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The Effects of Chemotherapeutic Agents on Cognitive Function: A Literature Review

Corinne Menz

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Eleanor Mann School of Nursing

University of Arkansas

Dr. Kelly Vowell Johnson

Abstract

With increasing cancer diagnoses and an increase of chemotherapy treatment, many patients complain of cognitive decline during the duration of treatment as well as once treatment has been completed. The purpose of this review is to compile relevant research regarding chemotherapy-related cognitive impairment and its implications for the care of cancer patients. Peer-reviewed articles and studies focusing on the impact of chemotherapy on cognitive function were evaluated, resulting in a total of 12 studies utilized in this review. Overall, it has been found that a large percentage of patients undergoing chemotherapy treatment report a subjective decline in cognitive functioning, but there is little evidence of objective decline shown by cognitive testing and fMRI data. While more research needs to be conducted to find whether there is measurable objective decline in patients receiving chemotherapy treatment, understanding and managing the symptoms should be a priority for healthcare providers delivering chemotherapy treatment.

Introduction

Chemotherapy is a commonly used treatment for a variety of cancers, and the long-lasting effects of chemotherapy treatment have been widely documented. One of the highest concerns is cognitive impairment during and after treatment and is commonly referred to as "chemobrain" (Perrier et al., 2018). The effects of chemotherapy vary according to each patient, however, in approximately 15-35% of cases cognitive dysfunction has been reported (Martin et al., 2020). Chemotherapy treatment most commonly affects memory, learning, attention, concentration, reasoning, processing speed, executive functions, and visuo-spatial skills (Mounier et al., 2020). In turn, the adverse effects of chemotherapy can result in anxiety, stress, depression, and fatigue, among other symptoms (Alhareeri et al., 2020). Due to the increasing life expectancy after cancer diagnosis, more effects of chemotherapy-related cognitive impairment (CRCI) are being recognized and reported, most often in breast cancer patients (Boscher et al., 2020).

The direct cause and etiology of chemotherapy-related cognitive impairment is still unknown, yet the occurrence is thought to be multifactorial (Kessler et al., 2019; Martin et al., 2020). Commonly reported causes include the direct neurotoxic effects, hormonal changes, oxidative stress, dysregulation of the immune system, and vascular damage (Martin et al., 2020). However, it has been found that cognitive impairment exists prior to the initiation of therapy in some cases, indicating that the cancer itself could be a contributing factor to cognitive decline (Mounier et al., 2020). Introduction of stress, anxiety, and depression related to cancer diagnosis and subsequent treatment may also impair cognitive function in cancer patients (Martin et al., 2020).

Due to the wide-reaching cognitive effects that chemotherapy can have on patients, improving and maintaining quality of life is of the utmost importance (Boscher et al., 2020). With an increased number of cancer survivors due to better detection and advances in cancer treatment, the long-term effects of chemotherapy need to be mitigated and researched more thoroughly (Fernandez et al., 2020). Providing care for patients with declining cognitive function presents a myriad of challenges for their nurses, doctors, and family members (Cheng et al., 2019). Because of these factors, there are many nursing implications for the care of cancer patients undergoing chemotherapy treatment and those in remission.

The purpose of this literature review is to investigate how chemotherapy treatment affects cognitive function in cancer patients. This review is presented using the following themes: potential causes of this cognitive decline, effects of chemotherapy treatment, and subjective patient reports. The Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) questionnaire has become widely used among providers, yet its use and scoring has not been standardized (Costa et al., 2018). Utilizing these topics, the question of whether chemotherapy affects cognitive function will be explored.

