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RESEARCH

Characterizing cancer-related cognitive impairments and impact on quality of life in women with metastatic breast cancer

Ashley M. Henneghan[1,11] · Kathleen M. Van Dyk[2,3] · Darren Haywood[4,5,6,7] · Mansi Patel[8] · Oscar Y. Franco-Rocha[1] · Soyeong Bang[9] · Tamsin Longley[10] · Rebecca Tasker[1] · Tara Kaufmann[11] · Emily W. Paolillo[12] · Raeanne C. Moore[13] · Nicolas H. Hart[4,14,15,16,17]

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Abstract

Purpose Little is known about cancer-related cognitive impairments (CRCI) in women with metastatic breast cancer (MBC). The purpose of this study is to (1) comprehensively describe CRCI and any associated psychosocial and behavioral symptoms, (2) determine observable sociodemographic and clinical risk factors for CRCI, and (3) explore cognitive and psychosocial predictors of quality of life and social functioning in women living with MBC.

Methods Using a cross-sectional design, women with MBC completed assessments (objective and subjective measures of CRCI including 3 open-ended questions, measures of psychosocial and behavioral factors, and assessments of quality of life and social function), and data were analyzed using descriptive statistics, qualitative content analysis, correlation analyses, *t* tests, analysis of variance, and linear regression models.

Results Data from 52 women were analyzed. 69.2% of the sample reported clinically significant CRCI and 46% of the sample scored < 1 standard deviation below the standardized mean on one or more cognitive tests. Those with triple-negative MBC (compared to HER2+), recurrent MBC (compared to de novo), and no history of chemotherapy had worse subjective CRCI, and those without history of surgery and older age had worse objective CRCI. Subjective CRCI, but not objective CRCI, was significantly associated with quality of life and social functioning.

Conclusion Subjective and objective CRCI are likely a common problem for those with MBC. Subjective CRCI is associated with poorer quality of life and lower social functioning. Healthcare providers should acknowledge cognitive symptoms, continually assess cognitive function, and address associated unmet needs across the MBC trajectory.

Keywords Cancer-related cognitive impairments · Metastatic breast cancer · Clinically meaningful thresholds · Quality of life · Social function

Introduction

Cancer-related cognitive impairments (CRCI) are common during and after breast cancer diagnosis and treatment and include symptoms, such as memory lapses and slowed thinking [1–6]. CRCI significantly reduce quality of life, worsen social and occupational function, and decrease survival [7–10]. Most CRCI research (in non-central nervous system cancers) have focused on early-stage breast cancer, leaving a critical knowledge gap about CRCI in people with metastatic breast cancer (MBC) who may be especially vulnerable to CRCI due to cycling on and off active treatment, high psychological burden [11–17], and the potential metastases to the brain.

Almost 30% of people with early stage of breast cancer (I–III) will experience recurrent metastatic disease, and approximately 10% of initial breast cancer diagnoses are advanced (stage IV; referred to as de novo MBC) [18–22]. Approximately 168,000 people in the U.S.A. live with MBC [18], requiring continuous and complex treatment and monitoring. MBC diagnosis and treatments are often associated with burdensome physical, psychological, emotional, and spiritual side effects that negatively impact quality of life (QoL) and disrupt participation in everyday life [11–16].

The few studies that have examined cognitive symptoms in MBC indicate the need for more research, with cognitive dysfunction identified as a significant problem, limiting

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engagement in daily activities [16]. Poorer perceived cognitive functioning is associated with higher depression, anxiety, and post-traumatic stress, particularly for younger women and those with less social support in women with MBC [23]. These studies provide valuable insights but are limited in scope and size, leaving questions about the link between CRCI and other important behavioral and social factors including fatigue, sleep, and social satisfaction, as well as associations between CRCI and QoL.

The study aims were to (1) comprehensively describe CRCI using patient-reported outcomes, objective cognitive evaluations, open-ended responses, and psychosocial and behavioral symptoms; (2) determine sociodemographic and clinical risk factors for CRCI; and (3) explore cognitive and psychosocial correlates of QoL and social functioning in women with MBC.

Materials & methods

Data presented here are part of a prospective observational cohort study that included an ecological momentary assessment (EMA) protocol not included in this analysis (see [24] for similar study protocol). This study was approved by the University of Texas at Austin Institutional Review Board (STUDY00002393). All participants provided written informed consent.

Recruitment and sample characteristics

We recruited women who had been diagnosed with MBC residing in the USA. Social media posts were distributed via administrators of METAvivor©, a national social media support group for those affected by metastatic breast cancer. Inclusion criteria were: (1) > = 21 years of age, (2) physically able to participate (i.e., confirmed ability to use a computer and smartphone; Karnofsky Performance Scale > = 70), (3) cognitively able to participate (Mini-Moca Telephone screening, > = 11) [25, 26]), 4) access to a computer with internet, 5) daily use of and access to a personal smartphone, and 6) English language proficiency. Those who might be pregnant, had major sensory deficits (e.g., deafness or blindness) that would interfere with data collection, had prior history of cancer with systemic treatment (other than breast cancer), or neurological or cognitive co-morbidities (e.g., dementia, substance abuse, unmanaged psychiatric conditions) were excluded.

Setting and study procedures

All study procedures were conducted remotely from the University of Texas at Austin between May 2023 and May 2024. Interested participants contacted the study team and self-scheduled telephone appointments for prescreening, followed by informed consent procedures if eligible.

Data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Texas at Austin [27, 28]. Baseline data collection included (1) a survey (written consent; sociodemographic/clinical variables; and cognitive and psychosocial variables) and (2) remote administration of a cognitive test battery (via BrainCheck, Inc.). Data from qualitative open-ended questions from the follow-up data collection (4 weeks after baseline) were also included.

