The Effect of Cancer Treatment on Cognitive Function

Arash Asher, MD, and Jamie S. Myers, PhD, RN, AOCNS

Dr Asher is the director of Cancer Survivorship and Rehabilitation at the Samuel Oschin Comprehensive Cancer Institute at the Cedars-Sinai Medical Center and an assistant clinical professor in the department of Health Sciences at University of California, Los Angeles. Dr Myers is a postdoctoral scholar in the School of Nursing at the University of Pittsburgh in Pittsburgh, Pennsylvania and an adjunct assistant professor in the School of Nursing at the University of Kansas in Kansas City, Kansas.

Corresponding author:
Arash Asher, MD
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center
University of California, Los Angeles
8700 Beverly Boulevard, AC 1109
Los Angeles, California 90048
E-mail: Arash.Asher@cshs.org
Tel: 310-423-2111
Fax: 310-854-5930

Keywords
Cancer, cancer treatment, chemobrain, cognitive impairment

Abstract: Cognitive dysfunction is an increasingly recognized complication of cancer and its treatment. Most research in this arena has found that a subset of patients appear to be vulnerable to this complication even after treatment has ended, and often have difficulties with multitasking, short-term memory, word-finding, attention, or concentration. The mechanisms underlying these cognitive changes are not fully elucidated but may include direct neurotoxic effects of therapy, oxidative damage, and genetic predisposition. Compelling evidence has accumulated for the role of immune dysregulation and neurotoxicity from inflammatory cytokines. A gold standard for subjective or objective assessment of cancer treatment–related cognitive changes has yet to be established. Current options to assess cognitive function include neuropsychological testing, functional neuroimaging, and subjective assessments. Pharmacologic treatment options for this clinical problem are modest and limited. Nonpharmacologic treatments, including cognitive rehabilitation programs, are an emerging area of research for the management of cancer treatment–related cognitive changes.

Introduction

More than 14 million Americans are alive today with a history of cancer.[1] This number is expected to approach 20 million in the United States alone by 2024.[1] Given the extraordinary number of individuals who are surviving after a cancer diagnosis, increased attention is being given to issues related to function, quality of life, and community integration after treatment. One key concern among cancer survivors is cognitive dysfunction, commonly referred to in the lay community as "chemobrain" or "chemo-fog." The purpose of this review is to provide clinicians with a scientific overview of the current state of this phenomenon among patients with cancer who do not have central nervous system (CNS) disease, including possible pathophysiology, assessment, and treatment approaches.

Table 1. Diagnostic Clues for Cancer Treatment–Related Cognitive Changes

Typical symptoms of chemobrain
Forgetfulness
Slower processing speed
Impaired concentration and attention
Difficulty with multitasking
Word-finding difficulties
Short-term memory challenges
Decreased reaction time
Memory deficits not affected by chemobrain
Reasoning
Problem solving
Talent
Old memories

Chemobrain is a phenomenon that refers to the general mental fog many patients with cancer experience during or after treatment. This condition encompasses a range of symptoms such as short-term memory loss, difficulty in thinking and concentration, impaired multitasking, and other subtle cognitive changes (Table 1). No single symptom or set of symptoms is pathognomonic for cognitive dysfunction due to cancer and its treatment. Moreover, cognitive complaints often are associated with persistent fatigue and depressive symptoms that historically have complicated evaluation and research. Over the last decade, the literature on cognitive changes after cancer treatment has rapidly expanded and been subjected to much more rigorous study. The research, in general, has demonstrated that cognitive concerns can negatively and sometimes dramatically impact function, quality of life, and community integration.[2,3] Fortunately, deficits in long-term memory and syndromes suggestive of cortical dysfunction, such as aphasia, agnosia, and apraxia, generally do not occur[4] (Table 1).

Most studies suggest that up to 75% of patients with cancer experience cognitive impairment during treatment, and 15% to 35% of cancer survivors experience cognitive problems months to years following treatment.[5,6] However, the prevalence of cognitive dysfunction varies widely in the literature, and multiple challenges impede the accurate assessment of the incidence of cognitive dysfunction, including the lack of prechemotherapy assessment of cognitive function, differences in the populations being studied, and the lack of standardized assessment tools and neuropsychological batteries. Measurement of cancer-related cognitive dysfunction in the literature is hampered further by differences in inclusion criteria, timing of cognitive assessments, and varying comparison groups (ie, published normative data, healthy matched controls, patients with cancer not treated with chemotherapy, etc). Furthermore, patients differ with respect to tumor type, stage of disease, concomitant treatment (nausea regimens, hormonal treatments, and multimodality treatments), and medical comorbidities—all of which could impact cognitive function.[7] Some researchers have reported that cognitive changes associated with cancer treatment often resolve within 1 year, whereas others have documented long-term changes that last for more than 20 years.[8-10]

Multiple studies using prechemotherapy cognitive assessments have demonstrated that some patients have cognitive dysfunction *prior* to receiving any treatment. For example, several studies have noted that approximately 20% to 35% of patients with breast cancer have lower than expected cognitive performance based on age and education at the pretreatment assessment.[5,11-13] Pretreatment cognitive dysfunction also has been found in other populations, including patients with acute myelogenous leukemia and lung cancer.[14,15] In addition, because cancer is generally an illness that affects older populations, it is not surprising that age is a confounding factor for cognitive challenges. One-fifth of geriatric patients with cancer screen positively for cognitive disorders.[16]

The majority of studies in this area have been conducted using women with breast cancer. Cross-sectional data suggest that 16% to 75% of patients with breast cancer experience cognitive impairment during chemotherapy, compared with 4% to 11% of healthy controls.[6] Jim and colleagues reported meta-analysis findings on cognitive function obtained from 17 studies of 807 survivors of breast cancer treated with standard-dose chemotherapy at least 6 months previously. Cognitive deficits were limited to verbal and visuospatial ability and were generally small in magnitude.[17] However, many experts purport that a subset of cancer survivors may be particularly vulnerable to more significant cognitive changes.[18] For example, one recent study used neuropsychological tests to demonstrate that a subgroup of breast cancer survivors continued to experience a decline in cognitive function over time after treatment.[19] Another recent report evaluating cognitive function among survivors of allogeneic stem cell transplantation found that, after 5 years, survivors continued to recover within some cognitive domains (eg, verbal fluency and executive function) but deficits remained for more than 40% of patients.[20]

