HHS Public Access

Author manuscript

CA Cancer J Clin. Author manuscript; available in PMC 2015 March 11.

Published in final edited form as:

CA Cancer J Clin. 2015 March ; 65(2): 123–138. doi:10.3322/caac.21258.

Clinical Characteristics, Pathophysiology, and Management of Noncentral Nervous System Cancer-Related Cognitive Impairment in Adults

Jeffrey S. Wefel, PhD[1,*], **Shelli R. Kesler, PhD**[2], **Kyle R. Noll, PhD**[3], and **Sanne B. Schagen, PhD**[4]

[1]Associate Professor, Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX [2]Associate Professor, Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX [3]Associate Professor, Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX [4]Associate Professor, Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Abstract

Over the past few decades, a body of research has emerged confirming what many adult patients with noncentral nervous system cancer have long reported—that cancer and its treatment are frequently associated with cancer-related cognitive impairment (CRCI). The severity of CRCI varies, and symptoms can emerge early or late in the disease course. Nonetheless, CRCI is typically mild to moderate in nature and primarily involves the domains of memory, attention, executive functioning, and processing speed. Animal models and novel neuroimaging techniques have begun to unravel the pathophysiologic mechanisms underlying CRCI, including the role of inflammatory cascades, direct neurotoxic effects, damage to progenitor cells, white matter abnormalities, and reduced functional connectivity, among others. Given the paucity of research on CRCI with other cancer populations, this review synthesizes the current literature with a deliberate focus on CRCI within the context of breast cancer. A hypothetical case-study approach is used to illustrate how CRCI often presents clinically and how current science can inform practice. While the literature regarding intervention for CRCI is nascent, behavioral and pharmacologic approaches are discussed.

Keywords

chemotherapy; psychological/behavioral oncology; breast neoplasms; complications and late effects of therapy

Corresponding author: Jeffrey S. Wefel, PhD, Department of Neuro-Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 431, Houston, TX 77030; jwefel@mdanderson.org.

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The remaining authors report no conflicts of interest.

Introduction

Advances in diagnosis and treatment of cancer have greatly improved survival. With reduced mortality, morbidity related to cancer and its treatment has garnered increased attention, and issues surrounding quality of life have become ever more important. Cancer survivors have long reported cognitive dysfunction at various stages of the disease course with associated consequences upon well-being and functional independence. Nonetheless, until relatively recently, cancer-related cognitive impairment (CRCI) in patients with noncentral nervous system (non-CNS) malignancies was largely unacknowledged.[1] The prevailing attitude was reinforced by the belief that chemotherapies were unable to cross the blood-brain barrier,[2–4] precluding the possibility of a direct neurotoxic effect of cancer therapies. However, since the 1990s, a growing body of literature has verified the existence of CRCI, with recent animal models and neuroimaging studies uncovering pathophysiologic correlates.[4–14]

CRCI research has largely focused on neurotoxicity associated with chemotherapy, often referred to as “chemobrain” or “chemofog.”[5] However, CRCI has also been documented in the absence of chemotherapy, leading to hypothesized associations with cancer itself,[15] surgery,[15–18] and other adjuvant therapies.[19–21] Estimates of the prevalence of CRCI vary widely, although current longitudinal studies suggest that approximately 40% of cancer patients have evidence of CRCI before any treatment, up to 75% may have cognitive decline during treatment, and up to 60% exhibit deterioration in cognition even after completion of therapies.[5,22–25] The pattern of CRCI differs across patients and disease course, although severity is typically mild to moderate in nature. Mild cognitive impairments are conventionally considered to be performances that are from −1.5 to −2 standard deviations below population normative means. However, mild to moderate CRCI may also refer to a psychometrically significant decline relative to a patient’s own pretreatment baseline performance (ie, a decline of approximately 1–2 normative standard deviations from baseline scores). Accordingly, these methods of determining impairment yield some difference in absolute impairment levels, depending on the individual patient’s premorbid level of function. Nonetheless, the severity of CRCI is generally milder than the cognitive impairment typical of common neurologic populations, including those with neurodegenerative diseases and stroke. Despite this, encephalopathies involving dementia have been observed in the context of treatment with some cytotostatic agents.[26,27] In addition, CRCI can persist for months to years after treatment,[28] and even subtle impairments can have profound consequences upon quality of life, including occupational and social functioning.[1]

To date, the majority of CRCI research in patients with non-CNS cancer has involved women with breast cancer,[29,30] who represent approximately 22% of the 14.5 million cancer survivors in the United States alone.[31] Investigations have also been conducted in patients with testicular cancer,[32,33] lymphoma,[28] multiple myeloma,[34] colorectal cancer,[35] ovarian cancer,[36] and prostate cancer,[37] among others. However, much of the literature regarding these populations is preliminary, with studies mostly consisting of small sample sizes. Future large, longitudinal, cohort studies are needed to better describe the prevalence and nature of CRCI in these patient populations. In light of the current state of the literature, this

review deliberately focuses on the findings from clinical and basic research on CRCI in adult patients with breast cancer or preclinical models thereof, which has rapidly grown over the past few decades. To illustrate this work, the cognitive functioning of a hypothetical breast cancer patient is described at various stages of her disease and treatment course, based upon published reports and our collective clinical experience. These clinical descriptions are supplemented by summaries of associated empirical findings and discussion of pathophysiological underpinnings and potential intervention strategies.

