Review Article

A narrative review of risk factors and interventions for cancer-related cognitive impairment

Lu Bai[1,2], **Enyan Yu**[1,2]

[1]Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China; [2]Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Beijing, China

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Correspondence to: Enyan Yu. Department of Clinical Psychology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), East Banshan Rd, Hangzhou, China. Email: yuenyan@aliyun.com.

Abstract: Cancer-related cognitive impairment (CRCI) refers to a series of cognitive impairment symptoms associated with alternations in brain structure and function, caused by a non-central nervous system malignant tumor and its related treatment. CRCI may present as memory loss, impaired concentration, difficulty in multitasking and word retrieval, and reduced comprehension speed. CRCI has become one of the prevalent factors that compromise the quality of life for cancer survivors. Different treatments, including surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted drugs, may contribute to CRCI. Meanwhile, patients' factors, including emotional challenges and genetic makeup, also contribute to the development of CRCI. The condition can be treated with using stimulants methylphenidate and modafinil, metabolites of nicotine: cotinine, antidepressants of fluoxetine and fluvoxamine, dementia drug of donepezil, and antioxidants ZnSO4, n-acetyl cysteine, propofol, and Chinese herbal of silver leaf medicine. Psychotherapies, including meditation and relaxation, cognitive rehabilitation training, along with physical therapies, including aerobic exercise, resistance training, balance training, yoga, qigong, tai chi electroencephalogram biofeedback, and acupuncture, are also beneficial in alleviating cancer-related cognitive impairment symptoms. In recent years, researchers have focused on factors related to the condition and on the available interventions. However, most research was conducted independently, and no review has yet summarized the latest findings. This review details and discusses the status of related factors and potential treatments for CRCI. We also supply specific recommendations to facilitate future research and integration in this field.

Keywords: Cancer; cognitive impairment; risk factors; treatment

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Introduction

The survival rate of cancer patients is increasing despite the advancements in cancer diagnosis and treatment technology. This has resulted in an increased focus on the quality of life of cancer survivors over recent years. The incidence of cancer-related cognitive impairment (CRCI) ranges from 16% to 75% (1). The number varies because of different cancer type, treatment, duration of follow-up, type of study design and definition of cognitive impairment (2). According to a 2019 web-based survey, the prevalence of CRCI complaints experience is 8.23% for breast cancer, 9.10% for gynecological cancer patients, 8.33% for hematologic cancer patients, and 8.86% for other cancer types (3). Most studies suggest this reversible condition is attributed to chemotherapy and is evident

within 18 to 36 months after treatment (4). However, some symptoms have been reported to be observed for up to 20 years (5). Although CRCI is usually mild to moderate in severity, it compromises the patient's treatment adherence, reduces work productivity, and impacts the quality of daily activities (cooking, driving, etc.) (6). The American Cancer Society indicates that cognitive domains of memory, attention, executive function, and processing speed might be impaired, although research has also found impairment in working memory, new learning, visuospatial skills, and language. One research showed that low IQ score, as well as high fatigue predicted baseline CRCI. IQ score also predicted individual cognitive ability, which were also influenced by age, sex, cancer diagnosis, and an active intervention for hypertension (7). CRCI symptoms are categorized as follows: attention, memory, psychomotor speed, and executive function (8). Memory refers to forgetfulness, including the inability to recall the names of individuals. Attention pertains to insufficient concentration while completing a task, losing track of thoughts, and the inability to grasp the main concepts from written material. Psychomotor speed refers to the sluggish movement, accompanied by an unclever mind. Executive function refers to indecision and the inability to multitask.

When CRCI exits, the condition of the brain and the specific manifestations of the changes is reviewed. DTI Network analyses showed cognitive deficits was related with altered global and local brain networks. Chemotherapy drugs, which is related to hippocampal and frontal lobes dysfunction, and suppression of neurogenesis, cause memory loss, attention, working memory, and strategic learning deficits (9,10). Studies have reported that CRCI patients shows increased level of functional activation and connectivity of brain regions, which might be explained as the cognition have been interpreted as compensatory processes for treatment induced brain injury (11). Several studies have shown widespread reductions in grey matter density or volume and white matter microstructure when there is CRCI (12-15). Furthermore, mitochondrial dysfunction and dysregulation of cytokine activity might be another reason (16). Other possibilities include direct neurotoxicity with damage to neurons or nerve cells from chemotherapy (particularly fluorouracil and methotrexate, which are more likely to cross the blood-brain barrier) or induced hormonal changes from chemotherapy that lead to cognitive change (17). Chemotherapy drug, radiotherapy combined with immunotherapy caused increased levels pro-inflammatory cytokines, such as IL-1b, IL-6, TNF-a, IL-10, which impact on the frontal lobe function (18,19). Multiple studies have linked serum inflammatory markers with cognitive performance. In patients with breast cancer receiving chemotherapy, Williams *et al*. found an association between increasing concentrations of soluble tumor necrosis factor receptors I and II and decline in short-term visual memory (13). Additionally, CRCI also can be explained by oxidative damage and decreased hypothalamic-pituitary adrenal axis activity, and reduced brain vascularization and blood flow (20).