Measures

Sociodemographic and clinical variables

A questionnaire was used to collect self-reported age, education, race, ethnicity, marital status, children or dependents, income, employment status, health history (co-morbidities, menstrual history, current medications), and cancer history (types of breast cancer treatment received, MBC type [receptor status; recurrent/de novo], date of diagnosis). Three items (FT6; FT8; FT10) from the FACIT-COST instrument were used to assess financial toxicity [29], where higher scores indicated worse financial toxicity.

Cognitive variables

FACT-Cog version 3 was used to assess self-reported cognitive function [30]. The Perceived Cognitive Impairments 20-item subscale (FACT-Cog PCI) operationalized self-reported CRCI, with clinically meaningful CRCI determined according to clinical thresholds [31]. A computerized battery of standardized cognitive tests were administered via BrainCheck and included the Trail Making Tests for attention and processing speed, the Digit Symbol Substitution Test and the Stroop Test for executive functioning, and the Recall Test (list learning) for immediate and delayed verbal memory [32]. Participants received detailed instructions for engaging with the online platform, including an introductory video. Individual and combined standardized scores were used to quantify objective cognitive performance. BrainCheck scores are standardized based on age and sex from a normative sample of 3500 + healthy participants and have been validated in clinical populations [32–35].

Cognitive open-ended questions

The follow-up REDCap survey included the three open-ended questions (Questions included in Table 3).

Psychosocial and quality of life

We administered the Patient-Reported Outcomes Measurement Information System (PROMIS) scales—Emotional Distress—Anxiety Short Form 8a ("PROMIS Anxiety"), Emotional Distress—Depression Short Form 8a ("PROMIS Depression"), Satisfaction with Social Roles & Activities Short Form 8a ("PROMIS Social"), and the UCLA Loneliness 3-item scale [36]. Perceived stress was assessed using the 10-item Perceived Stress Scale (PSS) [37]. The Social Difficulties Inventory (SDI) measured social functioning. SDI 16 total scores were calculated per instrument scoring instructions from Wright et al., 2011 [38]. Higher UCLA loneliness, PSS, and SDI-16 scores indicate worse symptoms or functioning.

Fatigue was assessed using the PROMIS Fatigue Short Form 8a ("PROMIS Fatigue") [39] and the PROMIS Sleep Disturbance 4a ("PROMIS Sleep") measured sleep disturbance [40]. All PROMIS scales were transformed to norm-based t-scores [39] with higher scores on negative scales indicating worse symptoms, and higher scores on positive scales indicating better function. The Functional Assessment of Cancer Treatment-General (FACT-G) assessed QoL across physical, social/family, and emotional domains [41]. General population and cancer patient norms on the FACT-G were used to determine clinically meaningful thresholds in the present study [42].

Data analyses

Quantitative

Data were checked for normality and outliers. Missing data were low in this study (< 10% for any one item across instruments and < 10% for any one participant). For multi-item self-report instruments with missing data at random, mean substitution were used (using all scale/subscale items) at the item level prior to summing total scores. Outliers for cognitive variables were identified and removed if > 3 SD below/above the mean. Descriptive statistics were used for sociodemographic variables and clinical history. Clinically meaningful thresholds (CMT) were used for self-reports of cognitive, psychosocial, and behavioral variables, determined by previous literature (FACT-Cog PCI, FACT-G, SDI-16) or 1 SD > or < the t scores (PROMIS scales). Impairment on cognitive tests were determined as 1 SD below the standardized mean, consistent with Mild Cognitive Disorder descriptions in the DSM-5 [43].

Sociodemographic and clinical differences in subjective (FACT-Cog PCI) and objective cognitive function (BrainCheck composite scores) were examined with independent samples *t* tests or 3-way analysis of variance (ANOVA). Pearson's correlations for cognitive outcomes and psychological, social, and behavioral variables were performed. These tests were exploratory, with an alpha set to 0.05.

Building on earlier findings, we explored subjective and objective cognitive correlates (FACT-Cog PCI; BrainCheck composite) of quality of life (FACT-G) and social functioning (SDI-16) within the context of psychological distress and fatigue, known to contribute to overall QoL in people with MBC [44, 45]. Two linear regression models (outcome variables: FACT-G; SDI-16) were then constructed with the same 5 predictors (FACT-Cog PCI; PROMIS Fatigue total scores, PROMIS Depression total scores, PSS total scores, and COST total scores). BrainCheck scores (objective CRCI) were not included in the models as no correlations were found (see Supplementary Fig. 2 and Supplementary Table 1). The backward stepwise method was used and model fit evaluated for each step of the regression models using adjusted r square values and F statistics. Collinearity diagnostics and assumptions for residuals (Durbin–Watson test for auto-correlation; Q–Q plots) were evaluated. Data cleaning and analyses were conducted using R Studio (Posit Software, version 2024.04.1 + 748; 'ggplot2,' 'ggcorrplot,' 'dplyer,' 'tidyverse,' 'magrittr' libraries) and JASP (Version 0.18.3).

Qualitative

Open-text box responses were independently reviewed and analyzed by 2 co-authors (AMH, SB) using a qualitative content analysis approach [46, 47]. This approach allows for manual distillation of words into fewer content-related categories [48]. Each co-author read the entire narrative and then initiated line-by-line coding (units of analysis were words and phrases). Codes were inductively grouped into larger categories that emerged from the data without a formal organizing framework [48], rather the question prompts were used for conceptual organization. Co-authors met to compare and collapse categories and complete the abstraction process, which involves forming general descriptions and meanings of the final categories [48].