Breast Cancer, Surgery, and Cognitive Functioning

The patient is a 53-year-old, married woman employed as an attorney in a busy corporate law firm. Upon self-examination, she noticed a mass in the outer upper quadrant of her right breast, prompting medical consultation. At the time of presentation, she reported that menopause occurred at age 50 years. She underwent lumpectomy with axillary lymph node dissection, and pathology revealed stage II, infiltrating, estrogen receptor-positive and progesterone receptor-positive (ER+/PR+) ductal carcinoma that was negative for human epidermal growth factor receptor 2 (HER2/neu). Her adjuvant treatment plan was discussed at her follow-up visit, including the role of chemotherapy. She stated that she had read about “chemobrain” and expressed concerns about treatment-related changes in her cognitive functioning. She was referred for formal neuropsychological evaluation by her oncologist to establish a baseline for monitoring her cognition throughout treatment. Her performances on neurocognitive testing were notable for subtle inefficiencies with attention and processing speed, although her endorsements on self-reported measures reflected greater cognitive complaints than objective cognitive impairments identified on neuropsychological testing. Inventories of emotional functioning revealed mild to moderate anxiety and future uncertainty.

In practice, patients rarely present to clinical neuropsychologists before the initiation of adjuvant therapy, although research suggests that the clinical picture described above is not uncommon. On objective testing before the initiation of chemotherapy, the patient evidenced some cognitive weaknesses, which may have been present to some extent even before surgery. While rates vary according to the cognitive instruments and impairment criteria used, studies assessing women with breast cancer before chemotherapy have documented that up to 40% exhibit CRCI before the initiation of therapy.[23,38] Some data suggest that CRCI is most commonly observed within the cognitive domains of learning and memory,[18] although others report a more nonspecific pattern of impairments.[24]

In the above example, the patient’s self-reported cognitive complaints exceeded the severity of deficits noted on objective testing. Such discrepancies between objective and subjective measures of cognitive functioning have been documented in patients with various neurological illnesses,[39–41] which is also an area of ongoing research in patients with non-CNS CRCI.[42–45] While evidence suggests that cognitive complaints do in fact bear some relationship to objective cognitive performance,[42] self-reported cognitive symptoms appear to be more strongly associated with affective symptoms (eg, depression and anxiety), coping and adjustment issues, and cancer-related fatigue.[43] This highlights the importance of comprehensive assessment of cognitive and emotional functioning using a battery of

measures that captures not only objective cognitive performances but also patient-reported symptoms of CRCI and emotional functioning.

Pathophysiological Underpinnings

Pretreatment CRCI identified on objective testing appears to be independent of emotional distress and fatigue,[28,46] medical comorbidities,[47] and surgical factors,[48] although no consistent explanation has been found for CRCI before the initiation of therapies. Hypothesized mechanisms have been proposed at a variety of levels, including the biology of cancer itself (eg, inflammatory responses triggering neurotoxic proinflammatory cytokine cascades) and shared underlying risk factors for the development of cancer and cognitive decline (eg, poor DNA repair mechanisms linked to both cancer and neurodegenerative disorders).[4,49] A recent rodent study demonstrated that a non-CNS tumor alone is sufficient to induce hippocampal dysfunction, possibly by reducing the rate of neurogenesis and the levels of BDNF (brain-derived neurotrophic factor) and COX-2 (cyclooxygenase 2), in addition to increasing stress-related parameters and circulating levels of proinflammatory cytokines.[50] However, patients participating in pretreatment cognitive studies do not likely represent a random sample of individuals confronted with cancer. Thus, it is possible that these samples are biased toward individuals with impairment. Confirmation of the observation of pretreatment CRCI in an unbiased sample is critical and will help disentangle the possible underlying pathophysiology.

Chemotherapy, Endocrine Therapy, and Cognition

After lumpectomy, the patient received 4 cycles of standard-dose adjuvant chemotherapy with doxorubicin and cyclophosphamide as well as weekly paclitaxel for 12 weeks. This was followed by locoregional radiation therapy. Throughout chemotherapy, the patient reported worsening fatigue and cognitive complaints, including greater difficulty with memory, trouble multitasking, and distractibility. She stated that her symptoms negatively impacted daily functions, as she occasionally forgot doses of medications and missed bill payments. Given the ER+/PR+ subtype of carcinoma and postmenopausal status, chemotherapy was followed by 5 years of endocrine therapy with anastrozole to reduce the risk of recurrence. Worsening in learning and memory was reported after the initiation of endocrine therapy and had an even greater adverse impact on her work functioning. Serial neuropsychological assessments were conducted after chemotherapy and again after 6 months of endocrine therapy. The results demonstrated postchemotherapy decline on measures of attention, processing speed, learning, and memory as well as executive functions, including mental flexibility. During endocrine therapy, performances on testing were largely stable, although slight worsening in learning and memory was noted. Mood assessment evidenced mild depression and continued anxiety.

A common challenge for both clinical assessment and cross-sectional research involves the reliance on normative comparison groups. Without pretreatment neuropsychological assessment for comparison, relative declines in cognitive functioning across the pretreatment to posttreatment interval may be undetected or underestimated. That is, patients may have declined during treatment despite post-treatment performances falling within the “normal” to “low normal” range compared with normative data. This is a particularly important

consideration when interpreting the test results of individuals with high levels of preillness functioning (eg, being well-educated), which presumably are indicative of greater cognitive reserve.[22] Unlike the situation faced by most neuropsychologists in the clinic, the patient in the above example had repeated neuropsychological evaluations, allowing the direct comparison of her pre-treatment and posttreatment cognitive test performances. With the use of modern statistical approaches (eg, reliable change indices) supplementing clinical analysis and inference, normal variation and treatment-related cognitive change can be distinguished with adequate confidence.[5]

