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Association of markers of tumor aggressivity and cognition in women with breast cancer before adjuvant treatment: The Thinking and Living with Cancer Study

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Abstract

Purpose—Tumor features associated with aggressive cancers may affect cognition prior to systemic therapy. We evaluated associations of cognition prior to adjuvant therapy and tumor aggressivity in older breast cancer patients.

Methods—Women diagnosed with non-metastatic breast cancer (n = 705) ages 60–98 were enrolled from August 2010-March 2020. Cognition was measured post-surgery, pre-systemic therapy using self-reported (FACT-Cog Perceived Cognitive Impairment [PCI]) and objective tests of attention, processing speed, and executive function (APE domain) and learning and memory [LM domain]. Linear regression tested associations of pre-treatment tumor features and cognition, adjusting for age, race, and study site. HER2 positivity and higher stage (II/III vs. 0/I) were a priori predictors of cognition; in secondary analyses we explored associations of other tumor features and cognitive impairment (i.e., PCI score < 54 or having 2 tests < 1.5 SD or 1 test < 2 SD from the mean APE or LM domain score).

Results—HER2 positivity and the hormone receptor negative/HER2 + molecular subtype were associated with lower adjusted mean self-reported cognition scores and higher impairment rates (p values < .05). Higher stage of disease was associated with lower objective performance in APE.

Other tumor features were associated with cognition in unadjusted and adjusted models, including larger tumor size and lower PCI scores ($p = 0.02$). Tumor features were not related to LM.

Conclusions—Pre-adjuvant therapy cognition was associated with HER2 positivity and higher stage of disease and other features of aggressive tumors. Additional research is needed to confirm these results and assess potential mechanisms and clinical management strategies.

Keywords

Breast cancer; Clinicopathological tumor features; Cognition; Older adults; Elderly

Introduction

Cognitive problems among cancer patients are commonly referred to as cancer-related cognitive decline (CRCD) and have now been well-documented in subsets of adults after treatment of non-central nervous system cancers [1, 2]. CRCD is, in turn, associated with declines in quality of life, work performance, and daily functioning of cancer patients [3–5]. Recommendations by the International Cognition and Cancer Task Force [6] to measure pre-treatment baseline cognition have led to several reports of cognitive problems even before starting adjuvant systemic therapy [7–9].

Pre adjuvant systemic-treatment cognitive problems have been attributed to a number of factors, including extant comorbidity burden and frailty [8, 10], biological stress associated with diagnosis and treatment [11, 12], and shared environmental exposures or genetic risk factors for both cancer incidence and cognitive dysfunction [13], while most do not find an association with underlying mood disturbance [2, 7].

There are few clinical studies examining the relationships of adjuvant systemic therapy cognition and tumor features and these have had relatively small samples and inconsistent results [7, 8, 14]. However, it is plausible that tumor features could themselves affect pre-treatment cognition since they may differentially affect the tumor microenvironment, systemic inflammatory and neuroinflammatory responses, and/or alter blood–brain barrier permeability [15–17]; notably, studies in preclinical models have found behavioral effects of tumor burden that are reversed with anti-inflammatory agents [18]. It has also been suggested that aggressive tumors are the most likely to generate responses that adversely affect cognition, including high levels of systemic inflammation [19]. In previous work from our group, we reported an association of stage of disease with executive dysfunction prior to adjuvant treatment, with stage II to III cancers exhibiting lower executive function compared to those with stage 0 or I disease [8]. Similarly, in another study, higher-stage patients were significantly more likely to be classified as having lower than expected overall cognitive performance than lower stage patients and healthy controls [7]. HER2 positivity, another marker of tumor aggressivity, has also been found to be associated with pre-adjuvant therapy cognition [19].