Hypotheses for Causal Mechanisms

Many mechanisms have been suggested to explain cognitive dysfunction in patients with cancer (Table 2), including direct neurotoxic effects of therapy (eg, inhibition of hippocampal neurogenesis), genetic predisposition, oxidative

Table 2. Factors Potentially Contributing to Cognitive Dysfunction Among Patients With Cancer

Depression/anxiety
Chronic social isolation/stress
Inactivity/deconditioning
Other medications (benzodiazepines, corticosteroids, certain antiemetics, opioids, etc)
Other medical problems (hypothyroidism, anemia, liver disease, etc)
Hormonal changes (androgen deprivation, estrogen deprivation)
Genetic factors (*APOE4*, *COMT*)
Inflammatory cytokines
Nutritional factors and deficiencies
Direct neurotoxic effects of chemotherapy
Poor cognitive reserve (due to age, education, etc)

damage, and immune dysregulation. Definitive evidence to support a single mechanism is absent, and discovering a final common mechanistic pathway may be unrealistic.

Direct neurotoxicity from chemotherapy is one obvious hypothesis for the etiology of cognitive dysfunction in this setting (hence the term chemobrain). However, determining the biggest offender in the various classes of chemotherapeutic agents is problematic. Because multiple classes of drugs often are used in combination, it is difficult to isolate the effects of chemotherapy from other aspects of treatment, such as radiation therapy and surgery. Nevertheless, we know that certain agents (eg, methotrexate and 5-fluorouracil) are particularly neurotoxic and cause diffuse white matter changes on neuroimaging.[4,21,22] Animal studies have suggested that certain chemotherapeutic agents (eg, carmustine, cisplatin, and cytarabine) may be more toxic to white matter progenitor cells and hippocampal stem cells than they are to actual cancer cells.[23,24] Anemia is also a well-known side effect of myelosuppressive chemotherapies. Anemia may cause cerebral hypoxia due to a decrease in hemoglobin concentration, and has been associated with fatigue and cognitive dysfunction.[25]

Genetic factors also may predispose some patients with cancer to cognitive dysfunction. Variants of genes encoding apolipoprotein E *(APOE)* and catechol-O-methyltransferase *(COMT)* have both been associated with age-related cognitive decline in the general population.[26] ApoE plays a role in neuronal repair and plasticity after injury, and one study suggested that long-term cancer survivors with at least 1 ApoE4 allele who were previously treated with chemotherapy had poorer cognitive function.[27] COMT plays a role in the breakdown of catecholamines. Small and colleagues found that patients with breast cancer who had the COMT-Val allele performed worse on tests of attention, verbal fluency, and motor speed than those without the allele.[28]

The appreciation that some patients with cancer have cognitive problems prior to receiving any chemotherapy has changed our understanding of the mechanisms behind this syndrome. One hypothesis to explain this phenomenon is that risk factors may be shared for cognitive dysfunction and certain cancers. For example, poor DNA repair mechanisms have been linked to both problems.[29] Another potential mechanism is known as the "accelerated aging hypothesis," which proposes that cancer treatment accelerates the aging process through a variety of mechanisms, including increased DNA damage, shortened telomeres, inflammation, and oxidative stress.[5] Different patients may be vulnerable to different mechanisms, which can account for the observations that older breast cancer survivors may be at elevated risk for cognitive dysfunction.[30]

The field of psychoneuroimmunology has shed light on the mechanisms of cognitive change after cancer treatment. Tissue trauma and inflammation from surgery, radiation, chemotherapy, biologic therapy, and targeted therapy can trigger systemic inflammation that can cross the blood-brain barrier and have deleterious effects on the CNS.[31,32] Circulating proinflammatory cytokines have been shown to impair learning and memory in animals.[33] In these studies, administration of proinflammatory cytokines to the brain increases the metabolism of key neurotransmitters, including noradrenaline, dopamine, and serotonin.[34] These neurotransmitters are central to the regulation of memory, learning, sleep, and mood. Moreover, administration of innate immune cytokines to laboratory animals has been shown to disrupt long-term potentiation in the hippocampus and thereby disrupt memory consolidation.[35] Once cytokines reach the brain, they stimulate the resident immune cells (ie, microglia) to produce other proinflammatory cytokines and inflammatory mediators.[36,37] This may explain why cognitive dysfunction is not limited to patients with brain tumors (primary or metastatic) or to treatment directly targeting the brain.

Psychological and emotional stress can alter the hypothalamic pituitary adrenal axis and sympathetic nervous system, which then can alter the immune system in a similar way.[38] In this light, some investigators have argued that chemobrain has a somatic component in some patients, such as may occur in fibromyalgia and chronic fatigue syndrome. This hypothesis purports that the physical and psychological distress of cancer treatment triggers biologic alterations (such as acute shifts in cytokines) that result in epigenetic alterations. These epigenetic modifications may create long-term homeostatic changes that are responsible for the neuroplastic alterations in cancer-related cognitive

dysfunction.[39] Recent evidence also has pointed to certain single nucleotide polymorphisms (eg, in *IL1R1*) that may significantly increase the chance for cytokine-induced changes in cognition after treatment.[40] This evidence supports the International Cognition and Cancer Task Force report, highlighting a consistent finding in the literature that subgroups of patients are more vulnerable to cognitive changes.[41]

Assessment Techniques

A gold standard for subjective or objective assessment of cancer treatment–related cognitive changes has yet to be established. Many challenges have been noted, including inconsistent correlation between objective and subjective measures, the lack of objective instruments sensitive enough to capture the subtle cognitive changes perceived by some survivors, and the lack of instruments that accurately simulate the real-world environment in which cancer survivors must function. Objective neuropsychological testing requires special training and significant time to administer, thus adding to survivors' burden. Neuroimaging has been used in the clinical trial setting to document cancer treatment–related changes in brain structure and function. Researchers continue to search for accessible, cost-effective measures of intervention efficacy.