Results

Sample description

Fifty-two participants enrolled and completed baseline data collection. Participants were on average 51.1 years of age (*SD*: 11.1) and received 16.1 years of education (*SD*: 2.2). Most identified as non-Hispanic White (84.6%) were married or living with a significant other (65.4%) and unemployed due to disability (38.5%) or laid off/fired or retired (13.5%). Clinically, the sample was on average 4.2 years

from diagnosis with MBC (*SD*: 3.4), and the majority had a de novo MBC diagnosis (57.7%). Most had been diagnosed with hormone receptor-positive, HER2-negative breast cancer (61.5%) and were post-menopausal (82.7%). See Table 1 for complete demographic and clinical characteristics.

Quantitative cognitive outcomes

The mean score on the FACT-Cog PCI subscale was 49.42 ($SD = 18.37$), and 69.2% of the sample reported clinically significant CRCI (< 60 [31]). Fifty of the 52 participants completed baseline BrainCheck cognitive batteries. Although the BrainCheck scores were, on average, in the normal range (Table 2), 46% of the sample scored < 1 SD below the standardized mean (100) on 1 or more of the 6 tests (See Fig. 1 for rates of impairment, and Supplementary Fig. 1 for frequency of impairment on 0 to 6 cognitive tests). See Table 2 for descriptive statistics for all the cognitive domains.

Qualitative cognitive outcomes

Five themes emerged during the content analysis of responses to the first question, four themes for the second question, and four themes for the third question. Themes are described and exemplar quotations provided in Table 3.

Psychosocial, behavioral, and QoL outcomes

Notably, 26.9% of the sample had clinically meaningful anxiety, 57.7% had clinically meaningful levels of fatigue, 53.8% met the CMT for social functioning difficulties (SDI-16), and 38.5% scored below the CMT for FACT-G [42] (Table 2).

Demographic and clinical correlates of cognitive function

Significant differences in cognitive scores were found for age groups, MBC diagnosis (de novo or recurrent), MBC pathology, history of surgical treatment for MBC, and chemotherapy treatment for MBC (See Table 4). On average, those aged 61–74 years old performed worse overall on the cognitive test batteries (adjusted for age) compared to those aged 40–60 years old ($p = 0.005$). Those with no history of surgery also performed worse on cognitive tests than those who did have surgery ($p = 0.046$). Those with a history of recurrent MBC compared to those with de novo MBC ($p = 0.015$), those who received no chemotherapy for their MBC compared to those who did receive chemotherapy ($p = 0.039$), and those with a history of triple-negative breast cancer compared to those with HER2 positive (*mean* 34.00 compared to *mean* 59.40, $p = 0.019$) reported worse subjective cognitive impairment.

Correlation analyses among cognitive variables, psychosocial variables, behavioral variables, financial toxicity, QoL, and social functioning revealed BrainCheck scores did not correlate with any of patient-reported outcome variables ($p's > 0.10$), whereas FACT-Cog PCI did significantly correlate with PSS and PROMIS Anxiety ($r's = -0.46$ to -0.48, $p's < 0.01$), PROMIS Social Satisfaction and UCLA Loneliness ($r's = |0.4–0.46|$, $p's < 0.01$), PROMIS Fatigue ($r = -0.40$, $p < 0.01$), COST scores ($r = -0.40$, $p < 0.01$), and SDI and FACT-G ($r's = |0.59–0.68|$, $p's < 0.001$). See Supplemental Fig. 2 for a correlation heat map, and Supplemental Materials, Table 1 for the correlation matrix.

Correlates of everyday functioning (social function and QoL)

FACT-Cog PCI, PROMIS Fatigue, PROMIS Depression, and PSS explained 69% of the variance in FACT-G scores ($R^2_{adjusted} = 0.69$, $F\ (4.46) = 24.21$, $p < 0.001$, See Fig. 2). PROMIS Fatigue was the strongest predictor in this model (*Standardized Beta* $= -0.39$, $SE = 0.18$, $t = -4.29$, $p < 0.001$), followed by PSS (*Standardized Beta* $= -0.28$, *SE*:0.28, $t = -2.51$, $p < 0.05$), then FACT-Cog PCI (*Standardized Beta* $= 0.24$, *SE*:0.07, $t = 2.61$, $p < 0.05$), and PROMIS Depression (*Standardized Beta* $= -0.23$, *SE*:0.27, $t = -2.30$, $p < 0.05$).

FACT-Cog PCI, COST, PROMIS Fatigue, and PROMIS Depression explained 66% of the variance in SDI-16 scores ($R^2_{adjusted} = 0.66$, $F(446) = 25.16$, $p < 0.001$, See Fig. 3). FACT-Cog PCI was the largest predictor in this model (*Standardized Beta* $= -0.42$, *SE*:0.04, $t = -4.29$, $p < 0.001$), followed by COST (*Standardized Beta* $= 0.32$, *SE*:0.22, $t = 3.54$, $p < 0.001$), then PROMIS Fatigue (*Standardized Beta* $= 0.23$, *SE*:0.11, $t = 2.55$, $p < 0.05$), and then PROMIS Depression (*Standardized Beta* $= 0.19$, *SE*:0.14, $t = 2.12$, $p < 0.05$).

Discussion

In this study, we provide a comprehensive evaluation of CRCI and the effects of CRCI on QoL and social functioning in women with MBC. We found that over half the sample had subjective or objective CRCI, consistent with prevalence rates reported of subjective CRCI (78% [5]) and objective CRCI (30–60% [2, 3]) in early-stage breast cancer. The rates are lower than what has been reported in cancer populations with brain metastases (up to 90% with neurocognitive dysfunction reported) [49]. While we did not measure number or location of metastases in this study, the brain is the least affected site in MBC [20], and the cumulative incidence of brain metastases in breast cancer is approximately 5% [50].