We use data from the Thinking and Living with Cancer (TLC) study, a large, multisite cohort of patients with breast cancer ages 60 and older [10, 20–23] to test hypotheses about tumor aggressivity and pre-systemic treatment cognition. Our primary hypotheses

were that higher tumor stage, and HER2 positivity (and HER2 positive molecular subtypes) would be associated with lower self-reported and objective cognition prior to systemic therapy. In secondary analyses, we explored the relationship between other tumor features considered markers of aggressivity (e.g., large tumor size, high grade, lymph node positivity, hormone receptor negativity) and cognition. The results are intended to guide future studies to understand how features of breast tumors may contribute to cognitive problems even prior to systemic adjuvant treatment and ultimately use that knowledge to guide supportive care and surveillance of cognitive function from the point of diagnosis through post-active treatment survivorship.

Materials and methods

This Institutional Review Board-approved study (ClinicalTrials.gov Identifier: NCT03451383) has been reported previously [2, 8] and was conducted at six US sites in Los Angeles, New York City, New Jersey, the DC metropolitan area, Indianapolis, and Tampa.

Setting, Population and Data Collection

We included all women with breast cancer recruited between August 1, 2010 and March 1, 2020; none of these women had COVID19 prior to initial enrollment. Eligible patients were 60 years of age or older, newly diagnosed with non-metastatic breast cancer and English-speaking. We excluded those with neurological disorders or any hearing or vision impairment that precluded assessment. Candidate participants with a history of other cancers were excluded if active treatment was recent (< 5 years) or included systemic therapy.

Patients were screened using the Mini-Mental State Examination (MMSE) [24] and the Wide Range Achievement Test, 4th edition (WRAT-4) Word Reading subtest [25]; those with scores of < 24 or < 3rd grade-equivalent reading level, respectively, were ineligible (1 patient). The analytic sample included 705 patients.

Baseline assessments were conducted by trained staff post-surgery and prior to systemic adjuvant treatment (or prior to neo-adjuvant therapy) using an interviewer-administered structured survey and neuropsychological testing [2, 8]. Medical records were abstracted using a structured tool at study enrollment and annually thereafter for tumor features, therapy, and surgery.

Measures

We use the protocol-specified primary cognitive outcomes: self-reported cognition measured using the Functional Assessment of Cancer Therapy–Cognition, Perceived Cognitive Impairment scale (FACT-Cog PCI) [26], and objective performance on the attention, processing speed, and executive function domain (APE; 6 tests) and learning and memory domain (LM; 5 tests) [2, 8]. The PCI is an 18-item scale often used in clinical trials and had excellent reliability in our cohort (Cronbach's alpha = 0.94). Scores range from 0 to 72, with higher scores representing better cognitive function; a 3–5 point difference in scores is considered a meaningful difference and a score of < 54 corresponds to mild cognitive impairment and is considered a clinically meaningful cut-point [27]. For the APE and LM domains, results are transformed into z-scores based on age- and education-matched

non-cancer control baseline means and standard deviations [2]. Z-scores have a mean of zero and range from – 3 standard deviations (SD) to + 3 SD. A positive score indicates better than average cognition and a negative score reflects worse than average scores. Domain-level impairment was defined based on having two tests in the domain < 1.5 SD or 1 test < 2 SD from the mean.

The primary tumor features of interest were stage of disease and HER2 status based on past reports and the association of these tumor features with aggressivity of disease [19]; other tumor features were secondary independent variables. For stage of disease, American Joint Committee on Cancer (AJCC) v6 stage (in place at the start of the cohort) was categorized as pathological stage 0/I vs. II/III. For HER2 status, cases were considered positive (vs. negative) if there was either a score of 3 + on HER2 IHC, a positive result on HER2 FISH, or the patient went on to receive trastuzumab treatment.

Hormone receptor (HR) status was categorized as positive if either estrogen (ER) and/or progesterone receptors (PR) were positive, otherwise hormone receptor status was negative. We also examined molecular subtype based on combinations of hormone receptor and HER2 status (i.e., HR + /HER2−, HR + /HER2 +, HR−/HER2 + and HR−/HER2− [triple negative]). Tumor grade was reported as low vs. moderate and high. Lymph nodes were considered positive for any positive nodes on sentinel node or full axillary dissection. Tumor pathological size was characterized as < 2 cm or 2 + cm.

