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Cognitive Effects of Chemotherapy and Cancer-Related Treatments in Older Adults

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Abstract

Advances in cancer treatment are producing a growing number of cancer survivors; therefore, issues surrounding quality of life during and following cancer treatment have become increasingly important. Chemotherapy-related cognitive impairment (CRCI) is a problem that is commonly reported following the administration of chemotherapy treatment in patients with cancer. Research suggests that CRCI can persist for months to years after completing treatment, which has implications for the trajectory of normal and pathologic cognitive aging for the growing number of long-term cancer survivors. These problems are particularly relevant for older individuals given that cancer is largely a disease of older age, and the number of patients with cancer who are age 65 years or older will increase dramatically over the coming decades. This review will briefly summarize empirical findings related to CRCI, discuss CRCI in older patients with cancer, potential causative hypotheses, and provide a canonical patient case to illustrate how CRCI presents clinically. Finally, potential intervention strategies for CRCI will be highlighted and issues to consider when evaluating older patients with a history of cancer will be discussed.

Keywords

chemotherapy-related cognitive impairment; chemotherapy; cognitive impairment; subjective cognitive decline

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1. Introduction

Advances in cancer treatment are producing a growing number of cancer survivors; therefore, issues surrounding quality of life during and following cancer treatment have become increasingly important. Chemotherapy-related cognitive impairment (CRCI) is one such quality of life issue that is commonly reported following the administration of chemotherapy in patients with cancer.¹ Although studies reporting cognitive impairments associated with chemotherapy have been reported in patients with non-central nervous system (non-CNS) cancers since the 1980s,² the phenomenon commonly referred to as ‘chemo brain’ or ‘chemo fog’ is poorly understood and, until relatively recently, was largely unacknowledged.³ Research suggests that CRCI can persist for months to years after finishing treatment,⁴ which may have implications for the trajectory of cognitive aging for the growing number of long-term cancer survivors.⁵ These implications are particularly relevant for older individuals as risk for not only cancer, but cognitive impairment increases with age. As of January 2016, 62% of cancer survivors (9.61 million) are currently 65 years or older,⁶ and this number is expected to increase dramatically over the coming decades.⁷ Therefore, as the number of older cancer survivors who will have to cope with CRCI is likely to increase, it is crucial to understand how CRCI presents clinically and to screen for symptoms of cognitive impairment. This article will briefly provide an overview of CRCI, discuss risk factors for CRCI, and will highlight potential intervention strategies and therapeutic targets for CRCI. A typical patient case summary is included to illustrate how CRCI often presents clinically, as well as to provide context for how current research can inform clinical practice.

Case Summary

The patient is a 68-year-old, married woman employed as a teacher at a high school with a history of breast cancer. At 65-years of age, she presented with an abnormal routine mammogram screening; subsequent diagnostic imaging revealed a suspicious abnormality in her right breast. She underwent lumpectomy with axillary lymph node dissection, and pathology revealed stage IIa (pT1c, pN1, cM0), estrogen receptor-positive and progesterone receptor-positive (ER+/PR+), human epidermal growth factor receptor 2-positive (HER-2/neu+), invasive ductal carcinoma. The patient received chemotherapy and targeted therapy consisting of 6 cycles of taxotere, carboplatin, and trastuzumab, as well as radiotherapy to the right breast and underarm. Chemotherapy and radiotherapy were followed by adjuvant endocrine therapy with letrozole and completion of one year of maintenance trastuzumab to reduce risk of breast cancer recurrence. During chemotherapy, the patient reported worsening fatigue and cognitive complaints, including greater difficulty with memory, attention, concentration, and ability to multitask. The patient was advised that cognitive complaints during chemotherapy are not uncommon and would likely improve following completion of chemotherapy.

Follow-up with the patient 2-years post-chemotherapy revealed that the patient’s cognitive complaints have not improved. She has stated that her symptoms have negatively impacted her job as a teacher. She denies receiving complaints about her work performance, but suspects that her coworkers are aware of changes. Upon questioning, she states that she has

difficulty with word finding, needs reminders and notes to complete tasks, frequently loses paperwork, reports being easily distracted, has forgotten events and conversations, has trouble learning new work-related tasks, and that it takes greater cognitive effort to complete work-related tasks. She denies trouble recognizing faces, getting lost while navigating in familiar places, or any change in ability to manage household chores. She ambulates, dresses, bathes, drives, and shops independently. She states that she has been less interested in socializing, due to anxiety and distress surrounding her cognitive functioning.

