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What Do Perceived Cognitive Problems Reflect?

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Abstract

Women with breast cancer frequently report cognitive problems to healthcare providers during and after adjuvant therapy. Patients' perceptions of their cognitive problems would be expected to relate to objectively measured cognitive impairments. We explored the relationship between perceived cognitive function and objective ratings of thinking ability in early-stage breast cancer patients receiving hormonal therapy. In particular, we targeted objective measures of learning and memory as the primary endpoints in this exploratory study. We included a comprehensive battery of objective measures of cognitive function to explore relationships between perceived cognitive problems and impairments in other domains of cognitive function. At a minimum, our results indicated that women's complaints of cognitive problems should prompt additional assessment to clarify the bases of the problem and initiate appropriate intervention.

Frequent reports of attention and memory problems during and after adjuvant breast cancer therapy have led to multiple studies that documented cognitive impairments related to systemic therapy for the disease.[1–8] Approximately 17%–50% of women with breast cancer who receive adjuvant chemotherapy experience cognitive impairment, particularly in the domains of memory, attention, concentration, executive function, and psychomotor efficiency.[8–10] Further, in two studies,[5,11] women treated with chemotherapy and the hormonal agent tamoxifen had more cognitive compromise than did those given only chemotherapy or no systemic therapy. Women with breast cancer who are prescribed hormonal agents generally continue therapy for 5 years with or without adjuvant chemotherapy after their primary surgery.

Batteries to measure cognitive function generally consist of several objective measures to evaluate the multiple domains of thinking ability. However, the ecologic validity of objective methods has been questioned; currently, there is a lack of consensus about what constitutes a clinically meaningful cognitive impairment.[12] Thus, some investigators include subjective measures of cognitive function that elicit patients' perceptions of their intellectual capacity and that also may assess the functional impact of cognitive impairments in their measurement batteries.

Intuitively, patients' perceptions of their cognitive problems would be expected to relate to objectively measured intellectual impairment. In fact, some clinicians may assume that patient complaints of cognitive decline reflect real impairment. However, some investigators found little to no correlation between subjective cognitive complaints and scores on objective measures of intellect.[13–16] Cognitive complaints apparently are related to depression and

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anxiety rather than to impairments in thinking function in cancer patients.[2,3,15–19] However, not all patients who complain of cognitive decline are depressed or anxious. Findings from these studies may result partially from approaches used to assess subjective cognitive function.

Other investigators found relationships between scores on subjective and objective measures of cognitive function. Poppelreuter et al[16] found significant relationships between self-reports of cognitive problems and scores on objective measures of learning and memory ($P < 0.05$) and mental flexibility ($P < 0.01$) in 119 patients receiving cancer rehabilitation. However, when they controlled for affective variables, they found that the previous correlations were no longer significant. In a similar study of 53 women given long-term breast cancer therapy, Castellon et al[11] found a significant relationship between subjective scores and objective measures of visuospatial ability ($P < 0.05$).

Relationships between complaints of cognitive problems and objective cognitive function scores also have been documented in other populations. Capuron et al[20] reported significant relationships between subjective mental fatigue and the domains of spatial working memory ($P < 0.05$) and sustained attention ($P < 0.05$) in individuals with chronic fatigue syndrome. However, they found no association linking cognitive impairment to mood.

Matotek and colleagues[21] also reported relationships between subjective complaints and working memory ($P < 0.01$) and verbal dysfluencies ($P < 0.05$) in patients with mild multiple sclerosis. Interestingly, patients' subjective cognitive complaints correlated with depression in healthy controls but not in patients afflicted with this disease.

The significance of patients' complaints of cognitive problems must be delineated to work toward a meaningful, practical assessment of cognitive function in clinical settings and to provide a basis for interventions to ameliorate, or compensate for, intellectual impairments. We sought to gain understanding of how perceived cognitive function relates to its objective measurement in early-stage breast cancer patients receiving hormonal therapy. Mainly, we targeted objective measures of learning and memory as the primary endpoints in this exploratory study. However, we included a comprehensive battery of objective measures of cognitive function to explore relationships between perceived intellectual problems and impairments in other domains of thinking ability.

Methods

This preliminary study used a cross-sectional design with subjective and objective measurement of cognitive function starting at least 3 months of adjuvant hormonal therapy (20 mg/d of tamoxifen or 1 mg/d of anastrozole [Arimidex]) in early-stage breast cancer patients. The women were able to speak and read English, had completed at least 8 years of education, and had no prior diagnosis of cancer or neurologic illness and no history of hospitalization for psychiatric illness within the previous 2 years. This study was approved by the University of Pittsburgh Institutional Review Board.