Table 1 Demographic and clinical characteristics of the sample ($N = 52$)

Demographic characteristic	Mean (SD)	Frequency (%)
Age	51.1 (11.1)	–
Age groups		
Ages 22–39	–	6 (11.5%)
Ages 40–60	–	34 (65.4%)
Ages 61–74	–	12 (23.1%)
Race/ethnicity		
White	–	44 (84.6%)
Asian/Asian American	–	2 (3.8%)
Black/African American	–	2 (3.8%)
Hispanic	–	4 (7.7%)
Married/Living with significant other	–	34 (65.4%)
Has dependents (children or parents)	–	28 (53.8%)
Employment		
Working full or part time	–	21 (40.4%)
Unemployed due to disability	–	20 (38.5%)
Laid off/fired/retired	–	7 (13.5%)
Other		4 (7.6%)
Household income		
Annual household income $0–50,000	–	15 (28.8%)
Annual household income $50,000–99,999	–	12 (23.1%)
Annual household income > $100,000	–	20 (38.5%)
Preferred not to answer		5 (9.6%))
Income decreased from pre diagnosis to now	–	20 (38.5%)
Years of education	16.1 (2.2)	–
< = 16 years of education	–	35 (67.3%)
> 16 years of education	–	17 (32.7%)
Clinical characteristic	Mean (SD) or frequency (percentage)	Frequency (Percentage)
Years since diagnosis with stage IV^	4.2 (3.4)	–
< 1.5 years since diagnosis with stage IV	–	13 (25%)
1.5–5.5 years since diagnosis with stage IV	–	25 (48.1%)
> 5.5 years since diagnosis with stage IV	–	13 (25%)
MBC diagnosis type		
De novo stage IV	–	30 (57.7%)
Recurrent stage IV	–	22 (42.3%)
MBC Pathological Type^		
HR + HER2-	–	33 (61.5%)
HER2 +	–	6 (11.5%)
HR + HER2 +		7 (13.5%)
Triple negative	–	5 (11.5%)
Post-menopausal	–	43 (82.7%)
History of surgery	–	33 (63.5%)
History of radiation	–	28 (53.8%)
Received any chemotherapy treatment(s)	–	30 (57.7%)
Received taxanes	–	25 (48.1%)
Received any hormonal treatment(s)	–	43 (82.7%)
Received SERM	–	10 (19.2%)
Received selective estrogen receptor degraders	–	13 (25%)
Received aromatase inhibitors	–	36 (69.2%)
Received lupron	–	13 (25%)
Received antibody drug conjugates	–	13 (25%)
Received CDK4/6 inhibitors	–	30 (57.7%)
Received HER2-targeted therapy	–	13 (25%)

Table 1 (continued) *HER2* human epidermal growth factor receptor 2, *SD* standard deviation
^$n=51$

Table 2 Baseline descriptive statistics for cognitive and psychosocial variables ($N=52$)

Cognitive Domain	Mean (SD)	Minimum	Maximum	Frequency worse than CMT
FACT-Cog PCI	49.42 (18.37)	15	77	36 (69.2%)
FACT-Cog abilities	18.64 (8.08)	7	36	–
FACT-Cog comments	14.23 (2.62)	4	16	–
FACT-Cog QOL	9.48 (4.66)	0	16	–
Cognitive test composite t score[1]	105.37 (12.88)	67	129	5 (10.2%)
Trails A standardized score[2]	105.34 (11.82)	75	123	3 (6%)
Trails B standardized score[2]	105.28 (13.24)	67	125	3(6%)
Digit symbol standardized score[1]	105.47 (12.7)	66	127	3 (6.1%)
Stroop tests standardized score[1]	98.74 (18.05)	58	127	15 (30.6%)
Immediate memory standardized score[2]	104.08 (15.9)	57	117	4 (8%)
Delayed memory standardized score[2]	101.78 (14)	57	118	7 (14%)
Psychological domain	Mean (SD)	Minimum	Maximum	Frequency worse than CMT
PROMIS anxiety *t* score	55.11 (8.11)	37.1	70.8	14 (26.9%)
PROMIS depressive *t* score	51.8 (7.387)	38.2	64.9	7 (13.5%)
Perceived stress scale	18.35	4	34	–
Social domain	Mean (SD)	Minimum	Maximum	Frequency worse than CMT
PROMIS social satisfaction 8a t score	46.49 (8.26)	30	65.6	12 (23.1%)
Social difficulties inventory-16 score	12.14 (7.99)	0	30	28 (53.8%)
UCLA Loneliness 3 item	5.14 (1.95)	3	9	–
Behavioral domain	Mean (SD)	Minimum	Maximum	Frequency worse than CMT
PROMIS fatigue *t* score	60.39 (7.24)	44.3	74.2	30 (57.7%)
PROMIS sleep *t* score	54.26 (7.91)	37.5	73.3	13 (25%)
FACT-G total	68.29 (14.39)	33	98	20 (38.5%)

CMT: clinically meaningful thresholds

CMT for all PROMIS scales (except PROMIS Cog) were determined as 1 SD below/above the t score (anxiety, depression, fatigue, higher scores are worse, so > 60 was used; cognitive function, social satisfaction, sleep quality higher is better, so < 40 used for threshold)

CMT for Fact Cog PCI 20 was a raw score less than 60 [31]

CMT for FACT-G total 1 SD below the published normative sample mean of 80 [42]

CMT for SDI 16 greater than 10 per published threshold [38]

FACT-Cog functional assessment of cancer therapy—cognitive function, *FACT-G* functional assessment of cancer therapy—general, *CMT* clinically meaningful threshold, *PCI* perceived cognitive impairment, *PROMIS* Patient-Reported Outcomes Measurement Information System, *SD* standard deviation, *QOL* quality of life, *UCLA* University of California Los Angeles

