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Cancer Related Cognitive Impairment in Breast Cancer Patients: Guidelines for Neuropsychological Evaluation and Management

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Abstract

Current literature indicates there is still some debate regarding the scope and severity of cancer treatment related cognitive impairment (CRCI), with a wide variety of complex factors contributing to cognitive decline and discrepancies between objective findings and patient self-report. This paper aims to provide guidelines for neuropsychological evaluation, management, and rehabilitation of CRCI in breast cancer patients based on current research. This paper also aims to discuss current research on proposed mechanisms of action for CRCI, the cognitive domains affected in CRCI, and significant bio-psycho-social risk factors impacting CRCI.

Introduction

"Chemobrain" is a term that has been used by patients to describe declines in cognitive abilities that coincide with cancer treatment, which may include radiation therapy, chemotherapy, hormonal therapy, or a combination of these therapies. Recent literature points to "cancer-related cognitive impairment" (CRCI) as the preferred term, as the former term "chemobrain" may create an expectation of negative outcome and avoidance for patients making important treatment decisions (Chao et al., 2021). Increasing evidence over the past 20 years suggests that treatment for non-central nervous system (non-CNS) cancer can have both acute and long-term effects on cognitive functioning, which can affect education, occupation, activities of daily living, and overall quality of life. The prevalence of pre-treatment cognitive impairment in women with breast cancer is estimated to range from 11% to 35% of patients, which underlines the important of pre-treatment baseline assessments in studies to accurately detect changes in cognitive function attributable to treatment (Bradshaw & Wefel, 2014). Longitudinal studies estimate the incidence of CRCI following systemic chemotherapy treatment in breast and

brain cancer patients ranges from around 19% to 78% (Bradshaw & Wefel, 2014). More recent studies have indicated that subjective cognitive complaints are reported in 50% or more of breast cancer patients following chemotherapy, while 15-25% of those patients demonstrated objective cognitive decline on testing (Lange et al., 2019). These wide estimates may partly be due to the use of different neuropsychological tests, reference data, and performance cutoffs for classifying results between studies (Wefel et al, 2011). Some of this variability may also be related to differences inherent to primary cancer type, site, and chemotherapy agents used (Noll et al., 2018). The specific cognitive deficits reported across these studies include attention, learning and memory, processing speed, and executive function, reflecting a frontal-subcortical profile of deficits. While many patients will have their cognitive issues subside over time following treatment, many others continue to experience ongoing, progressive decline following treatment.

Regardless of prevalence estimates, it is generally accepted that a significant portion of breast cancer patients experience persistent subjective and objective cognitive decline, and thus, effective detection and management of CRCI is an important goal for healthcare providers in increasing the quality of life for patients. It is important to note that in the literature objective impairment refers to demonstrated cognitive impairment with neuropsychological testing, while subjective impairment refers to patient reported cognitive impairment. This distinction should not invalidate a patient's subjective experience of cognitive decline, and there are numerous important factors that could be contributing to any discrepancy between objective and subjective decline, such as a lack of sensitivity of neuropsychological tests used in the battery, variations in the definition of impairment between providers, a lack of neuropsychological testing data on premorbid cognitive functioning, other health problems, medications, current levels of psychological distress and imprecise estimates of premorbid functioning (Hutchinson et al.,

2012). The terms "objective" and "subjective" are somewhat limited in that both patients and medical providers may infer from the term "subjective" that the patient's cognitive decline is not real. In this paper and in the literature, the term "subjective" indicates that a patient's experience of cognitive decline was simply not detected on neuropsychological testing, not that it does not exist or that the patient is misperceiving their reality. It is important for medical providers to be conscientious of using terms like these with patients to avoid invalidating their experience.

Given the complexity of CRCI, neuropsychologists conducting evaluations for breast cancer survivors may benefit from this paper as it will provide guidelines for testing, recommendations, and can help clarify and support clinical impressions. Providing a comprehensive overview of proposed mechanisms of action of CRCI as well as the bio-psycho-social risk factors that may impact CRCI can help neuropsychologists explain the etiology of cognitive impairments for patients.

Methods

The scope of this paper will be limited to breast cancer patients and not include research on CNS patients. A minor portion of relevant research that focuses on non-CNS cancer patients in general will also be utilized, as breast cancer fits under this umbrella. This narrowing of focus is due to important differences in typical presentation, course, treatment, and assessment considerations between these populations. Further, a significant portion of existing literature on CRCI involves breast cancer patients, which provides a foundation of research and information from which to build on. A review of peer-reviewed articles will be used to determine guidelines for neuropsychological evaluation and management of CRCI, bio-psycho-social risk factors, and proposed mechanisms of action. Literature used in this paper will be limited to articles published

within the last 12 years. Neuropsychological cognitive domains to be examined include all domains typically assessed in a neuropsychological assessment; attention and concentration, processing speed, executive functioning, language skills, visual-spatial ability, working memory, immediate and delayed verbal and visual memory, and motor functioning.

Proposed Neuropathological Mechanisms involved in CRCI

Accelerated aging has been proposed as a potential mechanism of progressive cognitive decline in non-CNS cancer patients. Aging is associated with a variety of biological changes that include DNA damage, oxidative stress, inflammation, and decreased telomere length and activity (which are located on chromosomes and involved in cell division), and chemotherapy has been associated with those same biological changes (Ahles et al., 2012). Past research has also implicated the above processes in the development of neurodegenerative disease and cognitive decline. Thus, research suggests the biological processes underlying cancer, the impact of cancer treatment, aging, neurodegeneration, and cognitive decline may all be linked, leading to the hypothesis that cancer treatments may accelerate the aging process (Ahles et al., 2012).

Significant progress has been made in neuroimaging research on cognitive functions for breast cancer patients in recent years. Imaging studies have confirmed that chemotherapy is associated with structural and functional changes, notably in the frontal regions involved in executive functioning and memory. Studies have shown a reduction in gray matter volume in frontal brain regions one month after chemotherapy completion when compared to baseline, and this reduction was associated with higher cognitive complaints in patients (Joly et al., 2015). Further, this structural change was accompanied by altered brain activation in these areas while performing a working memory task, which may suggest a decrease in efficiency of cognitive

function. One study estimated that in long-term brain cancer survivors, these changes in volume were equivalent to four extra years of aging (Koppelmans et al., 2012). Research exploring the long-term effects of chemotherapy on brain structure in a large cohort of breast cancer survivors spanning 20 years after chemotherapy found total brain and global gray matter volumes were smaller in survivors than in healthy controls, though no significant differences were found in hippocampal volume or white matter volume and integrity (Joly et al., 2015). However, other studies have observed white matter pathology in patients that have undergone chemotherapy for breast cancer. The reduction in white matter integrity is believed to be associated with axonal degeneration and demyelination evidenced in diffusion tensor imaging (Bradshaw and Wefel, 2014). These findings are significant because a decrease in gray matter volume is associated with declines in cognitive function, like memory, as well as motor functioning, depending on where the reductions are most prominent. A decrease in white matter integrity can lead to issues in areas like speed of information processing and motor skills, while a decrease in hippocampal volume is associated with learning and memory deficits.

