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Cancer-related cognitive impairment: updates to treatment, the need for more evidence, and impact on quality of life—a narrative review

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Background and Objective: Due to advances in early detection and treatment options, non-central nervous system (non-CNS) cancer survivors are living longer, even those with metastatic disease. Many of these survivors will experience enduring symptoms of breast cancer, such as cancer-related cognitive impairment (CRCI). Although CRCI is bothersome and, in some cases, potentially debilitating, little research has been done to address this symptom. Thus, the overarching goal of this narrative review is to provide both an overview of the problem of CRCI and its impact and focus on the latest research aimed at addressing CRCI in non-CNS cancer survivors.

Methods: A MEDLINE database (PubMed) search was conducted for terms related to non-CNS cancer, cognition, impacts of CRCI, and interventions. The English-language articles published until April 8th, 2024, were included in the search.

Key Content and Findings: CRCI includes self-reported cognitive complaints and/or impaired performance in multiple cognitive domains, including memory, processing speed, attention, and executive function. CRCI, in turn, can have a significant impact on everyday functioning, work ability, work engagement and productivity, and overall quality of life (QoL) of cancer survivors. While some researchers have examined pharmacological approaches, the vast majority of the interventional studies to date to address CRCI has focused on non-pharmacological approaches. Three of the most common non-pharmacological approaches are physical activity or exercise, mind-body approaches [e.g., mindfulness-based stress reduction (MBSR)], and cognitive rehabilitative approaches [e.g., cognitive training (CT) and cognitive behavioral therapy (CBT)].

Conclusions: Addressing the cognitive health of cancer survivors is imperative but has only recently been the focus of interventional research. More research in larger and more diverse samples of non-CNS cancer survivors is needed to identify effective ways to manage CRCI for all cancer survivors. Overall, maintaining cognitive health, especially in cancer survivors who are at increased risk for deficits, is a national health care priority that should not be ignored.

Keywords: Cancer-related cognitive impairment (CRCI); non-central nervous system cancer survivors (non-CNS cancer survivors); management of cognitive impairment

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Introduction

According to the American Cancer Society, the number of cancer survivors will continue to increase, reaching 22.5 million by 2032. In fact, it is anticipated that the number of cancer survivors living 5 or more years after a cancer diagnosis will increase by approximately 30% over the next decade (1). With the improved survival rate, more attention must be placed on addressing the late and long-term symptoms reported following cancer and cancer treatments (2) as well as their impact on survivors' quality of life (QoL) (2-5).

Cancer-related cognitive impairment (CRCI), a potentially debilitating symptom, is one of the most frequently reported symptoms by cancer survivors (6). Researchers have shown that 44.2% to 57.6% of cancer survivors will report CRCI (7). While this research has predominately focused on breast cancer survivors, CRCI is also noted across a wide range of other non-central nervous system (non-CNS) cancers (8-11). Early studies in this area focused on chemotherapy as the primary cause of CRCI and was often referred to as 'chemo brain' or 'chemo fog' (6) Chemotherapeutic agents have been shown to have a direct effect as well as an indirect effect by increasing proinflammatory cytokines [e.g., interleukin (IL)-6, IL-8, IL-10] (12,13), inducing DNA damage (14), and accelerating white matter and gray matter loss in the frontal lobes and hippocampus (15). However, a growing body of literature has demonstrated that CRCI may be associated with other cancer treatments (e.g., hormone therapy, targeted therapy, radiation therapy) (16). Estrogen plays an important role in neuronal cell growth and maintenance as well as the development of synapses in the brain involved in memory (17,18); thus, those treated with anti-estrogen therapies (e.g., aromatase inhibitors) may have an increased risk of CRCI. Targeted and radiation therapies have also resulted in impairments in learning, memory, and executive function (19-21). Investigators have theorized that dysregulation of the immune system after radiation can induce chronic oxidative stress and inflammation, affecting brain and cognitive function (18,22). Additionally, several studies have suggested that factors such as aging, comorbidities, psycho-social components, or inflammation can increase the risk for CRCI even before cancer treatments are initiated (23-28). Thus, while it remains unclear whether CRCI results from cancer itself, cancer treatments, or other factors, it has a significant impact on cancer survivors' QoL.