She stated that at a breast cancer support group, the topic of “chemobrain” was discussed, prompting her concerns that the changes in her cognitive functioning were a consequence of her breast cancer treatment. She was referred for neuropsychological evaluation by her primary care physician. Neuropsychological testing revealed that she performs below expectations for age and education level on measures of memory, executive function, and attention, however her performance was within the normative range. Despite performance within the normative range on objective cognitive testing, subjective cognitive (self-report) measures reveal endorsements of cognitive complaints.

2. Overview of Chemotherapy-Related Cognitive Impairment (CRCI)

The American Cancer Society defines CRCI as: increased forgetfulness, trouble concentrating and remembering details, difficulty with multi-tasking word finding, and taking longer to finish tasks.⁸ Although changes across various domains on objective testing have been reported for CRCI, effects have been reported most prominently in the domains of attention, working memory, executive function, and processing speed.⁵ To date, the majority of CRCI research has involved women with breast cancer,^{1,9} who (as of January 2016) represent approximately 23% (3.6 million) of the 15.5 million cancer survivors in the US alone.¹⁰ Although it is likely that patients who receive chemotherapy for any type of cancer may experience CRCI, much of the literature in populations other than breast cancer is preliminary.¹¹ However, research in patients with other types of cancer reveal similar results.^{4,12–17} Estimates of the prevalence of CRCI in cancer patients vary widely across studies.¹¹ Current longitudinal studies suggest that approximately 40% of breast cancer patients have evidence of cognitive impairment prior to cancer treatment, up to 75% exhibit cognitive decline during treatment, and 35–60% exhibit cognitive decline following completion of chemotherapy.¹¹ Severity of CRCI is typically mild to moderate in nature, such that impairments experienced would not typically qualify for a diagnosis of mild cognitive impairment (MCI)¹⁸ or dementia, however even subtle impairments in cognitive functioning can greatly influence quality of life.¹¹

3. Risk Factors for CRCI

Research suggests that the causes of CRCI are likely multifactorial and a number of biological mechanisms have been suggested to play a role in the development of CRCI, including blood brain barrier (BBB) damage, neurotoxic cytokines, changes in hormones, DNA damage, oxidative stress, reduced synaptic plasticity, altered growth factor levels, and impaired hippocampal neurogenesis.^{19–21} Additionally, certain alleles in the *Apolipoprotein E* (*APOE*) and *Catechol-O-methyltransferase* (*COMT*) genes have been associated with

increased risk for CRCI.^{22,23} Neuroimaging studies in patients with cancer have revealed white and gray matter loss, altered white matter integrity, altered resting state connectivity changes and brain activation during tasks.²⁴ The question of why some cancer patients continue to experience CRCI for years following completion of chemotherapy has led to the examination of additional risk factors for CRCI, discussed below.

Aging

Aging is the most significant risk factor for developing cancer.²⁵ Although the mechanisms that underlie the increased risk for cancer that accompanies increased age are not fully understood, there is considerable overlap in common biological changes that occur in the development of cancer, normal aging, and following chemotherapy treatment. Aging is associated with increased cell senescence, DNA damage, oxidative stress, inflammation, mitochondrial dysfunction, and decreased telomere length.^{26–31} Chemotherapy has been similarly associated with increased cell senescence,³² DNA damage,^{33,34} oxidative stress,³⁵ inflammation,^{36–42} mitochondrial dysfunction,⁴³ and decreased telomere length.^{35,44,45} It is important to note that all of the processes mentioned above, including age, have also been implicated as risk factors in cognitive decline and the development of neurodegenerative diseases, such as Alzheimer's disease (AD).^{19,29,35,46–51} There is also overlap in alleles in the *APOE* gene that have been associated with both increased risk for CRCI and AD.²² Further, neuroimaging studies have revealed similar changes observed following chemotherapy treatment and in normal aging, including gray and white matter loss, altered white matter connectivity, altered resting state connectivity changes and brain activation during tasks.^{19,24,52–57} Together, this research suggests that the biological processes that underlie normal aging, brain response to chemotherapy, cognitive decline, and neurodegeneration overlap, leading to the hypothesis that chemotherapy may modify the normal aging trajectory.^{3,5,35,52}