5-fluorouracil (5-FU), a major chemotherapy agent commonly administered to breast cancer patients, induced an alteration of cognitive flexibility and behavioral reactivity to novelty, indicating that long-term chemotherapy alters activity of selective brain areas connected to "hippocampal-cortical-frontal-cerebellar" networks in the dentate gyrus of the hippocampus (Joly et al., 2015). Research indicates that 5-FU and other cytotoxic drugs currently used in the treatment of cancer are shown to impact spatial memory, behavioral flexibility, and were associated with inhibiting proliferation of neural precursors and mature neuron integrity, leading to a reduction in brain tissue (Joly et al., 2015). Spatial memory deficits can result in difficulty

navigating to places or remembering the location of an object or event, while a decrease in behavioral flexibility would result in difficulty adapting to new situations (Lezak, 2012).

Further research in this area suggests that chemotherapy in breast cancer patients causes alterations in brain metabolites and brain network connectivity similar to processes that occur with normal aging. Specifically, the alterations in brain connectivity involve disruptions in frontal, striatal, and temporal areas, as well as reduced global connectivity in breast cancer patients treated with chemotherapy over healthy controls (Bradshaw and Wefel, 2014). The areas affected are implicated in executive function and memory, and cognitive dysfunction in these patients may be linked to disrupted coordination between brain regions, or a "disconnection syndrome," with lower white matter integrity and thus decreased processing speed and/or motor issues (Bradshaw and Wefel, 2014).

Other research in this area has examined the relationship between the body's inflammatory response to chemotherapy and cognitive complaints. Research has suggested a relationship between self-reported memory and attention complaints and immune system cytokine markers, like tumor necrosis factor alpha and interleukin 6, which are involved in immune system cell signaling. Brain glucose metabolism is thought to correlate with brain activity, and changes in metabolism in the medial prefrontal cortex and anterior temporal cortex of the brain was found to correlate with both memory complaints and cytokine marker levels in chemotherapy patients (Pomykala et al., 2013).

With respect to hormone therapy, research studies suggest that these treatments act on the estrogen and androgen receptors in the hippocampus and cerebral cortex. Imaging studies have demonstrated that women treated with Tamoxifen, a selective estrogen receptor modulator (SERM), had reduced hippocampal volumes and lower frontal lobe glucose metabolism

compared with controls and compared with women taking estrogen (Bradshaw and Wefel, 2014). Studies show that Tamoxifen also appears to affect neurotransmitter (serotonin and dopamine) and cytokine systems implicated in cognitive functioning. Animal studies in rodents revealed repeated administration of Tamoxifen or androgen deprivation has been shown to impair performance in learning and memory (Bradshaw and Wefel, 2014). Clinical research indicates that administering estradiol within a specific time window can stimulate neuroplasticity and improve cognition in breast cancer patients treated with SERMs and/or aromatase inhibitors (Schagen et al., 2014). SERMS and aromatase inhibitors work by blocking estrogen receptors and estradiol synthesis respectively, thus decreasing estrogen levels in the body.

Animal models have been useful in studying the impact of chemotherapy and cancer on brain function. Past animal studies support the hypothesis that chemotherapy affects brain structure and function and provide evidence for candidate mechanisms of chemotherapy induced cognitive changes (Ahles et al., 2012). Potential mechanisms for the effect of chemotherapy on the brain that have been demonstrated by animal studies include inhibition of hippocampal neurogenesis, oxidative damage, white matter damage, decreased hypothalamic-pituitary adrenal axis activity, and reduced brain vascularization and blood flow (Ahles et al., 2012).

Domains Impacted in CRCI

Research in breast cancer survivors indicates they experience objective impairments in memory, processing speed, attention, and executive functioning post-chemotherapy (Lange et al., 2019). Other research has listed the neuropsychological domains most affected as verbal working memory, psychomotor processing speed, and visual-spatial memory, with cognitive impairment found in cancer survivors years after completing chemotherapy, in contrast to

survivors of the same cancer type who did not receive chemotherapy (Ferguson et al., 2012). The most common cognitive deficits noted among breast cancer survivors include areas related to executive functions including working memory, cognitive flexibility, multitasking, planning, and attention. Executive functioning impairment can have a significant downstream effect on other cognitive domains, like language, social cognition, and declarative memory. Executive functioning deficits can also have negative impacts on psychosocial functioning, education achievement, career success, and has been shown to be associated with medication non-adherence (Kesler et al., 2012). These deficits can also lead to decreased self-esteem and self-efficacy.

Literature on subjective impairments has shown cancer survivors self-report problems with word retrieval, working memory, and increased mental fatigue. Patients may present with complaints of difficulty with short-term memory concerning conversations or misplacing items, as well as issues with concentration, organization, and multitasking. (Bradshaw & Wefel, 2014). Further, this notice of changes can elicit significant distress, anxiety, depression, and past studies indicate higher levels of emotional distress are correlated to greater severity of self-reported issues (Chao et al., 2021). Regarding quality of life and daily functioning, numerous studies indicate that life areas impacted include decreased effectiveness in work-related activities, caregiving, and driving (Chao et al., 2021). Other studies had reports of individuals who delayed or deferred educational pursuits, switched employment positions with less responsibility and pay, left employment, and withdrew from social activity due to fear of appearing cognitively impaired (Ferguson et al., 2012). With respect to trajectory of cognitive changes, studies indicate most patients with CRCI report changes during active treatment, 30% demonstrating objective CRCI

at the completion of chemotherapy, and up to 35% experiencing persistent symptoms in the months to years following treatment (Chao et al., 2021).

Hormone therapy is commonly used in the treatment of patients with breast cancer and has been found to negatively affect cognitive functioning, though results have been mixed. Specifically, breast cancer patients who receive Tamoxifen, a selective estrogen receptor modulator, Anastrozole, an aromatase inhibitor, or a combination of the two, performed worse on measures of memory, processing speed, and executive functioning compared to control group patients. Treatment with luteinizing hormone releasing hormone (LHRH) has also been associated with declines in visuospatial processing, visual memory, and executive functioning (Bradshaw and Wefel, 2014). Another study noted that breast cancer patients treated with Anastrozole had lower executive function scores compared to healthy controls up to 18 months following treatment, as well as decreased working memory and concentration 12 to 18 months following treatment (Lange et al., 2019).

A review of literature on CRCI found while evidence shows some cancer survivors experience cognitive difficulties following chemotherapy, subjective cognitive complaints are more frequently reported than cognitive deficits shown by objective neuropsychological assessments (Hutchinson et al., 2012). This study reviewed the relationship between subjective and objective measures of cognitive impairments following treatment and stated they failed to consistently find an association between subjective and objective measures of cognition, and this discrepancy may be partially explained by a lack of sensitivity in neuropsychological tests used, differing definitions of cognitive impairment between providers, and imprecise estimates of premorbid functioning. A lack of neuropsychological testing data on the patient's premorbid functioning could also be important, in that a patient's cognitive functioning may have dropped

from a superior or above average range to a low average range, and while low average would not be considered cognitive impairment, it is still a significant drop that could lead to understandable distress for the patient. The authors state that since discrepancies between subjective and objective impairment may be explained by variations in assessment methods and/or definitions of impairment, this underlines the need for some standardization of evaluation methods for CRCI, which will be discussed further in the section on neuropsychological evaluation of CRCI (Hutchinson et al., 2012). The authors also noted that subjective impairment may be an indicator of psychological distress rather than cognitive impairment, and that regardless of discrepancies, the patient's perceptions of impairment are no less important because they significantly impact quality of life and significant psychological distress can adversely impact cognition. It is the job of the neuropsychologist to translate the relative experiences of patients into normative labels of functioning based on all bio-psycho-social factors, not just test data alone.