CRCI in non-CNS cancer survivors—rationale and knowledge gap

CRCI includes temporary or persistent self-reported cognitive symptoms and/or objective changes in cognitive function assessed by neuropsychological tests (16). Self-reported cognitive symptoms include decreased mental sharpness, decreased ability to focus or concentrate, feelings of being scattered, feelings that thoughts or information processing is slow, and forgetfulness, characterized by difficulty retaining information and/or recalling familiar names or words (29-31). Objective cognitive performance, on the other hand, is assessed via standardized neuropsychological tests which can identify deficits in specific cognitive domains, including learning, attention, executive function, memory, and processing speed, using standardized objective cognitive measures (32).

Although both self-reported cognitive concerns and performance on neuropsychological tests are typically used to assess CRCI, these measures are often not highly correlated (33,34). There are several reasons for the discrepancy between subjective and objective assessments of CRCI. First, although neuropsychological assessments are often considered the 'gold standard', they may not identify the more subtle cognitive changes incurred by cancer survivors (35,36). Second, the neuropsychological assessments may not be tapping into the real everyday cognitive difficulties that cancer survivors face (35). And finally, the subject assessments or self-reported assessments may tap into other symptoms (fatigue, anxiety, and depression) that are commonly experienced by cancer survivors (14,37). Although these measures do not always align, the International Cancer and Cancer Task Force recommends the inclusion of both assessment measures when identifying CRCI in cancer survivors (32).

CRCI may be subtle and persist across the trajectory of cancer care (6). In fact, one recent meta-analysis reveals that the rates of CRCI were reported to be 30% just after cancer treatment, 23% up to 1 year following treatment, and 31% at greater than 1 year after treatment (6,38). Researchers have also shown that CRCI may persist up to 20 years after cancer treatments in a subset of cancer survivors with deficits noted in immediate and delayed verbal memory, processing speed, executive function, and psychomotor speed (39). As such, CRCI requires appropriate assessment and management throughout the entire cancer care continuum.

Although CRCI is a prevalent symptom impacting

Table 1 Search strategy summary

Items	Specification
Date of search	April 8th, 2024
Database and other sources search	PubMed
Search terms used	'Non-CNS solid tumors', 'neurocognitive function', 'cognitive function', 'cognitive impairment', 'everyday functioning', 'daily lives', 'work performance', 'quality of life', 'non-pharmacology interventions', 'pharmacology interventions', 'exercise', 'mind-body interventions', 'cognitive rehabilitation'
Timeframe	Until April 8th, 2024
Inclusion criteria	Studies that include: - Adults (>18 years old) with non-CNS cancers - Self-report questionnaire and/or objective neuropsychological tests - The impacts of CRCI, such as daily functioning, work performance, and QoL - Non-pharmacology and pharmacology interventions for CRCI - Published in English
Selection process	The inclusion of articles was discussed by two authors (D.V.A. and Y.Y.) until full agreement was reached

CNS, central nervous system; CRCI, cancer-related cognitive impairment; QoL, quality of life.

many cancer survivors, few studies have focused on identifying survivors who may be at greatest risk. One recent literature review suggests that racial and ethnic minoritized cancer survivors are more likely to experience CRCI compared to their counterparts (40). It has been suggested by researchers that this may be due to the fact that racial and ethnic minority groups have limited access to high-quality care (41,42) and, thus, cognitive outcomes could be negatively impacted by an inequitable health care environment (43,44). Further, researchers suggest that reduced health care access could increase uncertainty about future health outcomes during survivorship (45-47), resulting in sustained and chronic anxiety (48-50) ultimately, leading to increased vulnerability to CRCI (51,52). Regardless, understanding whether (and how) CRCI differs among minoritized cancer survivors is critical and will provide foundational knowledge in developing personalized medicine for CRCI treatments.

Despite ongoing research, substantial gaps in our understanding persist; thus, more studies that focus on CRCI and its impact on QoL of cancer survivors are needed. In addition, although the underlying mechanisms of CRCI are not clearly understood, there is a growing need for interventional research to identify efficacious treatments to guide clinical care and provide support for cancer survivors in need.

Objective

Therefore, the goal of this narrative review was to synthesize the literature regarding CRCI, including highlighting the cognitive domains affected, summarizing the impact CRCI has on non-CNS cancer survivors' everyday functioning, work performance, and QoL, and importantly synthesizing recent efforts in managing CRCI in non-CNS cancer survivors. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-24-70/rc).