Aging is also associated with increased risk for cognitive impairment. Increasing evidence suggests that older patients are more susceptible to cognitive decline associated with chemotherapy and adjuvant endocrine therapies for breast cancer than younger patients.^{58,59} Additionally, age appears to interact with cognitive reserve, a predictor of future cognitive decline, to increase risk for cognitive decline following chemotherapy.⁵⁸ A study by Ahles et al demonstrated that older patients with lower cognitive reserve prior to chemotherapy treatment showed reduced performance on measures of processing speed.⁵⁸ This point is illustrated in Figure 1a where the effect of chemotherapy on cognitive performance may differ depending on level of pretreatment cognitive reserve.³ Investigators have proposed several models illustrating how cancer treatment may modify the trajectory of normal cognitive aging (Figure 1b; for a more extensive review, see Mandelblatt et al., 2013).⁵ Briefly, the phase shift hypothesis postulates that cancer patients treated with chemotherapy will experience greater decline in cognitive function compared to non-cancer/chemotherapy treated persons, and that the trajectory of decline will parallel normal aging and will remain constant over time.³ Alternatively, the accelerated aging hypothesis proposes that treatment with chemotherapy may accelerate the normal aging process.³⁵ This model predicts that the slope of cognitive decline will be steeper for cancer patients treated with chemotherapy compared to non-cancer/chemotherapy treated patients. It is important to note that the phase

shift and accelerated aging hypotheses are not mutually exclusive hypotheses.⁶⁰ It is likely that some cancer patients may experience decline that follows the phase shift trajectory, while other cancer survivors may experience decline that follows the accelerated aging trajectory.

Whether or not cognitive decline associated with cancer treatments are similar to and/or increase the risk for MCI or dementia is a common concern voiced by older cancer patients. However, this issue appears to be complex given evidence that there may be an inverse relationship between risk of cancer and risk of developing dementia.⁶¹ In a prospective study of over 62,000 older women with breast cancer, no significant association between chemotherapy and drug-induced dementia or “other cognitive disorders” and in fact a significant reduction in the incidence of AD and vascular dementia was observed,⁶² however this finding should be further evaluated.

Pre-Morbid Cognitive Functioning

A common challenge for clinicians evaluating patients for CRCI is that, as in the case example, in normal clinical practice, cancer patients rarely receive cognitive assessment or neuropsychological testing prior to the initiation of chemotherapy. The importance of obtaining pretreatment neuropsychological assessment has been demonstrated by studies that have found that up to 41% of breast cancer patients perform below expectations for age and education prior to receiving chemotherapy,^{63–65} even when controlling for psychological factors, such as depression or anxiety, fatigue, or surgical factors.⁶³ Of additional importance, without pretreatment assessment for comparison, declines in cognitive functioning that occurred during and following completion of chemotherapy treatment may go unnoticed. This is of particular importance when interpreting the test results of individuals with greater pretreatment cognitive reserve, such as individuals with high education levels.²⁰ Individuals with high pre-morbid cognitive functioning prior to chemotherapy may also be more likely to express subjective cognitive complaints before objective cognitive measures can detect impairment,⁶⁶ as may be the situation for the above case example. That is, due to the case example’s high pre-morbid cognitive functioning, her lower than expected performance may reflect a change for a previously high to mid-range normal individual; therefore, the patient could be accurately perceiving an alteration in her perceived cognitive abilities, which is reflected as cognitive complaints on subjective (self-report) measures. fMRI studies have demonstrated the potential for compensatory activation after chemotherapy, which may maintain normal performance on neuropsychological testing, but reflect a change in resource utilization, similar to what is seen in normal aging.^{54,67–69} Such findings suggest that the patient’s neuropsychological testing may fall in the normal range despite being associated with additional resource utilization and experienced as more effortful by patients. Further, there is increasing evidence that subjective (self-report) cognitive complaints, even with normal performance on objective neuropsychological tests, is associated with an increased risk for developing late-life cognitive decline and AD.^{18,66}