Studying cognitive dysfunction associated with chemotherapy is a challenge since cognitive deficits can be present before the start of treatment, combinations of chemotherapy drugs can affect cognitive functioning more than others, and not all individuals are equally affected by the same chemotherapy regimen (Wefel et al, 2011). Variance among studies may also be due to assessment instruments used and criteria for defining change (Ahles et al., 2012). Further, lack of pre-chemotherapy evaluations also limits the conclusions that can be drawn from some of these studies (Ahles et al., 2013).

Table 1. Suspected Cognitive Impairments Induced by Cancer Treatments. Adapted from (Lange et al., 2019)

Cancer Treatment	**Cognitive Domains Affected (objective impairment on testing)**
Chemotherapy:	

Doxorubicin Taxol Methotrexate Fluorouracil	Memory, processing speed, attention and concentration, executive functioning
Hormone Therapy: Aromatase Inhibitors (Anastrozole) Anti-estrogen (Tamoxifen) Androgen Deprivation Therapy	Executive functioning, working memory, concentration, visuomotor functions

Risk Factors Impacting CRCI

Research suggests factors that increase risk of CRCI include premorbid cardiovascular conditions, older age, and lower cognitive reserve, which is determined by an estimated IQ derived from test performance, level of education, and demographic information (Chao et al., 2021). Longitudinal studies revealed that about 20-30% of breast cancer patients have cognitive impairments before the start of adjuvant treatment, and this is seen more frequently in elderly patients than younger ones (Joly et al., 2015). Since accelerated aging has been considered a potential mechanism of CRCI, elderly cancer patients may be particularly susceptible to CRCI in addition to being at risk for possible co-occurring neurodegenerative processes (Noll et al., 2018). Cognitive reserve, which represents innate and developed cognitive capacity influenced by education, occupational attainment, and lifestyle, has been associated with high resiliency to cognitive decline after brain insult in studies (Ahles et al., 2012). Research has demonstrated that age, as well as baseline cognitive reserve, are predictors of post treatment cognitive decline in processing speed among women treated with chemotherapy for breast cancer. Further, research has indicated that more than 60% of elderly breast cancer patients who report

preexisting memory problems are more likely to report worsening memory following chemotherapy (Joly et al., 2015).

Poor sleep and chronic bone pain, which are common during cycles of chemotherapy, are also associated with cognitive impairment in cancer patients. Medications taken for these problems can have side-effects that are associated with cognitive issues as well. Prior studies have noted 20-70% of breast cancer patients report sleep disturbance, with around 20% meeting diagnostic criteria for insomnia. Poor sleep has been associated with poorer performance in attention, memory, working memory, and executive functioning (Chao et al., 2021). Prior research shows prescribed sleep medications such as Zolpidem demonstrate mild to moderate negative effects on verbal memory, attention, processing speed, and working memory, while Trazadone has been found to mildly impact short-term memory (Stranks et al., 2014). It is estimated that 33-64% of patients experience cancer related chronic pain, which has been associated with worse performance in attention and executive functioning. Further, up to two-thirds of patients with cancer have reported their functional independence is significantly impacted by pain (Chao et al., 2021). Opioids, tricyclic antidepressants, and anti-convulsant medication taken for pain have all been associated with a decrease in cognitive performance, though results have been variable. Specifically, opioids have been associated with impairments in attention and concentration, memory, visuospatial skills, and psychomotor speed, and past studies suggest that a significant portion of breast cancer patients are prescribed opioid medication (Gruber et al., 2007). One study found that among about 25,000 patients with breast cancer included in the study sample, 46.8% had an opioid prescription during the one year prior to metastatic breast cancer diagnosis. During the one year after metastatic breast cancer diagnosis, 81.4% of patients received at least one opioid prescription, while 55.8% had at least

three opioid prescription claims, and 22.8% had at least seven filled opioid prescriptions (Shen et al., 2020).

There are several other medical issues that may contribute to CRCI as well. Anti-emetic medications prescribed to manage cancer treatment induced nausea and vomiting are not typically associated with cognitive impairments but are known to cause drowsiness. Further, corticosteroids used during treatment for nausea, vomiting, and suppressing the immune system have been found to have modest but significant negative effects in memory and executive functioning, and are also associated with insomnia (Chao et al., 2021). Diabetes and cardiovascular disease are associated with impairment among patients before adjuvant treatments, which underlines the importance of including a comprehensive assessment of comorbidities in future studies (Joly et al., 2015). Thyroid dysfunction and anemia, which are common during active treatment for cancer, have both been known to impact cognitive functioning in the general population. Genetic factors like apolipoprotein E (APOE4) were implicated as risk factors for chemotherapy-induced cognitive decline among breast cancer survivors (Joly et al., 2015).

Research studies have put forth the hypothesis of a dose-response relationship between chemotherapy and cognitive impairment in breast cancer patients. When controlling for baseline performance, age, education, and mood, one study found cognitive function progressively worsened with cumulative chemotherapy exposure (Joly et al., 2015). Another study observed that cognitive decline rates were higher in patients following high-dose chemotherapy compared to patients given conventional dose chemotherapy (Schagen et al., 2014). Administration of chemotherapy via intrathecal or intra-arterial methods may also be associated with increased risk of CRCI (Bradshaw and Wefel, 2014).

Mental Health Factors Impacting CRCI

Mental health factors impacting self-reported CRCI include greater baseline levels of anxiety, depression, and younger age. Additionally, research has shown that patients who were informed of the potential impact of chemotherapy on cognition were more likely to report higher levels of cognitive complains, while patients who reported not being educated on the possibility of CRCI prior to treatment noted higher levels of emotional distress following onset of cognitive symptoms (Chao et al., 2021). This phenomenon may suggest a "nocebo effect," a situation in which a patient's negative expectations regarding treatment cause the treatment to have a more negative effect than it otherwise would.

Due to the life-threatening context of the illness, cancer and its treatments can involve many stressful events and psychiatric symptoms like those reported in depression, anxiety, or post-traumatic stress disorder, which are known to induce adverse effects on cognition (Joly et al., 2015). Anxiety, depression, and fatigue frequently occur in cancer patients, and these variables should be considered in cognitive assessments, as several studies show associations between cognitive complaints and depression, anxiety, and PTSD (Lange et al., 2019). One study examined the mental health effects for breast cancer patients undergoing treatment, including surgical resection, chemotherapy, radiation therapy, or a combination of these treatments. The study found 38.2% met criteria for depression while 32.2% met criteria for anxiety based on a structured questionnaire and PHQ-2 and GAD-2 screeners, with other studies and systematic reviews having found results similarly in the 30-40% range for anxiety and depression (Tsaras et al., 2018). Further, studies indicate up to 70% of breast cancer survivors

report clinically significant fear of cancer recurrence, which is characterized by intrusive thoughts, substantial distress, and maladaptive coping (Johns et al., 2019).