Perceived cognitive function was evaluated with the Patient's Assessment of Own Functioning (PAOF),22 a multidimensional measure that assesses perceptions of memory, executive function, language/communication, orientation, use of hands, and sensorimotor ability. Higher PAOF scores indicate poorer perceived cognitive function. We evaluated cognitive function using a battery of objective measures—attention with the Digit Vigilance Test,23 the Trail Making Test (TMT)-A,24 and the Digit Span Forward and Backward Test25; learning and memory with the Rey Auditory Verbal Learning Test,26 the Rey Osterrieth Complex Figure Recall,27 the Rivermead Behavioral Memory Test Story Recall,[28] and the Four-Word Short-Term Memory Test[29]; psychomotor speed with the Grooved Pegboard Test[23] and the Digit Symbol Substitution Test[25]; mental flexibility with the TMT-B24; visuospatial ability with the

Rey Osterrieth Complex Figure Copy27; and estimated general intelligence with the National Adult Reading Test–Revised.28 These measures previously were described in detail.29 We also measured potential covariates of cognitive functioning in these women, including their ages, years of education, amount of time on hormonal therapy, and degree of depression (Beck Depression Inventory–II),[30] anxiety (Profile of Mood States [POMS]–Tension/Anxiety subscale), and fatigue (POMS–Fatigue/Inertia subscale).31

STATISTICAL ANALYSIS

Data were analyzed using SPSS® version 12.0 (SPSS Inc, Chicago, Ill). We used descriptive statistics to explain the sample characteristics and potential covariates of cognitive function. To explore relationships between scores on the PAOF and the objective measures of cognitive functioning, we conducted partial correlations, controlling for the selected covariates of age, education, time on therapy, depression, anxiety, fatigue, and type of hormonal therapy. We later conducted hierarchical linear regression analyses on scores of those objective measures of cognitive function, in which we noted significant relationships with the PAOF scores via the partial correlations and controlled for the selected covariates. An incremental R^2 statistic was computed as an effect size measure. The incremental R^2 was based on the change in R^2 with the addition of the PAOF score of interest where the selected covariates were controlled.

Results

Table 1 summarizes the descriptive characteristics of the sample (n = 31). Most women had stage I/II breast cancer, and 58% received adjuvant chemotherapy before beginning their hormonal therapy. Women received hormonal therapy an average of 19.19 months at the time of the cognitive function assessment; they were not depressed, anxious, or fatigued.

Controlling for age, education, depression, anxiety, fatigue, and time on hormonal therapy, partial correlations were computed between all PAOF subscale and total scores and the scores on all our measures of objective cognitive function. The most frequent significant correlations were found between the PAOF scores and the findings on the objective measures of verbal memory. Significant correlations were found between PAOF subscale and total scores and the Four-Word Short-Term Memory Test in the 5-, 15-, and 30-second condition[32] (P = 0.00–0.05) and the Story Recall from the Rivermead Behavioral Memory Test[33] (P = 0.04–0.05), suggesting that perceived poorer cognitive function was related to poorer verbal learning and memory. Scores on the PAOF Language/Communication subscale also were significantly marginally related to poorer mental flexibility as measured using the TMT-B.[24]

Counterintuitively, the remaining findings suggested relationships opposite to those anticipated. There were significant and marginally significant correlations between PAOF scores and the measure of visual memory Rey Complex Figure Test[27] in the immediate- (P = 0.03–0.05) and delayed-recall conditions (P = 0.05–0.08), suggesting that perceived poorer cognitive function may be associated with better visual learning and memory. Similarly, PAOF scores correlated significantly with attention measures, including the Digit Symbol Substitution (P = 0.04)[34] and the TMT-A (P = 0.02),[24] and with the measure of mental flexibility TMT-B[24] (P = *0.0*6), suggesting that perceived poorer cognitive function may be related to better attention and mental flexibility.

To further explore the relationships between scores on the PAOF and the objective cognitive-function measures, we conducted hierarchical linear regressions on all the significant and marginally significant relationships found via the partial correlations (Table 2). We controlled for age, education, depression, anxiety, fatigue, and time and type of hormonal therapy and found similar results with respect to verbal learning and memory. Higher PAOF subscale and total scores were significant and marginally significant predictors of performance on the Four-

Word Short-Term Memory Test in the 5-second (P = 0.02–0.07), 15-second (P = 0.00–0.04), and 30-second (P = 0.07–0.10) conditions, suggesting that perceived poorer cognitive function may predict poorer verbal learning and memory. Similarly, perceived poorer language/ communication was a marginally significant predictor of poorer mental flexibility (P = *0.07*).

