Published in final edited form as:

Breast Cancer Res Treat. 2017 October ; 165(3): 677–686. doi:10.1007/s10549-017-4353-y.

Cognitive Function and Discontinuation of Adjuvant Hormonal Therapy in Older Breast Cancer Survivors: CALGB 369901 (Alliance)

Shirley M. Bluethmann, PhD, MPH¹, Catherine M. Alfano, PhD², Jonathan D. Clapp, MS³, George Luta, PhD⁴, Brent J. Small, PhD⁵, Arti Hurria, MD⁶, Harvey J. Cohen, MD⁷, Steven Sugarman, MD⁸, Hyman Muss, MD⁹, Claudine Isaacs, MD¹⁰, and Jeanne S. Mandelblatt, MD, MPH^{3,10}

¹Department of Public Health Sciences, College of Medicine, The Pennsylvania State University, 500 University Drive, Hershey, PA, 17033

²American Cancer Society, Inc., 1875 Connecticut Ave NW, Washington, DC, 20009

³Department of Oncology, Georgetown University Medical Center and Georgetown-Lombardi Comprehensive Cancer Center, 3300 Whitehaven Street NW, suite 4100, Washington, DC, 20007

⁴Department of Biostatistics, Bioinformatics and Biomathematics, Georgetown University Medical Center and Georgetown-Lombardi Comprehensive Cancer Center, 3300 Whitehaven Street NW, suite 4100, Washington, DC, 20007

⁵School of Aging Studies, University of South Florida, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612

⁶Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, 1500 Duarte Rd, Duarte, CA 91010

⁷Department of Medicine and Center for the Study of Aging and Human Development, Duke University, Box 3003 DUMC, Room 3502 Busse Building, Blue Zone, Duke South, Durham, NC 27710

⁸Department of Medicine, Memorial Sloan-Kettering Cancer Center, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065

Corresponding author: Shirley M. Bluethmann, PhD, MPH, The Pennsylvania State University College of Medicine, Department of Public Health Sciences, 500 University Drive, Hershey, Pennsylvania 17036, szb332@psu.edu.
Drs. Isaacs and Mandelblatt served as dual senior authors

[ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT00068328

Compliance with Ethical Standards:

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: Informed consent was obtained from all individual participants included in the study. The protocol met Health Insurance Portability and Accountability Act standards and was approved by CALGB, the National Cancer Institute, and the institutional review boards at all sites. Each participant signed an IRB-approved, protocol-specific consent form in accordance with federal and institutional guidelines.

Conflict of Interest: All other authors declare no conflicts of interest.

⁹Department of Medicine, UNC-Chapel Hill School of Medicine, University of North Carolina, 321 South Columbia Street, Chapel Hill, NC 27514

¹⁰Department of Medicine, Georgetown University Medical Center and Georgetown-Lombardi Comprehensive Cancer Center, 3300 Whitehaven Street NW, suite 4100, Washington, DC, 20007

Abstract

Purpose—To investigate the effects of cognitive function on discontinuation of hormonal therapy in breast cancer survivors ages 65+ (“older”).

Methods—Older breast cancer survivors with invasive, non-metastatic disease and no reported cognitive difficulties were recruited from 78 Alliance sites between 2004–2011. Eligible survivors (n=1280) completed baseline interviews; follow-up was conducted annually for up to seven years. Survivors with estrogen-receptor positive (ER+) cancers who initiated hormonal therapy (n=990) were included. Self-reported cognitive function was measured using the EORTCQLQ30 scale; a difference of 8 points on the 0–100 scale was considered clinically significant. Based on varying rates of discontinuation over time, discontinuation was evaluated separately for three time-periods: early (<1 year); midpoint (1–3 years); and late discontinuation (>3–5 years). Cox models for each time-period were used to evaluate the effects of cognition immediately preceding discontinuation, controlling for age, chemotherapy, and other covariates.

Results—Survivors were 65–91 years old (mean 72.6 years), and 79% had stages 1 or 2A disease. Overall, 43% discontinued hormonal therapy before five years. Survivors who reported lower cognitive function in the period before discontinuation had greater hazards of discontinuing therapy at the treatment midpoint (HR 1.22 per 8-point difference, CI 1.09–1.40, p<.001), considering covariates, but cognition was not related to discontinuation in the other periods.

Conclusions—Self-reported cognitive problems were a significant risk factor for discontinuation of hormonal therapy 1–3 years post-initiation. Additional research is needed on the temporality of cognitive effects and hormonal therapy to support survivorship care needs of older survivors.