Neuropsychological Evaluation of CRCI patients

Literature on neuropsychological evaluation of cancer patients stress that during clinical interview and record review, efforts should be made to gather information regarding the onset and course of cognitive symptoms and how that timeline relates to the patient's cancer diagnosis and treatment. A robust understanding about the impact of specific cancers and treatments on cognition, with close examination of a patient's known risk factors and neuropsychological profile can help distinguish between cancer-related and other etiologies of cognitive impairment (Bradshaw & Wefel, 2014). CRCI is often observed alongside various other symptoms and issues, including fatigue, chronic pain, multiple strong medications, poor sleep, and emotional distress, and these comorbidities may impact test engagement and patient quality of life. Neuropsychologists are uniquely positioned to examine cognitive issues and other important bio-psycho-social contributors to patient well-being, thus identifying targets for intervention to improve overall quality of life (Noll et al., 2018).

Pre-treatment baseline evaluations for breast cancer patients undergoing chemotherapy provides a valuable point of comparison both in research and clinical practice. Baseline data helps to determine whether cognitive impairments are attributable to a specific treatment or are secondary to the cancer itself. Baseline data also allows for identification of subtle treatment related neurotoxicity for a patient who exhibits a meaningful post-treatment decline but continues to perform in the non-impaired range relative to normative expectations (Bradshaw & Wefel, 2014). However, in clinical practice, such baseline data is rarely available as a point of

comparison. Instead, neuropsychologists are usually presented with referral questions in the aftermath of cancer treatment without pretreatment data, and thus, pre-morbid level of functioning must be estimated based on education, occupational attainment, and neuropsychological tests that are robust to neurological insult and thus can predict level of functioning before the insult (Bradshaw & Wefel, 2014).

An example of such a test would be the Test of Premorbid Functioning, a revised and updated version of the Wechsler Test of Adult Reading (Noll et al., 2018). With respect to neuropsychological evaluations during or post treatment, this will vary depending on the patient's treatment course, functional status, and goals. Evaluation shortly after post-treatment recovery provides an opportunity to offer recommendations for rehabilitation planning or homecare needs. Timing evaluations in conjunction with patient goals and activities, like return to work evaluations, ensure that neuropsychological care is given at times of greatest need for the patient (Bradshaw & Wefel, 2014). It is important for the neuropsychologist to use best judgment and collaborate with the patient on determining when it is most appropriate to test, whether it be medical, psychological, or motivation factors that are impacting a patient's ability to put forth their best possible effort on testing.

Regarding neuropsychological tests, reliable, valid measures that are sensitive to subtle changes but robust to practice effects are crucial, since patients may be evaluated numerous times given the dynamic nature of cancer and treatment (Noll et al., 2018). Re-evaluation in relatively shorter time intervals than other patient populations and use of alternate forms to reduce practice effects are also recommended. In test selection, important factors to consider include a patient's disease status, expected prognosis, and physical stamina (Noll et al., 2018). For patients with short-estimated survival time, an extensive battery spanning many hours would

not be warranted or recommended, and an abbreviated battery tapping key cognitive domains would be indicated (Bradshaw & Wefel, 2014). For neuropsychological testing with non-CNS cancer patients, heavy emphasis on testing of frontal and subcortical network functioning is indicated, which includes executive functioning, processing speed, motor coordination speed, and learning and memory retrieval.

The International Cognition and Cancer Task Force in 2012 identified a brief core set of measures that meet the criteria discussed above, are appropriate for both CNS and non-CNS cancer patients, and can be supplemented with additional measures (Bradshaw & Wefel, 2014). The ICCTF test battery includes the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association of the Multilingual Aphasia Examination (COWA) (Wefel et al., 2011). The HVLT-R measures learning and memory, has adequate psychometric properties (i.e., reliability, validity), six alternate forms, and is translated in several languages. The TMT also has adequate psychometric properties, is not language dependent, has instructions translated in several languages, and measures psychomotor speed and executive functioning. The COWA is a measure of speeded lexical fluency which requires aspects of executive function, has adequate psychometric measures, and one alternate form. Neuropsychologists are encouraged to supplement this core battery with additional tests of working memory capacity based on their own preferences, since none of the available measures meets all the criteria outlined above (Wefel et al., 2011).

Noll et al. expanded on this battery by identifying several tests and measures that provide "a repeatable core battery with robust psychometric properties" for each cognitive domain (Noll et al., 2018, pg. 348). The tests for each domain are located in Table 1 below. Literature on test selection for CRCI stress that no test battery will be appropriate for every cancer patient, thus

flexibility around these core tests and measures is often necessary, with supplementation and adjustment varying according to comorbidities, diagnoses and referral questions. Further, tests with greater sensitivity, like continuous performance tests, are often supplemented, as deficits can be relatively subtle in some cases (Noll et al., 2018). Validity testing throughout the battery are also important in gauging patient engagement and effort, and Table 1 provides examples of short stand-alone and embedded validity measures that can be used in the battery.

A neuropsychological evaluation should also include an assessment of affective functioning and quality of life, which are commonly compromised in this patient population and can negatively impact subjective, self-reported cognitive functioning (Noll et al., 2018). It is notable that self-report of cognitive complaints has been shown to correlate more strongly with fatigue and mood disturbance than with objective evidence of cognitive dysfunction. Affective assessment should include assessment of suicidal ideation, as research suggests that the suicide risk of patients diagnosed with cancer is approximately two times higher than the general population, and increased risk of suicide can remain for up to 15 years after diagnosis (Bulotiene & Pociute, 2019). More extensive psychological testing can be administered if a mental health disorder or condition is indicated, like the Personality Assessment Inventory (PAI) or Minnesota Multiphasic Personality Inventory (MMPI). However, due to the length of these assessments, it may be beneficial to schedule these additional assessments on a different day to avoid patient fatigue.

As discussed previously, the broad estimates in prevalence of objective CRCI may be in part due to differences in neuropsychological test selection and reference data, but also differences in performance cutoffs for classifying results between studies (Wefel et al, 2011). The American Academy of Clinical Neuropsychology (AACN) noted that no universally

accepted system exists for assigning qualitative descriptors to scores in specific ranges, and the definition of the term "impairment" also lacks specificity and consensus. To address this, the AACN organized a consensus conference in which to recommend a universal system of qualitative labels to describe results and a definition of impairment (Guilmette et al., 2020). It may be beneficial for future research studies on CRCI to adhere to a similar core battery of tests like the one proposed in Table 1 and uniform labeling of performance test scores outlined by the American Academy of Clinical Neuropsychology consensus statement, as this will allow for a more streamlined comparison of results across studies.

Table 2. Core Battery for Assessment of Cognition in Cancer Patients (adapted from Noll et al., 2018).