However, contrary to the anticipated direction, perceived poor use of the hands predicted better performance on the immediate (P = 0.05) and delayed (P = 0.06) Rivermead Behavioral Memory Test story recall scores. Similarly, perceived poorer overall cognitive function predicted better attention (P = 0.01 and 0.02) and mental flexibility (P = 0.03).

Discussion

These findings showed that after controlling for anxiety, depression, and fatigue, perceived poor cognitive function predicted objectively measured poorer verbal learning and memory—the primary endpoint of this exploratory investigation. In contrast to the expected pattern of results, patients' self-reported complaints of cognitive impairment were related to better performance on measures of attention, mental flexibility, and visual memory.

The findings of this preliminary study are similar to those of Poppelreuter et al,16 who found significant relationships between scores on a measure of perceived cognitive function and those on measures of verbal memory (Logical Memory I and Digit Span Forward and Backward of the Wechsler Memory Scale)[25] and mental flexibility (TMT-B). However, these relationships were no longer significant when the investigators controlled for mood. Castellon et al11 found a significant relationship between scores on the Cognitive Failures Questionnaire35 and objective measures of visuospatial ability. No other significant relationships were found between subjective and any other objective measures in their battery.

Other investigators found no significant relationships between scores on subjective and objective measures of cognitive function.[2–4,13,18,19,36] For the most part, these investigators found that scores on subjective measures were significantly related to mood (anxiety or depression).[2,4,13,18,19,36,37]

Methodological differences between this study and those of previous investigators could account for these contradictory results. Other investigators evaluated subjective cognitive function with brief measures; some comprised only one or two items.[2,13,15,17,37] We used a more comprehensive, multidimensional assessment that may have been more sensitive to perceptions, particularly in specific cognitive domains. Poppelreuter et al[16] also used a more comprehensive measure of perceived cognitive function; they reported results similar to those we observed.

We also used a comprehensive battery of objective mea sures to assess cognitive function. Other investigators used screening measures[17] or a brief, mailed battery[36] or calculated an overall cognitive score.[2,37] These methods for evaluation and scoring of objective cognitive function may have lacked sensitivity, which may have had implications for the observed relationships with scores on subjective measures.

There are differences in the samples used in this study and other investigations of relationships between scores on subjective and objective measures of cognitive function. Our sample consisted of women with early-stage breast cancer who currently were receiving therapy. Other investigations included samples of individuals who had late-stage disease[14] or who were long-term (minimum, 5 years) cancer survivors.[4] The differences in these samples with respect to the extent of disease present and the duration of time since diagnosis and treatment may account partially for the differences in our results.

LIMITATIONS

There were limitations to this exploratory study. This project had a cross-sectional design involving measurement of women currently receiving hormonal therapy. The sample size was small; we conducted multiple statistical analyses on these data and found significant relationships with this small sample. We calculated incremental R^2 statistics as a measure of effect sizes. The incremental R^2 statistics were based on the changes in R^2 with the addition of the PAOF scores of interest where the selected covariates were controlled (Table 3). Moderate detectable effect sizes ranging from R^2 (incremental) = 0.129–0.177 were estimated for each of the relationships. These findings suggested that we would have sufficient power to detect clinically meaningful relationships.

The question of the clinical utility of cognitive complaints remains. Our findings suggested that such complaints may be related to poorer verbal learning and memory. In fact, memory complaints have been predictive for dementia[38] and have been related to the future development of cognitive decline in other populations, particularly the elderly.[39,40]

Clearly, a large-scale study of the relationships between perceived and objectively measured cognitive function is warranted in this population. Clarification of the utility of subjective measures of cognitive problems may lead healthcare providers to more appropriately target care for women who experience these problems.

Women with breast cancer frequently report cognitive problems to healthcare providers during and after adjuvant therapy. These reports should not be dismissed, and healthcare providers should not assume that such complaints indicate depression. At a minimum, our results indicate that women's complaints of cognitive problems should prompt additional assessment to clarify the bases of the problem and to initiate appropriate intervention.