In the case example, significant postchemotherapy declines were found across several cognitive domains. This phenomenon has been increasingly recognized in both the scientific literature and the clinic. Over the past decade, more than 20 longitudinal studies have been conducted involving both prechemotherapy and postchemotherapy assessment of cognition,[5,7,11,13–15,18,23–25,29,32,46,51–67] with nearly 70% of investigations reporting evidence of significant decline after therapy.[29] The incidence of CRCI after chemotherapy has been observed in 17% to over 70% of patients in longitudinal studies. Breast cancer patients treated with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC), a regimen similar to that received by the hypothetical patient, tend to show the most prominent decline in the cognitive domains of learning and memory, attention, and processing speed.[52] While CRCI within the context of chemotherapy is often mild to moderate in severity, several agents have been associated with severe encephalopathy and dementia in some patients, including methotrexate, BCNU (bis-chloroethylnitrosurea [carmustine]), fludarabine, cytarabine, 5-fluorouracil, and cisplatin.[29]

Specific risks for CRCI and patterns of CRCI by regimen are largely unknown. Nonetheless, considerable evidence suggests a dose-response relationship between chemotherapy and CRCI.[68–70] Collins and colleagues conducted neuropsychological assessments in 60 women with early stage breast cancer before the initiation of chemotherapy but after surgery, as well as after the completion of each cycle of chemotherapy.[70] Compared with matched healthy controls, progressive decline was noted at each subsequent time point, supporting a dose-response relationship in which patients demonstrated a linear worsening of CRCI with each cycle of chemotherapy. In addition, CRCI associated with chemotherapy may emerge at various stages of the disease course. In a longitudinal investigation of 42 patients with breast cancer receiving FAC (with or without paclitaxel), Wefel et al found that 21% of patients exhibited CRCI before the initiation of chemotherapy, 65% exhibited cognitive decline during or shortly after therapy, and 61% showed decline at approximately 1 year after the completion of treatment.[25] Of this 61%, a substantial subgroup demonstrated cognitive deterioration that was not previously apparent.

In our case example, slight worsening in cognitive functioning was noted during endocrine therapy. In contrast to the literature regarding chemotherapy and CRCI, few rigorous investigations have been conducted examining the impact of endocrine therapy on cognition. Nonetheless, some research suggests that treatment with selective ER modulators (SERMs) is associated with cognitive deterioration.[8,21] For instance, treatment with tamoxifen has been associated with significantly reduced performances on measures of memory, verbal fluency, visuospatial functioning, and processing speed,[71] and those receiving both

chemotherapy and tamoxifen may exhibit greater impairment than those treated with either alone.[8] Aromatase inhibitors, such as anastrozole in the case example, may also contribute to CRCI,[72,73] although the literature is inconsistent.[20,74] Evidence also suggests that the cognitive effects of aromatase inhibitors may be less than those of SERMs.[75] However, it is important to note that patients are often maintained on endocrine therapy for long durations, with some remaining on treatment for up to 10 years per recent American Society of Clinical Oncology guidelines.[76] As such, it is possible that CRCI associated with hormonal therapy may emerge over time, although large, well-controlled longitudinal studies are needed.

The patient we describe above reported some occupational difficulties and distress. While problems performing instrumental activities of daily living (eg, medication and financial management, occupational functioning) are associated with cognitive impairment in neurological populations,[77] these relationships are not as well studied in patients who have CRCI associated with non-CNS cancer. Nonetheless, some evidence suggests that acquired executive deficits (eg, difficulty planning and multitasking) contribute to reductions in community involvement and social functioning[78] as well as more general degradation of quality of life.[79] Those who exhibit postchemotherapy decline in cognition also tend to report greater occupational difficulties than those who remain stable throughout treatment,[52] with approximately 13% of cancer survivors ceasing to work within 4 years of diagnosis secondary to “cancer-related reasons,” including CRCI.[80]

Late Effects of Cancer Therapy

As evidenced by Wefel and colleagues, CRCI can be persistent and may even emerge in the months to years after completion of all therapies.[25] Koppelmans et al investigated the neuropsychological functioning of patients with breast cancer who received an average of 6 cycles of chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) and had a mean of 21 years since completion of treatment.[81] Compared with a healthy, population-based comparison group, significantly worse performances were noted in memory, processing speed, and executive functioning, although patients reported less symptoms of depression. However, despite evidence of persistent CRCI in some patients with breast cancer, other subsets of patients have been found to improve in the months to years after cessation of chemotherapy[51] and endocrine therapy.[13]

At present, it is not understood why some patients exhibit decline or persistent CRCI after treatment while others improve or remain stable. Premorbid cognitive capacity may play a role, as greater posttreatment decline in processing speed has been documented in breast cancer patients with lower preillness cognitive capacities.[4] Lifestyle and medical comorbidities as well as problems with fatigue and sleep may also represent risk factors for later cognitive decline, although existing studies have not found these to be strong predictors of cognitive decline. Geriatric research suggests that older individuals and carriers of variants of the apolipoprotein E (*APOE*) gene (eg, *APOEε*4) are at increased risk of cognitive decline and development of dementia.[82,83] Accordingly, it is possible that CRCI may become more pronounced later in life or in individuals with certain genetic vulnerabilities.[29] Further research is needed to clarify the risk factors associated with the development and maintenance of CRCI. Greater consistency across studies regarding

assessment, criteria for impairment, and analytical methods is required to facilitate the comparison of results across studies and cancer populations. Toward this end, the International Cognition and Cancer Task Force has proposed a useful set of guidelines for the assessment and study of CRCI, providing the groundwork for unification of future investigations.[84]