Introduction

Adjuvant hormonal therapy (including tamoxifen and aromatase inhibitors) is the standard of care for the 70% of breast cancer survivors with estrogen-receptor positive (ER+) disease, [1, 2] given evidence of significant reductions in recurrence and mortality. [3, 4] Despite recommendations for at least five years of hormonal treatment, up to 50% of survivors discontinue therapy prematurely. [5–7] Several factors have been shown to increase the risk of hormonal therapy discontinuation, including non-white race and healthcare access barriers, [8, 9] while management of medication-related side effects and greater patient-provider communication may reduce the risk of discontinuation. [5, 10]

Older age has also been shown to increase the risk of discontinuation of hormonal therapy, [11] perhaps related to high rates of multi-morbidities that interact with or interfere with ability to continue long-term medication regimens. [8, 9] One age-related condition that may be especially salient to premature discontinuation of hormonal therapy in older women is

cognitive decline, since cognitive problems could affect ability to comprehend medical instructions or create plans to manage daily medications. [12, 13]

While there has been some investigation of the effects of breast cancer treatment on cognition, especially related to chemotherapy, [14–16] few studies have specifically focused on cognitive function for older survivors taking hormonal therapy [17, 18] and none have prospectively examined the impact of pre-existing cognitive problems on the ability of older survivors to maintain hormonal treatment. [19, 20] To fill this gap, this study used data from a prospective cohort of older survivors to investigate the effect of self-reported cognitive function on subsequent discontinuation of hormonal therapy. These analyses are intended to contribute to the growing science on cognition and cancer treatment, generate new hypotheses, and suggest possible clinical interventions to address the chronic needs of the rapidly growing population of older adult cancer survivors. [21]

Methods

This study conducted an unplanned secondary analysis of data from an extant cohort of older survivors originally designed to investigate patterns of systemic therapy. [22, 23] The study was conducted at 78 hospitals or practices affiliated with the Cancer and Leukemia Group B (CALGB) cooperative group (presently part of the Alliance for Clinical Trials in Oncology). [23] The protocol met Health Insurance Portability and Accountability Act standards and was approved by CALGB, the National Cancer Institute, and the institutional review boards at all sites. Each participant signed an IRB-approved, protocol-specific consent form in accordance with federal and institutional guidelines.

Setting and Population

Survivors were registered between January 1, 2004, and April 1, 2011. Eligible survivors were 65 years or older, diagnosed with invasive (1 cm or more) non-metastatic breast cancer (AJCC-6 stages I–IIIA), and spoke English or Spanish. [24, 25] Survivors were required to pass an entry cognitive screen to be eligible for the study; those scoring <11 points using the Blessed Orientation-Memory-Concentration test were excluded. [25] Survivors were less than 20 weeks from their last definitive surgery. There were 1,703 survivors registered for the study; of these, 1,529 were eligible. A total of 1,280 baseline interviews (83.7%) were completed. The current analyses were restricted to survivors with ER+ tumors (n=1,063) that initiated hormonal therapy (n=1,015), and had follow-up data (n=990; 97.5% of initiators) (Figure 1).

Data Collection

Clinical research associates identified survivors, confirmed eligibility, and upon physician approval, obtained patient consent. Registration was managed by the Alliance Statistics and Data Center. Centrally trained interviewers administered 30- to 45-minute structured telephone interviews at baseline, 6 months, 12 months post-baseline, and then annually thereafter for up to 7 years.

Measures

The primary variables of interest for this analysis were cognitive function (primary predictor) and time to discontinuation of hormonal therapy (dependent variable). Self-reported cognitive function was assessed at baseline and at each subsequent follow-up interview using the cognition scale from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). [26] This scale includes two Likert-scored items: 1) “Have you had difficulty in concentrating on things, like reading a newspaper or watching television?”; and 2) “Have you had difficulty remembering things?” Scores were standardized to a scale of 0–100. Analyses examined the impact of cognition per 8-points, a clinically meaningful difference in scores. [26] To approximate temporal effects, the self-reported cognitive function score for the time period preceding discontinuation was used to predict subsequent discontinuation.

Data on adjuvant hormonal treatment use was collected over five years (i.e., the recommended duration of treatment during the study period). Initiation of any type of adjuvant hormonal therapy (and start date) was based on medical records. Subsequent hormonal therapy use was based on annual self-report. If the month and year of discontinuation was not known, the date of discontinuation was set at the midpoint between consecutive interviews. [27] Survivors who died or experienced a recurrence were censored at the date of the event ; these data were based on information from medical records. Survivors with recurrence who had discontinued hormonal therapy more than 18 months preceding the recurrence date were classified as discontinuing; discontinuation at recurrence was treated as a censored event.

Several potential confounding variables were considered, including age, race (white vs. non-white), frailty, receipt of systemic chemotherapy, and type of hormonal medication initiated. Frailty was measured by adapting the index developed by Searle et al., [28] and previously validated to predict mortality in community-dwelling elders. It includes self-reported limitations in activities of daily living, sensory deficits, functioning, and pre-diagnosis comorbidity. Cognitive function was *not* included in the frailty index. Frailty scores were categorized based on established cut points related to mortality outcomes [28, 29] as “robust”, 0 to 0.2; “pre-frail,” >0.2 to 0.35; and “frail” >0.35 to 1. Frailty was dichotomized into robust versus pre-frail/frail categories based on the sample distribution, similar to previous studies. [30] Chemotherapy use (yes vs. no) and type of hormonal therapy initiated was obtained from medical records. Data on changes in hormonal therapy regimens was not available.