[1] $n=49$, after outliers removed

[2] $n=50$ after outliers removed

Our findings suggest older age, recurrent MBC, triple-negative breast cancer, and not receiving certain MBC treatments (surgery or chemotherapy) may be risk factors for lower cognitive functioning. Older age is a risk factor for cognitive decline [51], thus standardized scores for tests administered in this study were adjusted for age. This finding may suggest that in this population, older age has an association with poorer cognition above and beyond that seen in normative samples and may be explained by accelerated aging observable in cancer survivors due to disease

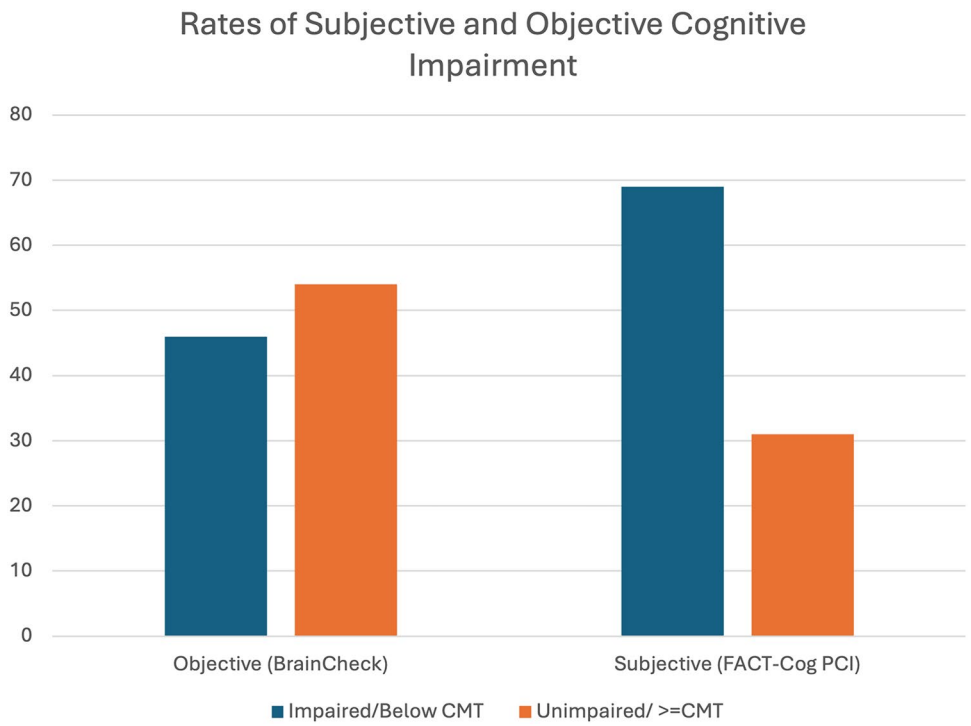

Fig. 1 Bar graph of those who had subjective or objective cognitive impairment. Objective impairment was determined by 1 standard deviation below the standardized mean on 1 or more tests and a clinically meaningful threshold (CMT) of < 60 used for subjective impairment

and treatments, also corresponding with CRCI [52]. Those with recurrent MBC had worse self-reported cognitive impairment, but not objective cognitive performance, than those with de novo MBC, which is consistent with broader MBC literature describing more aggressive tumor biology and worse outcomes in those with recurrent versus de novo MBC [53, 54]. A large prospective cohort study of people treated for MBC (n = 977) found those with recurrent MBC had a higher number of central nervous system metastasis than those with de novo MBC (13.5% versus 4.3%) [54]. Monitoring both subjective and objective cognitive symptoms is important in this group, given the higher risk for brain metastases.

Those with a history of triple-negative breast cancer had the greatest self-reported CRCI. Treatment protocols (first to third line) vary according to MBC subtypes (luminal/HR positive & HER2 negative vs. HER2 positive vs. or triple negative), thus cognitive consequences will likely differ across these variable treatment regimens[53]. Interestingly, the triple-negative group had the highest cognitive performance scores compared to HR + and HER2 + groups (though not statistically significant). Lack of correlation between self-reported CRCI and objective measures is common [55, 56]. Those in the triple-negative group likely had above average objective performance on their standardized cognitive tests, but still experienced functional cognitive deficits in their day-to-day life.

Our findings indicate lower cognitive functioning among those who did not undergo surgery or receive chemotherapy. These findings are contrary to what is known about surgical risk for cognitive function in general [57] and the effects of breast cancer chemotherapy on cognition [58, 59]. However, in the context of MBC, electing not to undergo treatment may reflect that this group had more aggressive disease [53] or treatment standards for subtypes of MBC. Almost 60% of this sample had de novo MBC, and systemic treatment (not surgery) is typically the first-line therapy for this type of MBC [21]. Regardless, the cognitive and psychosocial impact of specific MBC treatments needs to be prospectively evaluated in a larger cohort to untangle these complicated symptom trajectories.

We found patterns of medium to large correlations among self-reported cognitive impairments and worse psychosocial and behavioral symptoms or function and QOL, but no correlations among objective cognitive performance and patient-reported outcomes. These findings support the CRCI literature with consistent correlations among cognitive and other patient-reported outcomes [4, 60–63], and rarely finds objective cognitive correlates for QoL or everyday function [1, 55, 64]. Self-reported CRCI also correlated with worse financial toxicity in our study, providing new hypothesis generation insights for future studies focused on the impact of social constructs and environment on prevalence and persistence of CRCI.