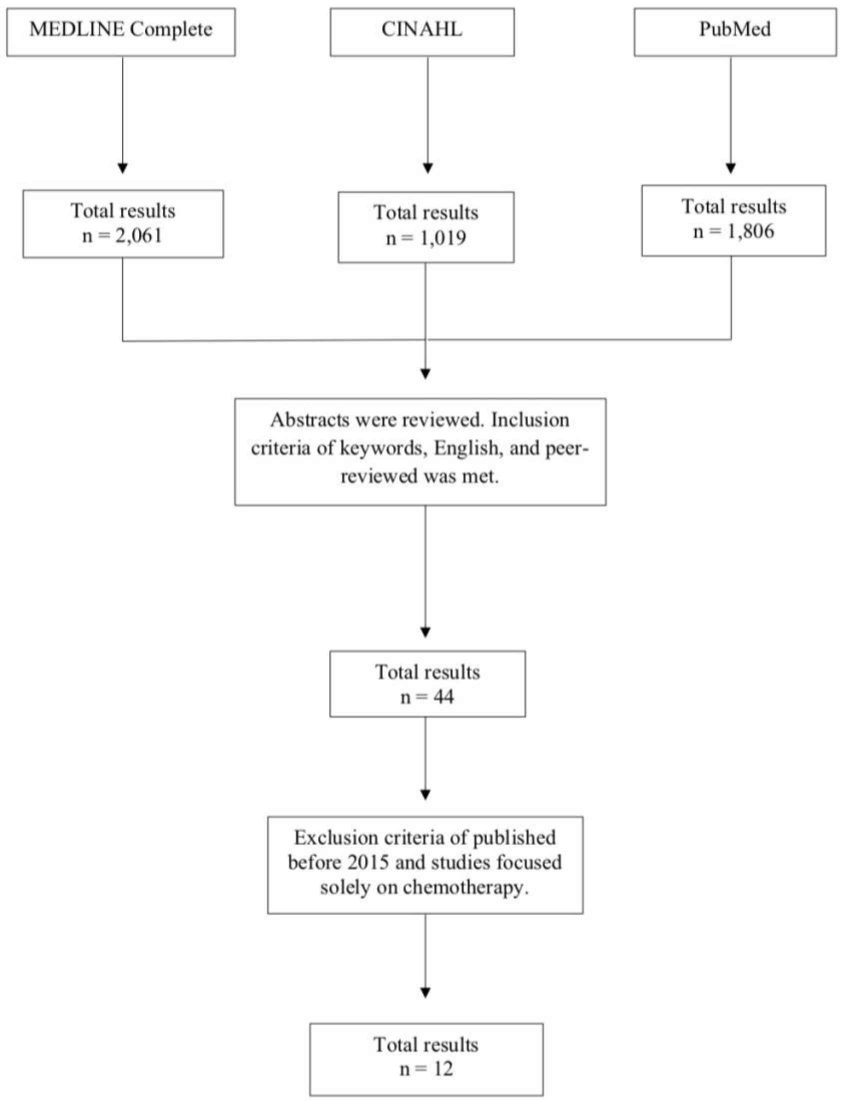
While there has been extensive research conducted on this topic, there are many gaps present within the literature. For instance, while the causes of cognitive dysfunction related to chemotherapy treatment are noted to be multifactorial, there has been little research conducted on the potential specific causes (Martin et al., 2020). In addition, many patients report subjective cognitive decline, but limited studies have carried out research on objective cognitive impairment as evidenced by alterations within the brain, and the studies that have focused on this area have not had compelling results (Cheng et al., 2019). Even with the use of FACT-Cog, compiling the incidence of CRCI among cancer patients has been inconsistent and the utilization of this assessment tool varies with each provider (Costa et al., 2018). Many of the studies presented in this review did not have statistically significant conclusions, which also indicate the need for further investigation on how chemotherapy affects cognitive function. While advances have been made in monitoring and treating this cognitive impairment, more needs to be done.

Methods

A thorough review of literature and data extraction was completed using MEDLINE Complete, CINAHL, and PubMed. A distinguished professor and health sciences librarian at the University of Arkansas provided expertise and support with finding applicable research articles that met the inclusion criteria. The key words used in all searches were: *chemotherapy, cancer, cognitive, cognitive impairment or dysfunction.* The inclusion criteria for the databases searched were articles that contained the keywords, written in English, and peer-reviewed. Excluded from the review were articles published before 2015. Additionally the criteria focused solely on chemotherapy treatments and outcomes. When using CINAHL, a total of 1,019 articles were relevant. These were reviewed and evaluated to ensure the inclusion criteria was met. Of these articles, three studies were found and were utilized in this review that focused on the use of magnetic resonance imaging in visualizing structural changes within the brain before, during and after chemotherapy. Searching PubMed produced a total of 1,806 results. After incorporating the inclusion and exclusion criteria, one article was used from this search. The study used the Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) version 3 in the assessment of cognitive function in patients undergoing chemotherapy treatment for cancer, which was analyzed for this review. MEDLINE Complete was used to search for additional articles. The keys words for the search were *chemotherapy and cancer and cognitive*.