Pathophysiological Underpinnings

Preclinical research—Preclinical studies have provided some insights into the pathophysiological mechanisms underlying CRCI associated with nontargeted delivery of chemotherapy.[85–88] It has been shown in animal models that cytostatic agents from different classes (eg, antimetabolites, DNA cross-linking agents, and alkylating agents) administered peripherally and in clinically relevant dosages can disrupt various neurobiological processes and induce cognitive impairment.[49] A direct toxic effect of chemotherapeutic agents on various cell populations has been proposed as etiology for these neurotoxicities. Specifically, many cytotostatic agents appear to be preferentially toxic to neural progenitor cells (the direct ancestors of all differentiated cell types in the CNS) and postmitotic oligodendrocytes (the myelin-forming cells of the CNS).[89,90] Reduced white matter integrity and impaired neurogenesis are also postulated as important mechanisms underlying the typical pattern of CRCI seen in patients.[87,89] A recent study in rats demonstrated that cytostatic agents may induce persistent neuroinflammation, which, in turn, is involved in changes in myelination and cognitive dysfunction.[91] Other etiologic factors comprise common indirect mechanisms, such as changes in oxidative balance[92] (a critical modulator of cellular functions in stem cells and progenitor cells),[93] neurotransmitter/monoamine release, and disruption of blood vessel density and blood supply.[94–96] While distinguishing between primary and secondary mechanisms is difficult, cytostatic agents likely exert their negative effect on cognition through multiple pathways.

Compared with the rapidly developing literature on the mechanisms of CRCI in the context of chemotherapy, less effort has been directed at understanding the cognitive consequences of endocrine therapies through preclinical experiments and animal models. The results of currently available studies are complex and inconclusive, with large variation across investigations. While preclinical research shows that SERMs like tamoxifen and raloxifene have mainly estrogenic agonistic effects on the serotonergic system after ovariectomy,[97,98] they also appear to exhibit neuroprotective functions in the dopamine and acetylcholine systems and to increase plasticity in the hippocampus.[98,99] Conversely, rodent studies with aromatase inhibitors like anastrozole and letrozole suggest that impaired estrogen synthesis in the brain is detrimental to the neuroprotective functions of estrogens, leading to impaired long-term potentiation, altered catecholamine levels (depending on the presence or absence of endogenous estrogen), and a decreased number of dendritic spines.[100,101] Based on these cellular effects, greater estrogenic effects within the brain would be expected from SERMs, resulting in positive effects upon cognition, including memory. However, preclinical behavioral research shows inconsistent results, ranging from increased anxiety,[102] to decreased memory consolidation and retrieval processes,[103] or to no effect, and even to improved cognition.[104] Interestingly, aromatase inhibitors also facilitate cognitive

improvement in rodents, contrary to reports of cognitive decline related to endocrine therapy in patients with breast cancer.[101,105]

Taken together, there are still large gaps between the preclinical and human data with respect to the effects of endocrine therapies on the brain and cognition. In addition, relatively little attention has been paid to the modeling of individual differences in cognitive vulnerability to cancer and cancer therapies. It is expected that studying the genetic factors that modulate CNS toxicity in preclinical models will be an area of increased interest and challenge in the near future.

Neuroimaging

The final common pathophysiologic pathway is altered neurobiologic status, which results in brain changes and cognitive dysfunction. To date, evidence for this pathway stems primarily from in vivo neuroimaging studies of breast cancer patients and survivors. Volumetric magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) studies demonstrate widespread reductions in gray matter volume and white matter connectivity.[66,106–118] For example, Deprez et al examined white matter connectivity using DTI in 16 patients with breast cancer before chemotherapy and again 3 to 4 months after chemotherapy.[110] These patients showed significantly reduced frontal, parietal, and occipital white matter tract integrity over time, whereas patients who did not receive chemotherapy showed no change. The chemotherapy-treated group also demonstrated decreased performance on tests of attention, processing speed, and memory compared with controls, and performance changes were correlated with reductions in white matter integrity.

Altered brain structure, such as changes in gray and/or white matter, reduces the brain network's ability to stabilize and support the dynamic functional networks that underlie various cognitive processes.[119,120] Multiple functional MRI (fMRI) studies have shown altered functional brain activation and connectivity associated with breast cancer and its treatments.[16,108,121–134] McDonald and colleagues measured brain activation associated with working memory using fMRI in 16 patients who received chemotherapy, 12 who did not receive chemotherapy, and 15 healthy female controls.[132] Participants were evaluated before chemotherapy, 1 month after chemotherapy, and 1 year later or at matched intervals for controls. Compared with controls, patients demonstrated overactivation of frontal regions.[132] Overactivation is believed to represent a deficient or inefficient neural response in which additional neural resources are required to perform the task. These frontal regions were also noted to have decreased gray matter from prechemotherapy to postchemotherapy in a previous study by the same authors.[117,118] Findings from fMRI studies are supported by results from complementary techniques, including positron emission tomography,[134–136] arterial spin labeling,[137] and electroencephalography (EEG).[138–141] Magnetic resonance spectroscopy imaging has also provided further insight regarding certain pathophysiologic mechanisms, including inflammation and demyelination.[109,142,143]

Brain injury has been observed in association with several putative CRCI mechanisms, including cancer pathogenesis and/or surgery,[16,121,122,129,132,133] chemotherapy,[66,109,110,113,115–118,124–126,129,130,132,134,137,144] locoregional radiation therapy,[145] endocrine therapy,[111,146] menopausal status,[123] and inflammatory

response.[114,135,147] Neuroimaging studies have also demonstrated neurobiologic alterations associated with specific symptoms that are often comorbid with CRCI, including fatigue, depression, and anxiety.[131,148–150] However, none of these studies distinguished among the specific effects of various potential CRCI mechanisms. Therefore, it is currently unclear whether certain mechanisms are more or less likely to result in CRCI and/or whether CRCI results from the cumulative effects of various mechanisms.

Previous studies have consistently demonstrated correlations between altered neurobiologic status and atypical neurocognitive testing performance.[66,106–108,110,113,114,123,134,137] While neurocognitive testing has shown an inconsistent correlation with patient self-report,[151,152] several studies have demonstrated significant associations between various neuroimaging metrics and subjective cognitive complaints.[66,118,120,125,129,139,142] Future investigations are needed that directly compare the imaging characteristics of patients with and without significant subjective and/or objective cognitive impairment.

