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Chemotherapy-related cognitive impairment in older patients with cancer

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Abstract

Chemotherapy-related cognitive impairment (CRCI) can occur during or after chemotherapy and represents a concern for many patients with cancer. Among older patients with cancer, in whom there is little clinical trial evidence examining side effects like CRCI, many unanswered questions remain regarding risk for and resulting adverse outcomes from CRCI. Given the rising incidence of cancer with age, CRCI is of particular concern for older patients with cancer who receive treatment. Therefore, research related to CRCI in older patients with cancers is a high priority. In this manuscript, we discuss current gaps in research highlighting the lack of clinical studies of CRCI in older adults, the complex mechanisms of CRCI, and the challenges in measuring cognitive impairment in older patients with cancer. Although we focus on CRCI, we also discuss

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cognitive impairment related to cancer itself and other treatment modalities. We highlight several research priorities to improve the study of CRCI in older patients with cancer.

Keywords

Chemotherapy; Cancer treatment; Cognitive impairment; Older patients; Research gaps

1. Introduction

Evidence suggests that cancer treatments can cause cognitive impairment that is subjectively reported or objectively measured using neuropsychological tests.[1–4] Patients with cognitive impairment may encounter challenges in daily functioning, decision-making and treatment adherence, leading to decreased quality of life and possibly shorter survival.[5–7] Cognitive impairment can also increase caregiver burden. Prevention of cognitive impairment in patients with cancer undergoing treatment is therefore especially important in older patients, given the increasing long-term survival with new treatments and the increasing numbers of older patients living with cancer as a chronic condition.

Cross-sectional and longitudinal studies often do not include enough older patients with cancer to evaluate the interactions that exist among cancer, its treatment, aging and effects on cognition. Assessing cognitive impairment is challenging in the clinical trial setting given lack of routine use of standardized, brief and accurate neuropsychological testing. When cognitive impairment is detected in clinical practice, oncologists are often unprepared to manage the abnormal results. Additionally, there is a lack of evidence-based preventive measures or interventions when cognitive impairment is detected in the cancer population. A study suggested that patients were less likely to accept treatments that may worsen their cognition, but it is unclear how the presence of cognitive impairment in a patient with cancer affects oncologists' decision-making process.[8] As a result, controversy exists regarding the benefits of screening patients for cognitive impairment in clinical practice. Therefore, the National Cancer Institute (NCI) has designated chemotherapy-related cognitive impairment (CRCI), often called “chemo brain” or “chemo fog,” as a high-priority area of research. In this manuscript, we discuss current gaps in research and highlight research priorities for the study of CRCI in older patients with cancer, with some mention of cognitive impairment related to cancer itself and also to other treatment modalities given that they frequently overlap.

The research gaps and priorities were initially discussed during a National Institute on Aging (NIA)/NCI sponsored U13 conference. The U13 conference provides a forum for a multidisciplinary team of investigators in geriatrics and oncology to review the present level of evidence in geriatric oncology, identify areas of highest research priority, and develop research approaches to improve clinical care for older adults with cancer. The research gaps were then further refined during monthly calls with the expert group over a 4-month period. The expert group is composed of 6 geriatric oncologists and 2 geriatricians who have expertise in the care of older adults with cognitive impairment and/or have conducted research in the area, 2 researchers with expertise in cognitive effects of cancer treatments

and 1 patient advocate. We performed a literature search on PubMed using the keywords “cognition”, “cancer”, “prevalence” and “chemotherapy”. For research gap 1, relevant studies which described prevalence of CRCI and included older adults with cancer were selected from the search results. For research gap 4, studies evaluating treatment and preventive strategies for CRCI were selected if they were randomized trials or pre- and post-intervention in design (keywords “cognition”, “cancer”, “chemotherapy” and “treatment or prevention”). The studies were presented to the group of experts in cognition who selected the ones to be included in the manuscript. The studies were chosen with the purpose of illustrating research gaps rather than providing a comprehensive review of the literature.