Potential pre-systemic therapy covariates that might affect the associations between cognition and tumor features included age, cognitive reserve (measured by WRAT-4 [25] scores), race, recruitment site, surgery type (mastectomy vs. breast conservation) and number of comorbid illnesses. We also examined other potential covariates, including reactive mood that might be associated with knowledge of a more aggressive disease and need for additional adjuvant treatment, using the STAI-State (score of 45 or more) [28] or CES-D (score of 16 or more) [29]. Finally, since larger or more advanced stage tumors may reflect access barriers not fully captured by social determinants like race and cognitive reserve, we explored years of education, usual occupation, and Medicaid status as possible covariates.

Statistical Analysis

We estimated the association of stage of disease or HER2 and self-reported cognition scores and objective performance on APE and LM domains in unadjusted linear regression models. Adjusted self-reported cognitive scores and objective performance (or rates of impairment) on APE and LM domains were estimated in multivariable linear regression models controlling for age, race, and recruitment site.

In secondary analyses, associations of HER2 + molecular subtypes and cognitive impairment rates were tested using ANCOVA or Chi-square tests. In other secondary analyses, we used similar analyses to explore the association of self-reported and objective cognitive scores or impairment and other tumor markers.

In all analyses, we tested whether additional variables might have confounded the association of specific tumor features and cognition through socioeconomic status or barriers to treatment (e.g., years of education, Medicaid status). Finally, since self-reported depression and anxiety were variably associated with tumor features and cognition, these were considered in secondary analyses.

Since stage of disease and HER2 status were our a priori primary hypotheses, results for each were considered significant at a two-sided p-value < 0.05. For secondary tumor features, no multiplicity correction was performed, and we report these results as exploratory for hypothesis generating purposes.

All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Participants

Patients were on average 68 years old (SD 5.8, range 60–98), well-educated (mean years of education 15.3 [SD 2.2]), and predominantly white (79.1%) (Table 1). The majority of patients had tumors that were HER2 negative (89.3%), hormone receptor positive (88.6%), < 2 cm tumor size (71.5%), and/or Stage 0/1 (72.6%) (Table 1). Tumor features were not related to sociodemographic or other covariates except for small differences in racial group ($p = 0.034$) and minor variation in education by tumor size ($p = 0.005$); anxiety and depression were associated with stage of disease (STAI: $p = 0.003$; CES-D: $p = 0.006$) (Online materials, Table 1); race is included in all adjusted models of cognition and tumor features; mood is included in all adjusted models in the supplementary materials.

Association of Tumor Features with Pre-systemic Therapy Cognition

Objective Cognitive Performance—As predicted, higher stage of disease was associated with lower attention, processing speed, and executive functioning (APE) domain scores in unadjusted models ($p < 0.001$) and this relationship persisted in models adjusted for age, race, and site: patients with stage II/III tumors had worse APE performance than those with stage 0/I tumors (− 0.369 [0.048] vs. − 0.222 [0.033], $p = 0.005$). HER2 positivity or having a HER2 positive molecular subtype was not associated with APE or LM scores or impairment rates in unadjusted or adjusted models (Tables 2 and 3 a, b).

In secondary analyses, larger tumor size was associated with lower APE performance in unadjusted models ($p = 0.008$), but this association decreased to marginal significance in models adjusted for age, race, and site ($p = 0.074$). Hormone receptor negativity was associated with lower LM performance in unadjusted models ($p = 0.043$), but this association did not persist in models adjusted for age, race, and site ($p = 0.163$) (Table 2). Measures of mood were variably associated with tumor features (Online materials, Table 1). However, with the exception of the association of tumor size and APE performance, when depression or anxiety were added to models all other associations between tumor features and objective cognition remained either significant or marginally significant with similar magnitude of effects (Online materials Tables 2a and 2b).

