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Cognitive function prior to systemic therapy and subsequent well-being in older breast cancer survivors: longitudinal findings from the Thinking and Living with Cancer Study

Running title: Cognitive function and well-being in older breast cancer survivors

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ABSTRACT

Objective: To investigate the relationships between self-reported and objectively measured cognitive function prior to systemic therapy and subsequent well-being outcomes over 24 months in older breast cancer survivors.

Methods: Data were from 397 women aged 60-98 diagnosed with non-metastatic breast cancer in the Thinking and Living with Cancer Study recruited from 2010-2016. Cognitive function was measured at baseline (following surgery, prior to systemic therapy) using neuropsychological assessments of attention, processing speed, and executive function (APE), learning and memory (LM), and the self-reported FACT-Cog scale. Well-being was measured using the FACT-G functional, physical, social, and emotional well-being domain scales at baseline and 12 and 24 months later, scaled from 0 (low) to 100 (high). Linear mixed-effects models assessed the relationships between each of baseline APE, LM, and FACT-Cog quartiles with well-being scores over 24 months, adjusted for confounding variables.

Results: At baseline, older survivors in the lowest APE, LM, and FACT-Cog score quartiles experienced poorer global well-being than those in the highest quartiles. At 24 months, older survivors tended to

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improve in well-being, and there were no differences according to baseline APE or LM scores. At 24 months, mean global well-being was 80.3 (95% CI: 76.2-84.3) among those in the lowest vs. 86.6 (95% CI: 83.1-90.1) in the highest FACT-cog quartile, a clinically meaningful difference of 6.3 points (95% CI: 1.5-11.1).

Conclusions: Among older breast cancer survivors, self-reported, but not objective cognitive impairments, were associated with lower global well-being over the first two years of survivorship.

Keywords: cancer; oncology; cognitive function; breast cancer; cancer survivors; aging; well-being; quality of life; self-reports

INTRODUCTION

Breast cancer survivors are the largest group of female cancer survivors in the United States, and three-quarters of these women are ≥60 years old ("older") at diagnosis (1–3). While survival rates are excellent, older cancer survivors live with the effects of cancer treatments, potential aging-related losses of physical and cognitive function, multi-morbidity, and changes to financial, social, and living situations (4–8). In particular, cancer-related cognitive impairment has gained attention as a central concern of older survivors (9–11). Cognitive problems at the time of diagnosis are important: although they may not be clinically obvious, they may affect women's abilities to manage their health after treatment, and may have substantial effects on daily function and well-being (11–15).

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However, the longitudinal well-being outcomes associated with self-reported cognitive changes or neuropsychological deficits at the time of diagnosis among older women with breast cancer have not yet been established. Prior reports have been based on younger women, used cross-sectional data, and/or did not include cognitive measures prior to systemic therapy (11,15–19). Few studies have compared the associations between objective and self-reported cognitive function with longitudinal well-being in older breast cancer survivors. Self-reports may reflect subtle changes in cognitive function that are not detected by formal neuropsychological assessments. Similar to self-reports of general health, they may also reflect many factors, including psychological health, in addition to true underlying cognitive function (20–24). Self-reported and objective cognitive assessments have been reported to have poor correlations within cancer survivor and general population samples (24), but their comparative associations with outcomes that are important to older cancer survivors have rarely been investigated.

To fill these evidence gaps, we used data from a national, prospective study of non-metastatic breast cancer survivors aged ≥60 years at the time of diagnosis: The Thinking and Living with Cancer (TLC) Study. We investigated the relationships between objective and self-reported cognitive function prior to systemic therapy (baseline) and changes in global, functional, physical, social, and emotional domains of well-being at 12 and 24 months later. We hypothesized that older breast cancer survivors with lower cognitive function prior to systemic therapy would have persistently lower well-being over time than those with higher cognitive function, and that these associations would be strongest for self-reports of cognitive function (24). These results are intended to help identify older breast cancer survivors who may be at risk for poorer well-being over time, and to inform the development and targeting of strategies to improve care and well-being for this growing older breast cancer survivor population.