This search yielded 2,061 articles. Of these articles, 39 were found that included the use of keywords and were applicable to the literature review. However, three were found that did not meet the publishing date of 2015, one was focused on the use of other cancer treatment rather than chemotherapy, and one had not yet been fully published and was unavailable to the public. In total, 35 articles were found that met the inclusion criteria. Once the literature was extensively review and examined, a total of 12 articles were chosen to be included and are the focus of this review.

Figure 1



Results

Causes of Cognitive Decline

As discussed previously, the causes of CRCI remain mostly unknown, however the incidence is likely to be multifactorial. Martin et al. (2020) proposes five different causes: the direct neurotoxic effects of chemotherapy, induced hormonal changes, oxidative stress, immune system dysregulation, and vascular damage. Underlying stress, anxiety, and depression may also play a role in advancing CRCI in many patients (Martin et al., 2020).

Some chemotherapeutic agents have been shown to cross the blood brain barrier (BBB) and can cause direct neurotoxic injury on the central nervous system (CNS) (Mounier et al., 2020). However, Hernandez et al. (2020) argues that most chemotherapeutic treatments do not readily cross the BBB, rather that the integrity of the BBB is harmed when peripheral molecules enter and cause injury of the CNS, not those directly associated with chemotherapy treatment. Chemotherapy can also impact hormone secretion and lead to cognitive problems (Martin et al., 2020). For example, estrogen and testosterone, which are neuroprotective hormones, are known to be affected by chemotherapy (Martin et al., 2020). With the decrease of these hormones, the process of cognitive decline can be accelerated (Mounier et al., 2020). Adding to the neurotoxicity effects, many chemotherapeutic agents induce oxidative stress both directly and indirectly (Hernandez et al., 2020). This is caused by an “imbalance between reactive oxygen species (ROS) production, including free radicals and peroxides, and the biological systems oxidant defense mechanisms” (Mounier et al., 2020). The byproducts of oxidative stress related to chemotherapy treatment can potentially cause damage to the CNS blood vessels which can impact perfusion to other blood vessels within the CNS, causing CRCI effects (Mounier et al., 2020). Inflammation due to the release of immune system mediators may be involved in promoting or exacerbating CRCI (Hernandez et al., 2020). Processing speed, executive function, spatial ability, and reaction time are all impacted by inflammatory cytokine release which crosses the BBB and causes cognitive impairment (Martin et al., 2020). The release of these mediators can cause neuroinflammation which negatively impacts neurogenesis and disrupts the myelination process, all impacting cognitive function (Mounier et al., 2020). Chemotherapy has the ability to damage blood vessels which can impact blood flow to blood vessels within the brain, henceforth causing a decline in cognition (Martin et al., 2020). This can cause a disruption of cerebral blood flow and blood vessel density, notably in the hippocampus which plays a large role in memory and learning (Mounier et al., 2020).

Effects of Treatment

Perrier et al. (2018) discovered with the use of fMRI that there was no statistical significance between healthy controls and those undergoing treatment for breast cancer related to changes in brain structure. However, the fMRIs did depict gray matter reduction in some areas of the brain, while in other areas of the brain, gray matter volume increased one year after chemotherapy treatment had stopped (Perrier et al., 2018). This indicates that a compensatory mechanism may be occurring in patients undergoing chemotherapy treatment, where the brain begins to adapt to the structural changes that the chemotherapy causes and therefore counteracts by increasing the volume of gray matter in other areas of the brain (Perrier et al., 2018). The fMRIs that were taken one month after cessation of therapy showed significant atrophy within the brain which recovered one year after therapy had completed, as shown by follow-up fMRI (Perrier et al., 2018). This supports the hypothesis that CRCI improves once the chemotherapy course has been completed.

Chen et al. (2019) discovered that there was a significant increase in resting state brain activity in some parts of the brain and a decrease in others from before the initiation of chemotherapy to one month after chemotherapy was completed. However, there were no differences between the controls and chemotherapy group in rs-fMRI results, which is an indicator of intrinsic brain activity associated with cognitive function (Chen et al., 2019).

Moreover, there was no significant difference in neuropsychological testing among groups, which shows that there was not a large gap present that signified cognitive decline in the domains of executive functioning, memory, language, processing speed, and attention (Chen et al., 2019). Again, these results indicate a compensatory mechanism by the brain to counteract the effects of chemotherapy, however in this study there was no statistically significant data present that indicated a decline in cognition in chemotherapy patients (Chen et al., 2019).