Self-Reported Cognition—As predicted, HER2 positivity ($p = 0.008$) was associated with self-reported cognition and this relationship remained after adjustment for age, race, and site ($p = 0.02$) (Table 2). Patients with HER2 + (vs. HER2−) tumors had a higher rate of self-reported cognitive scores at or below the cut-point indicating impairment (30% vs. 19%, $p = 0.049$). When considering combinations of tumor features based on common molecular subtypes (Table 3), patients with the HR−/HER2 + molecular subtype tumors had significantly and clinically meaningfully lower self-reported cognitive scores (50.9 vs. 59.7–61.0 in other subtypes, $p = 0.006$) (Table 3a). Patients with HR−/HER2 + molecular subtype tumors also had the highest level of impairment (37.5% vs. 18.9–28.3% for other subtypes) but this difference was not statistically significant (Table 3b). Stage of disease was not associated with self-reported cognition.

In secondary analyses, additional markers of tumor aggressiveness were also significantly associated with having more perceived cognitive problems, including hormone receptor negativity and larger tumor size ($p = 0.02$) (Table 2), but only larger tumor size ($p = 0.02$) remained significantly associated with having more perceived cognitive problems in models adjusted for age, race, and site (Table 2). Having a larger (vs. smaller) tumor was also associated with higher adjusted self-reported rates of pre-systemic therapy cognitive impairment (28% vs. 18%, $p = 0.006$). Associations between tumor features and self-reported cognition remained either significant or marginally significant with similar magnitude of effects considering mood (Online materials Tables 2a and 2b).

Discussion

To our knowledge, this is the largest study of the association between breast cancer molecular and clinicopathological tumor features and pre-systemic therapy cognition in older patients with breast cancer. Our results indicated that higher stage of disease and HER2 positivity were associated with cognition: higher stage of disease was associated with worse performance on measures of attention, processing speed, and executive dysfunction and HER2 positivity was associated with significantly more self-reported cognitive problems and higher rates of clinically meaningful cognitive impairment. Among other markers of tumor aggressiveness, larger tumor size was associated with self-reported cognitive dysfunction. Taken together, our results suggest that aggressive tumor features like stage of disease, HER2 positivity, and tumor size may have systemic effects that impact cognition.

These results confirm the limited previous reports from largely younger patients and smaller samples that suggest a role for higher tumor stage/later stage [7, 8] and HER2 status [19] in pre-systemic treatment cognition. However, not all past studies have observed associations between tumor features and cognition, but these may have been limited in power due to small sample sizes [14]. Our results from a large cohort add new data from older patients with breast cancer. While older patients are less likely to have aggressive, poor prognosis tumors than younger patients, when they do have these tumor types, they may be more likely to report cognitive problems than other age groups because older patients often have diminished age-related cognitive reserve and limited ability to compensate for even small cognitive changes. Ways to test these ideas further include new cohort studies, use of

pooled existing data, measuring self-reported cognition in clinical trials, and increasing the representation of older patients in those trials.

Since the tumor features we identified as associated with cognition are known to be highly intercorrelated and related to tumor aggressiveness [30], it is possible that there is a final common pathway for their effect on cognition. Chronic, heightened inflammatory responses to larger, more aggressive tumors may be one potential pathway affecting pre-systemic therapy cognition via peripheral inflammation and neuroinflammation [18, 31]. This seems plausible given evolving evidence about the role of inflammation in post-treatment cognitive problems [32–35], which are thought to be due to peripheral inflammation crossing the blood brain barrier and promoting neuroinflammation [13, 36, 37]. Alternatively, since HER2 is encoded by ERBB2 and ERBB2 plays a role in central and peripheral nervous system development and adult cognition [38], this may be another pathway of effect for higher stage of disease and tumor size seen with HER2 positive tumors. Alternative pathways are also plausible since a subset of features associated with aggressivity were not associated with cognitive outcomes, such as triple negative status, although this is a less common subtype in older age, limiting our power. As data evolve, it will be useful to examine whether different tumor features influence cognition via multiple, separate, and distinct pathways or through a final, common pathway.