2. Research Gaps

2.1. Gap 1: Very Few Studies Focus Exclusively on the Prevalence of CRCI in Older Adults With Cancer

CRCI has been reported in up to 12–75% of patients with cancer and is associated with cancer type, treatment, duration of follow-up, type of study design and definition of cognitive impairment.[1,2] Most of these published studies assessed prevalence of CRCI in a heterogeneous group of patients, including both young and old patients, illustrated by first three studies in Table 1.[9,10,11] However, since the impact of chemotherapy on cognition in older adults with cancer may be more significant given the higher prevalence of pre-existing cognitive impairment in this age group, studies that include older patients exclusively would provide more relevant information. Little is known about how chemotherapy influences the prevalence of cognitive impairment in older patients with cancer.

To date, there are only a few studies that focused on prevalence of CRCI in older patients with cancer (29–51% in Table 1). The limited number of studies may be because researchers are reluctant to study CRCI in older adults due to challenges in study accrual and high dropout rates compared to their younger counterparts.[12,13] Older adults are also more reluctant to participate in clinical trials due to comorbidities, economic constraints, communication issues such as impaired hearing and eyesight, cultural divisions, language barriers, physical immobility with constraints in transportation and lack of social support.[14]

To overcome the barriers for researchers and patients, a number of strategies can be explored. McMurdo et al. recommended improving recruitment of older adults to research through good practice, including proper planning and engaging older adults in the importance of research.[12] Proper planning may include simple, clear and legible reading materials that are appropriate for those with visual, hearing and cognitive impairment; adequate time allocation for appointments and breaks; and optimization of physical environment such as mobility and transportation assistance. To increase engagement of older adults in research, it may be meaningful to include the participants and their carers in the planning stages. McHenry et al. also presented three major themes in their recruitment strategies in older adults: communication and trust-building, providing comfort and security, and expressing gratitude.[15]

Older patients frequently have multiple barriers to limit their participation in research, and a team of members with different expertise within a multidisciplinary team (MDT) may help

address barriers that interfere with the representation of older adults in research studies. The MDT approach is used in the care of elderly patients clinically and it has been shown to improve functional outcomes.[16] In the research setting, the MDT team can include the physicians who introduce the studies, researchers and research assistants who provide information on the studies with proper planning, social workers who provide assistance with transportation and financial difficulties and caregivers who provide support in navigating the complex research process. However this approach can be resource and time-consuming, has not been studied in the recruitment of older adults in research, and needs to be investigated further.

2.2. Gap 2: Biologic Drivers of CRCI in Older Patients With Cancer are Unknown

Evidence from clinical and pre-clinical research suggests that many mechanisms play a role in the development of CRCI, including inflammation, hormonal changes, DNA damage, oxidative stress, reduced synaptic plasticity, altered growth factor levels, and impaired hippocampal neurogenesis.[17–37] Several neuroimaging studies in patients with cancer show the impact of cancer and chemotherapy on brain structure and function, revealing white and gray matter loss, altered resting state metabolism changes and altered white matter integrity, and brain activation upon cognitive task challenge.[38–55] Additionally, alleles in genes *APOE* and *COMT* have been linked to CRCI, suggesting that lipid metabolism, neural repair and neurotransmitter signaling also play a role in CRCI.[56,57] Other mechanisms that have been proposed including epigenetic effects, and genes involved in longevity and aging.

Due to multi-morbidity and polypharmacy, the investigations of the biological mechanisms of CRCI in older patients are more complex than in younger patients for several reasons: 1) many mechanisms that are involved in CRCI are also involved in comorbid conditions, 2) comorbid conditions can increase vulnerability to CRCI by biological mechanisms similar or dissimilar from the mechanisms causing the condition itself, 3) the use of multiple medications can impact the measurement of many biological factors that may be related to CRCI, and 4) older patients are more likely to need dose- and drug-related changes to treatments which could differentially impact cognition.

