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Cognition in breast cancer survivors: hormones versus depression

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Abstract

***Background*: *Objective*: Breast cancer survivors receiving hormone treatment and/or endorsing histories of receiving chemotherapy report changes in their cognitive capacity, which is often not supported by formal testing. To address these conflicting reports, this study examined survivors' applied cognitive capacity and its association with hormone treatment, depression, and selected demographics.**

***Methods*: A descriptive, correlational, cross-sectional survey design was employed. There were 357 women who completed a survey comprised of 69 questions. The survey included both investigator-developed questions and instruments from the PROMIS® system.**

***Results*: There were significant main effects for hormone therapy, race, and depression. Depression explained the largest portion of variance of the perceived decreases in cognitive function among breast cancer survivors.**

***Conclusions*: Survivor complaints of changes in cognitive function may be a predictor for evaluating the presence of mood disorders and less a function of hormone therapy or chemotherapy history.**

Introduction

Many breast cancer (BC) survivors report changes in memory and overall cognition during or after chemotherapy or hormone therapies [1,2]. Patients and health care providers refer to these changes as 'Chemo brain', associating the pathology with side effects of treatment. Chemo brain, chemotherapy-induced cognitive impairment, includes 'impairment of a patient's memory, learning, concentration, reasoning, executive function, attention, and visuospatial skills during and after discontinuation of chemotherapy. In most cases it has a subtle manifestation and induces short-term transient sequela' page 127 [3]. These symptoms have significant implications for the daily functions associated with many women's lives, including difficulty driving, paying bills, and reading dense or 'technical' material [4]. Studies exploring these symptoms have conceptualized them as alterations in applied cognitive ability and concerns seen in patient persons with chronic illnesses including cancer [5]. Although Chemo brain is frequently associated with treatment, the cause of this perceived decrease in cognitive function is unclear: some potential factors are systemic (chemotherapy) or adjuvant hormone therapies (aromatase inhibitors or tamoxifen), and others are associated with cancer diagnosis. For example, psychiatric comorbidities commonly accompany BC diagnosis and include acute stress disorder, depression, and anxiety disorders—all of which also present with complaints of changes in cognitive function [6]. There have been numerous empirical evaluations of the relationship between hormone/aromatase inhibitors, history of chemotherapy treatment, and measured cognitive ability that have failed to support or are ambiguous for loss of memory [7–10]. Upon reviewing the relevant literature in this field, the only unanimous conclusion is that further research is needed to assess the topical area. It is important to note that research studies have commonly reported patients' perceived experiences of cognitive decline but frequently suggest that there is no difference in actual, measurable cognitive function [7,11]. This has led many researchers to approach the question of cognitive function in cancer patients by addressing real cognitive loss versus perceived cognitive loss [7–10]. We strive to emphasize, however, that a perceived loss of cognitive function is equally detrimental to the patient's wellness and should be considered as such when assessing survivorship needs. Regardless of whether the patient experiences cognitive decline that is poorly measured by neuropsychological testing or the decline is psychogenic in origin, the distress experienced by the patient experience is real. The perception of having lost cognitive function impacts quality of life in a negative manner [12]. Thus, this study looked at the relationship of the perception of cognitive performance and a variety of indicators from the extant literature.

Studies that examined cognitive changes in affected populations demonstrate conflicting outcomes, with some

reporting early changes during chemotherapy and hormone treatment that resolve, others reporting persistent changes, and still others finding no significant change [13–17]. Minisini *et al*. (2008) found trending differences in several cognitive abilities but also noted great loss in those with prior cognitive changes and depression [18]. In 2011, Phillips *et al*. concluded that the assertion that the etiology of cognitive changes is a function of lower circulating estrogen induced by hormone treatment is not supported by current evidence [1,19]. They cautioned that many study designs that have addressed this question were deficient, making a definitive conclusion difficult [1]. Although the prevalence of research studies addressing cognitive capacity in cancer patients seems to suggest an unspoken importance, it is clear that this particular area of study is complex and has remained under investigated.