Although neuroimaging research offers significant insight regarding the biologic mechanisms underlying CRCI, neuroimaging is not currently part of the clinical standard of care for primary breast cancer. Given our increasing awareness of the potential adverse effects of many cancer therapies on brain and cognition, methods for predicting which patients are at highest risk are not only feasible but may also help prevent long-term disability. Neuroimaging is increasingly used to aid the prediction of outcomes for various brain-based disorders, including future cognitive decline.[153–155] Prediction algorithms have benefitted from the innovative application of machine learning to neuroimaging data. Machine learning is a branch of artificial intelligence involving methods that can effectively detect complex patterns in high-dimensional data and make predictions. This translates into marked potential for the diagnosis of neurodegenerative brain diseases.[156–158] Machine learning studies in breast cancer survivors provide support for the use of baseline neuroimaging data to predict which patients will have persistent and/or progressive CRCI.[120,128,130] These emerging approaches hold promise for identifying those at risk of CRCI, and the International Cognition and Cancer Task Force is currently working to create recommendations for methods and timing of neuroimaging acquisitions.

Intervention

Given the neurocognitive deficits identified on neuropsychological evaluation and reported difficulties with instrumental activities of daily living, the patient was referred for cognitive rehabilitation after initiation of endocrine therapy. She participated in 60-minute sessions, once per week for 12 weeks. The treatment plan included psychoeducation (eg, presentation of information regarding symptoms and mechanisms of CRCI), training in compensatory strategies (eg, using a smartphone), in vivo training of real-world skills (eg, planning a weekly schedule), and homework assignments (eg, workbook readings and skills practice). Homework also included a curriculum of computerized cognitive training focused on executive functioning and memory. She completed the exercises using her home computer for 20 to 30 minutes per day, 5 days per week, for 12 weeks. The patient was further prescribed a program of physical exercise to help with fatigue, sleep, and cognition. At the

recommendation of her neuropsychologist, her employer provided workplace accommodations, including a change within the law firm to a less demanding role.

Behavioral Strategies

Cognitive rehabilitation refers to a clinic-based, therapeutic program aimed at improving cognitive abilities, functional capacity, real-world skills, and/or internal metacognitive strategies (ie, internal plans of action for completing cognitive tasks). Programs can be inpatient or outpatient and involve patients meeting individually and/or in groups with a trained clinician (typically a neuropsychologist, psychologist, speech and language pathologist, or occupational therapist). Thus far, there have been a limited number of studies involving cognitive rehabilitation after breast cancer, but the majority have demonstrated significant improvement in both objective and subjective cognitive performance as well as quality of life (Table 1).[159–172] Cognitive domains showing intervention effects include executive functioning, working memory, attention, memory, processing speed, and visual-spatial skills. One study also included a quantitative EEG biomarker of intervention outcome and demonstrated increased global brain activity after cognitive rehabilitation.[160] Ferguson et al randomized 40 breast cancer survivors who were at least 18 months postchemotherapy and had subjective complaints of CRCI to a manualized cognitive rehabilitation program focusing on memory and attention or a waitlist control condition.[162] The intervention program consisted of 4 biweekly, individual office visits, 30 to 50 minutes in duration, with phone contacts between visits. Intervention participants received psychoeducation regarding memory and attention, as well as training in self-awareness, self-regulation, and cognitive compensatory strategies. Compared with the waitlist control group, the intervention group demonstrated significantly increased memory performance and improved self-reported quality of life. Participants rated the intervention as being most useful for helping them compensate for daily memory difficulties.

Cognitive rehabilitation can also be advantageous for improving achievement of real-world objectives and managing psychological comorbidities, such as the anxiety and depression experienced by the patient described above. The social aspects of this approach (eg, therapeutic alliance with the clinician and group participants) are believed to contribute significantly to the cognitive and psychological effects. Unfortunately, cognitive rehabilitation is not always feasible because it requires multiple in-person sessions and administration by trained clinical providers. In addition, cognitive rehabilitation is not widely available and has a history of unpredictable coverage by health insurance.[173] However, many studies of cognitive rehabilitation in breast cancer survivors involve a manualized treatment approach,[160–162,165] which improves intervention standardization and practicality of dissemination.

Cognitive training aims to improve and maintain cognitive skills via distributed, adaptive practice of specific cognitive domains. Unlike cognitive rehabilitation, cognitive training tends to focus on independent cognitive skills practice, without compensatory or metacognitive strategies, and frequently relies heavily on computerized exercises. These exercises are typically game-based, given that games require various degrees of active problem solving and decision making to progress.[174] Exercises also involve algorithmic

control of difficulty level to optimize the balance between challenge and motivation. Studies of cognitive training for CRCI after breast cancer, although preliminary, suggest that executive function, memory, processing speed, self-rated cognition, anxiety, and depression can improve with as few as 10 hours of distributed training.[164,166,167] In 2012, Von Ah et al randomized 82 breast cancer survivors who were at least 1 year postchemotherapy and had subjective complaints of CRCI to memory cognitive rehabilitation, processing speed cognitive training, or waitlist control conditions.[167] Memory rehabilitation consisted of training participants in various compensatory strategies, including in vivo practice of these strategies. Processing speed training involved adaptive, computerized exercises focusing on time-order judgment, discrimination, spatial match, forward span, instruction after, and narrative-memory tasks. Each intervention was delivered for a total of 10 hours and was conducted in small groups over 6 to 8 weeks. The memory training group demonstrated significant improvements in immediate and delayed memory performance compared with waitlist controls. The processing speed group demonstrated significantly improved processing speed as well as improved immediate and delayed memory performance compared with waitlist controls. Both intervention groups also demonstrated improved subjective cognition and reduced psychological distress.[167]