Statistical Analysis

We used a Kaplan-Meier survival curve [31] to illustrate the overall probability of continuation of hormonal therapy over five years (Figure 2). Informed by patterns of discontinuation from previous studies [14, 32] and the observed rates of discontinuation over time, we tested separate models for three periods of discontinuation of hormonal therapy: early (from initiation up to 1 year); midpoint (>1 year up to 3 years) and late (>3 years up to 5 years). Survivors that discontinued in one period were not considered for analysis in

subsequent periods (i.e., we used the cognitive function score that most closely preceded the start of the period being modeled).

Separate Cox proportional hazards models [33] for each time period were used to assess the univariable and multivariable relationships between time to discontinuation and covariates. Variable selection for the multivariable models was based on a significance level of $p < .15$ in univariable analysis. This cut-point level was selected because of the preliminary nature of the analysis and the decreasing sample size in each subsequent time-period model. Backward elimination was used to determine the final models for each time period, retaining variables that were significant at the $p < .15$ threshold. Age was retained in all models for face validity, regardless of significance. Analyses were conducted using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

The mean age of the cohort that initiated hormonal therapy for ER+ cancers was 72.6 years (SD 5.9, range 65–91). Most were married (58%), white (89%), and diagnosed with early-stage tumors (79% at stages 1 or 2A) (Table 1). One-third received chemotherapy as part of treatment and 87% initiated their hormonal therapy with aromatase inhibitors. The majority of survivors (77%) were robust based on Searle criteria. Given the cognitive screening requirement for study participation, baseline self-reported cognitive function was also high (mean 93, SD 12.6 on a scale from 0–100; higher scores indicating better function).

Overall, 43% ($n=427$) of older survivors who initiated treatment discontinued hormonal therapy before five years (mean 33 months) (Figure 2). Among the 427 discontinuing, 47.3% ($n=202$) discontinued in the early period; 15.7% (67) discontinued in the midpoint period; and 37% ($n=158$) discontinued in the late period (Table 1). In each period, survivors who discontinued tended to have lower mean cognitive function scores than those who continued treatment, but this difference was only statistically significant in the midpoint period (Table 1).

In univariable models, there were differences in factors that were associated with discontinuation in the different time periods (Table 2). While age and non-white race were associated with discontinuation in the early period, they were no longer significant factors in later periods. In contrast, cognition was not related to discontinuation in the early period, but it was associated with discontinuation of hormonal therapy in the midpoint period.

Considering covariates among those that continued taking hormonal therapy at the midpoint period, survivors with lower (vs. higher) cognitive scores, had greater adjusted hazards of discontinuation (HR 1.22 per 8-point difference, CI 1.09–1.40, $p < .001$). The effect of cognition on discontinuation in the midpoint period was independent of age or frailty. For those who continued treatment into the late period (>3 to up to 5 years), prior receipt of chemotherapy was the only variable associated with lower hazards of discontinuation in multivariable models.

Discussion

This is the first study to explore whether self-reported cognitive function after initiating hormonal therapy is related to older breast cancer survivors' subsequent treatment discontinuation. The results illustrate that the probability of hormonal therapy discontinuation is high and varies over the duration of the recommended treatment course. Cognition was associated with discontinuation during the midpoint of treatment, with older survivors reporting lower (vs. higher) cognitive function prior to that period being more likely to discontinue. However, cognitive function was not related to earlier or later discontinuation, and different factors predicted discontinuation of hormonal treatment in each time period.

Other studies have also noted suboptimal adherence to the full course of hormonal treatment of breast cancer, with rates and timing of discontinuation similar to those observed in this older cohort. [1, 8, 34, 35] Some studies have considered quality of life and physical symptoms (such as arthralgia) as potential reasons for discontinuation. [30, 36–38]. Other studies have explored the relationship between hormonal therapy and patterns of subsequent cognitive changes. [20, 39, 40] However, none have specifically examined cognitive function after initiation of hormonal therapy as a factor that could explain subsequent discontinuation in older survivors.

There are several explanations for the preliminary finding that self-reported cognitive function could have affected discontinuation in the midpoint of therapy, and not in the early or late periods of hormonal therapy use. Cognitive problems could have resulted in discontinuation at the midpoint due to difficulty remembering to take medications or other challenges related to executive function that survivors might have experienced at that time. [41, 42] The lack of statistically significant effect of cognition on discontinuation in the late period might reflect selection biases, with the healthiest survivors, including those without cognitive deficits, continuing treatment.

Discontinuation of treatment at the midpoint may also have occurred as a consequence of the survivor or her provider attributing cognitive symptoms to the hormonal therapy. Unfortunately, since this study was not originally designed to address medication adherence, there were insufficient data to determine with certainty the reasons for hormonal therapy discontinuation. However, there is an emerging body of research reporting that cognitive changes are associated with hormonal therapy for breast cancer, [14–16] although these observations are not universal. [43, 44] Nevertheless, the timing of cognitive effects on discontinuation seen in this study was consistent with the length of hormonal treatment exposure previously observed to produce cognitive effects, [19, 20] supporting the biological plausibility of the timing of effects.