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Table 1

Characteristics of Women Receiving Hormonal Therapy (n = 31)

CHARACTERISTIC	**MEAN (SD)**
Age, years	52.68 (6.69)
Education, years	15.68 (2.36)
Time on hormone therapy, months	19.19 (13.71)
BDI-II	6.54 (4.20)
POMS Tension/Anxiety	4.10 (5.70)
POMS Fatigue/Inertia	6.97 (5.05)

CHARACTERISTIC		n (%)
Marital status	Married	26 (84)
	Not married	5 (16)
Number of children	None	6 (19)
	1–2	21 (68)
	≥ 3	4 (13)
Stage	DCIS	3 (10)
	Stage I	13 (42)
	Stage IIa or IIb	15 (48)
Chemotherapy	Yes	18 (58)
	No	13 (42)

Abbreviations: BDI-II = Beck Depression Inventory-II; POMS Tension/Anxiety = Profile of Mood States–Tension/Anxiety Subscale; POMS Fatigue/Inertia = Profile of Mood States–Fatigue/Inertia Subscale Score; DCIS = ductal carcinoma in situ

Table 2

Hierarchical Linear Regression Results*

PREDICTOR VARIABLE: PAOF	DEPENDENT VARIABLE	ADJUSTED REGRESSION COEFFICIENT (*P* VALUE)	EXPLAINED VARIANCE INCREMENTAL $R^{2\dagger}$
Executive function	Rivermead Story, Immediate Recall	−0.29 (0.05)	9%
	Rivermead Story, Delayed Recall	−0.28 (0.07)	12%
	Four-Word Short-Term Memory, 5 s	−0.03 (0.07)	10%
Hand complaints	Digit Symbol Substitution	3.59 (0.02)	13%
	Trail Making Test-A	−6.87 (0.01)	19%
	Trail Making Test-B	−6.22 (0.03)	13%
	Four-Word Short-Term Memory, 15 s	−1.37 (0.00)	23%
	Four-Word Short-Term Memory, 30 s	−0.89 (0.06)	13%
Memory	Four-Word Short-Term Memory, 5 s	−0.93 (0.02)	10%
Language	Trail Making Test-B	2.25 (0.07)	10%
	Four-Word Short-Term Memory, 5 s	−0.24 (0.07)	10%
Total	Rey Complex Figure Test, Immediate Recall	0.24 (0.04)	10%
	Rey Complex Figure Test, Delayed Recall	0.21 (0.06)	9%
	Four-Word Short-Term Memory, 15 s	−0.15 (0.04)	15%
	Four-Word Short-Term Memory, 30 s	−0.11 (0.10)	9%

*Hierarchical linear regression results limited to those PAOF and/or objective cognitive function measure scores demonstrating significant or marginally significant relationships. Reported statistics are adjusted regression coefficients (*P* values) and additional percent explained variance after controlling for covariates (age, education, time on therapy, depression, anxiety, and fatigue).

†Incremental R^2, where age, education, time on therapy, depression, anxiety, fatigue, and type of hormonal therapy were entered in the first block and the PAOF variable of interest was entered in the second block.

Abbreviation: PAOF = Patient's Assessment of Own Functioning

Table 3

Observed R^2 Values for Selected Covariates and Incremental R^2 Values for the Cognitive Function Measures With Significant Relationships

PAOF	COGNITIVE FUNCTION MEASURE	R^2 COVARIATES ONLY*	INCREMENTAL R^2†
Memory	Four-Word Short-Term Memory, 5 s	0.283	0.156
	Rey Complex Figure, Immediate Recall	0.257	0.160
Use of hands	Digit Symbol Substitution	0.405	0.128
	Trail-Making Test-A time	0.291	0.154
	Trail Making Test-B time	0.260	0.160
	Four-Word Short-Term Memory, 5 s	0.283	0.156
	Four-Word Short-Term Memory, 15 s	0.194	0.175
	Four-Word Short-Term Memory, 30 s	0.181	0.177
Executive function	Four-Word Short-Term Memory, 15 s	0.194	0.175
	Rivermead Story, Immediate Recall	0.235	0.164
	Rivermead Story, Delayed Recall	0.200	0.173
Language	Trail Making Test-B time	0.260	0.160
Total score	Four-Word Short-Term Memory, 15 s	0.194	0.175
	Four-Word Short-Term Memory, 30 s	0.181	0.177
	Rey Complex Figure, Immediate Recall	0.257	0.160
	Rey Complex Figure, Delayed Recall	0.273	0.158

Abbreviations: R^2 = incremental effect size; PAOF = Patient's Assessment of Own Functioning

*Covariates only: age, education, time on hormonal therapy, fatigue, anxiety, depression, and type of hormonal therapy

†Incremental effect size (R^2) for the particular cognitive function measure with a sample size of 31 at a significance level of 0.05, based on the changes in R^2 with the addition of the PAOF score of interest where the covariates were controlled