Other factors have been proposed to contribute to cognitive problems after surgery but before systemic therapy, including effects of general anesthesia [39, 40], genotype [41], and differential inflammatory effects related to extent of resection [42]. This latter effect has been particularly pronounced in pre-clinical models with aged animals [43]. However, we did not find a difference in cognition by surgery type in the current study and previous work associating anesthetic dose with pre-systemic therapy cognition also failed to find an association [7].

Other possible contributors to the relationships of aggressive tumor features and cognition we observe include anxiety and depression in reaction to facing treatment for an aggressive cancer or sociodemographic factors creating barriers to screening, diagnosis and/or access to treatment. However, models including measures of mood showed a persistent or minimal attenuation of the association between aggressive tumor features and cognition. Race was included in all models and did not attenuate effects. Given the relatively small number of older patients with aggressive tumor features and the limited socioeconomic and demographic diversity of our cohort it will be important to conduct future studies to explore the multi-level inter-relationships between life course experiences, coping styles, tumor characteristics, and cognition.

Understanding pre-systemic therapy mechanisms and factors associated with cognitive problems may be useful in identifying those patients who are at heightened risk for further cognitive decline and could suggest interventions to treat early cognitive issues and/or prevent additional decline while undergoing life-saving systemic therapy. This is especially important because aggressive tumors require extensive treatments that may also impact longer-term cognition after active therapy. Identifying cognitive vulnerability is especially important in older adults who are already at risk for age-related cognitive decline and can

alert clinicians to the potential need to evaluate cognitive function and ability to complete complex treatment regimens. Our findings also underscore the importance of screening older adults with cancer for cognitive problems at all phases of care, from diagnosis to survivorship, using geriatric assessments or other approaches [44]. It will also be important to determine if pre-systemic therapy cognitive problems resolve over time or are a harbinger of continued declines.

The TLC study is the largest study examining cognition in older patients with breast cancer to date. We found consistent results suggesting that features related to tumor aggressiveness are associated with pre-systemic therapy objective and self-reported and cognitive problems. There are also caveats that should be considered in evaluating our results. The current sample is composed of largely white, well-educated participants and should be replicated in other populations to assess generalizability. While stage of disease and HER2 status were hypothesized to be associated with cognitive function, our secondary analyses explored several other tumor features and may have increased risk for Type 1 error. Additionally, we did not have the power to test for the role of genetic factors like APOE4 positivity or interactions between tumor features and APOE4 positivity since this was only seen in about one-fifth of our sample. Finally, we did not have any data on earlier life exposures that may have affected pre-systemic therapy cognition. These will be important areas to consider when designing new studies of cognition and cancer.

In summary, several breast cancer tumor features associated with aggressive disease were found to be significantly associated with pre-systemic treatment cognition, with the most significant effects found for stage of disease, HER2 positivity, including the HER2 + /HR− subtype, and tumor size. These findings expand the scope of potential cancer-related cognitive decline mechanisms beyond systemic chemotherapy and hormonal therapies. Until new data become available, our results suggest that cognitive function should be evaluated prior to and during clinically indicated systemic therapies to provide early supportive care and symptom management for older patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interest

Asma Dilawari has served on the Cardinal Health oncology summit advisor board, 2019. Claudine Isaacs has served as a consultant for Genentech, Seattle Genetics, PUMA, Novartis, AstraZeneca, Sanofi, and Pfizer, and received support for research (to institution) from Pfizer and Tesaro/GSK. Heather Jim has consulted for RedHill BioPharma, Janssen Scientific Affairs, and Merck, and has received grant funding from Kite Pharma. The other authors declare that they have no conflict of interest.