There was also variability in effects of other covariates associated with treatment discontinuation by time period of therapy. For instance, chemotherapy was associated with lower hazards of discontinuing hormonal treatment in the early or late, but not the midpoint period, extending results for earlier studies. [30] However, it is likely that survivors that had received chemotherapy did not have sufficient cognitive effects from primary treatment to

interfere with hormonal therapy use or that they had more advanced disease, and perceived a greater benefit of maintaining hormonal therapy to prevent recurrence. [10] It is also possible that those at risk of cognitive decline after chemotherapy did not receive a recommendation for hormonal therapy from their medical team. Future research is needed to understand the complex balance of outcomes of chemotherapy in older patients, including the selection of the healthiest patients to chemotherapy, the cognitive effects of chemotherapy, interactions of chemotherapy and hormonal treatment on cognitive outcomes, and the impact on biological aging. [45–48]

This study had several important strengths, including the large, longitudinal cohort of older survivors, and the ability to assess the impact of cognitive function in the period prior to discontinuation of treatment. There are also some limitations that could be considered in evaluating the results. First, while cognitive function for the period preceding discontinuation was used to approximate temporal effects, it is not possible to rule out the possibility that results reflect the effects of hormonal therapy on cognitive function. Next, the various classes of hormonal therapy may have different side effect profiles, including adverse cognitive effects. [4, 40, 49] Unfortunately, since this was a secondary analysis, data were only available on the initial hormonal regimen, and three-quarters of survivors initiated treatment with aromatase inhibitors, limiting the ability to find variations in effects on discontinuation by treatment type.

In addition, the EORTC instrument, though commonly used to assess cancer-related outcomes, [26, 50] has limited precision in measuring cognitive function, relies on self-report, and only captures two aspects of cognition (concentration and memory). The survivors in this cohort also had high cognitive function at baseline given study eligibility criteria, potentially limiting ability to detect smaller cognitive effects on discontinuation of treatment. The cohort may also not fully represent all older survivors, given the research setting. Hence, the results should be considered preliminary pending new studies with diverse participants and more robust cognitive measures, including neuropsychological testing and brain imaging. [48]

This study addressed a largely unexplored question about the impact of cognitive function on discontinuation of hormonal therapy for breast cancer. If confirmed, the results may have important implications for clinical care of older survivors, such as decisions about extension of the duration of hormonal treatment from five to ten years. [7] Another implication of the results is that routine cognitive assessment of older survivors undergoing hormonal therapy might be used to identify those in need of interventions like medication reminders or supportive care, or to identify those who might be considered for alternative regimens with fewer cognitive side effects. If any medication-induced cognitive changes are identified, promising evidence suggests that compensatory cognitive rehabilitation strategies [51, 52] may be effective in improving cognitive function and potentially promoting treatment adherence. Additionally, interventions that include physical activity can mitigate cognitive impairment and other treatment side effects, [53] and could be examined as methods to enhance hormonal therapy completion. Given the nascent state of knowledge about cancer and cognition, it will be important to conduct future studies of cancer-related cognitive

outcomes to inform care and guidelines for the growing number of older breast cancer survivors.

Acknowledgments

Earlier versions of this research were presented by Dr. Bluethmann at the International Association of Gerontology and Geriatrics World Congress, July 23–27, 2017, San Francisco, CA.

Support: This research was conducted under Alliance for Clinical Trials in Oncology (formerly Cancer and Leukemia Group B) Protocol #369901. The research infrastructure was supported by UG1CA189823 (Alliance for Clinical Trials in Oncology NCORP Grant), U10CA031946, U10C0A33601, U10CA032291, U10CA047559, U10CA047577, U10CA077597, U10CA077651, U10CA180791, U10CA180857, U10CA180867, U10CA180838, and U10CA84131 to the Alliance. The research was also supported, in part, by NCI Grants R35CA197289, R01CA129769, R01CA124924, and K05CA96940 to JSM; and the Biostatistics and Bioinformatics Shared Resources at Georgetown-Lombardi Comprehensive Cancer Center funded by the National Cancer Institute at the National Institutes of Health under grant P30CA051008. Dr. Bluethmann was funded through the Cancer Prevention Fellowship at the National Cancer Institute at the time this report was prepared. Earlier portions of the research were also funded in part by a grant to support patient accrual from Amgen Pharmaceuticals to the CALGB Foundation. The content of this manuscript is solely the responsibility of the authors and does not represent the official views of the National Cancer Institute at the National Institutes of Health or the Alliance for Clinical Trials in Oncology.

Dr. Isaacs received remuneration and funding from Astra Zeneca, Pfizer and Novartis. She is also a consultant/advisor for Astra Zeneca, Novartis and Nanostring Technologies. Dr. Hurria is a consultant for Pierian Bioscience and Boehringer Ingelheim. She has also received funded from Celgene, Novartis and GlaxoSmithKline.