Kessler et al. (2020) organized the patients into three different biotype groups, according to the most similar connectome features within their brain, which were found using fMRI. It was found that biotype 1 performed lower compared to the control group in all cognitive tests, biotype 3 did poorer on 4 out of 5 cognitive tests, and biotype 2 had a low performance on letter fluency only (Kessler et al., 2019). Furthermore, the subjects completed the Clinical Assessment of Depression (CAD) and the Behavioral Rating Inventory of Executive Function (BRIEF-A) to report subjective cognitive impairment (Kessler et al., 2019). Results from these questionnaires showed that biotype 1 had lower perceived cognitive function and lower psychological functioning, whereas biotype 2 only showed lower executive functioning, and biotype 3 had no significant difference compared to controls (Kessler et al., 2019). These results show that brain structure plays a large role in determining how chemotherapy will affect cognitive functioning in cancer patients (Kessler et al., 2019).

In assessing functional connection within the brain, it was found that breast cancer survivors who had received chemotherapy treatment and complained of cognitive impairment showed weaker functional connectivity within the frontoparietal system of the brain compared to breast cancer survivors who did not complain of cognitive decline (Piccirillo et al., 2015). The results from this were found using rs-fcMRI data and cognitive impairment was measured using the Global Rating of Cognition (GRC) (Piccirillo et al., 2015). Those who had the highest GRC scores, indicating cognitive impairment, had the lowest functional connection strength (Piccirillo et al., 2015). These results outline that while not every cancer patient will have cognitive impairment, those that do exhibit changes within the structure of their brain that may be the cause of declining cognition (Piccirillo et al., 2015).

Telomere lengths were also assessed to discover the impact of chemotherapy on cognition (Alhareeri et al., 2020). Using fluorescence in situ hybridization (FISH), chromosome-specific telomere values were analyzed in order to find whether chemotherapy caused telomere length changes and if those changes resulted in cognitive effects (Alhareeri et al., 2020). Throughout the duration of chemotherapy, telomere lengths were measured and 84.8% showed a decrease in length (Alhareeri et al., 2020). It was found that there is a significant association of seven cognitive domains with chromosome-specific telomere values (Alhareeri et al., 2020). In addition, a significant relationship was found between visual memory domain and numerous individual telomeres on specific chromosomes (Alhareeri et al., 2020). Therefore it can be hypothesized that the shortening of telomere length caused by chemotherapy can negatively impact cognitive function (Alhareeri et al., 2020).

Patient Reports

Janelsins et al. (2017) implemented the use of FACT-Cog to determine perceived cognitive decline in breast cancer patients treated with chemotherapy. From prechemotherapy to post-chemotherapy, 45.2% of breast cancer patients reported meaningful cognitive decline compared to the healthy controls (Janelsins et al., 2017). However, FACT-Cog scores improved within six months of cessation of chemotherapy (Janelsins et al., 2017). This indicates that while the incidence of perceived cognitive function is high, there is evidence of improvement once chemotherapy has ended (Janelsins et al., 2017).

Boscher et al. (2020) found that a variety of factors impacted patient's FACT-Cog scores, including age, employment, trouble sleeping, medical treatment for mental health, chemotherapy treatment, anxiety, depression, fatigue, and PTSD. It was shown that those who received chemotherapy were more likely to report and suffer from cognitive decline (Boscher et al., 2020). However, the cause of this cognitive dysfunction was proven to be multifactorial because it was shown that the patients' employment status, diagnoses of mental health issues, as well as sleep difficulties also contributed to subjective cognitive complaints (Boscher et al., 2020). Therefore, it is likely that the cause of cognitive impairment in patients undergoing chemotherapy treatment is due to a variety of external factors, rather than solely the administration of chemotherapy for cancer (Boscher et al., 2020).

The Blessed Orientation Memory Concentration Test was also used to assess perceived cognitive function in older adults with breast cancer (Nakamura et al., 2020). Through the use of this test along with subjective reports of patients, 27% suffered from cognitive impairment (Nakamura et al., 2020). However, those that reported this decline were older in age, had less education, and not employed full-time (Nakamura et al., 2020). This corresponds with the hypothesis that cognitive impairment is impacted by other factors rather than solely the administration of chemotherapy (Nakamura et al., 2020).

See Table 1 for an outline of the studies that were reviewed. Most of the studies utilized were longitudinal, therefore the strength of evidence is less than that of randomized controlled trials. This is because the patient population that is being studied is unable to participate in randomized controlled trials due to their diagnosis of cancer and the need to undergo chemotherapy treatment.