In addition to cognitive reserve, education, gender, and anxiety and depression that are often assessed for their contribution to cognitive change in CRCI, careful measurement and assessment of comorbid conditions and medications in older patients are particularly important to consider in biomarker studies due to their increased frequency compared to younger patients. For example, hypertension, hyperlipidemia, diabetes, arthritis, osteoporosis, respiratory conditions, and neurodegenerative disorders are all impacted by inflammatory processes—the same cytokines, chemokines, and cognate receptors implicated in these diseases are also implicated in CRCI.[19,20] It is not well-understood how chronic inflammation and resultant oxidative stress across the lifespan impact a new diagnosis of cancer in the older patient. Teasing apart these interactions is challenging and emphasizes the need for control groups of similar age and comorbidity level so that we can better understand the specific impact of cancer and chemotherapy treatments on cognition. It is important to appreciate that some biological mechanisms may already be at play impacting cognition as part of the normal aging process in this population. For example, studies

investigating cognition in patients with cancer prior to surgery and chemotherapy suggest that inflammation is associated with cognitive decline.[58]

While not yet studied, it is likely that other biological, genetic, and epigenetic pathways also play a role in cognitive changes in older patients with cancer. Having a grasp on the biological and cognitive status of the older patient prior to cancer treatment is essential, as is understanding how these change over time in the context of their treatment, disease status, and comorbid conditions. Although not limited to older patients, there are two other ongoing trials that will be of interest: (1) studying changes in size, shape and activity in some brain areas that can occur in women receiving different types of breast cancer therapy (NCT01949376) and (2) studying the pathological changes of the brain using PET in patients with prostate cancer after ADT (NCT00006349).

By understanding the risk factors for cognitive dysfunction and the interaction between cancer treatment and the aging process, we can develop tools to risk-stratify patients for likelihood of cognitive impairment. These tools could help oncologists weigh the benefits relative to the risks of cancer therapy and introduce interventions to reduce the risks of new or worsening cognitive impairment.

2.3. Gap 3: Impact of Treatment on Cognition is not Routinely Measured in Trials Involving Older Adults With Cancer

Traditionally, clinical trials in oncology have focused on cancer-specific clinical endpoints such as overall survival, progression-free survival and response rates. Cognitive function is often not included as an endpoint in intervention trials assessing chemotherapy in most cancer subtypes, despite the fact that patients value cognition as an important outcome.[8] Additionally, patients and caregivers want information on how cancer treatment affects cognition.[59,60] In a qualitative study of the cancer treatment decision-making process in older patients, most patients accepted treatments only if they felt they were physically and cognitively able to tolerate them.[60] Older patients with cancer also based their treatment decisions on anticipated adverse cognitive outcomes, independent from the burden of the treatment such as the length of the hospital stay, extent of testing, and invasiveness of interventions.[8] Fried et al. studied 226 adults age ≥ 60 years with a limited life expectancy due to cancer, congestive heart failure, or chronic obstructive pulmonary disease and found that if the treatment burden was low but resulted in survival with severe cognitive impairment, 89% would decline treatment.[8] These data highlight the importance of incorporating cognitive function as an endpoint in clinical trials involving older patients with cancer, especially if the interventions are known to have a risk of cognitive impairment.

Understanding how to best measure the impact of cancer and treatment on cognitive function in older patients is a research priority. Cognitive dysfunction and its effects in published studies are generally assessed via patient-reported outcomes through semi-structured interviews or through validated questionnaires or batteries of standardized neuropsychological tools. Examples of some validated questionnaires and neuropsychological tests are listed in Tables 2 and 3. The International Cognition and Cancer Task Force (ICCTF) recommended The Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of

the Multilingual Aphasia Examination as cognitive assessments to be used in patients with cancer.[61] However, the ICCTF did not make specific recommendations for the optimal assessments to use with older patients with cancer. Prior to the ICCTF recommendations, the Radiation Therapy Oncology Group (RTOG) has adapted a similar cognitive assessment battery in clinical trial of patients with cancer.[62,63] However, the administration of these standardized tests by neuropsychologists, trained investigators or research assistants required substantial training. Moreover, administration of these tests is time consuming and fatiguing and therefore can be challenging in older patients due to impaired hearing or vision or low education at baseline.[3,64]

As studies have shown that certain domains are more commonly affected in patients with cancer (such as memory, motor function, attention, processing speed, concentration and executive functioning), one possible solution is to utilize screening tools focused on these domains [e.g. mini–mental state examination (MMSE), Montreal Cognitive Assessment (MOCA) or Blessed Orientation-Memory-Concentration (BOMC)], and if the tests are positive, comprehensive neuropsychological testing can follow.[65–67] However, the Mini-mental State Examination (MMSE) has only rarely been used in studies of cognitive function screening in patients with cancer, and now requires a per use fee.[68] The MOCA test may be a superior screening test for multi-domains including executive functioning. Nevertheless, these tests have variable sensitivity and specificity in non-cancer populations,[69–71] therefore there is a definite need to validate the sensitivity and specificity of these screening tests in patients with cancer prior to wider usage.