Domain	**Test**
Premorbid Functioning	Wechsler Test of Adult Reading
Validity	Rey-15, DCT, RDS
Memory	Hopkins Verbal Learning Test – Revised Brief Visuospatial Memory Test – Revised
Language	Boston Naming Test MAE: Controlled Oral Word Association MAE: Token Test
Attention/Processing Speed	WAIS-IV Digit Span WAIS-IV Arithmetic WAIS-IV Coding WAIS-IV Symbol Search Trail Making Test Part A
Executive Functioning	WAIS-IV Similarities Trail Making Test Part B
Visuospatial	WAIS-IV Block Design
Motor	Grooved Pegboard
Mood/Symptoms/Quality of Life	Beck Depression Inventory – II Beck Anxiety Inventory EORTC QLQ C30/BN20 Insomnia Severity Index (ISI) PROMIS Pain Interference – Short Form

Additional Measures	Domains Assessed
Auditory Consonant Trigrams Letter Number Sequencing (WAIS) Paced Auditory Serial Addition Test (PASAT) Brief test of attention	Working memory, executive function, complex attention

Management and Rehabilitation of CRCI

Recommendations for management and rehabilitation of CRCI can vary greatly between patients depending on referral questions and overall profile. Research has shown that patients who demonstrate cognitive impairment can benefit from education and instructions on implementing environmental modifications, external aids, and internal strategies for optimizing cognitive functioning (Noll et al., 2018). For patients displaying more severe cognitive impairment, neurological rehabilitation is also commonly recommended, as well as home health services where cognitive impairment limits self-care. Research has demonstrated that depression and anxiety disorders are the most frequent psychiatric comorbidities in cancer patients (Mehnert et al., 2014). As such, individual psychotherapy, like CBT and other evidence-based psychological interventions, can be beneficial for patients (Noll et al., 2018). Further, to address potential fatigue and sleep disturbances that are commonly seen in this patient population, education regarding sleep hygiene and pacing, as well as referrals to sleep clinics when appropriate, may yield cognitive and quality of life benefits (Noll et al., 2018). For cancer patients with fatigue and cognitive impairment, participating in regular cardiovascular exercise has been shown to elicit improvement in cognition and energy levels (Mustian et al., 2012). In addition to the above recommendations, other more generalized recommendations may be useful for CRCI patients depending on their overall clinical picture, which include referrals for

neuroimaging, pharmacological interventions, workplace or academic accommodations, occupational, physical or speech therapy, and recommendations on decision making or driving capacity (Noll et al., 2018). The sections below discuss current literature on interventions for management and rehabilitation of CRCI; cognitive rehabilitation, cognitive behavioral therapy, acceptance and commitment therapy, physical exercise, mindfulness-based stress reduction, and behavioral health apps. Though research is ongoing, it should be noted that many of the studies currently available on the management of CRCI have methodological limitations that include lack of an active control group for comparison, small sample sizes, and selective reporting of findings, thus, study findings should be interpreted with caution (Chao et al., 2021).

Many of the interventions discussed below can be provided by a health psychologist specializing in psycho-oncology as part of a multidisciplinary treatment team. If a patient is not already connected to a health psychologist and is open to it, this would be an important recommendation/referral, since addressing the psychological factors contributing to cognitive impairment can lead to significant improvement.

Cognitive Rehabilitation

Cognitive rehabilitation broadly refers to improving cognitive capacity through skills training with progressively increasing levels of difficulty, as well as compensatory strategies, with the goal of maximizing daily functioning. Cognitive rehabilitation can occur in an individual or group treatment setting, and sometimes can include computer or web-based programs (Chao et al., 2021). Programs designed specifically for treating CRCI include components of cognitive behavioral therapy involving psychoeducation, emotional coping skills, and stress reduction techniques. A recent systematic review in 2021 found that participants

engaged in cognitive rehabilitation programs experienced objective improvements in at least one cognitive domain, including memory, executive function, and processing speed (Chao et al., 2021).

Cognitive training in either memory or speed of processing in breast cancer survivors demonstrated improvement in memory and processing speed at two months follow up compared to a control group. Both interventions were also associated with improvement in perceived cognitive functioning, distress from cognitive symptoms, and quality of life (Von Ah et al., 2012). Another computerized cognitive training program to improve executive functioning over 12 weeks for breast cancer survivors who were, on average, six years out from completing chemotherapy, found significant improvements in cognitive flexibility, verbal fluency, processing speeds, with marginal improvements in verbal memory. Self-reported cognitive improvements were also reported for executive function skills (Kessler et al., 2013). Attention retraining and instruction in the use of compensatory strategies, including memory aids like notebooks, phone alerts, and medication reminder systems to facilitate recall of important information, showed promise in addressing mental fatigue and cognitive complaints (Bradshaw and Wefel, 2014). A four-week cognitive rehabilitation program aimed to improve cognitive function and quality of life in patients after completion of cancer treatment found the program was effective in improving overall cognitive function, visuospatial constructional performance, and delayed memory that went beyond practice effects, when compared to non-cognitive rehabilitation and control groups. The program was also helpful in reducing patients' perceptions of cognitive impairment and psychosocial distress, as well as promoting social functioning and understanding of cognition (Schuurs and Green, 2013).

A Memory and Attention Adaption Training (MAAT) program described as a brief cognitive-behavioral approach designed to help cancer survivors learn and apply adaptive strategies to reduce the negative functional and quality of life impact of cognitive problems found participants significantly improved relative to controls on verbal memory and on the quality of life measure (Ferguson et al., 2012). Another cognitive rehabilitation pilot program for breast cancer survivors that consisted of five, weekly, two-hour sessions involving psychoeducation, in-group and home cognitive exercises, and goal setting found significant changes from baseline for motor and psychomotor speed tests. There were also improvements in self-report assessments of own functioning, with all cognitive functions except motor speed remaining significant two and four months after intervention (Ercoli et al., 2013). Altogether, these results suggest that cognitive rehabilitation can be an effective intervention for objective and subjective cognitive impairment in cancer patients.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a psychotherapy approach that focuses on unhelpful thought patterns and behaviors and is commonly used in conjunction with cognitive skills training within cognitive rehabilitation programs. One study showed self-reported improvements in memory at six months follow up for a brief, manualized, individual therapy program that addressed symptom management, communication with healthcare providers, changes in self and relations, sense of meaning and purpose, and concerns for mortality and the future (Chao et al., 2021).

CBT was also shown to be effective in treating depression, anxiety, sleep disturbance, and chronic pain, which are all factors suspected to contribute to CRCI symptoms. One meta-analysis study found skills training and education had a medium-size effect in reducing pain severity in cancer survivors (Gorin et al., 2012). Another meta-analysis study found Cognitive Behavioral Therapy for Insomnia (CBT-I) for cancer survivors with insomnia to significantly improve sleep efficiency, sleep latency, and wake after sleep onset relative to control conditions from pre to post intervention, with medium effect size (Johnson et al., 2016). The study also noted that large effect sizes were observed for self-reported insomnia severity for patients who received CBT-I, and effects were durable up to six months. The authors concluded that evidence supports a strong recommendation for the use of CBT-I among cancer survivors (Johnson et al., 2016).

Acceptance and Commitment Therapy

Acceptance and Commitment Therapy (ACT) is designed to maximize psychological flexibility in navigating difficulties and challenges in life, and emphasizes acceptance while living mindfully according to one's values (Hayes et al., 2011). Fear of cancer recurrence (FCR) can be a persistent and disruptive problem for many cancer survivors leading to reduced quality of life, and studies have shown that FCR affects up to 70% of breast cancer survivors (Johns et al., 2019). Past research has suggested that ACT may improve distress symptoms and quality of life in cancer patients, but there are few studies to date that have examined the effectiveness of ACT for FCR. A pilot study by Johns et al. conducted a trial for breast cancer survivors participating in either a group-based ACT intervention, survivorship education intervention, and enhanced usual care for breast cancer survivors with FCR. The ACT intervention was designed

to increase adaptive coping through acceptance, cognitive defusion, mindfulness, and perspective taking exercises while supporting the participant in aligning behavior with personal values (Hayes et al., 2013). The ACT group consisted of six, weekly, two-hour sessions, that included mindfulness exercises each session to develop awareness of the present moment, along with adaptive strategies for responding to FCR. The survivorship education intervention had a similar group format and time commitment and involved symptom management, weight management, physical activity, and survivorship care plans. The enhanced usual care participants continued receiving standard care from their health care providers and received a National Cancer Institute booklet with a list of supplemental resources and a review of strategies to manage physical changes, feelings, and social and working relationships (Johns et al., 2019). Outcomes were measured using the Fear of Cancer Recurrence Inventory, and the study found the ACT group demonstrated significant improvement regarding FCR severity while the SE and EUC groups showed minimal changes across outcomes. The authors state that although preliminary, these results suggest ACT is a promising intervention for reducing FCR in breast cancer survivors, particularly regarding reducing avoidant/maladaptive coping (Johns et al., 2019).