Self-Report

Self-reporting of perceived treatment-related changes in cognitive function provides important data to oncology health care professionals. Subjective data frequently are criticized as lacking the robustness of objective neuropsychological testing; however, evidence has shown that perceived cognitive decline precedes the objective evidence demonstrated with neuroimaging.[42] Results from some studies indicate that perceived cognitive function is affected by fatigue and mood, such as anxiety and depression, and self-report instruments actually may measure a different construct than objective testing.[13,43,44] Regardless, survivors' perceptions of cognitive decline, much like other symptoms that are difficult to quantify (eg, pain), are an important indicator of the impact of cancer treatment on daily function and quality of life. These data also are important to assess the efficacy of any interventions.

Numerous self-report instruments have been employed in clinical trials for this patient population. However, only a few were specifically designed to measure cancer and cancer treatment–related cognitive changes as a primary outcome; most studies tested cognitive decline merely as a subscale or component of the trial while measuring multiple symptoms.

The Attentional Function Index (AFI) was designed for use in individuals with cancer to assess their perceived effectiveness in daily activities that require attention, working memory, and higher-level executive functions, including setting goals, planning and carrying out tasks, and monitoring behavior to meet intended goals. The AFI assesses patients' perceived losses in their capacity to direct their attention.[45] The AFI consists of a 13-item visual analogue scale (0-100 mm) that can be converted to a numeric rating scale (0-10). Factor analysis revealed 3 subscales: effective action (7 items), attentional lapses (3 items), and interpersonal effectiveness (3 items). Higher scores indicate better perceived functioning and less attentional fatigue. Attentional fatigue can be categorized as high (<5.0), moderate (5.0-7.5) and low (>7.5).[46]

The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG, version 3) is a 33-item instrument designed to measure patients' self-reports of chemotherapy-related cognitive function.[47] Participants rank items for 4 scales: perceived cognitive impairments (18 items), perceived cognitive abilities (7 items), comments from others (4 items), and impact on quality of life (4 items) as applicable during the past 7 days. Items for perceived cognitive impairments and comments from others are ranked from 0 (never) to 4 (several times a day). Items for perceived cognitive abilities and impact on quality of life are ranked from 0 (not at all) to 4 (very much). Higher scores indicate better-perceived cognitive function and quality of life.

Developers of the FACT-COG recently expanded the items to create item banks for 2 Patient Reported Outcomes Measurement and Information System (PROMIS) scales.[48] These 2 scales, PROMIS v1.0-Applied Cognition-Abilities and PROMIS v1.0-Applied Cognition-Concerns, include 33 positively worded items and 42 negatively worded items, respectively. Both scales utilize 5-point intensity ratings in which higher numbers reflect survivors' perceptions of better cognitive function. These instruments were validated with data from 509 individuals diagnosed with cancers of the breast, colon, rectum, prostate, and lung. Validated short forms for both instruments (8 items, 6 items, and 4 items) are available as well.

The National Comprehensive Cancer Network (NCCN) Guidelines for Survivorship do not yet recommend any one brief screening tool for assessing cognitive function, but suggest screening survivors with questions regarding their ability to pay attention, find words, remember things, think clearly, and perform functions.[49] They also suggest ascertaining the time of onset for cognitive complaints and assessing the trajectory over time. Additionally, survivors should be assessed for concomitant conditions that may contribute to cognitive issues, such as anxiety, depression, fatigue, sleep disturbance, and pain. These conditions should be appropriately addressed.

Likewise, survivors' medications should be reviewed, because many medications can contribute to alterations in cognition.

Neuropsychological Testing

A lack of consistency among the neuropsychological tests for the various cognitive domains affected by cancer treatment has made comparisons across studies difficult. The International Cognition and Cancer Task Force (ICCTF) published the recommendation that 3 core tests be used in future studies so that meta-analyses would be possible. These recommended tests are the Hopkins Verbal Learning Test-Revised, the Trail Making Test, and the Controlled Oral Word Association Test of the Multilingual Aphasia Examination.[41] The ICCTF made these recommendations based on the adequate sensitivity of the tests in measuring the key cognitive domains affected (learning and memory, processing speed, and executive function), sufficient psychometric properties, suitability for multinational application, and the existence of alternative forms (to decrease practice effects). The task force acknowledged the need to reduce the time and energy necessary to conduct the neuropsychological testing battery so that undue burden is not placed on study participants or investigators.

Specific descriptions of the multitude of available neuropsychological tests are well summarized elsewhere.[50] The NCCN Guidelines recognize the importance of validating survivors' cognitive complaints and suggest that neuropsychological evaluation in itself can be reassuring to survivors. The guidelines also suggest referring patients to a neuropsychologist when clarity is needed about the nature of the impairment and/or the survivor is pursuing disability status related to limitations in cognitive function.

Neuroimaging

Considerable work has been done in the area of neuroimaging, both to objectively demonstrate structural and functional changes due to non-CNS cancer and the related treatments, and to investigate potential causal mechanisms.[51] However, the bulk of this work has been conducted in the breast cancer population.