References

1. Chlebowski RT, Geller ML. Adherence to endocrine therapy for breast cancer. *Oncology*. 2006; 71:1–9. [PubMed: 17344666]
2. Chlebowski RT, Kim J, Haque R. Adherence to endocrine therapy in breast cancer adjuvant and prevention settings. *Cancer Prev Res (Phila)*. 2014; 7:378–387. [PubMed: 24441675]
3. Gray RG, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. 2013; 31:5.
4. Buzdar A, Howell A, et al. Arimidex, Tamoxifen, Alone or in Combination Trialists' Group. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol*. 2006; 7:633–643. [PubMed: 16887480]
5. Murphy CC, Bartholomew LK, Carpentier MY, et al. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat*. 2012; 134:459–478. [PubMed: 22689091]
6. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol*. 2010; 28:3784–3796. [PubMed: 20625130]
7. Burstein HJ, Temin S, Anderson H, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *Journal of Clinical Oncology*. 2014; 32:2255–2269. [PubMed: 24868023]
8. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *J Clin Oncol*. 2010; 28:4120–4128. [PubMed: 20585090]
9. Hershman DL. Disparities and challenges in adherence to oral antineoplastic agents. 2013
10. Bluethmann SM, Murphy CC, Tiro JA, et al. Deconstructing Decisions to Initiate, Maintain, or Discontinue Adjuvant Endocrine Therapy in Breast Cancer Survivors: A Mixed- Methods Study. *Oncology nursing forum*. 2017; 44(3):E101–E110. [PubMed: 28635973]

11. Stanton AL, Petrie KJ, Partridge AH. Contributors to nonadherence and nonpersistence with endocrine therapy in breast cancer survivors recruited from an online research registry. *Breast Cancer Res Treat.* 2014; 145:525–534. [PubMed: 24781972]
12. Lange M, Rigal O, Clarisse B, et al. Cognitive dysfunctions in elderly cancer patients: A new challenge for oncologists. *Cancer Treat Rev.* 2014; 40:810–817. [PubMed: 24713425]
13. Karuturi M, Wong ML, Hsu T, et al. Understanding cognition in older patients with cancer. *Journal of Geriatric Oncology.* 2016; 7:258–269. [PubMed: 27282296]
14. Jenkins V, Shilling V, Deutsch G, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer.* 2006; 94:828–834. [PubMed: 16523200]
15. Agrawal K, Onami S, Mortimer JE, et al. Cognitive changes associated with endocrine therapy for breast cancer. *Maturitas.* 2010; 67:209–214. [PubMed: 20688441]
16. Ganz PA, Kwan L, Castellon SA, et al. Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. *J Natl Cancer Inst.* 2013; 105:791–801. [PubMed: 23606729]
17. Bellury L, Ellington L, Beck SL, et al. Older breast cancer survivors: can interaction analyses identify vulnerable subgroups? A report from the American Cancer Society Studies of Cancer Survivors. 2013; 40
18. Bailey M, Wang AC, Hao J, et al. Interactive effects of age and estrogen on cortical neurons: implications for cognitive aging. *Neuroscience.* 2011; 191:148–158. [PubMed: 21664255]
19. Phillips K, Aldridge J, Ribi K, et al. Cognitive function in postmenopausal breast cancer patients one year after completing adjuvant endocrine therapy with letrozole and/or tamoxifen in the BIG 1–98 trial. *Breast Cancer Res Treat.* 2011; 126:221–226. [PubMed: 21046229]
20. Bender CM, Merriman JD, Gentry AL, et al. Patterns of change in cognitive function with anastrozole therapy. *Cancer.* 2015; 121:2627–2636. [PubMed: 25906766]
21. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the “Silver Tsunami”: Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. *Cancer Epidemiology Biomarkers & Prevention.* 2016; 25:1029–1036.
22. Mandelblatt JS, Sheppard VB, Hurria A, et al. Breast cancer adjuvant chemotherapy decisions in older women: the role of patient preference and interactions with physicians. *Journal of Clinical Oncology.* 2010; 28:3146–3153. [PubMed: 20516438]
23. Mandelblatt JS, Faul LA, Luta G, et al. Patient and physician decision styles and breast cancer chemotherapy use in older women: Cancer and Leukemia Group B protocol 369901. *Journal of Clinical Oncology.* 2012; 30:2609–2614. [PubMed: 22614985]
24. Davis PB, Morris JC, Grant E. Brief screening tests versus clinical staging in senile dementia of the Alzheimer type. *J Am Geriatr Soc.* 1990; 38:129–135. [PubMed: 2299116]
25. Kawas C, Karagiozis H, Resau L, et al. Reliability of the blessed telephone information-memory-concentration test. *J Geriatr Psychiatry Neurol.* 1995; 8:238–242. [PubMed: 8561839]
26. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993; 85:365–376. [PubMed: 8433390]
27. Lash TL, Fox MP, Westrup JL, et al. Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat.* 2006; 99:215–220. [PubMed: 16541307]
28. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC geriatrics.* 2008; 8:24. [PubMed: 18826625]
29. Rockwood K, Mitnitski A, Song X, et al. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. *J Am Geriatr Soc.* 2006; 54:975–979. [PubMed: 16776795]
30. Sheppard VB, Faul LA, Luta G, et al. Frailty and adherence to adjuvant hormonal therapy in older women with breast cancer: CALGB protocol 369901. *J Clin Oncol.* 2014; 32:2318–2327. [PubMed: 24934786]
31. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American statistical association.* 1958; 53:457–481.