This study is guided by the self-theory of memory as a conceptual framework [20] and by Lachman and Agrigoroaei's report on self-beliefs of control [21]. The self-theory of memory explains one's perception of his or her own cognitive ability as based on isolated personal experiences and events. Additionally, individuals use the opinions of others and what they have been told about themselves as a foundation for building a perception of their own cognitive abilities. This perception is malleable and changes with situational or circumstantial observations [6]. An individual's beliefs about how much control one has over his or her own circumstances are a large factor in his or her abilities pertaining to concentration and memory [21]. Although scientific tools are in place to accurately assess the cognitive performance of individuals under investigation, it is pragmatic to suggest that perceived cognitive function is equally legitimate as a factor to be considered when assessing the overall mental status of an individual [22].

Applying these frameworks to cancer, 'Low perceived control' is associated with a BC diagnosis, with patients reporting that they felt they had minimal control from the moment of diagnosis through treatment and subsequent long-term effects and experiences into the survivorship trajectory. The resulting depressed mood and anxiety are more influential on the survivor's physical health than on his or her cognitive function [21]. A survivor's perceived uncontrollability over challenge follows other models of depressed mood such as learned helplessness [21].

Many cancer patients have reported suffering from depressed mood on the basis of multiple sources of stress, including constant threats to life, treatment, fatigue, and loss of sleep [9]. The proportion of BC survivors who are depressed is reported to vary with the time since initial cancer diagnosis. The highest prevalence of depression (36.6%) is reported as occurring during early treatment and subsequently declining after the first year to 0.6% at 13 years [23]. Interestingly, individuals suffering from major depression without cancer similarly have complained of cognitive deficits [24]. A cancer diagnosis can be the nidus for the onset of depression or an event triggering a recurrence [25]. BC is the most common cancer of women [26]; yet, among BC survivors, the prevalence rate of depression has been shown as similar to women in general with the exception of those who experience a recurrence of cancer [27]. This paradox may be the result of censoring on the basis of mortality within survivors. There is a general consensus in the psychology literature that depression negatively affects the perception of cognitive performance [28]. In Massie's 2004 review of depression in oncology patients referred for psychiatric consultation, a prevalence of major depression in 9% to 58% of patients was reported [9]. In 1997, Pasacreta found that 18% of a sample of 79 women with BC 3–7 months after diagnosis had a past or current history of depression [29].

Several critical complexities have been found to contribute to the problem of assessing cognitive function, including a woman's age and health status, supporting alternate etiologies for the perception changes in cognitive capacity. For example, young women with an early stage BC diagnosis who experienced depression and reduced perception of cognitive ability could be a result of the mental and/or emotional effects of diagnosis at an early age. However, in older or postmenopausal women, a decrease in cognitive function could have been an effect of menopause and/or natural aging processes [24].

Several qualitative reports suggest differences in the survivorship experiences of African American (AA) women [30]. Although AA women have lower rates for BC and come to care later resulting in higher death rates, few studies have evaluated the changes in their cognition [4,31]. Research on race differences is limited. AA women are less likely to report cognitive changes to their health care provider and more likely to cope with using humor or spirituality [32,33]. Many of the quantitative studies have acquired small numbers of AA subjects, which have not provided estimates of racial differences [31]. The most extensive examination of race difference was completed using data from the Women's Health Initiative observational study with 5021 cancer survivors, which included 465 AA women. AA survivors had a lower quality of life, poorer general health, and greater role limitations because of emotional health compared with Caucasian survivors, and no significant differences in depression were found [32].

The perceived decrease in cognitive function among BC survivors is a widely undisputed point [34]. Whereas many studies support tamoxifen and aromatase inhibitors specifically as an important contributing factor in the deterioration of perceived cognitive capacity, many pertinent studies do not support this concept. In all studies, regardless of causality, the literature has confirmed that depression is a prominent component of cancer survivorship and that depression causes limitations in cognitive

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functions, whether real or perceived. There is a dearth of literature that explores the association between perceived cognitive deficits, hormone treatments, race, a history of exposure to chemotherapy, and depression.