Methods

The literature search used PubMed as the primary database. Search methods are summarized in *Table 1*. The main keywords used for the search relate to non-CNS cancer (e.g., non-CNS solid tumors), cognition (e.g., neurocognitive function, cognitive function, cognitive impairment), impacts of CRCI (e.g., everyday functioning, daily lives, work performance, quality of life), and interventions (e.g., non-pharmacology interventions, pharmacology interventions, exercise, mind-body interventions, cognitive rehabilitation).

Findings—overview

In our review of the literature, we included research to

date in adult non-CNS cancer survivors. Notably, the large majority of studies assessing CRCI focused solely on breast cancer survivors or a mix of cancer diagnoses making separating findings by cancer populations difficult. Thus, in the following sections, we provide a narrative summary including the identifying the specific cognitive domains most affected; highlighting the impact of CRCI, including its impact on everyday functioning, work performance, and QoL; and pinpointing the most promising interventions for CRCI. Specifically, we summarize the current state of the science regarding pharmacological and non-pharmacological approaches (e.g., exercise, mind-body intervention, combination of exercise and mind-body intervention, cognitive rehabilitation, and co-related symptom interventions) to address CRCI.

Cognitive domains most affected

CRCI can have a pervasive impact on everyday functioning. Studies indicate that cancer and cancer treatments may primarily affect cognitive domains, including memory, processing speed, attention, and executive function (6). Memory impairments are related to hippocampal and frontal lobe dysfunction, and such impairments are frequently reported by cancer survivors who underwent cancer treatments, including chemotherapy (53-55). A recent review has further indicated that memory impairments are often reported in conjunction with problems in working memory and attention (55), and these impairments negatively influence work performance and QoL (6,56,57).

Impairments in attention and processing speed are also frequently reported after treatment (6,32,58-60), and these impairments have been shown to reduce proficiency in daily functioning (61-63). Specifically, processing speed (i.e., mental quickness) is a cognitive ability that has been reported to relate to functional performance and QoL in older cancer survivors (64). Lastly, impairments in executive function are the most common deficits noted by breast cancer survivors (65-70). Executive function, as the control system that interacts with many cognitive domains responsible for adapting to changes in environments (71), is critical to developing skills such as problem-solving and planning (72,73). Studies have found that individuals with executive deficits show rigid thinking patterns, failure to recognize mistakes, and difficulties in multi-tasking (70,74), with the consequences being adverse outcomes in social relationships (75), occupational success (76), and medication adherence (77).

Overall, the majority of studies have reported significant deficits in memory, attention, processing speed, and executive function, as they have the largest quantified effects (78-80). In addition, other cognitive domains (e.g., language, visuospatial, motor/psychomotor ability) (59) have also been reported. Variations in cognitive deficits reported across studies may be a function of the type of neuropsychological test used. Importantly, these cognitive impairments have shown negative impacts on cancer survivors' daily functioning, social relationship, work outcomes, and ultimately their QoL (81,82). Thus, understanding which cognitive domains are most impaired and the consequences of such impairments is critical for developing future interventional approaches to address CRCI.

Impact of CRCI

Many studies have focused on understanding the prevalence and nature CRCI, whereas less is known about its impact on cancer survivors' lives, functioning, and QoL. Regardless of its severity, even mild CRCI can negatively impact the lives of survivors.

Everyday functioning

CRCI is known to negatively impact cancer survivors' self-confidence, social relationship, physical functioning, and level of independence (82). According to a review of qualitative studies, cancer survivors with CRCI have reported decreased self-confidence, which ultimately negatively impacted their social relationships (81,82). Similarly, several qualitative studies (82) have described the tendency of survivors with CRCI to withdraw from participating in social activities and avoid social interactions because they often face embarrassing situations due to inability to remember things such as peoples' names, dates, or events (75,81,83). Further, those with CRCI reported increased family tensions and frustrations resulting from their cognitive changes (75,81,83). In addition to the impact on self-confidence and social relationships, some geriatric studies have reported that CRCI contributes to decline in the physical functioning of cancer survivors (84-86). Decrements in physical functioning, including difficulties in performing daily activities, balancing, and gripping things, are key factors in determining whether older cancer survivors can live independently (84-86). In addition, physical functioning and the ability to live independently are strongly related to QoL in older cancer survivors (84-86).

Thus, CRCI is strongly linked to everyday functioning in cancer survivors.