32. Bender CM, Sereika SM, Brufsky AM, et al. Memory impairments with adjuvant anastrozole versus tamoxifen in women with early-stage breast cancer. *Menopause*. 2007; 14:995–998. [PubMed: 17898668]
33. Cox D. Regression Models and Life-Tables. *Journal of the Royal Statistical Society. Series B (Methodological)*. 1972; 34:187–220.
34. He W, Fang F, Varnum C, et al. Predictors of Discontinuation of Adjuvant Hormone Therapy in Patients With Breast Cancer. *J Clin Oncol*. 2015; 33:2262–2269. [PubMed: 26033800]
35. Mayer EL, Burstein HJ. Adjuvant endocrine therapy for postmenopausal women: Type and duration. *The Breast*. 2015; 24:S126–S128. [PubMed: 26279133]
36. Neugut AI, Hillyer GC, Kushi LH, et al. The Breast Cancer Quality of Care Study (BQUAL): A Multi-Center Study to Determine Causes for Noncompliance with Breast Cancer Adjuvant Therapy. *Breast J*. 2012; 18:203–213. [PubMed: 22487337]
37. Neugut AI, Zhong X, Wright JD, et al. Nonadherence to medications for chronic conditions and nonadherence to adjuvant hormonal therapy in women with breast cancer. *JAMA oncology*. 2016
38. Hershman DL, Kushi LH, Hillyer GC, et al. Psychosocial factors related to non-persistence with adjuvant endocrine therapy among women with breast cancer: the Breast Cancer Quality of Care Study (BQUAL). *Breast Cancer Res Treat*. 2016; 157:133–143. [PubMed: 27086286]
39. Zwart W, Terra H, Linn SC, et al. Cognitive effects of endocrine therapy for breast cancer: keep calm and carry on? *Nature Reviews Clinical Oncology*. 2015; 12:597–606.
40. Ganz PA. Understanding the impact of breast cancer adjuvant endocrine therapy on cognitive function: a work in progress. *Br J Cancer*. 2016; 114:953–955. [PubMed: 27115566]
41. Daniel JM. Estrogens, estrogen receptors, and female cognitive aging: the impact of timing. *Horm Behav*. 2013; 63:231–237. [PubMed: 22587940]
42. Kesler SR, Kent JS, O'Hara R. Prefrontal cortex and executive function impairments in primary breast cancer. *Arch Neurol*. 2011; 68:1447–1453. [PubMed: 22084128]
43. Wefel JS, Vardy J, Ahles T, et al. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *The lancet oncology*. 2011; 12:703–708. [PubMed: 21354373]
44. Hurria A, Patel SK, Mortimer J, et al. The effect of aromatase inhibition on the cognitive function of older patients with breast cancer. *Clinical breast cancer*. 2014; 14:132–140. [PubMed: 24291380]
45. Kool M, Fontein D, Kranenbarg EM, et al. Long term effects of extended adjuvant endocrine therapy on quality of life in breast cancer patients. *The Breast*. 2015; 24:224–229. [PubMed: 25704982]
46. Mandelblatt JS, Hurria A, McDonald BC, et al. Cognitive effects of cancer and its treatments at the intersection of aging: what do we know; what do we need to know? 2013; 40:709–725.
47. Mandelblatt JS, Jacobsen PB, Ahles T. Cognitive effects of cancer systemic therapy: implications for the care of older patients and survivors. *Journal of Clinical Oncology*. 2014; 32:2617–2626. [PubMed: 25071135]
48. Cohen HJ. The Cancer Aging Interface: A Research Agenda. *Journal of Clinical Oncology*. 2007; 25:1945–1948. [PubMed: 17488995]
49. Cella D, Fallowfield LJ. Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. *Breast Cancer Res Treat*. 2008; 107:167–180. [PubMed: 17876703]
50. Fayers, P., Aaronson, N., Bjordal, K., et al. The EORTC QLQ-C30 scoring manual. 2001. Vol. 3. Brussels: European Organisation for Research and Treatment of Cancer; 2015.
51. Ercoli L, Petersen L, Hunter A, et al. Cognitive rehabilitation group intervention for breast cancer survivors: results of a randomized clinical trial. *Psycho-Oncology*. 2015; 24:1360–1367. [PubMed: 25759235]
52. Von Ah D, Carpenter JS, Saykin A, et al. Advanced cognitive training for breast cancer survivors: a randomized controlled trial. *Breast Cancer Res Treat*. 2012; 135:799–809. [PubMed: 22918524]
53. Mustian KM, Sprod LK, Janelins M, et al. Exercise Recommendations for Cancer- Related Fatigue, Cognitive Impairment, Sleep problems, Depression, Pain, Anxiety, and Physical Dysfunction: A Review. *Oncol Hematol Rev*. 2012; 8:81–88. [PubMed: 23667857]

Figure 1. Sample of Older Breast Cancer Survivors with Estrogen-Receptor-Positive Cancers
The figure provides the study schema for enrollment and analysis. The final cohort in the locked dataset included 1280 survivors with baseline data. From these, only survivors with estrogen- receptor-positive cancers who initiated adjuvant hormonal therapy were considered for inclusion in analyses of discontinuation over five years of follow-up (25 survivors with missing data on treatment status [2.5%] were excluded). The final analytic sample included 990 survivors.