Another challenge in studying cognitive impairment among patients with cancer is determining what magnitude of cognitive function change should be considered clinically relevant. The ICCTF recommends defining clinically significant cognitive impairment if the result is ≥2 SDs below the mean for one test, or ≥1.5 SDs below the mean for more than one test to facilitate between study-comparison.[61] The ICCTF also encourages investigators to report the frequency of impairment for each test, the number of patients showing impairment on one, two or three tests and so forth, and the most common patterns of impairment. However the task force only defines cognitive impairment using neuropsychological testing, not other clinical measures such decline in activities of daily living (ADL) or instrumental activities of daily living (IADLs). In other studies, impairment was defined as scoring below the lowest quartile on at least four tests, scoring below the tenth percentile on two cognitive domains and scoring below the fifth percentile on at least four tests.[72–74] The clinical relevance of these changes is unclear, as a systematic review by Hutchinson et al. found that only 8 of the 24 studies had a significant relationship between objective cognitive impairment measured by neuropsychological testing and patient-reported cognitive impairment.[75] A European task force recommends the use of changes in ADL as a co-primary outcome for Alzheimer's trials, but this recommendation has not been widely adopted in cancer research.[76] One possible explanation may be that a significant decline in cognitive function is required for a change in ADLs.[77] More research is needed to associate changes in measurements of cognitive function with outcomes meaningful to older patients with cancer.

2.4. Gap 4: Few Randomized Clinical Trials Study Treatment and Preventive Strategies for CRCI in Older Patients With Cancer

Clinical trials of CRCI interventions have focused mostly on cancer survivors with cognitive impairment after cancer treatment, and few studies have evaluated how to prevent or decrease cognitive impairment during treatment for cancer.[44,78–80] Additionally, most intervention studies have included only a small number of patients. These interventions can be grouped into pharmacological and non-pharmacological categories. Examples of pharmacological agents investigated included donepezil, methylphenidate, modafinil and erythropoietin.[78,79,81,82] Non-pharmacological interventions include specific exercise programs and cognitive training.[80,83,84] Selected studies are shown in Table 4.

Only three intervention studies included patients with a mean age above 60[69,70,72]; two of these studies evaluated non-pharmacological interventions. Trials evaluating the safety and efficacy of pharmacological agents for cognitive impairment typically do not include many older patients with cancer. Modafinil is a wake-promoting agent that is effective in the treatment of excessive sleepiness associated with narcolepsy and in persons with shift-work sleep disorder. Lundorff et al. randomized 28 patients with advanced cancer (not specific to CRCI; mean age 62, range 40–79) treated in palliative care settings to modafinil or placebo.[85] Compared to placebo, the modafinil group demonstrated improvement in executive function and motor speed.

More data support non-pharmacological interventions such as exercise and cognitive behavioral training in older patients. A randomized study by Oh et al. evaluated the effects of medical Qigong (combination of gentle exercise and meditation) in 81 patients with cancer (mean age 64.6, SD 12.3) who either had received chemotherapy (66%) or were undergoing chemotherapy (34%). The intervention group participated in a 10-week Qigong program.[84] Compared to placebo, the intervention group reported significantly better cognitive function. Another study by Reid-Arndt evaluated the use of Tai-chi in 23 women (mean age 62.3, SD 10.8) who had been diagnosed with any cancer and had undergone chemotherapy, with treatment completed at least 12 months prior to the start of the study. Study participants received 60 minute Tai-Chi classes two times/week for 10 weeks.[83] At the end of the study, improvements were noted in memory, verbal fluency and attention. A clinical trial is currently ongoing to evaluate the use of acupuncture to prevent “chemo brain” in patients with breast cancer (NCT02457039) but it is not limited to older patients.