The majority of the neuroimaging work to date has employed magnetic resonance imaging (MRI) to measure white and gray matter volume and functional MRI to measure neural activity.[51] Some studies have employed proton MR spectroscopy to measure brain metabolite levels and neurochemical changes. Brain activity and metabolism also have been measured with positron emission tomography. Most breast cancer studies have demonstrated decreased gray and white matter volumes, changes in brain activation during memory tasks, and a correlation between self-reports and objective deficits on neuropsychological batteries. Both hyperactivation and hypoactivation have been noted, appear to be task dependent, and may be compensatory. These differences have been more pronounced in women who have received chemotherapy, and have been shown to persist for many years after completion of cancer treatment. Neuroimaging studies conducted in mixed cancer populations also have demonstrated decreased metabolism in patients with cancer (both treated and untreated with chemotherapy). Further longitudinal work is needed to compare patients receiving chemotherapy, patients not receiving chemotherapy, and healthy controls. The NCCN Guidelines suggest that neuroimaging outside of the clinical trial setting be restricted to patients who demonstrate focal neurologic deficits or those at high risk for CNS disease.[49]

Overview of Intervention Research

The search for efficacious interventions for cancer treatment–related cognitive changes is critically important to cancer survivors and oncology health care providers. Relatively modest results have been demonstrated for pharmacologic interventions and no agents have been granted US Food and Drug Administration (FDA) approval to date for this indication. Likewise, research conducted to investigate nonpharmacologic interventions is in preliminary stages; however results have been interesting in a number of areas. Categorizations of the intervention studies conducted to date are listed in Tables 3 and 4.

Pharmacologic Interventions

Neurostimulants. Research results thus far have been equivocal regarding the use of neurostimulants (such as methylphenidate and modafinil) as interventions for cancer-related cognitive changes. Both drugs have been of interest owing to their FDA-approved indications for attention deficit disorder (methylphenidate) and narcolepsy (modafinil). Early work with methylphenidate looked promising for patients with advanced disease; both subjective and objective improvements were seen for alertness, attention, memory, executive function, and psychomotor function. These studies were very small (N≤30) and included patients receiving continuous intravenous opioids[52] or those with hypoactive delirium.[53] However, later studies have been negative for efficacy[54,55] or the results have been mixed.[56] Modafinil studies also have been equivocal because of small sample sizes, noncontrolled designs, differences in dose and duration of therapy, and variations in which cognitive domains show improvement. Additionally, many of these studies do not use cognition as the primary endpoint.[57] At this time, neither drug has sufficient evidence of efficacy to move forward with an approved indication.[57]

Table 3. Pharmacologic Intervention Studies

	Agent	Design (N)	Reference No.
Neurostimulants	Methylphenidate	DBPC, crossover (20)	52
		RDBPC, 2-period, crossover (33)	56
		Prospective, nonrandomized (14)	53
		Systematic review and meta-analysis (498)	82
		RDBPC, parallel group (154)	54
		RDBPC, placebo run-in (57)	55
		Prospective, nonrandomized (12)	83
		Systematic review, 8 studies (255)	84
	Modafinil	Prospective (19)	85
		Prospective (82)	86
		RDBPC, crossover (28)	87
Erythropoiesis-stimulating agents	Erythropoietin	Prospective, randomized (354)	88
		Prospective, nonrandomized (50)	89
		Prospective, observational (42)	90
		Prospective, nonrandomized (87)	91
		Prospective, nonrandomized (10)	92
		RDBPC (94)	93
Antioxidants	Ginkgo biloba	RDBPC (166)	60
	Melatonin	RDBPC (54)	61

DBPC, double-blind, placebo-controlled; RDBPC, randomized, double-blind, placebo-controlled.

Antioxidants. One hypothesis is that cognitive decline may be caused by DNA damage from antineoplastic agents and the production of reactive oxygen species. For this reason, antioxidants have been investigated as possible therapeutics. Both vitamin E and ginkgo biloba have been studied in the cancer population. High doses of vitamin E (1000 mg twice a day for 12 months) were shown to positively impact executive function, verbal memory, and visual memory.[58] However, concerns have been expressed that doses greater than the recommended daily allowance (400 international units) may be associated with increases in mortality.[59] No positive impact on cognition has been demonstrated with the use of ginkgo biloba in patients with breast cancer.[60] A recent secondary analysis of a randomized, double-blind, placebo-controlled trial for the effect of melatonin on cognitive function and sleep showed improved sleep efficiency, but no effect on cognitive function.[61]

Erythropoiesis-stimulating agents. Initial interest was shown in the investigation of erythropoietin owing to the associations seen between anemia (lower oxygen carrying capacity to the brain and fatigue) and cognitive complaints. Despite encouraging results, these agents are no longer being studied because of safety concerns, including an increased risk for cardiovascular and thrombotic events and decreased survival.[57]

None of the pharmacologic agents are without side effects and toxicities. As such, the investigation of nonpharmacologic interventions is very appealing from an economic and patient satisfaction perspective.

Nonpharmacologic Interventions

Cognitive rehabilitation. Cognitive rehabilitation encompasses a number of interventions with different (or different combinations of) foci. In very general terms, cognitive training typically involves a series of exercises to enhance attention, concentration, and memory skills. These exercises may be computerized, and repetition and practice are important to the success of the intervention. Cognitive behavioral training is focused more on adaptive strategies to compensate for deficits in the various cognitive domains, and may also focus on confounding factors such as anxiety, depression, and fatigue. Many study designs include a combination of cognitive training and cognitive behavioral training. Additional terminology that is used includes psychoeducation, which involves providing didactic information about the challenges of cancer and cancer-related cognitive changes in addition to content about adaptive strategies and exercises to

Table 4. Nonpharmacologic Intervention Studies

Intervention Type		Design (N)	Reference No.
Cognitive rehabilitation	Cognitive training	Randomized, controlled (41)	94
		Randomized, controlled, single-blind (82)	95
	Cognitive behavioral training	Prospective, nonrandomized (29)	96
		Prospective, randomized (40)	97
		Randomized, controlled (98)	98
		Prospective, nonrandomized (22)	99
		Prospective, nonrandomized (53)	100
	Combination	Prospective, randomized (28)	101
		Prospective, nonrandomized (27)	102
		Randomized, controlled (90)	103
	Residential rehabilitation programs	Randomized, controlled (394)	104
Biofeedback	Electroencephalography or neurofeedback	Prospective, nonrandomized (23)	81
Exercise: aerobic		Cross-sectional, nonrandomized (37)	71
		Prospective, nonrandomized (26)	65
		Prospective, nonrandomized (408)	74
Exercise: resistance		Prospective, nonrandomized (17)	70
Exercise: mindfulness-based	Yoga	Randomized, controlled (200)	72
		Case series (4)	105
	Tai chi	Prospective, nonrandomized (23)	75
	Qigong	Prospective, randomized, controlled (81)	73
Physical activity intensity		Prospective, nonrandomized (15)	106
Biofeedback/exercise combination	Speed feedback with bicycle ergometer	Randomized, controlled, single-blind (78)	107
Meditation/mindfulness-based stress reduction		Prospective, randomized (42)	80
		Prospective, randomized, controlled (229)	79
Natural restorative environment		Prospective, nonrandomized (32)	76
		Prospective, randomized, controlled (157)	77
Guided imagery	Telemedicine delivery of imagery intervention	Randomized, controlled (118)	78
Combination therapy	Exercise and psychoeducation	Prospective, nonrandomized (658)	108