Clinically concerning levels of anxiety, social dysfunction, fatigue, and low levels of QoL were identified in our study using clinically meaningful thresholds. Linear regression models revealed better self-reported cognitive function, and lower

Table 3 Themes from qualitative content analysis of open-ended questions

Theme	Description	Exemplar(s) quotes
Responses to, "If you are experiencing cognitive symptoms related to your breast cancer diagnosis and treatment, what strategies have you tried to cope with and/or manage these symptoms?" ($n=42$)		
Compensatory strategies	Strategies to compensate for cognitive deficits such as making lists, using smartphone alarms, calendar reminders, planners, writing things down, and putting things (e.g., keys, purse, car) in the same place, three participants mentioned trying prescription medications (e.g., Ritalin, antidepressants)	"[I] make lists, set audible reminders on my calendar on phone and computer, put a list by the door to remember keys, money, phone, grocery list, burners turn off, thermostat off"
Grace and acceptance	Several described being grateful for what they can still do; being patient with self; and resorting to prayer to cope with cognitive challenges	"I try to do heavy brain things in the morning when I first wake up because as day goes on, I have brain fatigue." "I always am grateful and choose to always focus on that"
Cognitive load reduction	Described taking one moment/day/week at a time; managing expectations	"I only focus on one week at a time. I do not plan ahead because then I get disappointed when I am unable to do them"
Cognitive enrichment	Cognitive enrichment activities described included brain games and crossword puzzles, physical activity (e.g., yoga, walks, cycling), use of alternative and integrative therapies (e.g., Reiki, acupuncture), and employing meditation/mindfulness	"Doing crossword puzzles and playing brain games with the Lumosity app." "Taking spinning and yoga classes at home, meditating every night, talking to a therapist"
Enlisting help from others	Telling others, primarily partners and family members, about their cognitive changes and need for help	"Sharing frustration, and being open about symptoms and frustrations with family and friends"
Responses to, "What kinds of information or support would you like to receive to help you manage any cognitive concerns?" ($n=35$)		
Unsure of needs or no needs	Nine participants responded that they don't know or are unsure of what information/support they need, and three indicated that they do not need any information right now	"I don't even know what I could use"
Information on how/ why cognitive changes occur	Described wanting more information on how medications impact cognitive function, more research on this issue, better explanation of how and why breast cancer affects cognitive function	"More research on quantitative findings and common experiences"
How to improve/ cope with cognitive changes	Information on supplements, strategies, techniques to prevent or mitigate cognitive decline	"I think information on how to cope with memory loss would be helpful. Perhaps a list of brain game apps would be helpful"
Engaging social support	Descriptions of how to explain cognitive changes to others and to receive empathy and understanding and patience from others	"Support in letting family members know that this is REAL and things THEY can do to help. Support in how to tell others in the world that I have to encounter—doctors, teachers, bankers, insurance, etc. that I'm not stupid or dumb."
Responses to, "Is there anything else you would like to share with us related to your cognitive concerns or cognitive changes?" (n=23)		
Challenges and concerns related to cognitive changes	Specific challenges that impact cognitive function include treatment for brain metastases, poor sleep, uncertainty about possibility of cancer spreading to the brain, coping with an 'invisible' disability, being physically capable but not cognitively able	"When I forget things, I don't think "Oh, I'm getting older." I think, "Is my cancer in my brain?" "Cognitive changes are unpredictable and dynamic. The unexpected aspects is what feels like I'm climbing up a hill."
Wishes and	Wishing things were easier, having affairs in order when still cognitive capable, that they were informed about cognitive changes, and that they can focus on their health	"I wish doctors would've discussed possible cognitive changes with me."

Table 3 (continued)

Theme	Description	Exemplar(s) quotes
Emotional challenges and struggles	Struggling and feeling frustrated, and tired of feeling tired and forgetful	"I pretty much having a crying episode by myself just about every day when I do something related to my cognitive decline"
Positive reflections/ gratitude	Grateful to participate in the study and for what they do have and are able to do	"I am glad you're doing this as it makes me feel heard. This has been the most difficult for me to deal with"

fatigue, depression, and stress explain a large proportion of the variance in higher overall QoL in women with MBC. Our findings suggest that fatigue may be the strongest contributor to QoL. However, it is worthwhile noting there is nesting between the measures of the domains assessed, where the FACT-G incorporates two fatigue items, and one item for depression and stress. Thus, associations between the predictor domain and QoL must be interpreted in this context. Regarding cognitive functioning, however, it is possible that the relationships among these predictors and their impact on QoL are more complex. For example, qualitative studies have reported that the primary source of meaning to individuals living with MBC were family, relationships, and social connection, all areas in which cognitive dysfunction can negatively interfere [16].

Our model of social functioning showed that worse self-reported cognitive function, higher fatigue, and greater financial toxicity explained over half the variance in worse social functioning, with cognitive function the largest predictor followed by financial toxicity. Financial toxicity and social functioning were expected to be significantly associated due to their conceptual and item level overlap, as three items within the social functioning measure (SDI-16) reference financial challenges. Our self-reported cognitive functioning finding supports those reported by Chapman and colleagues [65], where higher-quality work life (component of social functioning) was related to better subjective CRCI in women with MBC, adding that this relationship may be bidirectional with better subjective cognitive function more broadly correlated with social functioning (not just occupational functioning). The contribution of financial toxicity to social functioning is also consistent with Chapman and colleagues who reported that financial difficulty was associated with a poorer quality of working life, greater depression, and worse perceived cognitive function in women with MBC [65]. Taken together, these findings confirm knowledge about fatigue, distress, and QoL in persons with MBC and provide new insights on the severity of social dysfunction and correlated financial toxicity.