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METHODS

Study Design

This study was conducted at Georgetown University and affiliated practices in the Washington, DC area, Memorial Sloan Kettering Cancer Center in New York, Moffitt Cancer Center in Tampa, City of Hope Comprehensive Cancer Center in Los Angeles, Hackensack University Medical Center in New Jersey, Indiana University (IU) School of Medicine in Indianapolis, and the University of California at Los Angeles (UCLA). IU and UCLA joined the study for laboratory support and IU for participant recruitment in 2016; data in this report are from the five other sites. All Institutional Review Boards approved the protocol (NCT03451383). Details about the study are provided elsewhere (25). The present analysis uses data from all participants enrolled from 2010 through 2016 who completed follow-up at 12- and 24-months post-baseline.

Study Participants

Eligible study participants were English-speaking women aged 60 years and over with a new, primary non-metastatic breast cancer (AJCC v.6 stage 0-3). Exclusion criteria were having a history of stroke, head injury, a major Axis I psychiatric disorder, or neurodegenerative disorder. Women were ineligible if they had a history of other cancers with active treatment in the past five years or any systemic therapy. Women were screened for ability to complete the study based on hearing, vision, and baseline MMSE scores of 24+ and WRAT-4 reading level of 3rd grade or higher. The consent rate among eligible women was 39.2% (range across sites: 17.2% to 83.9%; median 67.6%). Among those who remained alive and eligible for inclusion, follow-up rates were 75.2% and 74.9% at 12 months and 24 months, respectively. TLC also recruited frequency-matched controls (based on 5-year age groups, education level, race, and site) using the same eligibility criteria and assessments. Consent rate among eligible

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controls was 96.2% (range across sites: 92.8% to 100%; median 95.0%), with 89.2% retention at 12 months and 81.8% at 24 months (Figure 1).

Measures

Well-being Outcomes

The well-being outcomes were measured using the FACT-G functional, physical, social, and emotional domain scales at baseline and 12 and 24 months later, scaled from 0-100 with higher scores representing better well-being (26–28). The domains were considered separately, and combined to create a global score. As per Webster et al. (26), minimum clinically important differences (MCID) in scores on the 0-100 scale were considered to be: ≥3.6 points (global well-being); ≥8.3 points (functional well-being), ≥8.3 points (physical well-being), and ≥12.5 points (emotional well-being). General population and cancer survivor norms on these scales for US adults are available from Brucker et al (27).

Neuropsychological Assessments

A neuropsychological assessment was administered during the baseline (pre-systemic therapy) study interview to assess domain-specific cognitive functions. The assessment included six tests of attention, processing speed, and executive functioning (collectively, APE) and five tests of learning and memory (collectively, LM). We used tests of cognitive domains that are sensitive to aging-related changes and that have established validity and reliability in older populations (25). Using principal components analysis, we previously confirmed the domain structure of the APE and LM measures and their reliability over time within this sample (25). We z-standardized the composite APE and LM scores using the baseline age- and education-group matched healthy control means and standard deviations (SDs), to give a mean of 0 and SD of 1. We categorized the scores into quartiles, in order to compare

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changes in well-being over time among older women across the baseline distribution of cognitive function.

Self-Reported Cognitive Function

Self-reported cognitive function was assessed using the FACT-Cog scale at baseline (28). The FACT-Cog has excellent test-retest reliability and has been validated among breast cancer survivors as reflecting cognitive functions assessed by neuropsychological measures and quantitative electroencephalography, independently of depressive symptoms (29). The FACT-Cog items assess perceived cognitive functioning over the past 7 days according to four sub-scales: 1) *Perceived Cognitive Impairments*; 2) *Perceived Cognitive Abilities*; 3) *Impact on Quality of Life*; and 4) *Comments from Others*. The total scale has a Chronbach's alpha of 0.96. A previous validation study indicates a minimum clinically important difference of 6.9 points on the FACT-Cog scale among breast cancer survivors (30).

The range of the FACT-Cog scale was 0 (low) to 148 (high); we categorized scores into quartiles to allow comparability with estimates for well-being outcomes for individuals at equivalent locations on the distributions of each of FACT-Cog, APE, and LM scores. The quartile cut-off values were <121 points (lowest), 121 to 134 points, 134 to 141 points, and >141 points (highest). Examination of the domain-specific scores within each quartile of the total FACT-Cog scale score indicated that the Perceived Cognitive Impairments and Perceived Cognitive Abilities domains were the primary drivers of variability in total scale score. The Impact on Quality of Life and Comments from Others domains demonstrated ceiling effects, with little differences in these domain-specific scores between individuals in the lowest versus highest total FACT-Cog score quartiles (Supplementary Table 1).