RDBC, randomized, double-blind, controlled.

improve various domains. Likewise, some programs are referred to as psychosocial or residential rehabilitation and provide psychoeducational content within the context of a retreat setting. This overlap in terminology makes review of studies somewhat difficult when attempting to synthesize the evidence in support of cognitive rehabilitation interventions. An attempt at differentiating the various studies conducted to date can be seen in Table 4. Promising preliminary results have been demonstrated in a number of studies. The Oncology Nursing Society's Putting Evidence Into Practice (PEP) panel for cognitive impairment recently published an update stating that cognitive training research has reached a level of evidence to imply this intervention is "likely to be effective." By contrast, the evidence from studies evaluating cognitive behavioral training requires additional research to achieve the same level of recommendation because of the need for additional larger randomized, controlled trials.[57]

Exercise. Exercise is currently an exciting area of research for this patient population. Evidence continues to build in support of aerobic, resistance, and mindfulness-based exercise as potential interventions for cancer and cancer treatment–related cognitive changes. The primary rationales proposed for the success of physical activity and exercise are: (1) a reduction in markers of inflammation that accompany cancer and cancer treatments and (2) an increase in brain-derived neurotrophic factor levels and hippocampal volume.[62-64] Exercise is known to combat fatigue and sleep disturbances[65,66] and has been shown to improve cognitive performance in a variety of patient populations, such as the elderly,[67] those with Alzheimer disease,[68] those with Parkinson disease,[69] and preliminarily those with various types of cancer.[65,70-74]

Mindfulness-based exercises (such as yoga, tai chi, and qigong) are postulated to have additional benefits, possibly because they tap into different pathways than aerobic or resistance exercise alone.[72,73,75] Likewise, other mindfulness-based interventions such as meditation, natural restorative environments, and guided imagery have shown efficacy in the reduction of cognitive complaints.[76-80]

Exercise intervention studies thus far have been preliminary in nature and many questions remain regarding the most effective type(s) of exercise regimens, timing, duration, frequency, and intensity (ie, dosage).

Electroencephalography biofeedback. Pilot study results regarding the feasibility of electroencephalography biofeedback to reduce subjective cognitive complaints for breast cancer survivors demonstrated significant improvements in perceived cognitive function (N=23).[81] This intervention involves the use of a "real-time display of the brain's electrical activity, fed back as visual or auditory information" enabling the participant to "modify that brainwave activity." This intervention is based on the premise that the brain's neuroplasticity can be used to restore brain function.

Nonpharmacologic interventions show promise, but a great deal of research still is needed to provide appropriate levels of evidence to recommend specific interventions to cancer survivors with cognitive complaints, or to justify preventative measures to be employed prior to and during treatment for cancer.

Future Research Needs

Over the last decade, mounting evidence for the biologic effects of cancer treatment on behavioral symptoms have validated patient complaints of persistent cognitive difficulties after cancer treatment ends. In general, the magnitude of impairment appears to be modest, although the symptoms may have a major impact on quality of life. A subset of cancer survivors may be most profoundly affected, with negative implications for community reintegration, social pursuits, and viability of returning to the workplace. Future research is needed to further refine our understanding of underlying mechanisms and identify those patients who might be most vulnerable to cognitive changes. Many potential confounders, including fatigue, insomnia, medication side effects, and hormonal changes, need to be accounted for before arriving at a definitive conclusion on the pathophysiology of this important clinical problem. Most studies of cognitive change after cancer treatment have excluded those who would presumably be the most vulnerable to cognitive decline—ie, geriatric patients and those with a history of head injury, neurological disorders, or depression. More research is needed to determine the effects of cancer treatment on these susceptible patients to allow for better decision making in the real-world clinical setting. Finally, larger studies are needed to find effective rehabilitation and treatment strategies for this important clinical problem.

Disclosures

The authors have declared no relevant conflicts of interest.

References

1. American Cancer Society. Cancer Facts & Figures 2015. Atlanta: American Cancer Society; 2015.
2. Argyriou AA, Assimakopoulos K, Iconomou G, Giannakopoulou F, Kalofonos HP. Either called "chemobrain" or "chemofog," the long-term chemotherapy-induced cognitive decline in cancer survivors is real. *J Pain Symptom Manage*. 2011;41(1):126-139.
3. Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB. Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. *Ann Oncol*. 2008;19(4):623-629.
4. Wefel JS, Witgert ME, Meyers CA. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychol Rev*. 2008;18(2):121-131.
5. Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. *J Clin Oncol*. 2012;30(30):3675-3686.
6. Janelsins MC, Kohli S, Mohile SG, Usuki K, Ahles TA, Morrow GR. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Semin Oncol*. 2011;38(3):431-438.
7. Nelson WL, Suls J. New approaches to understand cognitive changes associated with chemotherapy for non-central nervous system tumors. *J Pain Symptom Manage*. 2013;46(5):707-721.
8. Collins B, Mackenzie J, Stewart A, Bielajew C, Verma S. Cognitive effects of chemotherapy in post-menopausal breast cancer patients 1 year after treatment. *Psychooncology*. 2009;18(2):134-143.
9. Ahles TA, Saykin AJ, Furstenberg CT, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol*. 2002;20(2):485-493.
10. Koppelmans V, Breteler MM, Boogerd W, Seynaeve C, Gundy C, Schagen SB. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol*. 2012;30(10):1080-1086.
11. Ahles TA, Saykin AJ, McDonald BC, et al. Cognitive function in breast cancer patients prior to adjuvant treatment. *Breast Cancer Res Treat*. 2008;110(1):143-152.
12. Wefel JS, Lenzi R, Theriault R, Buzdar AU, Cruickshank S, Meyers CA. 'Chemobrain' in breast carcinoma?: a prologue. *Cancer*. 2004;101(3):466-475.
13. Hermelink K, Untch M, Lux MP, et al. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. *Cancer*. 2007;109(9):1905-1913.
14. Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine

levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer*. 2005;104(4):788-793.
15. Meyers CA, Byrne KS, Komaki R. Cognitive deficits in patients with small cell lung cancer before and after chemotherapy. *Lung Cancer*. 1995;12(3):231-235.
16. Rodin MB, Mohile SG. A practical approach to geriatric assessment in oncology. *J Clin Oncol*. 2007;25(14):1936-1944.
17. Jim HS, Phillips KM, Chait S, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol*. 2012;30(29):3578-3587.
18. Rodin G, Ahles TA. Accumulating evidence for the effect of chemotherapy on cognition. *J Clin Oncol*. 2012;30(29):3568-3569.
19. Wefel JS, Saleeba AK, Buzdar AU, Meyers CA. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. *Cancer*. 2010;116(14):3348-3356.
20. Syrjala KL, Artherholt SB, Kurland BF, et al. Prospective neurocognitive function over 5 years after allogeneic hematopoietic cell transplantation for cancer survivors compared with matched controls at 5 years. *J Clin Oncol*. 2011;29(17):2397-2404.
21. Schagen SB, Muller MJ, Boogerd W, et al. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. *Ann Oncol*. 2002;13(9):1387-1397.
22. Winocur G, Vardy J, Binns MA, Kerr L, Tannock I. The effects of the anticancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. *Pharmacol Biochem Behav*. 2006;85(1):66-75.
23. Dietrich J, Han R, Yang Y, Mayer-Pröschel M, Noble M. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. *J Biol*. 2006;5(7):22.
24. Seigers R, Fardell JE. Neurobiological basis of chemotherapy-induced cognitive impairment: a review of rodent research. *Neurosci Biobehav Rev*. 2011;35(3):729-741.
25. O'Shaughnessy JA, Vukelja SJ, Holmes FA, et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. *Clin Breast Cancer*. 2005;5(6):439-446.
26. Harris SE, Deary IJ. The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends Cogn Sci*. 2011;15(9):388-394.
27. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology*. 2003;12(6):612-619.
28. Small BJ, Rawson KS, Walsh E, et al. Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. *Cancer*. 2011;117(7):1369-1376.
29. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer*. 2007;7(3):192-201.
30. Yamada TH, Denburg NL, Beglinger LJ, Schultz SK. Neuropsychological outcomes of older breast cancer survivors: cognitive features ten or more years after chemotherapy. *J Neuropsychiatry Clin Neurosci*. 2010;22(1):48-54.
31. Ganz PA. "Doctor, will the treatment you are recommending cause chemobrain?" *J Clin Oncol*. 2012;30(3):229-231.
32. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. *Nat Rev Cancer*. 2008;8(11):887-899.
33. Holden JM, Overmier JB, Cowan ET, Matthews L. Effects of lipopolysaccharide on consolidation of partial learning in the Y-maze. *Integr Physiol Behav Sci*. 2004;39(4):334-340.
34. Shintani F, Kanba S, Nakaki T, et al. Interleukin-1 beta augments release of norepinephrine, dopamine, and serotonin in the rat anterior hypothalamus. *J Neurosci*. 1993;13(8):3574-3581.
35. Maier SF, Watkins LR. Immune-to-central nervous system communication and its role in modulating pain and cognition: implications for cancer and cancer treatment. *Brain Behav Immun*. 2003;17(suppl 1):S125-S131.
36. Vitkovic L, Konsman JP, Bockaert J, Dantzer R, Homburger V, Jacque C. Cytokine signals propagate through the brain. *Mol Psychiatry*. 2000;5(6):604-615.
37. Banks WA. The blood-brain barrier in psychoneuroimmunology. *Neurol Clin*. 2006;24(3):413-419.
38. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat Rev Immunol*. 2011;11(9):625-632.
39. Wang XM, Walitt B, Saligan L, Tiwari AF, Cheung CW, Zhang ZJ. Chemobrain: a critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy. *Cytokine*. 2015;72(1):86-96.
40. Merriman JD, Aouizerat BE, Cataldo JK, et al. Association between an interleukin 1 receptor, type I promoter polymorphism and self-reported attentional function in women with breast cancer. *Cytokine*. 2014;65(2):192-201.
41. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12(7):703-708.
42. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology*. 2006;67(5):834-842.
43. Correa DD, Hess LM. Cognitive function and quality of life in ovarian cancer. *Gynecol Oncol*. 2012;124(3):404-409.
44. Pullens MJ, De Vries J, Roukema JA. Subjective cognitive dysfunction in breast cancer patients: a systematic review. *Psychooncology*. 2010;19(11):1127-1138.
45. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index—a self-report cognitive measure. *Psychooncology*. 2011;20(2):194-202.
46. Cimprich B, So H, Ronis DL, Trask C. Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. *Psychooncology*. 2005;14(1):70-78.
47. Wagner L, Sweet J, Butt Z, Lai J, Cella D. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. *J Support Oncol*. 2009;7:W32-W39.
48. Lai JS, Wagner LI, Jacobsen PB, Cella D. Self-reported cognitive concerns and abilities: two sides of one coin? *Psychooncology*. 2014;23(10):1133-1141.
49. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®). Survivorship. v.1.2015. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Updated February 27, 2015. Accessed May 15, 2015.
50. Myers JS. Neuropsychologic testing for chemotherapy-related cognitive impairment. *Adv Exp Med Biol*. 2010;678:55-69.
51. Holohan KN, Von Ah D, McDonald BC, Saykin AJ. Neuroimaging, cancer, and cognition: state of the knowledge. *Semin Oncol Nurs*. 2013;29(4):280-287.
52. Bruera E, Miller MJ, Macmillan K, Kuehn N. Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. *Pain*. 1992;48(2):163-166.
53. Gagnon B, Low G, Schreier G. Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. *J Psychiatry Neurosci*. 2005;30(2):100-107.
54. Lower EE, Fleishman S, Cooper A, et al. Efficacy of dexmethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. *J Pain Symptom Manage*. 2009;38(5):650-662.
55. Mar Fan HG, Clemons M, Xu W, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. *Support Care Cancer*. 2008;16(6):577-583.
56. Escalante CP, Meyers C, Reuben JM, et al. A randomized, double-blind, 2-period, placebo-controlled crossover trial of a sustained-release methylphenidate in the treatment of fatigue in cancer patients. *Cancer J*. 2014;20(1):8-14.
57. Von Ah D, Jansen CE, Allen DH. Evidence-based interventions for cancer- and treatment-related cognitive impairment. *Clin J Oncol Nurs*. 2014;18(suppl):17-25.
58. Chan AS, Cheung MC, Law SC, Chan JH. Phase II study of alpha-tocopherol in improving the cognitive function of patients with temporal lobe radionecrosis. *Cancer*. 2004;100(2):398-404.
59. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA*. 2007;297(8):842-857.
60. Barton DL, Burger K, Novotny PJ, et al. The use of Ginkgo biloba for the prevention of chemotherapy-related cognitive dysfunction in women receiving adjuvant treatment for breast cancer, N00C9. *Support Care Cancer*. 2013;21(4):1185-1192.
61. Hansen MV, Madsen MT, Andersen LG, et al. Effect of melatonin on cognitive function and sleep in relation to breast cancer surgery: a randomized, double-blind, placebo-controlled trial [published online August 27, 2014]. *Int J Breast Cancer*. doi:10.1155/2014/416531.
62. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017-3022.
63. Fairey AS, Courneya KS, Field CJ, et al. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. *Brain Behav Immun*. 2005;19(5):381-388.
64. Szuhany KL, Bugatti M, Otto MW. A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *J Psychiatr Res*. 2015;60:56-64.
65. Knobf MT, Thompson AS, Fennie K, Erdos D. The effect of a community-based exercise intervention on symptoms and quality of life. *Cancer Nurs*. 2014;37(2):E43-E50.
66. Mustian KM. Yoga as treatment for insomnia among cancer patients and survivors: A systematic review. *Eur Med J Oncol*. 2013;1:106-115.
67. Erickson KI, Kramer AF. Aerobic exercise effects on cognitive and neural plasticity in older adults. *Br J Sports Med*. 2009;43(1):22-24.
68. de Andrade LP, Gobbi LT, Coelho FG, Christofoletti G, Costa JL, Stella F. Benefits of multimodal exercise intervention for postural control and frontal