Pre-Existing Cognitive Impairment

As our population ages, increasing numbers of patients with pre-existing MCI or dementia will be diagnosed with cancer, which represents a challenge in studying the role that cancer diagnosis and cancer treatment may play in the exacerbation of cognitive impairment in older adults.⁷⁰ SEER Medicare studies suggest that the estimated prevalence of dementia in cancer patients age 65 and over ranges from 3.8 to 7%,^{71–73} although these estimates may be lower than true prevalence due to lack of reporting of these diagnoses within Medicare claims.⁷⁰ Few studies have examined how a prior diagnosis of MCI or dementia specifically impacts treatment decision-making for cancer and what percentage of these patients are offered various types of cancer therapies, such as surgery or chemotherapy.⁷⁰ Gupta and Lamont found that colon cancer patients with a pre-existing dementia diagnosis were more likely to be diagnosed without biopsies and less likely to be treated with curative intent, compared to non-dementia colon cancer patients.⁷¹ Chemotherapy and radiation are administered less frequently to breast cancer patients with a preexisting dementia diagnosis compared to non-dementia breast cancer patients.⁷² Raji et al found that presence of a preexisting dementia diagnosis was associated with decreased survival after a diagnosis of breast, colon, or prostate cancer, increased mortality from cancer and from non-cancer causes, and increased odds of being diagnosed at an unknown stage of cancer.⁷³ The issue of providing cancer treatment to patients with pre-existing dementia is a complex balancing act in terms of considering quality of life vs. quantity of life for the patient, and certainly stage of dementia at the time of cancer diagnosis should be taken into consideration. However, further research on the overall benefits, risks, and tolerance of cancer treatment in dementia patients at different stages of cancer is needed to better inform treatment decision making for such patients and to better inform the role of health care professionals involved in the care of cancer patients with preexisting dementia.

Effects of Endocrine Therapy on CRCI

While the majority of evidence for cognitive difficulties in cancer patients and survivors is attributed to chemotherapy, there is growing evidence to suggest that adjuvant endocrine therapy for hormone-receptor positive (HR+) breast cancer, which account for approximately 70–75% of breast cancers,⁷⁴ may impact cognitive function, either alone or in combination with chemotherapy.^{75–81} However, such effects observed may not occur equally with all endocrine therapies.⁵ Adjuvant endocrine therapies for HR+ breast cancer act by blocking or lowering hormonal levels in patients with ER/PR+ tumors and include: 1) selective estrogen receptor modulators (SERMs), such as tamoxifen and 2) aromatase inhibitors (AIs), such as letrozole, which our case example received. Typically, studies provide evidence that tamoxifen adversely affects cognitive functioning,^{79,82,83} but have yielded inconclusive results with respect to AIs.^{77,79,83,84} However, it is important to note that breast cancer patients are often maintained on endocrine therapy for extended periods of time; the current American Society of Clinical Oncology guidelines now recommend 10 years total duration.⁸⁵ Therefore, it is possible that CRCI associated with endocrine therapy for breast cancer may develop over time as patients age, although more research is needed.

Another area of growing concern is the effect of androgen-deprivation therapy (ADT) in men with prostate cancer. As of January 2016, there are more than 3.3 million men

estimated to be living with prostate cancer in the United States, with the majority (64%) of these prostate cancer survivors over the age of 70 years.¹⁰ ADT is used to lower male androgens in order to treat prostate cancer and is a mainstay of treatment for both metastatic and localized disease.^{86,87} ADT can produce effects, such as depression and fatigue,^{88,89} that may indirectly affect cognitive functioning, and may also directly affect cognitive functioning as studies suggest that lower testosterone levels are associated with worse cognitive functioning in healthy older men⁹⁰. In addition, both low testosterone levels and ADT increase the risk of cardiovascular disease,^{91,92} which is a known risk factor for dementia.⁹³ Studies examining the effects of ADT on cognitive functioning have yielded inconclusive results,^{94–97} however a meta-analysis of 14 studies concluded ADT in patients with prostate cancer had a significant impact on visuomotor ability,⁹⁸ and ADT has been associated with increased risk for dementia.⁹⁹

Effect of Targeted Therapies on Cognition

The majority of CRCI research has focused on understanding the effects of traditional chemotherapy on cognition. By contrast, there is little to no published data on the effects of newer targeted therapies on cognitive performance after treatment. Types of targeted therapies include immunotherapies, such as monoclonal antibodies and checkpoint inhibitors, and small molecule signaling pathway inhibitors, such as tyrosine kinase (TK) inhibitors. The appeal of targeted therapies is that they aim at targeting genes or proteins specific to cancer cells or activating immune mechanisms to attack cancer cells, thus reducing off-target side effects in normal tissues.