Covariates

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Potential confounding variables were: age (continuous), race/ethnicity (white non-Hispanic, and non-white), marital status (married or living as married; not married), word reading score as a marker of cognitive reserve (continuous score on the Wide Range Achievement Test Word Reading sub-test, 4th edition, or WRAT-4), receipt of radiation (yes; no), receipt of chemotherapy (yes; no), number of comorbidities, number of limitations to instrumental activities of daily living (IADLs), and study recruitment site. Because the study participants predominantly identified as white non-Hispanic, we could not further stratify the "non-white" group in statistical analyses.

Statistical Analysis

Baseline descriptive characteristics of the study sample at baseline were calculated. We examined the unadjusted correlations between baseline APE, LM, and FACT-Cog scores (continuous) and baseline well-being domain scores (continuous). With separate models for each of the three cognitive measures, we used linear mixed-effects models to test the hypotheses that older breast cancer survivors with lower baseline APE, LM, and FACT-Cog scores would have persistently poorer global, functional, physical, social, and emotional domain scores over the 24-month follow-up. The linear mixed-effects models allowed us to account for the within-person correlations in the outcomes due to the repeated measures over time by incorporating subject-specific random effects. The models were adjusted for age, race/ethnicity, marital status, word reading score, receipt of radiation (yes vs. no), receipt of chemotherapy (yes vs. no), study recruitment site, in addition to a variable for time (in years) and a statistical interaction between time and the baseline cognitive measure, to allow the well-being outcome slopes (rate of change over time) to vary by baseline level of cognitive function.

Since study drop-out or death after the baseline can be informative with respect to the outcome, we calculated inverse probability of censoring weights (IPCWs) to account for any differential loss to

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follow-up due to study attrition or mortality (31). The IPCW is the inverse of the probability of study

attrition through a given study time point, for person *i* at time point *t*. We estimated these probabilities

using logistic regression models including baseline covariates as predictors of study attrition: age,

race/ethnicity, marital status, study recruitment site, pre-diagnosis self-reported physical function, fatigue

symptom score, number of comorbidities, number of prescription medications, FACT-Cog score,

depressive symptom score, and timed get-up-and-go. All models incorporated the IPCWs.

For each model set, we extracted the predicted adjusted mean values and their 95% confidence

intervals for each well-being outcome scale at each time point, and estimated the differential between the

highest and lowest baseline cognitive function quartiles for each time point. We graphically presented

change over time for each of the well-being outcomes according to baseline cognitive function quartiles,

and added the corresponding fully adjusted slope for the healthy cancer-free controls, to visually

benchmark the degree of change over time in well-being outcomes that may be attributable to breast

cancer, over and above aging over time alone. All statistical analyses were completed using SAS 9.0

(SAS Institute, Cary, NC).

Sensitivity Analyses

We conducted sensitivity analyses with mixed-effects models that were adjusted for our original

model covariates, plus two iterative adjustments for baseline physical health and mental health indicators:

first, we included number of comorbidities and limitations to instrumental activities of daily living

(IADLs), and second, we included depressive symptom score (Center for Epidemiologic Studies

Depression Scale) and anxiety symptom score (State-Trait Anxiety Inventory Scale). Because the causal

directions of associations between these factors and cognitive function remain uncertain and could be

bidirectional (20,21), we consider these analyses exploratory and hypothesis-generating for future studies.

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RESULTS

The mean age of the breast cancer survivors was 68 years (SD: 6 years; range: 60-98 years).
Mean years of education was 15.2 years (SD: 2.2 years), and 79.1% reported that they were white and
non-Hispanic (Table 1). Table 2 shows the unadjusted correlation coefficients between baseline APE,
LM, and FACT-Cog scores with baseline well-being domain scores.