Work performance

Cancer survivors described that work represents a return to normal activities (87,88), gives a meaningful and purpose-driven life (89), and improves overall well-being and self-esteem (90). Returning to work is therefore viewed as a sign of full recovery from cancer and its treatments (90). Despite the benefits associated with working, cancer survivors often report difficulty in returning to work and/or completing the task (91). Specifically, those with CRCI have more frequently reported taking longer time and more effort to complete job tasks compared to others and having a diminished overall ability to complete a job task (92-94), leading to lower self-confidence at work (81). In line with these findings, a study has shown that cancer survivors who demonstrated persistently low work functioning reported more cognitive problems than those who demonstrated moderate to high work functioning (76). This study has further found that cancer survivors report stable but persistent cognitive problems that affect work tasks during the first 18 months after treatment (76).

Due to lowered ability or capacity for work, those with CRCI may not be assigned to an important project or take a managerial role (95). Job loss and financial difficulties could result and, in their turn, negatively impact personal and family lives (88,96-98). Given that the number of young cancer survivors of working age is increasing, the impact of CRCI on work-related outcomes in this age group should be investigated (99). Achieving a comprehensive understanding of how CRCI affects job performance, ability and capacity to work, return to work, income, job opportunities, and work satisfaction in young survivor groups would be a critical step for future interventions related to work outcomes and for clinical guidelines for the care of those with CRCI (100).

QoL

QoL can be defined as a subjective perception of well-being that includes physical, psychological, environmental, social, and spiritual aspects (101). Studies have found that QoL is affected by diminished physical, social, and occupational aspects of cancer survivors' functioning (102). Furthermore, reduced QoL has been predominantly found in cancer survivors with cancer-related symptoms, including CRCI (102). With the improved survival rate due to advances in cancer detection and treatments, QoL becomes an essential indicator for health outcomes for cancer survivors (103-105).

Several studies have shown that CRCI can negatively influence QoL in cancer survivors (31,106-108). The possible explanation for this relationship is that cancer survivors with CRCI often experience difficulties in employment, social functioning, and independence, and such difficulties can decrease QoL (109,110). Early studies in this area have shown that CRCI can have devastating effects on the personal and professional lives of cancer survivors and negatively impact their QoL (111-113). Specifically, a qualitative study exploring the effect of CRCI on cancer survivors' lives, found that cancer survivors attributed their diminished QoL to CRCI and expressed poorer outcomes on an economic, emotional, and interpersonal levels (83). Consistent with these findings, recent studies have further shown that CRCI causally relates to QoL of cancer survivors (86,108,114).

Need for the identification and treatment for CRCI

The downstream effects of CRCI are compounded by the fact there is a lack of definitive evidence-based clinical support for cancer survivors in need. Interviews with cancer survivors have revealed that clinicians often fail to assess for CRCI after treatment. Instead, cancer survivors reported that they were left to raise their concerns regarding CRCI, but even then, their concerns were often met without assistance or even acknowledgment (75). A summary of 17 qualitative studies regarding the patient experience with CRCI reported that survivors wanted more information regarding CRCI and recognition of its effects by the health care team (81). To address this concern, the National Comprehensive Cancer Network Guidelines for Survivorship now call for the assessment of cognitive concerns as the initial step in identifying and treating cognitive impairment in non-CNS cancer survivors (115). These guidelines recommend clinicians screen for cognitive symptoms by asking a series of questions about cognitive health, and identify and treat any co-occurring symptoms, and conduct further cognitive testing to identify CRCI. Importantly, these guidelines highlight the need to identify other common cancer-related symptoms, such as depression, anxiety, or sleep disturbances as each may contribute to CRCI. In addition, these guidelines offer some recommendations to address CRCI, albeit the level of evidence for these interventions remains equivocal (115).

Treatment updates for CRCI

Addressing CRCI is a clinical need and a current research priority. Interventions for CRCI for cancer survivors fall into two main categories: pharmacological and non-pharmacological and each has multiple strengths and limitations. Future research is needed to build the level of evidence of CRCI interventions for cancer survivors to be administered across the cancer care continuum.