Figure 2. Cumulative Probability of Continuing Hormonal Therapy Over Time among Older Breast Cancer Survivors

Kaplan-Meier curve of the cumulative probability of continuing hormonal therapy by time period. The solid black line represents the point estimate and the lighter solid lines indicate the lower and upper 95% confidence intervals around the probability of continuing therapy. Dashed lines indicate designated time periods for separate analyses of the effects of cognitive function and duration of hormonal therapy use (<1 year, 1–3 years, >3–5 years).

Table 1

Characteristics of a Cohort of Older Estrogen-Receptor-Positive Breast Cancer Survivors that Initiated Hormonal Therapy by Time Period of Discontinuation¹

	Overall Sample (n=990)	Early (<1 year from initiation) (n=990)			Midpoint (1 year up to 3 years from initiation) (n=711) ¹			Late (>3 years up to 5 years from initiation) (n=496) ¹		
		Continued (n=788)	Discontinued (n=202)	P-value	Continued (n=644)	Discontinued (n=67)	P-value	Continued (n=338)	Discontinued (n=158)	P-value
Age (mean, SD)	72.6 (5.9)	72.4 (5.9)	73.6 (5.8)	<.01	72.2 (5.7)	73.4 (6.1)	0.13	71.6 (5.4)	72.8 (5.8)	0.03
Race										
White	885 (89.4)	712 (90.4)	173 (85.6)	0.05	586 (91.0)	62 (92.5)	0.67	302 (89.3)	147 (93.0)	0.19
Non-white	105 (10.6)	76 (9.6)	29 (14.4)		58 (9.0)	5 (7.5)		36 (10.7)	11 (7.0)	
Education										
</= High School	414 (41.8)	330 (41.9)	84 (41.6)	0.94	257 (39.9)	29 (43.3)	0.59	129 (38.2)	56 (35.4)	0.56
Some College +	576 (58.2)	458 (58.1)	118 (58.4)		387 (60.1)	38 (56.7)		209 (61.8)	102 (64.6)	
Marital status										
Married	556 (56.2)	451 (57.2)	105 (52.0)	0.18	380 (59.0)	36 (53.7)	0.40	205 (60.7)	95 (60.1)	0.91
Single	434 (43.8)	337 (42.8)	97 (48.0)		264 (41.0)	31 (46.3)		133 (39.3)	63 (39.9)	
Primary Surgery										
Lumpectomy	672 (67.9)	538 (68.4)	134 (66.3)	0.58	440 (68.4)	47 (70.1)	0.77	226 (67.1)	108 (68.4)	0.78
Mastectomy	317 (32.1)	249 (31.6)	68 (33.7)		203 (31.6)	20 (29.9)		111 (32.9)	50 (31.6)	
Chemotherapy										
Yes	319 (32.2)	276 (35.0)	43 (21.3)	<.01	224 (34.8)	18 (26.9)	0.19	143 (42.3)	35 (22.2)	<.01
No	671 (67.8)	512 (65.0)	159 (78.7)		420 (65.2)	49 (73.1)		195 (57.7)	123 (77.8)	
Stage										
I	466 (47.1)	360 (45.7)	106 (52.7)	0.05	299 (46.4)	33 (49.3)	0.20	147 (43.5)	91 (57.6)	<.01
2A	312 (31.5)	248 (31.5)	64 (31.8)		199 (30.9)	25 (37.3)		99 (29.3)	48 (30.4)	
2B or 3	211 (21.3)	180 (22.8)	31 (15.4)		146 (22.7)	9 (13.4)		92 (27.2)	19 (12.0)	
Cognition, baseline ²	93.0 (12.6)	93.1 (12.5)	92.5 (13.0)	0.55	92.2 (11.9)	86.8 (16.3)	<.01	90.1 (14.4)	90.4 (15.1)	0.81
Frailty ³										

	Overall Sample (n=990)	Early (<1 year from initiation) (n=990)			Midpoint (1 year up to 3 years from initiation) (n=711) ¹			Late (>3 years up to 5 years from initiation) (n=496) ¹		
		Continued (n=788)	Discontinued (n=202)	p-value	Continued (n=644)	Discontinued (n=67)	p-value	Continued (n=338)	Discontinued (n=158)	p-value
Pre-frail/trail	224 (22.9)	168 (21.6)	56 (27.7)	0.07	126 (19.8)	21 (31.8)	0.02	68 (20.4)	25 (16.1)	0.27
Robust	756 (77.1)	610 (78.4)	146 (72.3)		511 (80.2)	45 (68.2)		266 (79.6)	130 (83.9)	
Hormonal Rx Initiated										
Aromatase inhibitor	859 (87.0)	678 (86.1)	181 (90.5)	0.10	549 (85.2)	56 (84.8)	0.93	305 (90.2)	120 (75.9)	<.01
Tamoxifen	128 (13.0)	109 (13.9)	19 (9.5)		95 (14.8)	10 (15.2)		33 (9.8)	38 (24.1)	
Mean continuation, months (SD)	33.1 (23.0)	40.8 (19.4)	3.2 (3.2)	<.01	46.9 (15.2)	21.6 (6.5)	<.01	55.3 (7.3)	52.2 (6.4)	<.01