cognitive functions in individuals with Alzheimer's disease: a controlled trial. *J Am Geriatr Soc*. 2013;61(11):1919-1926.
69. Murray DK, Sacheli MA, Eng JJ, Stoessl AJ. The effects of exercise on cognition in Parkinson's disease: a systematic review. *Transl Neurodegener*. 2014;3(1):5.
70. Baumann FT, Drosselmeyer N, Leskaroski A, et al. 12-Week resistance training with breast cancer patients during chemotherapy: effects on cognitive abilities. *Breast Care (Basel)*. 2011;6:142-143.
71. Crowgey T, Peters KB, Hornsby WE, et al. Relationship between exercise behavior, cardiorespiratory fitness, and cognitive function in early breast cancer patients treated with doxorubicin-containing chemotherapy: a pilot study. *Appl Physiol Nutr Metab*. 2014;39(6):724-729.
72. Derry HM, Jaremka LM, Bennett JM, et al. Yoga and self-reported cognitive problems in breast cancer survivors: a randomized controlled trial. *Psychooncology*. 2014.
73. Oh B, Butow PN, Mullan BA, et al. Effect of medical Qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. *Support Care Cancer*. 2012;20(6):1235-1242.
74. Sprod LK, Mohile SG, Demark-Wahnefried W, et al. Exercise and cancer treatment symptoms in 408 newly diagnosed older cancer patients. *J Geriatr Oncol*. 2012;3(2):90-97.
75. Reid-Arndt SA, Matsuda S, Cox CR. Tai Chi effects on neuropsychological, emotional, and physical functioning following cancer treatment: a pilot study. *Complement Ther Clin Pract*. 2012;18(1):26-30.
76. Cimprich B. Development of an intervention to restore attention in cancer patients. *Cancer Nurs*. 1993;16(2):83-92.
77. Cimprich B, Ronis DL. An environmental intervention to restore attention in women with newly diagnosed breast cancer. *Cancer Nurs*. 2003;26(4):284-292.
78. Freeman LW, White R, Ratcliff CG, et al. A randomized trial comparing live and telemedicine deliveries of an imagery-based behavioral intervention for breast cancer survivors: reducing symptoms and barriers to care [published online August 22, 2014]. *Psychooncology*. doi:10.1002/pon.3656.
79. Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of mindfulness-based stress reduction in mood, breast- and endocrine-related quality of life, and well-being in stage 0 to III breast cancer: a randomized, controlled trial. *J Clin Oncol*. 2012;30(12):1335-1342.
80. Milbury K, Chaoul A, Biegler K, et al. Tibetan sound meditation for cognitive dysfunction: results of a randomized controlled pilot trial. *Psychooncology*. 2013;22(10):2354-2363.
81. Alvarez J, Meyer FL, Granoff DL, Lundy A. The effect of EEG biofeedback on reducing postcancer cognitive impairment. *Integr Cancer Ther*. 2013;12(6):475-487.
82. Gong S, Sheng P, Jin H, et al. Effect of methylphenidate in pateints with cancer-related fatigue: a systematic review and meta-analysis. *PLoS One*. 2014;9(1):e84391. doi:10.1371/journal.pone.0084391.
83. Schwartz AL, Thompson JA, Masood N. Interferon-induced fatigue in patients with melanoma: a pilot study of exercise and methylphenidate. *Oncol Nurs Forum*. 2002;29(7):E85-E90.
84. Stone P, Minton O. European Palliative Care Research collaborative pain guidelines. Central side-effects management: what is the evidence to support best practice in the management of sedation, cognitive impairment and myoclonus? *Palliat Med*. 2011;25(5):431-441.
85. Blackhall L, Petroni G, Shu J, Baum L, Farace E. A pilot study evaluating the safety and efficacy of modafinal for cancer-related fatigue. *J Palliat Med*. 2009;12(5):433-439.
86. Kohli S, Fisher SG, Tra Y, et al. The effect of modafinil on cognitive function in breast cancer survivors. *Cancer*. 2009;115(12):2605-2616.
87. Lundorff LE, Jønsson BH, Sjøgren P. Modafinil for attentional and psychomotor dysfunction in advanced cancer: a double-blind, randomised, cross-over trial. *Palliat Med*. 2009;23(8):731-738.
88. Chang J, Couture FA, Young SD, Lau CY, Lee McWatters K. Weekly administration of epoetin alfa improves cognition and quality of life in patients with breast cancer receiving chemotherapy. *Support Cancer Ther*. 2004;2(1):52-58.