Hypothesis

Applied cognitive capacity in BC survivors is associated with a survivor's current hormone treatment, history of treatment with chemotherapy for BC, level of depression, and race.

Methods

To address the primary aim of characterizing perceptions of cognitive changes in BC survivors, a descriptive, correlational, cross-sectional survey design was employed. BC survivors (357 women) were recruited from three sources: offices of the members of the Susan G. Komen (SGK) Medical Advisory Board, which included academic and community breast surgery clinics; emails inviting survivors on the SGK mailing lists; and women who attended SGK Spring 2012 events. Subjects who participated at the clinics or SGK events completed a pencil and paper version of the survey. Subjects invited by email completed the survey online using REDCap™ (a secure web application). This study involved an assessment of perceived cognitive function, as well as other cognitive factors including anxiety, depression, mood, and sleep patterns. Overall quality of life and satisfaction in various other domains were assessed as well.

Instruments and measures

The SGK BC Survivorship Needs Assessment Survey consisted of 69 questions and was developed in collaboration with the SGK Philadelphia-affiliated Medical Advisory Board. The Board was a panel comprised of physicians with expertise in breast health who represented nearly all of the major health systems with BC treatment programs in a 15-county region. The survey included questions from the Patient Reported Outcomes Measurement Information System (PROMIS®) Profile 29 [35], applied cognition instrument [36], additional demographics, current and previous treatments received, selected late effects of cancer treatment, and psychosocial needs. PROMIS is a system that provides 'highly reliable precise measures of patient-reported health status for physical, mental, and social well-being' for use as an endpoint of clinical studies 'across a wide variety of chronic diseases and conditions and in the general population' [37]. It provides comparability, reliability and validity, flexibility, and inclusiveness. The PROMIS raw score for depression and cognitive function are normed against a national sample and are converted to *t*-scores with a mean of 50 and standard deviation of 10. The PROMIS instruments are available in several lengths, and within this study, the short forms were used consisting of four questions. The short form has reported 0.90 reliability compared with 0.98 for the long form [36].

Applied cognitive functioning

As described by PROMIS developers, 'the applied cognition—abilities is generic rather than disease specific. The item bank uses the time frame "In the past 7 days" when assessing applied cognition—abilities…The PROMIS Applied Cognition—Abilities instruments assessed patient-perceived functional abilities with regard to cognitive tasks including the perception that one's cognitive abilities with regard to the domain of inquiry (e.g., concentration, memory) has not changed' [18]. The PROMIS applied cognition measure was found to be highly correlated with the FACT-cognition and EORTC cognition items [5].

Depression

The PROMIS depression item bank assesses negative mood (e.g., sadness, guilt), negative views of the self (e.g., self-criticism, worthlessness), negative social cognition (e.g., loneliness, interpersonal alienation), and decreased positive affect and engagement (e.g., loss of interest, loss of meaning and purpose). Depression is reflected in high levels of negative affect and low levels of positive affect and is often characterized by the experience of loss and feelings of hopelessness, helplessness, and worthlessness. Somatic symptom items (e.g., changes in appetite, sleep, psychomotor functioning) were excluded from the PROMIS depression item bank on the basis of psychometric properties and poor fit of these items to the other items in the bank. Therefore, the PROMIS depression item bank does not reflect the full range of symptoms commonly considered in a diagnosis of major depressive disorder, but the exclusion of somatic items from this bank eliminates the confounding effects of these items when assessing depression in patients with comorbid physical conditions [38].

Current hormone treatment

Current hormone treatment was determined by a subject selecting the hormonal therapy used. This list of hormone therapies commonly used to treat BC included, for example, tamoxifen, aromatase inhibitor, and ovarian suppression. The sample included 357 BC survivors with a mean age of 56.92 and standard deviation (SD) = 10.83 and had a mean time in survivorship of 7.44 years (SD) = 6.19 years. There were 212 (55.1%) Caucasians and 173 (44.9%) AAs. The BC stage at diagnosis included 78 (20.3%) *in situ*, 125 (32.5%) Stage 1, 100 (26%) Stage 2, and 49 (12.7%) Stage 3 and Stage 4 combined. Survivors were a mean of 7.56 years, and SD = 6.22 from their initial diagnosis of BC. Approximately 29% ($n = 113$) of the survivors were currently prescribed hormone treatment

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(e.g., tamoxifen, aromatase inhibitor, ovarian suppression), and 61.62% ($n = 220$) reported prior histories of receiving chemotherapy.