None of the aforementioned studies were exclusive to older patients with cancer. Additionally, most of the studies had small sample size, and only included a small number of older adults. Sprod at al. conducted a secondary analysis of a longitudinal study of 408 newly diagnosed older patients with cancer (mean age 73, range 65–92) who underwent chemotherapy and/or any radiation therapy.[86] The group found that the oldest patients (≥80 years) who exercised during treatment self-reported less memory loss during treatment.

To date, no studies have looked at strategies to prevent CRCI. Therefore, we need randomized trials to evaluate interventions for prevention of cognitive impairment in patients with cancer undergoing chemotherapy, especially among older patients who have a high risk for cognitive decline with cancer treatments.

3. Conclusion and Research Priorities

CRCI is increasingly recognized but research focused on older patients with cancer is limited, which may be due to the difficulty of studying this group due to underlying medical complexities and the effect of aging as a potential confounder. The development of cognitive impairment is likely multifactorial, with contributing factors including, but not limited to, aging, comorbidities, underlying cancer, cancer treatment, psychoactive medications, and psychosocial, environmental and genetic risk factors. Yet this is an essential area of research given its clinical importance. Effective interventions for patients with cancer with CRCI are also lacking, as are guidelines on how to care for older patients with cancer and CRCI.

Addressing the following research priorities will help close gaps in knowledge by illuminating how to best prevent or improve cognitive outcomes in older patients with cancer. These priorities are: 1) design a longitudinal study to evaluate the prevalence of cognitive impairment exclusively in older patients with cancer; 2) investigate the role of the MDT approach to increase the participation of older adults with cancer in clinical studies; 3) delineation of the mechanisms of injury in older patients with cancer and examine the complex interactions of cognition with cancer, cancer treatments and psychosocial, lifestyle and genetic risk factors in parallel to aging; 4) develop tools to risk-stratify the likelihood of developing cognitive impairment; 5) develop validated cognitive screening and neuropsychological tests as well as patient-reported outcomes that are feasible and meaningful for older patients with cancer; 6) implement randomized controlled trials on the prevention and treatment of cognitive impairment in older patients with cancer. It is crucial that we design studies exclusively for older adults with cancer to fill the gaps illustrated above and to better understand the interplay between CRCI and aging.

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Table 1

Selected studies on prevalence of CRCI in younger and older adults.

Reference	Population	Treatment	Age (years)	Time during which testing was performed	Tests use/ measures	Cognitive domains tested	Results
Cruzado et al., 2014[10]	81 colon cancer patients	Chemotherapy	Mean 67.0 (range 38–85)	Pre-chemotherapy. T2: post-chemotherapy. T3: 6 months from last chemotherapy	Neuropsychological tests[a]	Attention and visual-motor ability, executive function, verbal memory and verbal learning	Cognitive dysfunction in 37% at baseline, 37% at T2 and 39% at T3
Wefel et al., 2010[11]	42 T1–3, N0–1, M0 breast cancer patients	Chemotherapy	Mean 48.8 (range 33–65)	At baseline: before chemotherapy. T2: during and shortly after chemotherapy [2.9 (SD, 0.59) or 7 (SD, 1.4) months after baseline). T3: 7.7 months (SD, 3.1) after completion of chemotherapy	Neuropsychological tests[a]	Attention, processing speed, learning and memory, executive function	– Cognitive dysfunction in 21% at baseline, 65% at T2 and 61% at T3. – At T3, 29% has evidence of new delayed cognitive decline. – Cognitive decline most common in learning and memory, executive function, and processing speed.
Kohli et al., 2007[9]	595 newly diagnosed solid tumor patients	Chemotherapy or radiation therapy or both	Mean 56.3 (range 29–92)	At baseline: within 2 weeks before initiation of chemotherapy. T2: within 2 weeks of completing treatment. T3: 6 months after completing treatment	Symptom Inventory	Concentration, memory	– Concentration problems in 48% at baseline, 67% at T2 and 58% at T3. – Problems with memory in 53% at baseline, 67% in T2 and 68% in T3.
Hurria et al., 2006[59]	45 stage I–III breast cancer patients; 84	Chemotherapy	Mean 70 (range 65–84)	Before chemotherapy. T2: 6 months after chemotherapy	Squire Memory Self-rating Questionnaire	Self-reported learning, working memory and remove learning	51% perceived decline in memory from baseline to T2.
Hurria et al., 2006[3]	31 stage I–III breast cancer patients	Chemotherapy	Mean 71 (range 65–84, SD 5)	Before chemotherapy. T2: 6 months after chemotherapy	Neuropsychological tests[b]	Attention, verbal memory, visual memory; and verbal, spatial, psychomotor and executive functions	Cognitive dysfunction in 11% at baseline, 29% at T2.