Cognition and Global Well-Being

Figure **2** shows the longitudinal trends in fully adjusted global well-being scores, according to
baseline APE (Panel A), LM (Panel B), and FACT-Cog quartiles (Panel C). The model generating the
estimates for this figure included the cancer-free controls to provide a visual benchmark for comparison
with the trends in survivors. As shown in Figure **2**, at baseline, the adjusted mean global well-being
scores going from the highest to lowest APE quartile were: 85.9 (SE: 1.29), 85.9 (SE: 1.78), 84.3 (SE:
1.84), and 80.1 (SE: 1.83). For LM quartiles, the adjusted mean global well-being values were: 85.1 (SE:
1.29), 82.2 (SE: 1.68), 83.7 (SE: 1.82), and 78.5 (SE: 1.98). For FACT-Cog quartiles, the adjusted mean
global well-being values were 87.99 (SE: 1.20), 86.03 (SE: 1.88), 82.26 (SE: 1.64), and 74.90 (SE: 1.78)
(Figure 1). The differences in adjusted baseline global well-being between survivors in the lowest versus
highest APE, LM, and FACT-Cog quartiles were 5.8, 6.6, and 13.1 points out of 100, respectively, which
were all clinically meaningful differences. At the 24-month follow-up, there were no statistically or
clinically meaningful differences in global well-being according to baseline APE or LM scores (Table 3;
Supplementary Table **2**). The mean predicted 24-month global well-being score in the highest baseline
FACT-Cog quartile was 86.6 (95% CI: 83.1-90.1), and in the lowest FACT-Cog quartile was 80.3 (95%

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CI: 76.2-84.3), a clinically meaningful difference of 6.3 points (95% CI: 1.5, 11.1; Table 3; Supplementary Table **2**).

Cognition and Domain-Specific Well-Being

Changes over time in the functional and physical well-being domains were similar to those observed for global well-being for all three cognitive measures (Supplementary Figures **1** and **2**). The fully adjusted baseline differences between the highest versus lowest FACT-Cog quartiles were considered clinically meaningful for these two domains (16.8 for functional well-being; 16.4 for physical well-being; Supplementary Figures 1 and 2). Social well-being declined over time and emotional well-being improved over time, on average, among the breast cancer survivors (Supplementary Figures 3 and 4). At the 24-month follow-up, there were negligible differences in predicted well-being domain scores according to baseline APE and LM (Table 3). The predicted differences between the highest vs. lowest baseline FACT-Cog score quartiles at the 24-month follow-up were statistically significant but not clinically meaningful for physical, social, and emotional well-being (Table 3).

Sensitivity Analyses

When physical health indicators and mental health indicators were added to models, the physical health indicators generally changed the effect estimates very little, and the mental health indicators attenuated the effect estimates towards the null for the FACT-Cog (Supplementary Table 3).

DISCUSSION

This is the first large, prospective study of self-reported and objective cognitive function prior to systemic therapy and their relationships with changes in multi-domain well-being among older women over the first two years of breast cancer survivorship. Prior to systemic therapy, older breast cancer

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survivors with poorer objective and self-reported cognitive function had clinically meaningfully poorer global well-being scores, after accounting for key confounders. The women in this study tended to improve in well-being over time, and the observed differences in well-being narrowed. However, there were persistent clinically meaningful differences in global well-being over time for women who reported the most cognitive impairments and lowest perceived cognitive abilities prior to their systemic therapy. Well-being was more closely related to self-reported cognitive function than to the neuropsychological test measures, consistent with prior research indicating that self-reported and objective cognitive function do not consistently correlate (24). We add new evidence indicating that, among older breast cancer survivors, self-reported cognitive function prior to systemic therapy is associated with a clinically meaningful decrement in global well-being over the first 24 months of survivorship.

Comparison to other literature

Our results are consistent with a cross-sectional study that correlated self-reports of cognitive function with well-being measures in older breast cancer survivors (32). We identified three studies that investigated cross-sectional and longitudinal associations between neuropsychological test scores and well-being among breast cancer survivors (17,18,33), however, their findings are inconsistent. Previous research has indicated that self-reported cognitive function is associated with depressive symptoms, but also has relationships with well-being outcomes independently of depressive symptoms (29). In our sensitivity analysis, we observed that mental health indicators attenuated the relationship between self-reported cognitive function and well-being, but since these measurements were all taken at the same time, we cannot discern whether mental health is a confounder or mediator of this relationship. The role of mental health in the relationships between self-reported cognitive function and survivorship outcomes among older breast cancer survivors warrants further investigation.