Analysis

To address the hypothesis of this study, data were first evaluated using descriptive and graphical statistical methods. A model was constructed using the applied cognition ability percentile score from the Profile 29 as the dependent variable and the depression percentile score from the Profile 29, the presence or absence of current hormone treatment, a prior history of receiving chemotherapy, and race and age as an independent factor and covariate, respectively. The model was evaluated using multiple regression with an alpha of 0.05.

Results

A standard multiple regression was performed between applied cognitive *t*-scores as the dependent variable and age, race, current treatment with hormones, history of chemotherapy, and depression as independent variables. The mean values for depression and cognition by race and treatment groups can be seen in Table 1. The number of cases without missing data was $N = 357$. Table 2 displays the correlation between the variables, the unstandardized regression coefficients (β), and intercept, the standardized regression coefficients (β), the semi partial correlations (sr_i^2) and R^2 and adjusted R^2. R for regression was significantly different from zero, $F = 17.08$, d.f. = 5, $p < 0.001$. The 95 % confidence limits were calculated for the three regression coefficients that significantly differed from zero. The confidence limits for depression were −0.478 to −0.275; for race −3.791 to −0.429; and currently using hormone treatment −3.95 to 0.237. Three of the independent variables significantly predicted applied cognitive ability depression ($sr_i^2 = 0.114$), race ($sr_i^2 = 0.014$) and current hormone treatment ($sr_i^2 = 0.011$). These three independent variables contributed another 0.57 in variability. Altogether, 19.6% (18.4% adjusted) of the variability in applied cognitive ability was predicted by depression, race, and current hormone treatment.

Although the correlation applied cognition between age and was 0.20 did not contribute to the regression. Post hoc evaluation of the correlated revealed that it was significantly different from zero, $F(1, 375) = 17.39$, $p < 0.001$. Apparently, the relationship between applied cognition and age was mediated by the relationship between depression, race, current hormone treatment, and prior chemotherapy treatment.

Discussion

The results suggest a potential explanation for the conflicting views of the relationship between hormone treatment and cognitive ability. A number of studies that tested survivors' cognitive capacity did not support the conjecture that their capacity is impacted by hormone treatment. [8,29,32] Yet many survivors reported a feeling that their

Table 1. Mean *t*-scores by group for depression and cognition

		Race			Current hormone treatment				History of chemotherapy treatment			
		N	Mean	SD	Status	*N*	Mean	SD	Status	*N*	Mean	SD
Cognitive	Caucasian	204	52.99	8.49	No	251	52.97	8.85	No	137	53.69	8.07
	African American	153	50.97	8.91	Yes	106	50.12	8.07	Yes	220	51.15	8.97
Depression	Caucasian	204	49.75	7.93	No	251	49.58	7.82	No	137	47.86	7.36
	African American	153	50.47	7.92	Yes	106	51.17	8.11	Yes	220	50.65	8.22
Age	Caucasian	204	57.00	10.29	No	251	57.91	10.65	No	137	59.64	11.42
	African American	153	50.47	11.67	Yes	106	54.50	11.13	Yes	220	55.19	10.21

Table 2. Standard multiple regression of age, race, depression, current hormone treatment, and history of chemotherapy treatment on perceived cognitive ability