Role of the funders

The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Data availability

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Table 1

Characteristics of older patients with non-metastatic breast cancer at enrollment, prior to systemic therapy (n = 705)

	Percent (n) or mean (SD)
Age	68.0 (5.8), range 60–98
Race[a]	
White, non-Hispanic	79% (558)
Non-White	18% (124)
Hispanic	3% (23)
Years of education	15.3 (2.2)
Number of comorbidities	2.8 (2.0)
Surgery	
Mastectomy	32.6% (228)
Lumpectomy	67.4% (471)
Time from surgery to enrollment, days	44.2 days (51.4)
STAI-A Anxiety above cutoff (> 44)[b]	6.1% (40)
CES-D score indicting depression (≥ 16)[c]	12.6% (81)
HER2 positivity[d]	
Negative	89.3% (552)
Positive	10.7% (66)
Hormone receptor status[e]	
Positive	88.6% (620)
Negative	11.4% (80)
Triple negative status (ER−, HER2−, PR−)	
Not triple negative	91.9% (634)
Triple negative	8.1% (56)
Tumor grade	
Low	20.1% (110)
Moderate	61.1% (334)
High	18.8% (103)
Lymph node	
Negative	82.2% (560)
Positive	17.8% (121)
Tumor size	
< 2 cm	71.5% (487)
2 + cm	28.5% (194)
AJCC v. 6 stage	
Stage 0/II	72.6% (504)
Stage II/III	27.4% (190)

[a]Non-White includes Black and Asian

[b] Scores on the State-Trait Anxiety Inventory range from 20 to 80, with higher scores reflecting more anxiety. A cut point of > 44 is used to define clinical anxiety

[c] Scores on the Center for Epidemiologic Studies Depression Scale range from 0 to 60, with higher scores representing more depressive symptoms; a cut point of 16 is used to define clinical depression

[d] HER2 positivity was defined as scoring 3 + on HER2 IHC, or tested positive on HER2 FISH, or going on to receive Herceptin treatment

[e] Hormone receptor positive was defined as being estrogen receptor (ER) positive and/or progesterone receptor (PR) positive

Table 2

Crude and adjusted enrollment, pre-systemic therapy cognitive function by tumor characteristics among older patients with non-metastatic breast cancer

	FACT-Cog PCI score[a]				Attention, processing speed, executive function[b]				Learning and memory[b]			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
Stage												
Stage 0/1	60.9 (0.5)	$p = 0.452$	61.0 (0.6)	$p = 0.171$	**−.052 (0.029)**	**$p = < .001$**	**−.222 (0.033)**	**$p = 0.005$**	−.041 (0.037)	$p = 0.699$	−.295 (0.042)	$p = 0.733$
Stage 2/3	60.2 (0.8)		59.7 (0.9)		**− .242 (0.047)**		**− .369 (0.048)**		− .069 (0.061)		− .272 (0.061)	
HER2[c]												
Negative	**61.2 (0.5)**	**$p = 0.008$**	**60.9 (0.6)**	**$p = 0.023$**	− .113 (0.028)	$p = 0.946$	− .284 (0.034)	$p = 0.786$	− .052 (0.035)	$p = 0.170$	− .322 (0.042)	$p = 0.292$
Positive	**57.3 (1.4)**		**57.6 (1.4)**		− .107 (0.081)		− .262 (0.079)		− .201 (0.102)		− .428 (0.098)	
Tumor size												
< 2 cm	**61.3 (0.5)**	**$p = 0.024$**	**61.2 (0.6)**	**$p = 0.021$**	− .063 (0.029)	$p = 0.008$	− .238 (0.034)	$p = 0.074$	− .038 (0.038)	$p = 0.669$	− .301 (0.043)	$p = 0.595$
2 + cm	**59.1 (0.8)**		**59.0 (0.9)**		− .210 (0.046)		− .331 (0.047)		− .068 (0.060)		− .267 (0.059)	
Hormone receptor												
Positive	61.0 (0.5)	$p = 0.034$	60.9 (0.6)	$p = 0.131$	− .100 (0.026)	$p = 0.534$	− .265 (0.031)	$p = 0.915$	− .026 (0.033)	$p = 0.043$	− .272 (0.039)	$p = 0.163$
Negative	58.2 (1.3)		58.9 (1.3)		− .148 (0.073)		− .257 (0.070)		− .227 (0.093)		− .400 (0.088)	
Grade												
Low	61.2 (1.0)	$p = 0.562$	61.7 (1.4)	$p = 0.545$	− .039 (0.062)	$p = 0.609$	− .140 (0.078)	$p = 0.439$	− .003 (0.079)	$p = 0.352$	− .096 (0.098)	$p = 0.310$
Moderate	60.3 (0.6)		60.7 (1.2)		− .109 (0.036)		− .224 (0.064)		0.018 (0.045)		− .122 (0.079)	
High	59.6 (1.1)		60.1 (1.5)		− .076 (0.064)		− .182 (0.080)		− .117 (0.082)		− .241 (0.100)	
Lymph node												
Negative	60.9 (0.5)	$p = 0.907$	60.8 (0.6)	$p = 0.946$	− .097 (0.028)	$p = 0.588$	− .262 (0.032)	$p = 0.528$	− .043 (0.035)	$p = 0.990$	− .281 (0.040)	$p = 0.805$
Positive	60.8 (1.0)		60.9 (1.1)		− .133 (0.059)		− .301 (0.060)		− .044 (0.076)		− .300 (0.075)	