Although such strategies may be generally less cytotoxic than traditional chemotherapy drugs, targeted cancer therapies are not without risk and can have substantial, and in some cases, life-threatening side effects. Targeted therapies also have the potential to either directly affect brain function or indirectly effect cognition through peripheral extra-CNS mechanisms. For example, sunitinib, a TK inhibitor capable of crossing the BBB used to treat a number of cancers, has been shown to have negative effects on cognitive functioning, specifically in the areas of learning, memory, and executive functioning in treated cancer patients.^{100,101} A subsequent mouse study revealed that sunitinib impaired spatial cognition as evidenced in Morris water maze, T-maze, and a passive avoidance task, and adversely affected cortical and hippocampal neurons.¹⁰² In a study evaluating the effect of antiangiogenic targeted therapy (primarily TK inhibitors), more than 30% of patients treated with such drugs developed cognitive decline.¹⁰³

As targeted therapy use becomes increasingly more common, how these drugs affect cognition will need to be addressed, especially given that they are often used in conjunction with traditional chemotherapy. In the case example, the patient received trastuzumab in conjunction with chemotherapy followed by completion of one year of maintenance trastuzumab. Trastuzumab, a monoclonal antibody, is the most commonly used targeted therapy to treat HER-2/neu+ breast cancer, however there is no published data on the effects of trastuzumab on cognition. As the role of targeted therapy expands, cognitive performance follow-up will become increasingly important.

4. Intervention

Non-Pharmacological Interventions

There is some evidence that suggests that nonpharmacological interventions such as cognitive behavioral therapy, cognitive brain training, mindfulness based stress reduction, and physical activity may be beneficial for patients with patients with CRCI.^{20,104} Two pilot studies examining cognitive behavioral therapy in breast cancer patients demonstrated improvement on both objective and subjective (self-report) measures of cognitive function.^{105,106} Computerized cognitive brain-training studies suggest improvement in executive functioning,¹⁰⁷ and yoga may reduce subjective memory complaints.¹⁰⁸ The application of non-pharmacological interventions may be promising and should be tailored to each individual patient.

Pharmacological Interventions

Currently, there is no pharmacological treatment that is specific for CRCI. Most pharmacological treatment studies of cancer patients and survivors have centered on treating side effects of chemotherapy such as fatigue^{109–112} and anemia,^{113,114} and have largely not focused on treating cognitive symptoms associated with chemotherapy. Studies evaluating the efficacy of stimulants, such as methylphenidate, dexamethylphenidate, and modafinil, for the treatment of CRCI have yielded mixed results with respect to cognition, therefore it remains unclear whether these medications are useful in treating CRCI.^{109–114} Other pharmacologic treatment studies have evaluated donepezil, an acetylcholinesterase inhibitor, approved to treat mild to severe AD.^{115,116} Both open-label and placebo controlled studies in glioma patients suggested statistically significant improvements in cognitive performance.^{115,116} Additionally, a study in breast cancer survivors suggested improved verbal memory in those who had poorer cognitive functioning at baseline.¹¹⁷ Cholinesterase inhibitor studies provide support for the cholinergic system as a therapeutic target for improving cognitive functioning in CRCI.^{115–117} More selective cholinergic stimulation may potentially be useful for certain cognitive symptoms. For example, a randomized, placebo-controlled study evaluating the use of transdermal nicotine treatment as a therapeutic strategy for persistent CRCI is currently underway (NCT02312934).

6. Factors to Consider When Evaluating Older Cancer Survivors for CRCI

Depression

Depressive symptoms have been found to occur in up to 15% to 25% of cancer patients.^{118,119} Although depression is frequently associated with cancer, the role of depression as a risk factor for CRCI is not fully understood. Differentiation between cause and effect is particularly challenging when assessing older patients with depression for CRCI since depression by itself is associated with a number of cognitive deficits, including difficulty concentrating, distractibility, forgetfulness, reduced reaction time, memory loss, and indecisiveness¹²⁰. For patients with a history of cancer, a cognitive assessment at the time the patient begins treatment for their depression may be valuable. If cognitive impairment continues, even with successful treatment of depression, a search for other causes can be commenced and separate treatment may be warranted.

Subjective Cognitive Decline (SCD)

In the AD literature, greater emphasis on early detection and diagnosis of cognitive impairment has led to the conceptualization of ‘subjective cognitive decline’ (SCD), in which individuals perceive changes in their cognitive abilities but perform within normal limits on cognitive tests, as in the case example.^{18,121} There is increasing evidence that subjective cognitive complaints, even with normal performance on objective tests, is associated with an increased risk for developing late-life cognitive decline and AD.^{18,66} This is of particular importance to older cancer patients due to the age-associated increase in the risk for dementia.