Pharmacological interventions

The use of pharmacotherapies for CRCI in non-CNS cancer survivors is relatively limited (116). Studies to date have focused primarily on psychostimulants, cholinesterase inhibitors, and N-methyl-D-aspartate (NMDA) receptor antagonists. Psychostimulants (such as dexmethylphenidate or methylphenidate (117) and modafinil (118) have produced some improvement in attention, alertness/awareness, and psychomotor speed, with the largest study showing sustained benefit (118). Yet, the majority of studies have small sample sizes, varying duration of medication, and limited follow-up periods to determine long-term efficacy; thus, more research is needed to establish effectiveness (116). Donepezil, a cholinesterase inhibitor, reduces inflammation, regulates catecholamine, supports neuroplastic activity, and has been used to slow the progression of dementia and Alzheimer's disease. Animal models and clinical trials also show some promise for the use of donepezil for CRCI (54,119,120). In one study, Lawrence and colleagues [2016] administered donepezil for 24 weeks, (5 mg daily for the first 4 weeks and 10 mg daily for 20 weeks) in breast cancer survivors' post-chemotherapy. The group receiving donepezil demonstrated significant improvement in memory compared with the placebo group (120). In another preclinical trial, Winocur and colleagues [2011] noted donepezil improved hippocampal-dependent memories, including spatial memory (119). However, previous trials have demonstrated mixed and varied responses from no treatment effect (121) to some improvement in measures of attention, concentration, and memory (116). Consequently, more research is needed to determine the efficacy of donepezil for improving CRCI in cancer survivors. Memantine, a NMDA receptor antagonist, has been shown to reduce radiation-induced neuronal stimulation and excitotoxicity in brain tumor patients; suggesting that memantine may prevent whole-brain radiation therapy-induced cognitive decline. However, more research is needed to understand the role of memantine for reducing cognitive impairment in non-CNS cancer survivors, especially in those with brain metastasis (122).

Additional innovative pharmacological intervention trials to address CRCI are ongoing. The focus of these clinical trials includes testing neurostimulating, neuroprotectants, or antineuroinflammatory therapeutic agents (116). Most of this work is in the pre-clinical stages. For example, work in animal models suggests that the antidepressant, fluoxetine (123,124), cotinine, a derivative of nicotine (125), and the antioxidant zinc sulfate ($ZnSO_4$) (126), may also improve cognitive performance following chemotherapy; however, further clinical research is required to establish their efficacy in cancer survivors (116,127).

Non-pharmacological interventions

In recent years, more attention has been focused on developing and testing non-pharmacological interventions to address CRCI. The most promising non-pharmacological interventions have been broadly categorized as physical activity/exercise (e.g., aerobic and anaerobic activities), mind-body interventions [e.g., mindfulness-based stress reduction (MBSR), meditation, etc.], and cognitive rehabilitative approaches [e.g., cognitive behavioral therapy (CBT) and cognitive training (CT)]. While most of these approaches have demonstrated some improvement in subjective and/or objective cognitive function, conclusions are limited due to study design (lack of active attention control comparator arms or control for confounding factors, such as other correlated symptoms), sample limitations (small sample size, single-site studies, lack diversity), and outcomes measured (failure to identify impact on everyday function ability). Further research is needed to identify evidence-based treatments for clinicians to recommend or cancer survivors to address CRCI.

Exercise/physical activity interventions

Exercise has been increasingly recognized as important to cancer survivors' overall health and in reducing symptoms (128). Exercise entails planned or structured physical activity involving repetitive bodily movement to improve or maintain cardiorespiratory endurance, muscular strength, muscular endurance, flexibility, and/or body composition. Exercise interventions, such as aerobic exercise, resistive training, yoga, qigong, and tai chi have been shown to have some benefits for addressing CRCI and improving QoL of cancer survivors (129-133). In a study of sedentary breast-cancer survivors, those who were assigned to a 12-week exercise program showed improved

processing speed and reduced cognitive symptoms within 2 years of diagnosis compared to a waitlist control group that received emails regarding general health topics (healthy eating, stress reduction, and general brain health) (134). Furthermore, in a recent systematic review of 26 studies of interventions that included aerobic or resistance exercise as well as mindfulness-based exercise, the majority were associated with positive cognitive outcomes. However, many of these studies did not include objective tests of cognitive performance. In addition, due to the heterogeneity of the studies, no specific type of exercise, exercise dose (duration, intensity, or frequency), or timing to initiate the exercise could be determined (135). Thus, more research is needed to identify the optimal exercise training prescriptions to mitigate CRCI in cancer survivors.