In-clinic[167] and home-based[166] cognitive training programs appear to show very similar effect sizes in breast cancer survivors, consistent with previous research in healthy older adults.[175] Cognitive training programs by Posit Science Corporation (San Francisco, CA; brainhq.com/)[167] and Lumosity (Lumos Labs, Inc. San Francisco, CA; lumosity.com)[166] have been tested in breast cancer, and both showed similar effects. Cognitive training programs are widely available, relatively inexpensive, and allow for remote administration with improved feasibility and access. Previous studies of healthy adults have claimed that cognitive training is neuroprotective with respect to improvement and conservation of cognitive performance.[175,176] These findings may be particularly salient for breast cancer survivors, given that previous research suggests cancer and/or its treatments may accelerate the aging process.[12,177,178] However, cognitive training may not be suitable for individuals with more severe cognitive deficits or significant psychological comorbidities.

Some studies of cancer and noncancer groups have shown transfer of benefits to nontrained skills[179–181] and improvement in symptoms other than cognitive difficulties, such as sleep quality, psychological distress, and fatigue.[166,167,182,183] Given that emotional regulation strategies are not typically included in cognitive training approaches, the improvement of other symptoms may reflect training-induced increase in general brain health. These improvements may also reflect the effects of user-game-experience and positive psychology principles,[184,185] which increase internal locus of control, self-efficacy, and distraction from real-world problems. However, in general, transfer effects of cognitive training remain inconsistent.[186] In addition, “training to the test” can confound cognitive training effects, as certain training exercises resemble the cognitive tests that are used to evaluate their effectiveness.

Physical Activity

Physical activity (PA) is associated with improved cognitive function in both human and animal studies.[188–190] In healthy adults, executive functions show the largest and most consistent exercise-related increases, while improvements in memory and other cognitive skills have been less reliable thus far.[190] PA increases neurogenesis[188–190] and the levels of neurotransmitters and neurotrophins that promote cognitive function,[188,191] it reduces inflammation,[192] and it stimulates positive brain vasculature changes.[188] Reduction of psychological and chronic medical conditions (eg, depression, sleep disruption, diabetes, obesity) associated with PA[193] may also indirectly improve cognitive function. PA is also believed to moderate the signaling pathways involved in neuroprotection,[194] such as increasing the expression of neuroprotective genes.[191] Importantly, animal studies suggest that PA can improve cognitive function after breast cancer treatment.[195]

Human studies of PA as an intervention for CRCI in breast cancer (Table 1) have involved Hatha yoga, Iyengar yoga, Qigong, and Tai Chi.[168–171] Improvements were noted in processing speed, memory, executive function, and quality of life. In 1 study,[169] cognitive effects were observed after as little as 1 month of intervention with PA, which is consistent with results from previous studies in healthy adults.[196] Specifically, Janelsins and colleagues randomized 358 cancer survivors (75% breast cancer) to a yoga intervention or a no-treatment condition.[169] The intervention consisted of breathing exercises, gentle Hatha and Restorative yoga postures, and meditation twice per week for 75 minutes across 4 weeks. The intervention group demonstrated significantly improved subjective memory functioning and quality of life as well as reduced fatigue compared with the no-treatment group.

Thus far, PA studies in breast CRCI have focused on specific types of nonaerobic interventions, despite national guidelines suggesting that moderate to vigorous intensity aerobic exercise is recommended for brain health.[196] PA interventions have also involved relatively short durations (ie, 2–10 weeks), which may not result in lasting benefit among older adults.[197] In addition, most of the existing studies did not include objective cognitive tests, and none have adequately evaluated executive function, although this domain is among the most commonly impaired after breast cancer and the most amenable to PA intervention. The relationship between PA and cognitive function, especially executive function, is bidirectional. In healthy adults, executive function has been shown to moderate PA adherence.[198–201] In addition, decreased prefrontal cortex activity has been associated with reduced self-regulation of PA behavior in healthy adults.[202] This is unsurprising given that core executive functions, including working memory, inhibition, and task switching, are believed to be critical for successful self-regulation.[203] Individuals with executive dysfunction often have difficulty changing ideas or behaviors,[204,205] and cognitive dysfunction can be a barrier to PA engagement after cancer.[206] Accordingly, the combination of PA with cognitive interventions may prove more optimal for some cancer survivors, particularly those with significant CRCI.

Both physical and cognitive exercise increase neuroplasticity but do so through different pathways. PA results in an increased number of new neurons; however, roughly 50% of these die within a few weeks, never reaching full maturity or becoming connected with other neurons.[207] Based on emerging animal studies, many of these neurons may be rescued with

cognitive training, which enables them to form functional connections within brain networks.[207] Therefore, the combination of PA and cognitive training may result in greater cognitive benefit compared with either approach alone. Preliminary human and animal studies provide additional support for this hypothesis.[190,207–213]

Regular mental activity is known to be neuroprotective by increasing cognitive reserve.[214] As such, it is theoretically possible that cognitive interventions conducted before and/ or during cancer therapy could help prevent cognitive difficulties. However, the optimal timing of behavioral interventions for CRCI remains unaddressed within the literature. It is also unknown how natural neural recovery and response to behavioral intervention are affected by different cancer types and treatments. Only 1 study of cognitive rehabilitation and cognitive training in breast cancer conducted thus far demonstrated no intervention effects. In that study, the breast cancer group showed a decline in verbal memory from post-intervention to 6-month follow–up, suggesting that early cognitive rehabilitation/cognitive training intervention may not have stable effects.[164] That study was unique in that participants were only off-therapy an average of 2 months. As in other forms of acquired brain injury, cognitive impairment after breast cancer treatment is often characterized by initial deficit occurring within the first 6 months followed by a 1-year to 2-year recovery/ stabilization period.[62,215] The majority of the other intervention studies reviewed above involved long-term survivors and several years off-therapy, with a minimum time off-therapy (excluding endocrine therapy) ranging from 0.5 to 3 years. The rationale for the minimum time off-therapy, when provided, was consistently to allow for neurologic and medical/health stabilization.