SCD, like CRCI, is not a discrete syndrome and could potentially reflect numerous conditions such as normal aging, psychiatric conditions, neurologic and medical disorders, substance use, and medication effects. Current evidence suggests that the following factors increase the likelihood of future cognitive decline in older individuals with SCD: 1) subjective decline in memory, rather than other domains of cognition, 2) new onset of SCD within the last 5 years, and 3) age at onset of SCD > 60 years.¹²¹ Therefore, if patients with CRCI show additional factors that increase risk for future cognitive decline, periodic follow-up and testing is warranted.¹⁸

Mild Cognitive Impairment (MCI) & Dementia

MCI is a syndrome defined as subjective and objective decline in cognition and function greater than expected for an individual’s age and education level that does not meet criteria for a diagnosis of dementia.¹⁸ Elderly patients with MCI constitute a high-risk population for developing dementia, in particular AD. The concept of MCI originally evolved out of the effort to characterize the pre-dementia phase of cognitive impairment for which, at the time, there was no clinical definition. Older patients that meet criteria for MCI (for a more extensive review, see Vega and Newhouse, 2014¹⁸) should be evaluated as to the potential cause. Comprehensive neuropsychological testing, screening for depression, brain imaging (MRI and/or PET), and neurological examination will assist in differentiation from CRCI¹⁸. Patients with predominantly amnesic-MCI or evidence for AD pathology may be considered for cholinergic or investigational therapies as well as nonpharmacological interventions, such as cognitive training or aerobic exercise.¹⁸ Regardless of treatment, longitudinal follow-up is indicated.

Structured Assessments

Older patients with a cancer history should be routinely asked about their cognitive functioning. If available, informants should be asked to confirm any reports of cognitive decline experienced by the patient. Clinicians should consider using a structured instrument that examines diverse aspects of functional abilities, psychiatric signs and symptoms, and cognitive functioning, such as the Older Adult Self-Report (OSAR) and the informant-based Older Adults Behavior Checklist (OABCL) which have been validated to correlate with evaluations of cognitive impairment.¹²² The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)¹²³ is an assessment tool that was developed to assess subjective cognitive function specifically in cancer patients. The FACT-Cog has been used to monitor change in CRCI subjective complaints in a number of studies, can be administered

repeatedly, and therefore may be useful in a clinical setting.^{124–126} This 37-item questionnaire is a self-report measure of cognitive function that aims to evaluate the “real world” impact of CRCI. The scale evaluates subjective memory, concentration, mental acuity, verbal fluency, functional interference, and multitasking ability. Reports from patients and their family members and/or care-givers about subjective changes in cognitive functioning should prompt more focused clinical evaluation and structured assessment instruments will be valuable in initial and longitudinal assessment.

7. Conclusion

CRCI is a complex and evolving concept. While there is now general agreement that chemotherapy and other cancer treatments may induce cognitive impairments, current knowledge is limited by the lack of consistent findings in the identification of risk and progression factors, specific pathological and clinical markers, as well as difficulties in finding effective treatments. Although the phenomenon of CRCI is better recognized among patients and has been widely publicized in the popular press, patient reports suggest that the cognitive effects of cancer treatments are not routinely discussed and cognitive assessments are not routinely incorporated into the evaluation and management of older patients with cancer. Therefore, as in our case example, primary care physicians and/or psychiatrists have an opportunity to discuss, diagnose, and offer intervention strategies for patients with CRCI. For clinicians, making the distinction between cognitive impairment that may indicate future cognitive decline and changes in cognition related to either psychiatric illness (e.g., depression) or normal aging can be challenging. However, CRCI may be of particular importance for older patients with a history of cancer due to the age-associated increase in the risk for dementia. CRCI may have numerous contributing factors, such as interaction with normal aging, co-development of dementia, endocrine therapy, and targeted therapy. Several brief cognitive assessment tools, including the FACT-Cog and OASR/OABCL, can be used in the evaluation of older adults with cancer. Older patients with a cancer history should be routinely asked about their cognitive functioning and assessment for CRCI should be assessed at regular intervals. Interventions are still under investigation but may include specific pharmacologic and non-pharmacologic approaches.

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Figure 1. Interaction of chemotherapy with factors that affect normal cognitive aging
a) Effect of chemotherapy on cognitive performance may differ depending on pretreatment level of cognitive reserve. **b)** Possible trajectories of cognitive decline based on theories how chemotherapy interacts with normal cognitive aging. Figures adapted from Ahles et al. 2012.³