	Cognitive	Depression	Hormone	Chemotherapy history	Age	*B*	β	sr_i^2
Cognitive	1	−0.39	−0.149	−0.142	0.201			
Depression	−0.39	1	0.092	0.095	−0.208	−0.381**	−0.0347	0.114
Hormone	−0.149	0.092	1	0.16	−0.143	−0.209**	−0.11	0.011
Chemotherapy	−0.142	0.095	0.16	1	−0.199	−1.42	−0.79	
Age	0.201	−0.208	−0.143	−0.199	1	−0.76	−0.0.95	
Race	−0.115	0.045	−0.154	−0.062	−0.011	−2.11**	−0.12	0.014
						Intercept = 71.38	$R = 0.442$	
Mean	52.13	50.06	0.3	0.62	56.9	0.429	$R^2 = 196$	
Standard deviation	8.72	7.93	0.46	0.49	10.89	0.496	Adjusted $R^2 = 0.184$	

**$p < 0.05$.

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capacities had been impacted by their treatment. To evaluate the question of the genesis of women's memory complaints, this study posited that changes in perceived cognitive capacity could be explained using the self-theory of memory and self-belief of control in cancer survivors as conceptual frameworks.

The findings supported statistically significant main effects for depression, race, and current hormone treatment impacting applied cognitive ability in BC survivors. What is of clinical significance in these finding is not that the main effects were statistically significant, but in the final model, depression's role was the largest contributor to differences in applied cognitive ability. The relationship between depression and the perception of cognitive capacity was consistent with the theoretical frameworks of the study and could be one putative explanation for the differences in patient reports and neuropsychiatric evaluation studies. Depression imparts a negative skew of a person's abilities, which could be further eroded by the perception of lack of control of one's future during cancer treatment. Suggesting a connection between the perception of cognitive loss seen in major depression and that seen in cancer survivors, interestingly, in both, conditions are reports that the perceived loses were not apparent on formal testing. Depressed persons without cancer have complaints of cognitive changes as part of their psychiatric presentation; thus, the report of reduced memory as an indicator of depression demonstrates a potential link, which parallels the results of this study. Findings from research on assessments of memory complaints in persons with major depression have reported the similar clinical picture of the perceptions of poor cognitive performance not supported by neuropsychological testing [33].

Race differences seen in this study were statistically significant, but the magnitude of the difference was small. Few studies have reported on cognitive changes in AA survivors or compared their experience with Caucasian survivors. These finding suggest a small difference between AA and Caucasian survivors, which we would consider clinically unimportant. Age was not significant in this study but appears to be mediated by depression, race, and current hormone treatment. There was also no significant effect for prior exposure to chemotherapy, which both differs and supports prior reports.

There are several limitations of this study. The design did not support means of testing the potential for cognitive decline to be the cause of depression, rather than the opposite. This alternative is demonstrated by the depressive mood states in persons who have suffered strokes and other neurological conditions. The study did not find cognitive changes associated with age, which may be a function of the use of internet collection methods. This could have led to the exclusion of certain population with experiencing cognitive decline, such as older adults. Additionally, those survivors with more advanced cancer may have been censored by their ability to complete the survey or have been unavailable as they were hospitalized for treatment.

Given the heterogeneity of reports in the literature, one could postulate the cognitive changes associated with BC treatment are likely to arise from multiple etiologies [19]. This study suggests depression is likely to be a major contributor, but there are other clinical trial studies that support changes in estrogen levels that may be involved [19]. The diversity of the reports within the literature suggests multiple etiologies [19]. Even with the etiologic difference unanswered, this study has underscored the importance of depression screening during BC survivorship and suggests memory complaints could be a 'bell weather' symptom for the oncologist or primary care provider to initiate an evaluation to determine the presence of mood disorders or other neurologic changes. This concurs with the recommendation of Bender *et al*. (2008) that perceived cognitive impairment should trigger additional evaluation to determine the etiology of these changes [39].

The results support the hypothesis that BC survivors' applied cognitive ability is significantly associated with exposure to hormone treatment, level of depression, and race. However, after reviewing the statistical outcomes, the findings revealed that depression was the largest factor explaining perceived cognitive function in this sample. The literature suggests the presence of other etiologies for cognitive changes in survivors, all of which merit additional screening. Depression and distress associated with BC have historically often gone undetected and not treated in oncology and primary care supporting the use of survivor complains of cognitive changes as bell weather for additional screening.

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