of future research. Finally, because our sample consisted of well-educated women who were predominantly Caucasian, our findings may not be generalizable to the overall population of older women with BC and should be replicated in a more representative sample.

Conclusions

Despite these limitations, this study contributes to our growing understanding of the cognitive effects of ET, and importantly, adds to the very sparse literature pertaining to these effects in older women. Given that ET is typically prescribed for a course of 5 to 10 years, and that the current study suggests adverse effects on verbal memory after just 1 year of treatment, it is critical that additional studies examine longer-term effects on cognition. While ET undoubtedly represents an important therapeutic option for many women with HR+ BC, the information provided by this and future studies examining the cognitive effects of ET in older BC patients will be essential in allowing these women and their clinicians to make informed treatment decisions.

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Compliance with ethical standards

Conflict of interest K.I.P. has served in consulting and advisory roles for and received honoraria and travel support from AstraZeneca, Pfizer, Roche, Amgen, Novartis, and Eisai. K.J.J has served as a consultant for and/or attended advisory boards for Genomic Health Inc., Novartis, Purdue Pharma and Roche. No other authors have any conflicts of interest to report. M.C.T has full control of all primary data and agrees to allow the journal to review the data if requested.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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