Further research is needed regarding cognitive interventions conducted before treatment and/or during the acute recovery phase (approximately 0–6 months) after adjuvant cancer therapies (ie, chemotherapy and radiation). Cognitive rehabilitation or cognitive training programs may require currently unknown modifications to be effective preventive approaches. It is also possible that exercise interventions may have greater potential for prevention, given that the majority of exercise studies conducted to date occurred during or shortly after cancer therapy.

Neuromodulation Strategies

Cognitive neuroscience-based interventional research offers new, noninvasive approaches for ameliorating cognitive dysfunction. Neurofeedback is a method that involves providing a participant with feedback regarding her brain activity as a means of training her to control the up-regulation and down-regulation of brain activity using metacognitive strategies. Various cognitive-behavioral symptoms are potentially reduced by targeting appropriate brain regions. Neurofeed-back is provided via EEG, functional near-infrared spectroscopy (NIRS), or real-time fMRI. Neurofeedback studies conducted in noncancer populations demonstrate that participants can learn to control the activation of specific brain regions related to motor function, attention, pain response, and emotion regulation, among others.[216] One study has been conducted in breast cancer survivors and demonstrated positive effects on subjective cognitive function using EEG neurofeedback (Table 1), suggesting potential for this and similar neurofeedback techniques.[172]

Repetitive transcranial magnetic stimulation (rTMS) uses magnetic fields to modulate neuronal excitability. During the procedure, a TMS coil is suspended over a specific area of the head to deliver short electromagnetic pulses. The technique is currently approved by the US Food and Drug Administration for the treatment of depression, but it is also being investigated as a means of improving cognitive performance.[217,218] Currently, there have been no studies of rTMS for CRCI, although positive effects on memory and attention impairments have been documented in other populations,[219,220] making it a promising potential intervention for future studies.

Pharmacotherapy

Very few psychopharmacologic agents have proven effective in reducing or preventing cognitive impairment in non-CNS cancer patients. Psychostimulants like methylphenidate, dexmethylphenidate, and modafinil have produced mixed results; and, at present, the effectiveness of these agents is not well established. Another example of an agent that received attention after initial preclinical findings is donepezil, an acetylcholinesterase inhibitor. However, its effectiveness remains uncertain, as only 2 small studies with conflicting findings have been published so far.[221–223] More rigorous clinical trials with sufficient sample sizes are necessary to definitively assess the potential of such pharmacologic agents in the treatment of CRCI.

Unraveling the precise mechanisms underlying CRCI may facilitate the identification of novel pharmacologic treatment strategies. Several animal studies focusing on the impact of chemotherapy on cognition have suggested promising interventions, such as preventing oxidative stress associated with chemotherapy using 2-Mercaptoethane sulfonate,[224] N-acetylcysteine, or melatonin[225]; stimulating neurogenesis with insulin-like growth factor-1,[226] fluoxetine, or glucose[227,228]; and treatments with glutamate receptor antagonists, such as dextromethorphan[229] or memantine,[230] that ameliorate chemotherapy-induced CRCI. The arrival of new targeted agents and immunotherapies that may influence cognition, either alone or in combination with traditional anticancer agents, will necessitate further preclinical work to understand and potentially improve adverse side effects on cognition. In addition, tumor-bearing model systems will be essential in the evaluation of potential adverse effects of promising agents on antitumor efficacy.

Summary

CRCI is a frequent adverse effect of non-CNS cancer and systemic anticancer therapies in adults. While predominantly investigated in women with breast cancer, these adverse outcomes are common to many other cancer patient populations (eg, colorectal carcinoma, leukemia, lymphoma, multiple myeloma, ovarian carcinoma, prostate carcinoma, testicular cancer). Clinical observational studies have characterized the most typical pattern of cognitive dysfunction associated with CRCI (ie, memory loss, slowed processing speed, and executive dysfunction), have provided some early estimates of incidence (ranging from17% to over 70%), and have identified potential clinical and patient factors that modify risk (eg, chemotherapy dose, cognitive reserve, presence of an *APOEε*4 allele). It has been demonstrated that this neurotoxicity adversely impacts patients' and survivors' quality of

life, including occupational and social functioning, and results in increased health care and societal costs.

More recently, various preclinical and neuroimaging studies have begun to shed light on the pathophysiologic mechanisms that may underlie CRCI. It is anticipated that continued research in these areas will create translational science opportunities to develop and test pharmacologic and behavioral interventions to prevent, reduce, or eliminate this untoward neurotoxicity. Currently, few intervention studies involving CRCI after breast cancer have been conducted, and many of these are limited by methodological concerns, including small sample sizes, lack of objective cognitive testing, inclusion of other cancer types, limited public health dissemination potential, and/or lack of proper control conditions. In addition, no effective prevention strategies have been identified to date. However, many promising lines of research are emerging that offer hope and promise to future cancer patients and the clinicians who care for them.

Acknowledgments

DISCLOSURES: Supported by the National Institute of Nursing Research of the National Institutes of Health under Award Number R01NR014195 (Dr. Wefel and Dr. Kesler); the National Cancer Institute under Award Number R01CA172145 (Dr. Kesler); and the Dutch Cancer Society under Award Numbers 2009-4284, 2010-4829, and 2012-5495 (Dr. Schagen). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Dutch Cancer Society. Dr. Kesler reports grants from the National Institutes of Health and personal fees for lectures at academic institutions.