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Study Limitations

A limitation of this study is that it was conducted among mostly white, highly educated women who presented to mainly academic medical centers in urban areas. We observed higher mean global well-being scores in our sample relative to the established norms for the FACT scales (mean: 81.2; SD: 12.9 in our sample, versus mean: 73.7; SD: 17.2 in the US general adult female population and mean: 76.02; SD: 15.09 in the US adult female cancer survivor population), which was mostly driven by higher than average scores in the functional and social domains (27). The higher mean well-being scores that we observed may reflect the sociodemographic composition of our study, and we caution the generalization of our findings outside of this population subgroup. A high priority for future research on cancer and aging is to include diverse older population samples to improve the generalizability of findings, and to characterize and understand any potential health disparities in well-being and other outcomes that are relevant to older cancer survivors.

Clinical Implications

In this study population, older women with relatively low objective and self-reported cognitive function prior to systemic therapy tended to recover somewhat in well-being over time, which should be a reassuring finding. However, older women who reported the lowest pre-systemic therapy cognition had clinically meaningful decrements in global well-being over the first two years of breast cancer survivorship. In this study, perceived cognitive impairments and perceived cognitive abilities were the sub-domains of self-reported cognitive function that appeared to primarily drive the observed associations. A next step is to determine whether older women who present with cognitive complaints at the time of their diagnosis might need detection and intervention to improve well-being over the course of

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cancer survivorship care. Our findings are consistent with literature supporting the use of geriatric assessments in oncology practice, which include brief self-reports of cognitive function (34–36).

Conclusions

Prior to systemic therapy, older breast cancer survivors with poorer objective and self-reported cognitive function had clinically meaningfully poorer global well-being scores, after accounting for key confounders. These women tended to improve in their well-being over time throughout the first two years of cancer survivorship. However, there were persistent clinically meaningful differences in global well-being over time for women who reported the most cognitive problems prior to systemic therapy. Well-being domains were more strongly associated with self-reported than objective cognitive function measures, supporting the clinical utility of self-reports of cognitive function for understanding well-being over the early phase of survivorship for older breast cancer survivors. The present study is a novel early contribution in this area, at a time when older cancer survivors make up an increasing share of the general population in the United States and elsewhere.

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Data Availability Statement

In accordance with the NIH Data Sharing Policy, de-identified data collected as part of this study and supporting documentation will be made available to other researchers who contact the Principal Investigator directly and complete a material transfer agreement.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Disclosure

The views expressed in this article are those of the authors and do not necessarily reflect the official views of the National Cancer Institute.

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Table 1. Baseline characteristics, Thinking and Living with Cancer Study, 2010-2016, N=397

Baseline characteristic	Total N (%) or Mean (SD)
Age (Mean; SD)	68.0 (6.0)
Years of education (Mean; SD)	15.2 (2.2)
Race/ethnicity	
White (Non-Hispanic)	314 (79.1%)
Non-White	83 (20.9%)
Marital status	
Married or living as married	229 (60.6%)
Not married	149 (39.4%)
WRAT-4 literacy score (Mean; SD)	111.5 (15.3)
Number of comorbidities (Mean; SD)	2.6 (1.9)
Number of IADL limitations (Mean; SD)	0.44 (1.02)
Fatigue scale score	
Mean (SD)	43.15 (8.49)
Presence of depressive symptoms	
No	306 (86.9)
Yes	46 (13.1)
Anxiety scale score	
Mean (SD)	29.2 (8.2)

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Table 1. Baseline characteristics, Thinking and Living with Cancer Study, 2010-2016, N=397