Unadjusted scores for each individual categorical tumor characteristic were calculated from simple linear regression models, with significance testing based on Type III tests. Adjusted cognitive scores for each individual categorical tumor characteristic were controlled for age, race, and recruitment site in linear regression models

[a] Scores on the FACT-Cog perceived cognitive impairment scale range from 0 to 72, with higher scores represent better cognitive function

[b] Z-scores for neurological tests within each domain range from − 3 to + 3, with a mean of 0. A positive score indicates better cognitive performance and a negative score reflects worse than average scores

[c] HER2 positivity was defined as scoring 3 + on HER2 IHC, or tested positive on HER2 FISH, or receiving Herceptin treatment

Table 3

Pre-systemic therapy cognition by molecular sub-type among older patients with non-metastatic breast cancer

a. Mean (SE) adjusted baseline cognitive scores by molecular subtype

Mean scores	**HR +, HER2−(*n* = 493)**	**HR +, HER2 + (*n* = 51)**	**HR−,HER2 + (*n* = 15)**	**HR−, PR−, HER2− (triple negative) (*n* = 56)**	***p*-value[1]**
Self-reported cognitive problems (FACT cog PCI) *	60.8 (0.7)	59.7 (1.6)	50.9 (2.8)	61.0 (1.5)	0.006
APE z-score **	− .296 (0.036)	− .237 (0.090)	− .350 (0.159)	− .197 (0.084)	0.621
LM z-score **	− .306 (0.045)	− .377 (0.112)	− .578 (0.199)	− .430 (0.104)	0.370

b. Mean rates of baseline cognitive impairment by molecular subtype

Percent impaired	**HR +, HER2− (*n* = 460) (%)**	**HR +, HER2 + (*n* = 46) (%)**	**HR−, HER2 + (*n* = 14) (%)**	**HR−, PR−, HER2− (triple negative) (*n* = 53) (%)**	***p*-value[2]**
Self-reported cognitive problems (FACT cog PCI) *	19.4	28.3	35.7	18.9	0.245
APE domain **	17.2	15.7	20.0	10.7	0.636
LM domain **	14.2	7.8	13.3	23.2	0.150

Adjusted for age, race, site; p values based on ANCOVA

p-values based on Chi-square tests

*Scores on the FACT-Cog perceived cognitive impairment scale range from 0 to 72, with higher scores represent better cognitive function. 3–5 point differences are considered clinically meaningful and a score of < 54 is considered impaired

**Z-scores for neuropsychological tests within each domain range from − 3 to + 3, with a mean of 0. A positive score indicates better cognitive performance and a negative score reflects worse than average scores. Having one of the tests within the domain with a score of < 2SD from the mean or two tests < 1.5 SD from the mean are considered impairment