Impairment defined as:

[a]Scoring 2.0 SDs below published norms on one test or 1.5 SDs below published norms on two tests;

[b]Scoring ≥ 2.0 SDs below published norms on two or more tests.

Table 2

Examples of cognitive domains and neuropsychological tests.

Cognitive domain	Neuropsychological test
Verbal/visual learning and memory	Rey Auditory Verbal Learning Test
	Hopkins Verbal Learning Test
	Wechsler Memory Scale
	Verbal Memory Subtest of the Barcelona Test
	Brief Visuospatial Memory Test
	Luria MemoryWords Test
	Spanish Adaptation Barcelona Test
Executive function	Controlled Oral Word Association Test
	Timed Instrumental Activities of Daily
	Living Test
	Stroop Test
	Interference Score of the Stroop Color and
	Word Test
	Trail Making Test B
Intelligence	National Adult Reading Test
	Wechsler Adult Intelligence Scale
Language	Boston Naming Test
Concentration/ Attention	Digit Span of the Wechsler Adult
	Intelligence Scale
	Trail Making Test
	D2 Test of Attention
	Color Trails
Fluency	Word Fluency Subtest from the Dutch
	Aphasia Society Test
Motor speed	Fepsy Finger Tapping Task

Table 3

Examples of validated questionnaires in assessing cognitive function.

Subjective assessment of cognition	Description	Scores
Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)[87]	37-Item questionnaire is divided into six cognitive domains: memory, concentration, mental acuity, verbal fluency, functional interference, and multitasking ability.	Range from 0 to 148, with higher scores indicating better cognitive functioning
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30)[77,88]	30-Itemquestionnaire, two items [cognitive functioning scale (EORTC-CF)] that assess the cognitive domains of concentration and memory	Range from 0 to 100, with higher scores indicating better perceived cognitive function
Cognitive Failures Questionnaire[89]	25-item, 4 point Likert scale, self-report measure of everyday cognitive lapses such as forgetting appointments or where one has left things (e.g. keys, wallet), lapses in concentration or attention, or word-finding difficulty	Range from 0 to 100, higher scores on the CFQ are indicative of greater number or severity of cognitive complaints.
Multiple Abilities Questionnaire (MAQ)[90]	Self-report measure of cognitive problems encountered in daily life. Each of the 48 items is rated on a 5-point scale for frequency of cognitive lapses or successes yielding a total score, as well as scores for 6 domains (attention, language, remote memory, verbal memory, visual–spatial memory, and visual–spatial perception).	Range from 0 to 240, higher scores indicating worst perceived cognitive function
Self-perceived deficits in attention (FEDA) and for subjectively experienced everyday memory performance (FEAG)[73,74]	27 items in FEDA and 29 items in FEAG, each item is rated on a 5-point scale. FEDA assesses self-rated distractibility and retardation of mental processes, fatigue and retardation in activities of daily living and decrease in motivation. FEAG assesses forgetfulness.	Range from 27 to 135 in FEDA, 29–145 for FEAG, lower scores indicating worst perceived cognitive function
Mini-mental State Examination (MMSE)[68]	Brief screening test for cognitive deficits, covers a number of domains in orientation, registration, attention and calculation, recall, language, and copying.	Range from 0 to 30, higher scores indicating better cognitive function
Montreal Cognitive Assessment (MOCA)[91]	Screening test for cognitive deficits, covers a number of domains in short-term memory, visuospatial abilities, executive functions, attention, concentration, and working memory	Range from 0 to 30, higher scores indicating better cognitive function

Table 4

Selected studies on pharmacological and non-pharmacological interventions for CRCI that included older adults.