Mind-body interventions

Mind-body interventions are designed to reduce stress by encouraging participants to focus on one's individual potential for healing or restoration. Mind-body interventions used to address CRCI include guided imagery, meditation, MBSR, neuro/biofeedback, acupuncture, and restorative environments (20). These approaches have shown some positive effects in addressing CRCI. For example, MBSR has shown promise in improving both patient-reported subjective and objective measures of working memory and meditation has been shown to improve short-term memory and speed of processing (136-138). While encouraging, research is still quite limited. Further research, including both patient-reported subjective cognitive function and objective cognitive performance outcomes, is needed to establish efficacy of these mind-body interventions.

Combination of mind-body exercise

Interestingly, while researchers have been singly focused on either exercise or mind-body interventions, those interventions that combine the two may be most effective. Mind-body exercise is defined by the dictionary of cancer terms as "*a form of exercise that combines body movement*, *mental focus*, *and controlled breathing to improve strength*, *balance*, *flexibility*, *and overall health*" (139). In a recent systematic review of eleven studies, covering 1,032 cancer survivors, it was noted that mind-body exercise interventions, including yoga, tai chi, and qigong, improved both objective and subjective cognitive function in cancer survivors (138). However, most of the studies included small samples and substantial heterogeneity in the type and duration of the intervention. Because of these limitations, the authors call for adequately powered trials to inform practice (140).

Cognitive rehabilitative approaches

Cognitive rehabilitative approaches most commonly used to address CRCI include CT programs and/or cognitive behavioral training programs (141,142). CT programs provide structured practice on cognitive tasks with the intent of improving and/or maintaining cognitive function. Characteristics of most CT programs include repetitive, standardized, problem-oriented tasks that may target a specific cognitive domain or multiple cognitive domains (143). Multiple-domain CT has shown promise in older adults with mild cognitive impairment and mild dementia. CT can be delivered on an individual basis or in a group setting and can be computer-assisted. CT has shown improvement in both subjective (self-reported) and objective cognitive performance (144-146), specifically in improvements in speed of processing and memory (145). In fact, Bray and colleagues conducted the largest trial to date testing computerized CT compared to usual care in a pragmatic trial of 242 breast cancer survivors and noted significant improvement in perceived cognitive function post-intervention. The trial suggests CT offers much promise for improving CRCI (144). CBT programs, on the other hand, are designed to change a person's beliefs, expectations, appraisals, and attributions of CRCI (142). CBT focuses on retraining of lost cognitive abilities and compensatory strategies but also may provide psychoeducation and counseling regarding patients' distress related to their cognitive concerns. One of the most well-tested CBT programs for improving memory in breast cancer survivors is the Memory and Attention Adaptation Training (MAAT) program (147). In a series of studies using the MAAT program, Ferguson and colleagues demonstrated the acceptability of the MAAT program as well as demonstrated improvements in verbal memory and QoL outcomes in breast cancer survivors, suggesting that CBT may be a viable option to address CRCI (147,148). In a recent systematic review regarding both CBT and CT, Fernandes and colleagues reported that these cognitive rehabilitative approaches are feasible to deliver to cancer survivors, that cancer survivors were satisfied using the intervention programs, and that improvements in objective cognitive performance, including memory, attention, executive function, and processing speed, were noted (142). However, more work is needed to definitively test these programs. Research is needed in larger, more diverse samples of cancer survivors. In summary, while cognitive rehabilitative approaches clearly have promise,

more research is needed to inform evidence-based practice in this area.

CRCI interventions and other co-related symptoms

Addressing CRCI in cancer survivors has only recently gained momentum. The studies in this narrative focused on interventions primarily aimed at addressing CRCI. However, it should be noted that many of the intervention studies utilizing exercise/physical activity, mindfulness interventions, and cognitive rehabilitation (e.g., CBT and CT) have also shown promise in addressing other common correlated cancer symptoms that impact cancer survivors. For example, Von Ah *et al.* [2012] not only demonstrated significant and positive improvements in subjective and objective cognitive assessments with CT compared to waitlist control, but also documented significant small to large positive effects on other symptoms (e.g., fatigue, anxiety, and depression) and health-related QoL (145). Similarly, Bray *et al.* noted significantly lower levels of fatigue, anxiety, and depression utilizing the same CT program (144). This improvement in secondary outcomes as a result of the intervention (also known as transfer effects) may be due to the fact that CRCI has been shown to highly 'correlate with' or 'cluster' with other cancer-related symptoms including fatigue, anxiety, depression, sleep disturbance, and pain to form the psychoneurological symptom cluster (149-151). It is believed that these symptoms may share common underlying mechanisms, including biological, social, or psychological underpinnings. Thus, identifying promising interventions that target multiple symptoms simultaneously has the advantage of improving multiple symptoms while avoiding unnecessary burdensome interventions (152).