Physical Exercise

Animal model studies on physical exercise and CRCI suggest that exercise can promote neuroplasticity and reduce the effects of chemotherapy on cells in the hippocampus (Chao et al., 2021). A randomized controlled trial in breast cancer survivors showed improved cognitive processing speed following an exercise program, though this result was limited to survivors with diagnoses in the past two years. Another study compared a group of cancer survivors that underwent a 12-week high intensity interval training (HIIT) exercise program, a group of cancer

survivors that underwent a moderate intensity continuous (MOD) exercise program, and a wait-list control group (Northey et al., 2019). The study indicated that both the HIIT and MOD groups demonstrated improvement in executive function and working memory, with a large effect size for the HIIT group and a medium effect size for the MOD group. Notably, this particular study only included patients within two years of diagnosis and had a relatively small sample size (Chao et al., 2021). A recent study compared cognitive function in sedentary breast cancer survivors randomized to either a 12-week exercise program or a wait-list control group. The exercise group set specific goals with a clinical psychologist to gradually increase aerobic exercise to at least 150 minutes of moderate to vigorous physical activity per week, and were monitored by a Fitbit device throughout the 12 weeks (Hartman et al., 2018). The exercise program group demonstrated objective neurocognitive improvements in processing speed for those diagnosed within the previous two years, as well as a reduction in cognitive symptoms (Hartman et al., 2018). Another study of cancer survivors randomized to eight sessions of yoga or a control group showed improvements in cognitive complaints in the yoga group (Lange et al., 2019).

Overall, research suggests physical exercise may be useful for processing speed, executive function, and working memory for cancer survivors with diagnoses within the past two years. There is also evidence that exercise can have a positive impact for cancer-related fatigue and quality of life.

Mindfulness Based Stress Reduction

Mindfulness-based stress reduction (MBSR) utilizes guided mindfulness and meditation practices focused on improving attentional control and enhancing self-awareness and awareness

of one's environment. MBSR has been a treatment of interest for cancer and many other illness related quality of life problems for patients for many years, and several studies have shown some effectiveness for improving psychological distress.

A recent meta-analysis investigated MBSR and cognitive function among breast cancer survivors. This study focused on research that used a MBSR program similar to the one developed by Kabat-Zinn specifically for chronic pain and anxiety, but modified for breast cancer survivors (Cifu et al., 2018). This modified program, referred to as MBSR(BC) involves two-hour sessions for six to eight weeks that focus on controlling and self-regulating attention to help control and reduce stress and associated symptoms. Participants are given education materials on mind-body practices, meditations, and instructed to practice 15 to 45 minutes of formal meditation six days a week, as well as 15 to 45 minutes of informal meditation while doing usual activities like walking or eating (Cifu et al., 2018). Attention on breathing, focused body-scans, yoga, and walking meditation are also emphasized as mind-body practices. Participants are also given audio recordings of daily, guided meditations and asked to keep a daily meditation diary. MBSR(BC) programs were instructed by doctoral level clinical psychologists or physicians with MBSR experience, and most groups ranged from 10 to 15 participants (Cifu et al., 2018). The investigators found that MBSR showed some evidence for improving cognition among breast cancer survivors, but further research using validated and comprehensive cognitive assessments is required, as well on the timing, duration, and content of mindfulness interventions (Cifu et al., 2018). Another meta-analysis by Cramer et al. on MBRS for breast cancer patients came to similar conclusions, in that there is some evidence for the effectiveness of MBSR in improving psychological health, and existing data was promising, but

evidence was limited by shortcomings in methodology, and more rigorous research was needed (Cramer et al., 2012).

Behavioral Health Apps

Further, there are several mindfulness-based apps currently available to the public, such as Headspace, Calm, and the VA-based Covid-Coach and CBT-I Coach, though academic research is currently limited on evaluating the effectiveness of these applications. However, some studies are currently in progress examining the effectiveness of these applications, and a pilot study has indicated that a mindfulness and relaxation app intervention for cancer patients was feasible, with acceptable adherence and largely positive feedback from patients (Mikolasek et al., 2018).

Cultural and Ethnic Diversity Considerations

Literature indicates more research is needed on the psychosocial impacts of breast cancer for women from diverse ethnic and socioeconomic backgrounds. Studies suggest that cultural stigmas, taboos, and myths about cancer, as well as cultural competence in health care providers, can significantly impact cancer treatment (Daher, 2012). A qualitative study involving breast cancer survivors that included Black, Asian, Latinx, and White participants found differences in specific beliefs about breast cancer etiology, particular among older and less acculturated participants. For example, some women considered cancer to be contagious, or caused by breast trauma. Some held strong spiritual beliefs that the diagnosis was willed by God or a form of divine punishment, or took a fatalistic attitude towards their diagnosis (Ashing-Giwa et al., 2004).

Across all participants, survivors expressed similar fears regarding recurrence, survival, pain, and loss of autonomy. Fears about changes in body image, scarring, and the effect of chemotherapy and surgery were also areas of concern. Many survivors described negative feelings about their bodies after breast cancer treatment, with common sentiments including decreased self-worth and attractiveness, inadequacy, embarrassment, sadness, frustration, and a sense of loss. Concerns about the diagnosis affecting their roles as caregivers and the impact on their families were also important. Black women expressed specific fears related to unfamiliarity with breast cancer as well as racism within the health care system. Latinx, Black, and Asian American women also noted they experienced barriers and/or discriminatory treatment in accessing care (Ashing-Giwa et al., 2004).

In considering cultural and ethnic diversity factors, it is important to note that every individual experiences their culture and ethnicity differently. These identifiers are informative, but not defining, and part of the overall picture. The information above demonstrates that being aware and sensitive to cultural diversity considerations when providing care, educating the patient and family about expected symptoms and their management, clarifying information about interventions, and facilitating patient and family communication with the care team are vital for providers working with cancer patients. It is also important to note that not every patient will be as open to or willing to engage in western medicine interventions.

Conclusions

Though research in this area is ongoing, proposed mechanisms of action regarding CRCI include an acceleration of the aging process through DNA damage, oxidative stress, inflammation, and decreased telomere length and activity (Ahles et al., 2012). Neuroimaging

indicates structural and functional changes in frontal brain regions, with reductions in gray matter volume and white matter integrity (Joly et al., 2015). Hormone therapy acting on estrogen receptors has been associated with reduced hippocampal volumes, reduced neurogenesis, and decreased frontal lobe glucose metabolism (Bradshaw and Wefel, 2014).