Table 1					
Alhareeri, A. A., Archer, K. J., Fu, H., Lyon, D. E., Elswick, R. K., Jr., Kelly, D. L., Starkweather, A. R., Elmore, L. W., Bokhari, Y. A., & Jackson-Cook, C. K.	2020	United States	Longitudinal cohort study	Certain chemotherapy agents shortened telomere lengths which caused lower cognitive scores.	Level 4 Evidence
Chen, B. T., Jin, T., Patel, S. K., Ye, N., Ma, H., Wong, C. W., Rockne, R. C., Root, J. C., Saykin, A. J., Ahles, T. A., Holodny, A. I., Prakash, N., Mortimer, J., Waisman, J., Yuan, Y., Li, D., Sedrak, M. S., Vazquez, J., Katheria, V., & Dale, W	2019	United States	Longitudinal cohort study	Chemotherapy may impact intrinsic brain activity in breast cancer patients, negatively affecting their cognitive function.	Level 4 Evidence
Boscher, C., Joly, F., Benedicte, C., Humbert, X., Grellard, J., Binarelli, G., Tron, L., Licaj, I., Lange, M.	2020	France	Qualitative Study	About half of breast cancer patients undergoing chemotherapy reported cognitive complaints, which could be impacted by age, employment status, or mental health issues.	Level 6 Evidence
Costa, D., Loh, V., Birney, D. P., Dhillon, H. M., Fardell, J. E., Gessler, D., Vardy, J. L.	2018	Australia	Qualitative Study	The Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) can be used to assess the perceived cognitive function in cancer patients and its use should be standardized in order to assess the cognitive domains of those undergoing chemotherapy	Level 6 evidence
Fernandez, H. R., Varma, A., Flowers, S. A., & Rebeck, G. W.	2020	United States	Case-Control Study	The APOE gene related to the development of Alzheimer's disease could make those who carry this gene more susceptible to developing CRCI while undergoing chemotherapy treatment for cancer	Level 4 Evidence
Janelsins, M. C., Heckler, C. E., Peppone, L. J., Kamen, C., Mustian, K. M., Mohile,	2017	United States	Longitudinal Study	Patients receiving chemotherapy treatment for breast cancer reported a significant increase in cognitive impairment from	Level 4 Evidence

S. G., Magnuson, A., Kleckner, I. R., Guido, J. J., Young, K. L., Conlin, A. K., Weiselberg, L. R., Mitchell, J. W., Ambronsone, C. A., Ahles, T. A., Morrow, G. R				prechemotherapy to postchemotherapy. This was also likely impacted by anxiety, depression, and decreased cognitive reserve.	
Kesler, S. R., Petersen, M. L., Rao, V., Harrison, R. A., Palesh, O.	2020	United States	Longitudinal Study	Using fMRI data, different biotypes among breast cancer patients were identified and studied which show that certain genetic markers make some patients more susceptible to CRCI.	Level 4 Evidence
Martin, B. R., Fernandez Rodriguez, E. J., Rihuete Galve, M. I., Cruz Hernandez, J. J.	2020	Spain	Longitudinal Study	Cognitive performance declined in patients diagnosed with breast cancer and receiving chemotherapy and did not completely recover two months after the cessation of treatment. Those who had anxiety or depression had worse cognitive performance.	Level 4 Evidence
Mounier, N. M., Abdel-Maged, A. E.-S., Wahdan, S. A., Gad, A. M., & Azab, S. S.	2020	Egypt	Systematic Review	Explored the underlying causes of CRCI including neurotoxicity, blood brain barrier disruption, oxidative stress, vascular damage, and immune system dysregulation.	Level 5 Evidence
Nakamura, Z. M., Deal, A. M., Nyrop, K. A., Damone, E. M., Muss, H. B	2020	United States	Qualitative Study	27% of those receiving chemotherapy reported cognitive impairment. This was associated with an increase of age, less education, and not being employed full-time	Level 6 Evidence
Perrier, J., Viard, A., Levy, C., Morel, N., Allouache, D., Noal, S., Joly, F., Eustache, F., & Giffard, B.	2020	France	Longitudinal Study	Breast cancer patients undergoing chemotherapy had gray matter atrophy in some areas of the brain with an increase in gray matter volumes in other areas. The atrophy either persisted or recovered after one year of treatment, depending on the location of the atrophy.	Level 4 Evidence
Piccirillo, J. F., Hardin, F. M., Nicklaus, J., Kallogjeri, D., Wilson, M., Ma, C. X., Coalson, R. S., Shimony, J., Schlaggar, B. L.	2015	United States	Case-Control Study	Using fMRI, it was found that those who reported cognitive impairment after chemotherapy treatment had disrupted resting-state functional connectivity within the brain which may impact attention and executive functioning.	Level 4 Evidence