Based on the literature to date, exercise/physical activity appears to be a promising intervention to address multiple symptoms. The importance of exercise or physical activity and overall health has grown significantly in the last few years (153). An expert panel of the American College of Sports Medicine concluded that the evidence was strong enough that exercise was efficacious in improving many of the cancer-related symptoms that cluster with CRCI, including fatigue, anxiety, depression, sleep, and physical functioning as well as improving overall health-related QoL (154-156). In fact, the Moving Through Cancer initiative sets a goal for exercise to be standard of care in oncology practice by 2029 (153,156). Therefore, while more research is needed to identify its impact on exercise in addressing CRCI (157), the overall benefit of exercise for cancer survivors should not be ignored.

Future directions for research and practice

Building on the evidence to date, more research is needed to address CRCI. Research efforts need to focus on fully characterizing and identifying those cancer survivors at greatest risk for CRCI. To accomplish this goal, brief and reliable cognitive assessment tools must be developed and implemented in busy oncology clinics. The current assessments used in research are not conducive to a busy oncology practice. In addition, research is needed with a variety of cancer populations and treatments. To date, most of the research in non-CNS cancer survivors has been done in breast cancer survivors. More research is needed in a variety of other cancer populations to identify their unique concerns and develop interventions tailored to those needs. Also, the number of newly available treatments [e.g., immune checkpoint inhibitors, chimeric antigen receptor (CAR)-T cell therapy, etc.] has been increasing. More research is needed to identify their impact on cognitive function among cancer survivors. Overall, it is essential to identify those at greatest risk so that we can begin to target and tailor interventions to those most in need.

It is also important that we understand our changing demographics. As our population ages, the number of older adults diagnosed and treated for cancer will continue to increase (158). By 2040, it is projected that 74% of all cancers will occur in older adults, with the greatest increase expected in adults aged 75 years and older (158). Thus, the focus on maintaining cognitive health in older cancer survivors who may already be vulnerable because of lower cognitive reserve is paramount.

And finally, the cost of cancer care has also increased dramatically, leaving many cancer survivors and their families in financial ruin. Thus, it is essential that we begin to embed interventions or restorative programs within our oncology practices to promote uptake and reduce opportunity costs and other associated costs of these programs. Designing programs that are conducive to a cancer survivor's everyday life is critical. Programs such as Moving through Cancer, which has shown benefit for other symptoms, are being designed to be embedded in oncology practices and available for all cancer survivors. Another option would be to deliver programs remotely and asynchronously so that cancer survivors can participate at their convenience. Nevertheless, it is critical that interventions are codesigned in partnership with cancer survivors and their families to ensure that they are feasible and translatable. Importantly, to date, most interventions

for CRCI occur after treatment is completed and cancer survivors are already expressing cognitive concerns. Research is needed to determine whether cancer survivors would engage in interventions that could prevent or stave off cognitive decline. This approach would be similar to the long-standing National Institutes of Health (NIH)-funded trial, Advance Cognitive Training in the Vital Elderly (ACTIVE), in which Ball and colleagues identified the positive effects of CT on cognitive function and health-related QoL for up to 10 years post-treatment (159,160). Intervening earlier may have several cognitive and health benefits, but trials to stave off cognitive decline in cancer survivors are needed.

Conclusions

In summary, CRCI is a prevalent and potentially debilitating symptom for a subset of non-CNS cancer survivors. It has been associated with downstream negative effects on everyday functioning, work ability and productivity, and overall QoL. Addressing the cognitive health of cancer survivors is imperative but has only recently been the focus of interventional research. Many interventional strategies such as exercise, mind-based interventions and their combination (mind-based exercises), and cognitive rehabilitative approaches, including CT and CBT have shown promise, but require further testing. In addition to increasing sample sizes, clinical trials need to address the limitations of previous studies. These limitations include lack of attention control comparators, failure to mask intervention assignment, and insufficient sample size and diversity. Overall, CRCI is a complex symptom and will require a multidisciplinary approach to ameliorating its impact on cancer survivors.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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