Baseline characteristic	Total N (%) or Mean (SD)
Treatment modality	
Chemo +/- HT	111 (29.0)
HT only	272 (71.0)
AJCC tumor stage	
Stage 0	50 (12.7)
Stage 1	214 (54.3)
Stage 2	109 (27.7)
Stage 3	21 (5.3)
FACT-G Global well-being score (Mean; SD)	81.15 (12.86)
FACT-G Functional well-being score (Mean; SD)	74.43 (20.22)
FACT-G Physical well-being score (Mean; SD)	83.37 (16.27)
FACT-G Social well-being baseline score (Mean; SD)	85.96 (16.88)
FACT-G Emotional well-being baseline score (Mean; SD)	82.04 (17.23)

Note: US general adult female population FACT-G norms, scaled from 0-100, are: 73.7 (global), 65.35 (functional), 78.93 (physical), 70.71 (social), and 80.83 (emotional). US adult female cancer survivor FACT-G norms, scaled from 0-100, are: 76.02 (global), 69.64 (functional), 77.14 (physical), 79.64 (social), and 77.92 (emotional). From Brucker et al., 2005 (18).

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Table 2. Unadjusted correlation coefficients between baseline APE, LM, and FACT-Cog scores with global and domain-specific well-being scores, Thinking and Living with Cancer Study, 2010-2016, N=397

Baseline cognitive score	Baseline well-being score				
	Global well-being	Functional well-being	Physical well-being	Social well-being	Emotional well-being
APE	0.11	0.13	0.14	0.02	-0.01
P-value	(0.03)	(0.02)	(0.01)	(0.70)	(0.92)
LM	0.08	0.12	0.10	-0.01	0.06
P-value	(0.11)	(0.12)	(0.05)	(0.82)	(0.27)
FACT-Cog	0.43	0.39	0.39	0.15	0.27
P-value	(<0.0001)	(<0.0001)	(<0.0001)	(0.004)	(<0.0001)

Note: APE: attention, processing speed, and executive function; LM: learning and memory; The well-being outcomes are scaled from 0 (low) to 100 (high).

Table 3. Differences in mean 24-month well-being scores according to baseline cognitive measures, Thinking and Living with Cancer Study, 2010-2016, N=397

Baseline cognitive measure	Adjusted mean 24-month well-being score (95% CI)				
	Global well-being	Functional well-being	Physical well-being	Social well-being	Emotional well-being
APE (Q4-Q1 difference)	-0.01 (-5.59, 5.58)	-5.89 (-14.48, 2.69)	-0.72 (-6.6, 5.15)	8.67 (-0.61, 17.95)	-0.93 (-6.75, 4.89)
P-value	0.997	0.178	0.809	0.067	0.754
LM (Q4-Q1 difference)	0.41 (-5.09, 5.91)	-1.32 (-9.85, 7.21)	1.51 (-4.25, 7.27)	0.96 (-8.28, 10.2)	0.56 (-5.02, 6.15)
P-value	0.884	0.761	0.607	0.838	0.843

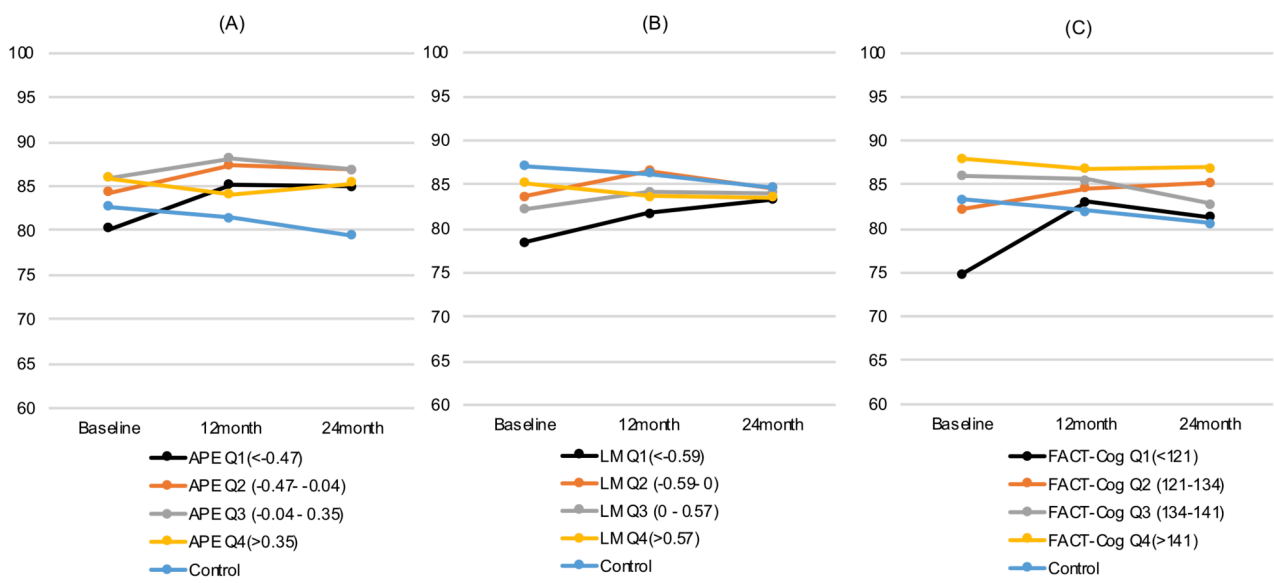|					
FACT-Cog (Q4-Q1 difference)	6.31 (1.49, 11.14)	5.97 (-1.61, 13.56)	5.41 (0.3, 10.53)	8.64 (0.4, 16.89)	5.95 (1.06, 10.84)
P-value	0.011	0.122	0.038	0.040	0.017