Study	Design	N	Population	Intervention group	Comparison group	Outcome
Lawrence et al., 2015[78]	Randomized, double-blind, placebo controlled	62	Patients with invasive breast cancer who completed adjuvant chemotherapy 1 to 5 years previously and who reported significant cognitive symptoms	Median age 55.8 (range 41–78, 35% ≥ 60) Donepazil 5 mg/day vs. placebo for 6 weeks, if tolerated 10 mg/day for 18 weeks	Median age 55.8 (range 39.79, 43% ≥ 60) Placebo	Improvement in recall and discrimination
O'Shaughnessy et al., 2005[92]	Randomized, double-blind, placebo controlled	100	Women ≥18 years of age diagnosed with stage I, II, or III breast cancer scheduled to receive 4 cycles of anthracycline-based adjuvant or neoadjuvant chemotherapy	Mean age 53.3 (SD 9.7) 40,000 units of EPO weekly throughout chemotherapy	Mean age 54.3 (SD 12) Placebo	Prior to cycle 4 of chemotherapy, executive functioning was improved in EPO-treated group compared to placebo but no difference was noted at 6 months
Fan HG et al., 2008[93]	Randomized, double-blind, placebo controlled	57	Patients with fully resected early breast cancer undergoing adjuvant chemotherapy	Median age 50 (range 36–73) D-Methylphenidate 5–10 mg until the end of chemotherapy	Median age 51 (range 37–74) Placebo	No change in cognitive function
Kohli et al., 2009[79]	Randomized, double-blind, placebo controlled	82	Breast cancer patients who completed chemotherapy for a month	Mean age 22.1 (SD 22.7) Modafinil 200 mg/day one-month after chemotherapy and/or radiation treatment	Mean age 22.1 (SD 22.7) Placebo	Improvement in memory and attention skills
Lundorff et al., 2009[85]	Randomized, double-blind, cross-over	28	Advanced cancer patients treated in palliative care settings	Median age 62 (range 40–79) Modafinil day 1 then cross-cover to placebo on day 8, placebo day 1 then cross-cover to modafinil on day 8	NA	Improvement in executive function and motor speed
Oh B et al., 2012[84]	Randomized trial	81	Cancer patients who had received or undergoing chemotherapy	Mean age 64.6 (SD 12.3) Qigong (combination of gentle exercise and meditation) for 10 weeks	Mean age 61.1 (SD 11.0) Usual care	Improved cognitive function
Reid-Arndt et al., 2012[83]	Before and after intervention	23	Cancer patients who had completed chemotherapy at least 12 months	Mean age 62.3 (SD 10.8) Tai-chi 60-min class twice/week for 10 weeks	NA	Improvement in memory, verbal fluency and attention
Kesler et al., 2013[80]	Randomized, placebo trial	41	Breast cancer survivors (stage I–IIIA) who on average completed chemotherapy for 6 years	Mean age 55 (SD 7) Online executive training program for 12 weeks	Mean age 56 (SD 6) Waitlist	Improvement in cognitive flexibility, verbal fluency and processing speed
Ferguson et al., 2012[94]	Randomized, double-blind, placebo controlled	40	Stage I and II breast cancer who had received adjuvant chemotherapy	Mean age 51.2 (SD 7.3) Cognitive behavioral therapy (Memory and Attention Adaptation Training)	Mean age 49.4 (SD 5.1) Waitlist	Improvement in verbal memory
Janelsins et al., 2015[95]	Randomized trial	328	Cancer survivors after adjuvant treatment	Mean age 55.2 (SD 11.0) Standard care and YOCAS©® yoga—a program of breathing, gentle Hatha and	Mean age 54.0 (SD 8.7) Standard care	Reduced patient-reported memory difficulty

Study	Design	N	Population	Intervention group	Comparison group	Outcome
				restorative postures, and meditation		