Research on CRCI in breast cancer patients points to demonstrated cognitive impairments on neuropsychological testing in attention, learning and memory, processing speed, and executive function, reflecting a frontal-subcortical profile of deficits (Lange et al., 2019). Common cognitive deficits are in areas related to executive functions, including working memory, cognitive flexibility, multitasking, planning, and attention (Ferguson et al., 2012). Executive functioning impairment can have a significant downstream effect on other cognitive domains and can also have negative impacts on psychosocial, education, and career functioning (Kesler et al., 2012). Studies indicate the majority of patients with CRCI report changes during active treatment, 30% demonstrate objective CRCI at the completion of chemotherapy, and up to 35% experiencing persistent symptoms in the months to years following treatment (Chao et al., 2021).

Risk factors involved in objective CRCI include cognitive reserve, premorbid IQ, premorbid cardiovascular conditions, older age, poor sleep, chronic pain and fatigue, pain and sleep medications, thyroid dysfunction, anemia, genetic factors (APOE4), and higher dosing or repeated exposure to chemotherapy (Ahles et al., 2012; Chao et al., 2021; Joly et al., 2015; Noll et al., 2018). Risk factors involved in subjective CRCI include emotional status and younger age. Patients informed of the potential negative impact of chemotherapy on cognition tended to report higher levels of cognitive complaints, while those not given education on the possibility of

CRCI reported higher levels of emotional distress following onset of symptoms (Chao et al., 2021).

Current guidelines on neuropsychological evaluation of CRCI state that pre-treatment baseline evaluations can provide valuable points of comparison to help determine the etiology of cognitive issues (Bradshaw & Wefel, 2014). Evaluations during or post-treatment will vary depending on the patient's treatment course, functional status, and goals. Evaluation shortly after post-treatment recovery provides an opportunity for rehabilitation planning and/or homecare needs (Noll et al., 2018). Timing evaluations in conjunction with patient goals and activities, like return to work evaluations, ensure that neuropsychological care is given at times of greatest need for the patient (Bradshaw & Wefel, 2014). It is important for the neuropsychologist to use best judgment and collaborate with the patient on determining when it is most appropriate to test, whether it be medical, psychological, or motivation factors that are impacting a patient's ability to put forth their best possible effort on testing.

Regarding test battery, reliable, valid measures that are sensitive to subtle changes are indicated. Re-evaluation in shorter time intervals and the use of alternate forms to reduce practice effects are also important (Noll et al., 2018). An abbreviated battery tapping key cognitive domains of frontal and subcortical functioning is indicated, including executive functioning, processing speed, motor coordination speed, and learning and memory retrieval (Bradshaw & Wefel, 2014). A recommended test battery adapted from The International Cancer and Cognition Task Force and subsequent literature on CRCI testing is provided above in Table 2. Assessment of emotional functioning and quality of life should also be included in a test battery (Noll et al., 2018). The American Academy of Clinical Neuropsychology recommends a universal system of qualitative labels to describe results and define impairment, which can allow

for more streamlined comparison of results across studies on CRCI (Guilmette et al., 2020). During interview and record review, information on onset and course of cognitive symptoms, timeline of cancer diagnosis and treatment, risk factors, and comorbidities should be gathered. Neuropsychologists are uniquely qualified to measure cognitive changes, evaluate the impact of bio-psycho-social factors, provide educational information, and make broad recommendations beyond the medical treatment (Bradshaw & Wefel, 2014).

In communicating with patients, clinicians should be mindful of using terms like objective or subjective impairment so as not to invalidate or otherwise impact the patient. Providers should explain to patients that there may be a number of significant factors that can contribute to discrepancies between objective and subjective decline, and communicate that the patient's perceptions of impairment are no less important, as they significantly impact quality of life and can adversely impact cognition.

Research on management and treatment of CRCI suggest that cognitive rehabilitation programs have shown that patients experience objective improvements in at least one cognitive domain, as well as improvements in subjective complaints. CBT has been shown to be effective in treating subjective complaints, depression, anxiety, sleep disturbance, and chronic pain related to CRCI (Chao et al., 2021). Preliminary results suggest ACT may be a viable intervention for reducing fear of cancer recurrence in breast cancer survivors, particularly in regard to reducing avoidant or maladaptive coping behaviors (Johns et al., 2019). Physical exercise may be useful for processing speed, executive function, and working memory for cancer survivors, especially those with diagnoses within the past two years. There is also evidence that exercise can have a positive impact for cancer-related fatigue and quality of life (Chao et al., 2021). Mindfulness based stress reduction has been a treatment of interest for cancer-related quality of life problems

and several studies have shown some effectiveness in reducing psychological distress (Cifu et al., 2018). Health psychologists specializing in psycho-oncology can be great assets in a multidisciplinary treatment team in delivering the above interventions to cancer patients.

Ultimately, the goal is to help patients maintain independence, dignity, cultural or spiritual practices, and hope in the face of their illness. It is important for neuropsychologists to partner with the patient, health psychologist, support system, and other healthcare providers to maximize cognitive functioning and quality of life. Further research is needed to determine the significant risk factors and appropriate interventions for CRCI, generally with more diverse demographic populations, larger sample sizes, adequate power, and appropriate control groups.

References:

Ahles TA, Root JC, Ryan EL. (2012). Cancer- and cancer treatment– associated cognitive change: an update on the state of the science. J Clin Oncol. 2012;30(30):3675–86.

Ashing-Giwa, K.T., Padilla, G., Tejero, J., Kraemer, J., Wright, K., Coscarelli, A., Clayton, S., Williams, I., Hills, D. (2006). Understanding the breast cancer experience of women: A qualitative study of African America, Asian American, Latina and Caucasian cancer survivors. Psychooncology. 2004 Jun: 13(6): 408-428.

Bradshaw, M.E., Wefel, J.S. (2014). The Neuropsychology of Oncology. Parsons, M.W., Hammeke, T.A (Ed.). Clinical Neuropsychology: A Pocket Handbook for Assessment (Third Edition). The American Psychological Association.

Bulotiene, G., Pociute, K. (2019). Interventions for reducing suicide risk in cancer patients: A literature review. European Journal of Psychology. 2019 Sep; 15(3): 637-649.

Chao, D., Hale, A., Henry, N.L, Kratz, A.L., Gabel, N.M. (2021). Cancer-Related Cognitive Impairment or "Chemobrain:" Emerging Assessments, Treatments, and Targets for Intervention. Current Physical Medicine and Rehabilitation Reports.

Cifu, G., Power, M.C., Shomstein, S., Arem, H. (2018). Mindfulness-based interventions and cognitive function among breast cancer survivors: a systematic review. BMC Cancer. 2018;18(1):1163.

Cramer, H., Lauche, R., Paul, A., Dobos, G. (2012). Mindfulness-based stress reduction for breast cancer – a systematic review and meta-analysis. Current Oncology. 2012;19(5): 343-52.

Daher, M. (2012). Cultural beliefs and values in cancer patients. Annals of Oncology. 2012 Apr;23 Suppl 3:66-9.

Ercoli, L.M., Castellon, S.A., Hunter, A.M. (2013). Assessment of the feasibility of a rehabilitation intervention program for breast cancer survivors with cognitive complaints. Brain Imaging Behavior 2013;7:543-553

Ferguson, R.J., McDonald, B.C., Rocque, M.A., Furstenberg, C.T., Horrigan, S., Ahles, T.A., Saykin, A.J. (2012). Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. Psychooncology. 2012 February; 21(2): 176-186.