Note: All estimates are adjusted for baseline age, race/ethnicity, marital status, WRAT-4 literacy score, study recruitment site, receipt of radiation, receipt of chemotherapy, time (in years) and the interaction between time (in years) and the baseline cognitive measure. Inverse probability of censoring weights (IPCWs) were applied to all models to account for differential loss-to study follow-up. APE: attention, processing speed, and executive function; LM: learning and memory; Q4: quartile 4 (highest); Q1: quartile 1 (lowest). The well-being outcomes are scaled from 0 (low) to 100 (high).

Figure 1. Study flow diagram, older breast cancer survivors, Thinking and Living with Cancer Study (recruitment to end of 2016 calendar year)

Figure 2. Adjusted global well-being scores over 24 months of follow-up, according to baseline APE quartile (Panel A), baseline LM quartile (Panel B), and baseline FACT-Cog quartile (Panel C), all with cancer-free controls included for comparison.

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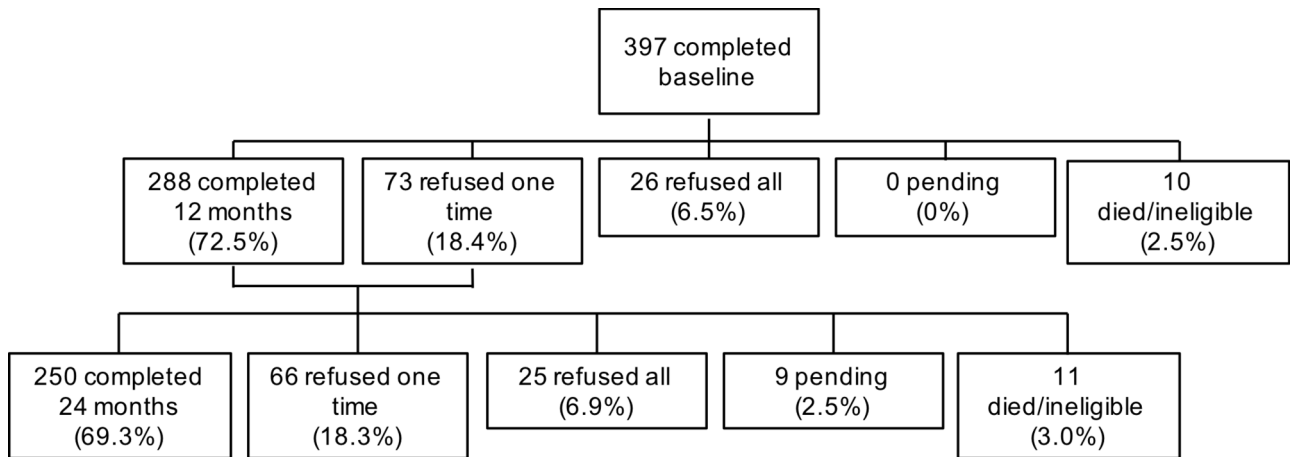
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