¹ Only survivors that continued to the start of the time period are included. So, if a survivor discontinued hormonal therapy at 9 months after initiation, she would not have been counted in the denominator for the two subsequent periods.

² Cognition scores are based on the EORTC-cog scale (0–100; higher scores indicate better self-reported cognition).[26] Score for the assessment immediately preceding the time of discontinuation are used in each model. For example, if a survivor discontinued hormonal therapy at 2 years, her cognition score from the 1-year follow-up assessment was used.

³ Frailty based on Searle's index.[28]

Hazards¹ of Discontinuation of Hormonal Therapy among Older Estrogen-Receptor Positive Breast Cancer Survivors that Initiated Hormonal Therapy by Time Period of Discontinuation²

Table 2

	Early (< 1 year from initiation)			Midpoint (1 year up to 3 years from initiation)			Late (> 3 years up to 5 years from initiation)		
	Univariable (n=990)	HR (95% CI)	p-value	Univariable (n=977)	HR (95% CI)	p-value	Univariable (n=711)	HR (95% CI)	p-value
Age (per one year increase)	1.03 (1.01–1.05)	1.03 (1.00–1.04)	0.12	1.02 (1.00–1.04)	1.03 (0.99–1.07)	0.12	1.03 (1.01–1.06)	1.02 (0.98–1.07)	0.24
Non-white (vs. white) race	1.48 (1.00–2.19)	1.46 (0.98–2.16)	0.06		0.83 (0.33–2.06)	0.68	0.80 (0.44–1.48)	0.80 (0.44–1.48)	0.48
<= High School (vs. college) education	1.02 (0.77–1.34)		0.91		1.19 (0.73–1.93)	0.48	0.98 (0.70–1.35)	0.98 (0.70–1.35)	0.88
Single (vs. married)	1.23 (0.93–1.62)		0.14		1.23 (0.76–1.99)	0.39	1.12 (0.81–1.54)	1.12 (0.81–1.54)	0.49
Surgery									
Mastectomy (vs. lumpectomy)	1.08 (0.81–1.44)		0.61		0.90 (0.53–1.52)	0.70	1.02 (0.73–1.43)	1.02 (0.73–1.43)	0.91
Chemotherapy (vs. none)	0.55 (0.39–0.77)	<0.1	0.59 (0.41–0.83)	<0.1	0.69 (0.40–1.19)	0.18	0.49 (0.34–0.72)	0.49 (0.34–0.72)	<0.1
Stage 2A (vs. 1)	0.90 (0.66–1.23)	0.51			1.18 (0.70–1.98)	0.54	0.89 (0.63–1.26)	0.89 (0.63–1.26)	0.51
Stage 2B/3 (vs. 1)	0.64 (0.43–0.95)	0.03			0.58 (0.28–1.21)	0.14	0.44 (0.27–0.72)	0.44 (0.27–0.72)	<0.1
Cognition, prior assessment (per 8-points) ³	1.02 (0.94–1.11)	0.59	1.04 (0.95–1.13)	0.39	1.22 (1.08–1.37)	<0.1	1.00 (0.92–1.09)	1.00 (0.92–1.09)	0.93
Pre-frail/frail (vs. robust) ⁴	1.36 (1.00–1.85)	0.05	----		1.82 (1.09–3.06)	0.02	0.99 (0.64–1.52)	0.99 (0.64–1.52)	0.96
Initiated with Tamoxifen (vs. AI)	0.66 (0.41–1.06)	0.09			1.03 (0.53–2.02)	0.93	2.05 (1.42–2.95)	2.05 (1.42–2.95)	<0.1

¹Univariable or multivariable Cox proportionate hazards models. For multivariable models, models were constructed by considering factors significant at p < .15 and using backwards elimination; resulting hazards are adjusted for the other variables shown. Since surgery, stage, and chemotherapy were very strongly correlated, we included chemotherapy given its potential effects of cognition.

²Only survivors that continued to the start of the time period are included. So, if a survivor discontinued hormonal therapy at 9 months after initiation, she would not have been counted in the denominator for the two subsequent periods.

³Cognition scores are based on the EORTC-cog scale (0–100, higher is better self-reported cognition). [26] Score for the assessment immediately preceding the time of discontinuation are used in each model. For example, if a survivor discontinued hormonal therapy at 2 years, her cognition score from the 1 -year follow-up assessment was used.

⁴Frailty based on the Searle's index. [28]

HR = Hazard Ratio

AI = Aromatase Inhibitors