Discussion

In analyzing these studies, it is evident that more research over CRCI needs to be completed. While it has been widely thought that chemotherapy is a direct cause of cognitive impairment, research has found that many factors may play a role in CRCI and that the type of cancer and chemotherapy treatment may determine the extent of symptoms, along with genetic predispositions (Fernandez et al., 2020). The results of many of these studies differed: while some reported statistically significant objective cognitive decline, others did not, but many subjects reported subjective cognitive impairment. A major finding in many of the studies presents that while patients may perform within normative ranges on cognitive tests, they subjectively report cognitive decline that is relevant to that patient, even though it cannot be objectively analyzed (Piccirillo et al., 2015). Martin et al. (2020) found that "all cognitive domains studied were affected during chemotherapy, although not all shared the same impairment" and this was found through the use of subjective questionnaires that were completed by the subjects. On the other hand, the shortening of telomere lengths was visualized after chemotherapy treatment, which may be related to cognitive impairment among cancer patients (Alhareeri et al., 2020). As is evident, the occurrence of CRCI varies among patient population and is more often subjectively reported, rather than objectively measured.

Due to the various types of studies that were reviewed, there is an inconsistency of results. Nakamura et al. (2020) had a small sample size and was limited to a more active and educated cohort that did not suffer from other variables that could impact cognitive impairment, such as depression, anxiety, and stress. Due to the lack of variability among patients in this study, a comprehensive view on how chemotherapy affects cognitive function was not achieved (Nakamura et al., 2020).

The FACT-Cog scoring tool implementation has not yet been standardized and may lead to discrepancies among cognitive function in cancer patients (Costa et al., 2018). Along with this, FACT-Cog scores have a statistically insignificant relationship with objective cognitive function analysis, such as testing and fMRI data, meaning that more research needs to be done as to the efficacy of this tool in measuring cognitive function in cancer patients (Costa et al., 2018). In one of the studies utilizing fMRI to analyze brain changes throughout the course of chemotherapy, limitations were present which included a short follow-up duration, small sample size, different stages of cancer, and different chemotherapy treatment which could have contributed to the insignificant relationship between the neuropsychological testing and intrinsic brain activity associated cognitive function (Chen et al., 2019). All of these studies reviewed and presented had limitations that could have impacted the results.

Conclusion

Regardless of whether objective cognitive decline exists in cancer patients undergoing chemotherapy, there continue to be subjective reports of cognitive decline that need to be addressed. Even though the evidence is inconclusive supporting changes in brain structure due to chemotherapy, the occurrence of CRCI and fear of "chemobrain" remain prevalent among cancer patients. Because of this, guidelines for clinical practice are needed. For example, developing interventions, both pharmacological and behavioral, should be a priority among providers who give care to those undergoing chemotherapy treatment (Piccirillo et al., 2015). In addition, the use and structure of FACT-Cog should be standardized across clinical practice so that subjective cognitive complaints can be better monitored before, during, and after treatment (Costa et al., 2018). With the proper use of the FACT-Cog clinical questionnaire, the incidence of CRCI may be better understood and managed within the clinical setting (Costa et al., 2018).

Moving forward, it is evident that more research needs to be done. Studies focusing on both subjective cognitive complaints through the use of questionnaires, as well as objective cognitive complaints through the use of fMRI should be completed. A better understanding may be gained through comparing and contrasting both sides of cognitive impairment using the same group of subjects. Furthermore, adequate timing and follow-up should be performed in all studies, as that was a limitation in multiple studies.

After reviewing all of the articles presented, it is evident that the occurrence CRCI is clinically relevant and warrants further investigation. While the specific causes of CRCI remain unknown and may be difficult to identify, there are many implications for caring for patients suffering from cognitive decline. More studies evaluating how chemotherapy affects cognitive function need to be completed so that evidence-based interventions could be utilized for better patient outcomes. Overall, those undergoing chemotherapy for cancer treatment may suffer from cognitive impairment, and therefore more needs to be done to address this issue.

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