Cognitive changes and symptoms were prevalent and problematic, consistent with previous qualitative studies in MBC [16]. Participants described using cognitive compensatory strategies (e.g., list making, using reminders, reducing and managing daily cognitive loads), engaging in cognitively enriching activities, and wanting more information on why cognitive changes occur during MBC, similar to previous breast CRCI studies [9, 66, 67]. Participants also engage and enlist social support and spirituality to cope with CRCI and would like their family and partners to also receive information on CRCI to improve their outcomes. This extension beyond the individual to their social systems is illustrative of the widespread impact of MBC, consistent with previous studies [16, 68]. Half the participants offered to share more about their cognitive concerns when prompted, where cognitive changes were especially distressing as they may

Table 4 Demographic and clinical differences in objective (Braincheck) and subjective (FACT-Cog PCI 20) scores

Variables	Groups	Mean Braincheck combined score (SD)	*P* value for independent *t* test or ANOVA	Mean FACT-Cog PCI score (SD)	*P* value for independent *t* test or 3-way ANOVA
Age	–	–	–	–	–
	22–39	102.6 (11.28)	–	58.67 (16.98)	–
	40–60	109.15 (11.07)	–	45.88 (18.21)	–
	61–74	95.27 (13.78)	0.005	54.83 (17.93)	0.15
Race/ethnicity			–		–
	NH White	105.28 (13.07)	–	49.80 (18.20)	–
	Minority	106.00 (12.55)	0.90	47.0 (20.76)	0.71
Partner status	–	–	–	–	–
	Married/ significant other	106.67 (13.36)	–	51.88 (19.06)	–
	unpartnered	103 (12.27)	0.36	46.24 (15.75)	0.30
Dependents	–	–	–	–	–
	Has dependents	107.7 (11.58)	–	50.25 (19.75)	–
	No dependents	102.5 (14.05)	0.16	48.46 (16.99)	0.73
Employment˜	–	–	–	–	–
	Unemployed	105.87 (12.70)	–	47.36 (18.67)	–
	Employed	104.58 (12.70)	0.74	52.48 (18.67)	0.33
Household income	–	–	–	–	–
	< $100 K	105.08 (11.75)	–	45.26 (15.92)	–
	> $100 K	105.42 (17.70)	0.95	48.39 (18.95)	0.59
Years of education	–	–	–	–	–
	< = 16	104.63 (13.37)	–	48.34 (17.75)	–
	> 16	106.77 (12.17)	0.59	51.65 (17.75)	0.55
Years since diagnosis	–	–	–	–	–
	< 1.5 years		–	52.23 (18.91)	–
	1.5–5.5 years		–	46.64 (17.05)	–
	> 5.5 years		0.70	49.92 (20.27)	0.70
MBC diagnosis type	–	–	–	–	–
	De novo	105.64 (13.15)	–	54.63 (17.81)	–
	Recurrent	105.00 (12.81)	0.87	42.32 (17.01)	0.015
MBC pathological type	–	–	–	–	–
	HR + HER2-	104.33 (13.91)	–	47.18 (17.50)	–
	^HER2 +	105.08 (10.55)	–	59.40 (15.56)	–
	Triple Negative	111.60 (13.89)	0.52	34.00 (18.67)	0.016
Surgery	–	–	–	–	–
	Surgery for MBC	108.03 (11.24)	–	49.79 (18.91)	–
	No surgery for MBC	100.35 (14.55)	0.046	48.79 (17.88)	0.85
Radiation	–	–	–	–	–
	Radiation for MBC	103.89 (10.25)	–	49.61 (17.71)	
	No radiation for MBC	107.18 (15.58)	0.38	49.21 (19.49)	0.94
Chemotherapy	–	–	–	–	–
	Chemotherapy for MBC	105.33 (10.51)	–	53.90 (17.88)	–
	No chemotherapy for MBC	105.42 (16.20)	0.98	43.32 (17.62)	0.039
Hormones		–	–	–	–
	Any hormonal treatment for MBC	105.35 (12.76)	–	50.12 (17.94)	–
	No hormonal treatment for MBC	105.44 (14.21)	0.98	46.11 (21.12)	0.56
CDK4/6 inhibitors	–	–	–	–	–
	CDK4/6 Inhibitors for MBC	103.37 (13.78)	–	47.07 (17.06)	–
	No CDK4/6 Inhibitors for MBC	107.82 (11.50)	0.23	52.64 (17.06)	0.28

˜Unemployed includes those not working because of disability, fired, or retired

^HER2 positive includes hormone receptor negative and hormone receptor positive/HER2 positive ($n = 13$)

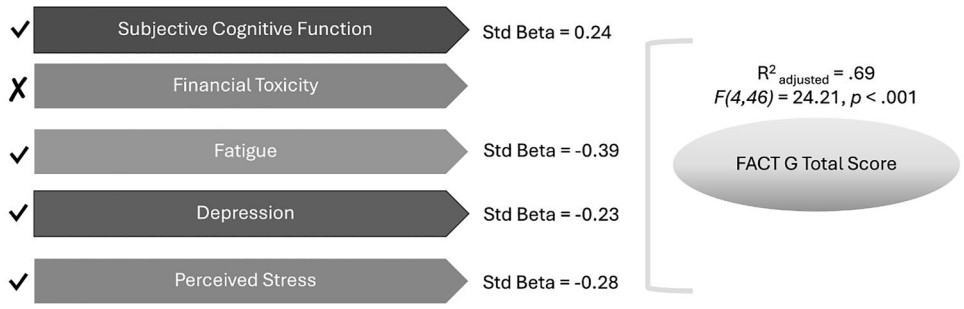

Fig. 2 Visualization of the linear regression model of quality of life. Financial toxicity (COST) was not included in the final model. Durban–Watson test was not significant. Tolerance values ranged from 0.51 to 0.78, and VIF values ranged from 1.41 to 1.97. The mean of the standardized residuals was − 0.004 (SD 1.01)