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CA Cancer J Clin. Author manuscript; available in PMC 2015 March 11.

TABLE 1

Summary of Intervention Studies for Cancer-Related Cognitive Impairment After Breast Cancer[a]

AUTHORS	NO. OF PARTICIPANTS	INTERVENTION	FINDINGS
Cherrier 2013[159a]	CR, n = 12; NTCs, n = 16; RD; OffTx 4.8 y (≥6 mo)	Seven weekly 1-h group sessions focused on memory aids and skills, mindfulness meditation, homework	Improved working memory, attention, QOL, and SR cognition
Ercoli 2013[160]	CR, n = 27; OffTx ≥18 mo	Five weekly 2-h, manual-guided sessions focused on attention, memory, and executive functioning; homework	Improved attention and executive functioning, SR memory, and cognition; increased global brain EEG activity
Ferguson 2007[161]	CR, n = 29; OffTx ≥3 y	Four monthly 30-min to 50-min, manual-guided sessions focused on attention and memory, CBT, self-awareness, and self-regulation; manual-guided homework; 3 total telephone contacts for support and review	Improved verbal memory, processing speed, response inhibition, executive function, attention, SR cognition, and QOL
Ferguson 2012[162]	CR, n = 19; NTCs, n = 21; RD; OffTx ≥18 mo	Same as above	Improved verbal memory, QOL
McDougall 2011[163a]	CR, n = 8; AC, n = 14; NRD; OffTx not specified	Eight 50-min sessions focused on anxiety, depression, health, metamemory, memory self-efficacy; 4 weekly 2-h booster sessions for 1 mo within 3 mo of completing initial training	Improved SR memory
Popplereuter 2009[164]	CR, n = 33; CT, n = 34; NTCs, n = 29; RD to CT or CR (but NTCs not randomized); OffTx 2.1 mo	Four 1-h inpatient sessions per wk for 3–5 wk; CR: attention, memory processes, skills, and compensatory strategies; CT: unspecified computerized program for attention, memory	No intervention effects
Schuurs and Green 2013[165a]	CR, n = 23; NTCs (cancer), n = 9; NTCs (noncancer), n = 23; NRD; OffTx 36–48 mo	Weekly 2-h, manual-guided group sessions over 6 wk focused on psychoeducation, thematic group discussion, memory and attention skills training, and compensatory strategies with homework; CBT: emotional adjustment, fatigue, sleep, self-care	Improved immediate memory, visuospatial memory, and delayed memory
Kesler 2013[166]	CT, n = 21; WLCs, n = 20; RD; OffTx 6 y (≥18 mo)	Forty-eight 20-min to 30-min sessions over 12 wk of home-based, computerized Lumosity program for executive function, processing speed, verbal fluency	Improved executive function, verbal fluency, processing speed, SR executive function behaviors
Von Ah 2012[167]	CT memory, n = 26; CT processing speed, n = 27; WLCs, n = 29; RD; OffTx 65.5 mo (≥1 y)	Ten 1-h small group sessions over 6–8 wk; computerized Posit Science program for memory or processing speed	Improved verbal memory, SR cognition, SR memory; anxiety in CT memory group vs WLCs; improved processing speed, memory, depression, anxiety, mental health in CT processing speed group vs WLCs
Galantino 2012[168]	PA, n = 4 (case studies); OffTx, n = 0 (enrolled prechemotherapy)	Iyengar yoga 2 × wk for 12 wk	Improved cognitive speed and accuracy, QOL
Janelsins 2012[169a]	PA, n = 168; NTCs, n = 160; RD; OffTx 2–24 mo	Biweekly 75-min sessions for 4 wk; breathing exercises; gentle Hatha and Restorative yoga postures and meditation	Improved SR memory
Reid-Arndt 2012[170a]	PA, n = 23; OffTx not specified, but participants were 6.5 y postdiagnosis	Biweekly 1-h Tai Chi classes for 10 wk	Improved verbal memory, attention, verbal fluency, executive function, SR verbal and visual memory
Oh 2012[171a]	PA, n = 37; NTCs, n = 44; RD; OffTx not specified, but some patients were still undergoing chemotherapy	Biweekly 90-min sessions for 10 wk of medical Qigong group class	Improved SR cognition, QOL; reduced C-reactive protein levels

AUTHORS	NO. OF PARTICIPANTS	INTERVENTION	FINDINGS
Alvarez 2013[172]	Neurofeedback, n = 23; participants served as their own WLCs; OffTx 6–60 mo	Biweekly 30-min sessions for 10 wk of Zengar approach, whole-brain EEG neurofeedback	Improved SR cognition, QOL, fatigue, sleep function, psychological symptoms

AC indicates active/attention control; CBT, cognitive-behavioral therapy; CR, cognitive rehabilitation; CT, cognitive training; EEG, electroencephalography; NRD, nonrandomized; NTCs, no treatment controls; OffTx, time off-therapy (chemotherapy, radiation; presented as the mean time if available or the minimum requirement as indicated by study methods); PA, physical activity; QOL, quality of life; RD, randomized; SR, self-rated; WLCs, waitlist controls.

[a] References for our literature review of intervention studies were identified via PubMed and Google Scholar searches using combinations of the keywords cognit*, rehabilitation, training, remediation, neuropsycholog*, intervention*, trial, cancer, radiation, chemotherap*, chemobrain, brain, exercise*, “physical exercise,” “physical activity,” neuroplasticity, enhance*, learn*, memory, executive, speed, and attention. Searches were limited to human subjects and articles written in English.

[b] The sample for this study included participants with other cancer diagnoses in addition to breast cancer.