89. Iconomou G, Koutras A, Karaivazoglou K, et al. Effect of epoetin alpha therapy on cognitive function in anaemic patients with solid tumours undergoing chemotherapy. *Eur J Cancer Care (Engl)*. 2008;17(6):535-541.
90. Mancuso A, Migliorino M, De Santis S, Saponiero A, De Marinis F. Correlation between anemia and functional/cognitive capacity in elderly lung cancer patients treated with chemotherapy. *Ann Oncol*. 2006;17(1):146-150.
91. Fan HG, Park A, Xu W, et al. The influence of erythropoietin on cognitive function in women following chemotherapy for breast cancer. *Psychooncology*. 2009;18(2):156-161.
92. Massa E, Madeddu C, Lusso MR, Gramignano G, Mantovani G. Evaluation of the effectiveness of treatment with erythropoietin on anemia, cognitive functioning and functions studied by comprehensive geriatric assessment in elderly cancer patients with anemia related to cancer chemotherapy. *Crit Rev Oncol Hematol*. 2006;57(2):175-182.
93. O'Shaughnessy JA. Effects of epoetin alfa on cognitive function, mood, asthenia, and quality of life in women with breast cancer undergoing adjuvant chemotherapy. *Clin Breast Cancer*. 2002;3(suppl 3):S116-S120.
94. Kesler S, Hadi Hosseini SM, Heckler C, et al. Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. *Clin Breast Cancer*. 2013;13(4):299-306.
95. Von Ah D, Haberman B, Carpenter JS, Schneidr BL. Impact of perceived cognitive impairment in breast cancer survivors. *Eur J Oncol Nurs*. 2013;17(2):236-241.
96. Ferguson RJ, Ahles TA, Saykin AJ, et al. Cognitive-behavioral management of chemotherapy-related cognitive change. *Psychooncology*. 2007;16(8):772-777.
97. Ferguson RJ, McDonald BC, Rocque MA, et al. Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. *Psychooncology*. 2012;21(2):176-186.
98. Goedendorp MM, Knoop H, Gielissen MF, Verhagen CA, Bleijenberg G. The effects of cognitive behavioral therapy for postcancer fatigue on perceived cognitive disabilities and neuropsychological test performance. *J Pain Symptom Manage*. 2014;47(1):35-44.
99. McDougall GJ, Becker H, Acee TW, Vaughan PW, Delville CL. Symptom management of affective and cognitive disturbance with a group of cancer survivors. *Arch Psychiatr Nurs*. 2011;25(1):24-35.
100. Schuurs A, Green HJ. A feasibility study of group cognitive rehabilitation for cancer survivors: enhancing cognitive function and quality of life. *Psychooncology*. 2013;22(5):1043-1049.
101. Cherrier MM, Anderson K, David D, et al. A randomized trial of cognitive rehabilitation in cancer survivors. *Life Sci*. 2013;93(17):617-622.
102. Ercoli LM, Castellon SA, Hunter AM, et al. Assessment of the feasibility of a rehabilitation intervention program for breast cancer survivors with cognitive complaints. *Brain Imaging Behav*. 2013;7(4):543-553.
103. Poppelreuter M, Weis J, Bartsch HH. Effects of specific neuropsychological training programs for breast cancer patients after adjuvant chemotherapy. *J Psychosoc Oncol*. 2009;27(2):274-296.
104. Rottmann N, Dalton SO, Bidstrup PE, et al. No improvement in distress and quality of life following psychosocial cancer rehabilitation. A randomised trial. *Psychooncology*. 2012;21(5):505-514.
105. Galantino ML, Greene L, Daniels L, Dooley B, Muscatello L, O'Donnell L. Longitudinal impact of yoga on chemotherapy-related cognitive impairment and quality of life in women with early stage breast cancer: a case series. *Explore (NY)*. 2012;8(2):127-135.
106. Fitzpatrick TR, Edgar L, Holcroft C. Assessing the relationship between physical fitness activities, cognitive health, and quality of life among older cancer survivors. *J Psychosoc Oncol*. 2012;30(5):556-572.
107. Miki E, Kataoka T, Okamura H. Feasibility and efficacy of speed-feedback therapy with a bicycle ergometer on cognitive function in elderly cancer patients in Japan. *Psychooncology*. 2014;23(8):906-913.
108. Korstjens I, Mesters I, van der Peet E, Gijsen B, van den Borne B. Quality of life of cancer survivors after physical and psychosocial rehabilitation. *Eur J Cancer Prev*. 2006;15(6):541-547.