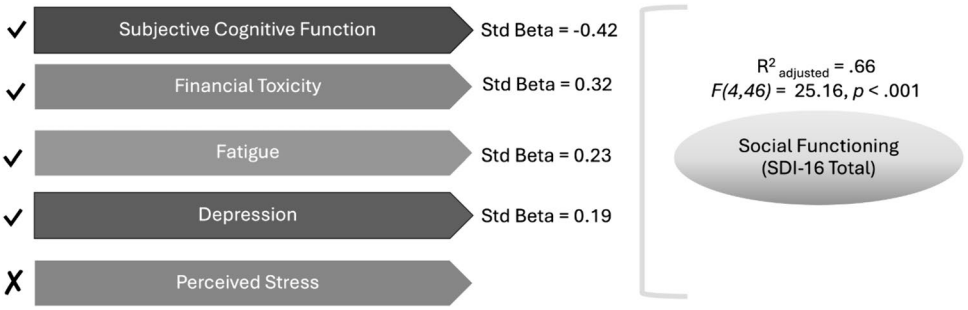

Fig. 3 Visualization of the linear regression model of social functioning. Perceived stress was not included in the final model. Durban Watson test was not significant. Tolerance values ranged from 0.73 to 0.87, and VIF values ranged from 1.15 to 1.37. The mean of the standardized residuals was 0.01 (SD 1.01)

represent metastasis to the brain; that information about the potential for cognitive changes at the onset of MBC diagnosis would facilitate decision-making; and that cognitive changes are most difficult change they are facing.

Limitations

Data are cross-sectional and do not account for time. Another potential limitation is a lack of control group to compare the cognitive findings of this group of women with MBC to; however, this was not the objective of the present study, which was to characterize CRCI in MBC. Future studies should assess CRCI in individuals living with MBC using a prospective design and including a control group, to maximize internal validity. Time since MBC diagnosis ranged from 4 months to 14 years, with half the sample less than 3.5 years since diagnosis. The average survival rate for MBC is approximately 36 months [69], thus it is possible our sample reflects a larger proportion of those experiencing above average survival rates and may not generalize to the larger MBC population. We did not measure number or location of metastases, also limiting the interpretability of the findings. Additionally, our inclusion criteria required a computer with internet access and ownership of a smartphone, so our findings may not generalize to women without this equipment or access, who may be representative of an under-resourced population.

Conclusion

Despite these limitations, this study provides valuable new insights on CRCI within the context of MBC, suggesting CRCI is a serious problem for over half of this population, with important research and clinical implications. CRCI research in larger cohorts of MBC patients starting from the initial diagnosis and through the different lines of treatment should include subjective and objective cognitive measures to better understand the cognitive risks associated with treatment across time. Healthcare providers should acknowledge cognitive symptoms and continually assess cognitive function across the MBC trajectory [70]. People with MBC would like information and support from healthcare providers and families to better cope with cognitive changes and are interested in incorporating evidence-based cognitive interventions into their daily lives.

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Author contributions AMH and KVD are responsible for the manuscript's conception and design. SB and AMH conducted the qualitative content analysis. AMH was the PI on this study and conducted the data analyses. AMH, KVD, RCM, DH, OFR, RT, TL, SB, MP, TLK, EWP, and NHH contributed to revisions of the manuscript. All authors approved the final version.

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Data availability De-identified data will be made available upon reasonable requests to the corresponding author and with data use agreements in place.

Code availability Open-source statistical software was used for these data analyses. Code will be made available upon reasonable requests to the corresponding author.

Declarations

Conflict of interest R.C.M. is a co-founder of KeyWise AI, Inc. and a co-founder of NeuroUX. The terms of this arrangement have been reviewed and approved by UC San Diego in accordance with its conflict-of-interest policies. A.M.H is a consultant for Prodeo, Inc. The terms of this arrangement have been reviewed and approved by University of Texas at Austin in accordance with its conflict-of-interest policies.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. The University of Texas at Austin Institutional Review Board reviewed and monitored all study related procedures (STUDY00002393).

Consent to participate Participants provided informed written consent.

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Authors and Affiliations

Ashley M. Henneghan[1,11] · Kathleen M. Van Dyk[2,3] · Darren Haywood[4,5,6,7] · Mansi Patel[8] · Oscar Y. Franco-Rocha[1] · Soyeong Bang[9] · Tamsin Longley[10] · Rebecca Tasker[1] · Tara Kaufmann[11] · Emily W. Paolillo[12] · Raeanne C. Moore[13] · Nicolas H. Hart[4,14,15,16,17]

✉ Ashley M. Henneghan
ahenneghan@nursing.utexas.edu

[1] School of Nursing, University of Texas at Austin, Austin, TX, USA

[2] Semel Institute of Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

[3] Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA, USA

[4] Faculty of Health, Human Performance Research Centre, INSIGHT Research Institute, , University of Technology Sydney (UTS), Sydney, NSW, Australia

[5] Department of Mental Health, St. Vincent's Hospital Melbourne, Fitzroy, VIC, Australia

[6] Department of Psychiatry, Melbourne Medical School, Dentistry and Health Sciences, University of Melbourne, Parkville, VIC, Australia

[7] Faculty of Health Sciences, School of Population Health, Curtin University, Bentley, WA, Australia

[8] Department of Neuroscience, College of Natural Sciences, University of Texas at Austin, Austin, TX, USA

[9] School of Nursing, Columbia University, New York, NY, USA

[10] The Royal Marsden Hospital, London, UK

[11] Dell Medical School, University of Texas at Austin, Austin, TX, USA

[12] Department of Neurology, Memory and Aging Center, University of California, San Francisco, San Francisco, CA, USA

[13] UC San Diego Health Sciences, University of California San Diego, San Diego, CA, USA

[14] School of Medical and Health Sciences, Exercise Medicine Research Institute, Edith Cowan University, Perth, WA, Australia

[15] Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Adelaide, SA, Australia

[16] Faculty of Health, Cancer and Palliative Care Outcomes Centre, School of Nursing, Queensland University of Technology (QUT), Brisbane, QLD, Australia

[17] Institute for Health Research, University of Notre Dame Australia, Perth, WA, Australia