Gorin, S., Krebs, P., Badr, H., Janke, E.A., Jim, H.S.L., Spring, B., Mohr, D.C., Berendsen, M.A., Jacobsen, P.B. (2012). Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. Journal of Clinical Oncology. 2012;30(5):539-47.

Gruber, S.A., Silveri, M.M., Yurgelun-Todd, D.A. (2007). Neuropsychological consequences of opiate use. Neuropsychology Review. 2007, 17(3): 299-315.

Guilmette, T.J., Sweet, J.J., Hebben, N., Koltai, D., Mahone, E.M., Spiegler, B.J., Stucky, K., Westerveld, M. (2020). American Academy of Clinical Neuropsychology consensus conference statement on uniform labeling of performance test scores. The Clinical Neuropsychologist. https://doi.org/10.1080/13854046.2020.1722244

Hartman, S.J., Nelson, S.H., Myers, E., Natarajan, L., Sears, D.D., Palmer, B.W., Weiner, L.S., Parker, B.A., Patterson, R.E. (2018). Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The Memory & Motion study. Cancer. 2018 January 01; 124(1):192-202.

Hayes, S.C., Levin, M.E., Plumb-Vilardaga, J., Villatte, J.L., Pistorello, J. (2013). Acceptance and commitment therapy and contextual behavioral science: examining the progress of a distinctive model of behavioral and cognitive therapy. Behav Ther. 2013; 44: 180-198.

Hayes, S.C., Strosahl, K.D., Wilson, K.G. Acceptance and Commitment Therapy: The process and Practice of Mindful Change. Guilford Press; 2011.

Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C. (2012) Objective and

subjective cognitive impairment following chemotherapy for cancer: a systematic review. Cancer Treatment Reviews. 2012;38(7):926–34.

Johns, S.A., Stutz, P.V., Talib, T.L., Cohee, A.A., Beck-Coon, K.A., Brown, L.F., Wilhelm, L.R., Monahan, P.O., LaPradd, M.L., Champion, V.L., Miller, K.D., Giesler, R.B. (2019). Acceptance and Commitment Therapy for Breast Cancer Survivors With Fear of Cancer Recurrence: A 3-Arm Pilot Randomized Controlled Trial.

Johnson, J.A., Rash, J.A., Campbell, T.S., Savard, J., Gehrman, P.R., Perlis, M., Carlson, L.E., Garland, S.N. (2016). A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia in cancer survivors. Sleep Medicine Review. 2016:27:20-8.

Joly F., Giffard B., Rigal O., De Ruiter M.B., Small B.J., Dubois M. (2015). Impact of cancer and its treatments on cognitive function: Advances in research from the Paris International Cognition and Cancer Task Force Symposium and Update Since 2012. Journal of Pain and Symptom Management. 2015;50(6):830–41.

Kesler, S., Hosseini, S.M.H, Heckler, C., Janelsins, M., Palesh, O., Mustian, K., Morrow, G. (2013). Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clin Breast Cancer. 2013 August; 13(3): 299-306.

Koppelmans, V., Groot, M.D., de Ruiter, M.B. (2012). Global and focal white matter integrity in breast cancer survivors 20 years after adjuvant therapy. Human Brain Mapping 2012; 25:889-899.

Lange, M., Joly, F., Vardy, J., Ahles, T., Dubois, M., Tron, L., Winocur, G., De Ruiter, M.B.,

Castel, H. (October 2019) Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. Annals of Oncology 30: 1925–1940, 2019. doi:10.1093/annonc/mdz41

Lezak, M. D. (2012). Neuropsychological assessment (5th ed.). Oxford University Press.

Mehnert, A., Brahler, E., Faller, H., Harter, M., Keller, M., Schulz, H. (2014). Four-week prevalence of mental disorders in patients with cancer across major tumor entities. Journal of Clinical Oncology, 32, 3540-3546.

Mikolasek, M., Witt, C.M., Barth, J. (2018). Adherence to a Mindfulness and Relaxation Self-Care App for Cancer Patients: Mixed-Methods Feasibility Study. Journal of Medical Internet Research, Vol 6, No 12 (2018).

Mustian, K.M., Sprod, L.K., Janelsins, M., Peppone, L.J., Mohile, S. (2012). Exercise recommendations for cancer-related fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction: A review. Oncology & Hematology Review, 8, 81.

Noll, K.R., Bradshaw, M.E., Rexer, J., Wefel, J.S. (2018). Neuropsychological Practice in the Oncology Setting. Archives of Clinical Neuropsychology 33 (2018) 344-353.

Northey, J.M., Pumpa, K.L., Quinlan, C., Ikin, A., Toohey, K., Smee, D.J., Rattray, B. (2019). Cognition in breast cancer survivors: A pilot study of interval and continuous exercise. Journal of Science and Medicine in Sport 22 (2019) 580-585.

Pomykala, K.L., Ganz, P.A., Bowers, J.E., Kwan, L., Castellon, S.A., Mallam, S., Cheng, I., Ahn, R., Breen, E.C., Irwin, M.R., Silverman, D.H.S. (2013). The association between pro-inflammatory cytokines, regional cerebral metabolism, and cognitive complaints

following adjuvant chemotherapy for breast cancer. Brain Imaging Behav. 2013 Dec; 7(4): 511–523.

Schagen, S.B., Klein, M., Reijneveld, J.C., Brain, E., Depre, S., Joly, F., Scherwath, A., Schrauwen, W., Wefel, J.S. (2014). Monitoring and optimizing cognitive function in cancer patients: Present knowledge and future directions. EJC 12 (2014) 29-40.

Schuurs, A., Green, H.J. (2013). A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. Psychooncology 2013;22:1043-1049.\

Shen, C., Thornton, J.D., Newport, K., Schaefer, E., Zhou, S., Yee, N.S., Dodge, D., Leslie, D. (2020). Trends and patterns in the use of opioids among metastatic breast cancer patients. Scientific Reports 10:21698 2020.

Stranks, E.K, Crowe, S.F. (2014). The acute cognitive effects of zopiclone, zolpidem, zaleplon, and eszopiclone: a systematic review and meta-analysis. Journal of Clinical and Experimental Neuropsychology. 2014; 36(7): 691-700.

Tsaras, K., Papathanasiou, I.V., Mitsi, D., Veneti, A., Kelesi, M., Zyga, S., Fradelos, E.C. (2018). Assessment of depression and anxiety in breast cancer patients: Prevalence and associated factors. Asian Pac J Cancer Prev, 2018; 19(6): 1661-1669.

Von Ah, D., Carpenter, J.S., Saykin, A., Monahan, P., Wu, J., Yu, M., Rebok, G., Ball, K., Scheider, B., Weaver, M., Tallman, E., Unverzagt, F. (2012). Advanced cognitive training for breast cancer survivors: a randomized controlled trial. Breast Cancer Res Treat (2012) 135: 799-809.

Wefel, J.S., Vardy, J., Ahles, T., Schagen, S.B. (February 2011). International Cognition and

Cancer Task Force Recommendations to Harmonize Studies of Cognitive Function in Patients with Cancer. Lancet Oncology: 12(7): 703-8.