Neuropsychological assessments usually help to determine the various domains of cognitive in objective methods. According to the International Cognition and Cancer Task Force (ICCTF), the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination are the typica scales to measure cancer patients' cognitive deficits (21). The ICCTF suggests ≥2 test scores ≤1.5 standard deviations from the normative mean or one test score ≤2.0 standard deviations indicates cognitive impairment. Apart from that, Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment Scale (MOCA), Wechsler Adult Intelligence Scale, California Verbal Learning Test-II, Revised Rey-Osterrieth Complex *Figure T*est are commonly used in clinical department (22). However, no consensus has been reached for a specific tool to assess CRCI, and therefore a general, precise and effective CRCI scale is in need.

A strong interest in CRCI-related factors and interventions has developed in recent years, with reports linking the incidence of CRCI with the period after diagnosis, surgery, radiotherapy and endocrine therapy, and targeted drug therapy. Other areas of interest in CRCI have included interventions and the individual differences impact on CRCI. However, most of these reports do not collectively present the data in a combined manner. This is the first literature review that summarizes and discusses the latest findings of CRCI, with a focus on related risk factors and interventions. This paper will analyze and discuss the influence of different cancer treatments and individual factors on CRCI, along with the underlying mechanisms. Also, the treatment of CRCI is comprehensively expounded on drug treatment, psychotherapy, and physiotherapy, to supply directions for future research.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6443).

Methods

We conducted a literature search for papers published up to Oct 2019 on the risk factors and interventions aspects of CRCI using PubMed. The following medical subject heading terms were included for a MEDLINE search: "CRCI", "cancer cognitive impairment", "cancer cognitive defecit", "chemobrain ", "endocrine therapy cognitive", "radiotherapy cogntive", "targeted therapy cogntive", "drug CRCI", "psychotherapy CRCI", "physical therapy CRCI", "CRCI APOE", "CRCI TMS", "CRCI genetic factor", "CRCI Cognitive rehabilitation". Qualitative and quantitative data was extracted through interpretation of each article.

Risk factors for CRCI

Treatments of cancer

CRCI, also known as chemobrain and chemofog, mainly refers to cognitive impairment caused by chemotherapy, which may lead to nerve toxicity (23). Longitudinal studies, with neuropsychological assessments, have determined that the incidence of CRCI has been observed in approximately 40%, 75%, and 60% of patients before, during, and months to years after treatment, respectively (24). Findings in recent years support the notion that CRCI exists before chemotherapy. The studies indicated that the development of CRCI originated from cancer and surgery (25-27). Another study found that up to 33% of patients reported cognitive impairment before chemotherapy, including difficulty in expression and slowness in response (28). Also, malignant tumors and surgery were suggested to increase the level of cytokines, causing inflammation and tissue destruction, leading to cognitive decline (29).

A meta-analysis of 30 studies (838 participants) identified significant changes in executive function and verbal memory in patients that underwent chemotherapy when compared to the control group (30). In another meta-analysis, Falleti *et al.* reported small to moderate cognitive decline concerning memory, executive function, and attention tests in breast cancer patients, post-chemotherapy (31). Another meta-analysis of 7 studies found that over 300 breast cancer patients showed decreases in short-term memory, verbal and spatial language ability after undergoing chemotherapy (32). As previously mentioned, chemotherapy may cause cognitive decline in four areas: memory, attention, psychomotor speed, and executive function.

Furthermore, the dose of chemotherapy affects the severity of CRCI. One study showed 32% and 17% of patients who received high- and standard-dose chemotherapy, respectively, developed cognitive impairment compared to 9% of the control group in cancer patients post-treatment (33). Another investigation found that patients who received high-dose chemotherapy displayed more severe cognitive deterioration than those who were administered low-dose chemotherapy (34). Collins *et al.* evaluated the cognitive status of 60 patients with early-stage breast cancer before and upon completion of chemotherapy, along with after surgery. They demonstrated a linear deterioration of CRCI at each subsequent time point when compared to healthy controls (35). However, Schagen's follow-up study revealed that the cognitive function of patients in both the high- and low-dose groups improved in the following four years, and considered the chemotherapy-induced change in cognitive function as transient (36,37). However, another study examined the effects of the chemotherapy combination CMF group [cyclophosphamide, methotrexate, 5-fluorouracil (5-fu), CMF] on cognitive function. A neuropsychological evaluation indicated that the CMF chemotherapy groups impaired cognitive functions on immediate and delayed memory, psychomotor speed, executive function, and processing speed, which were present for up to 20 years (5).

Another study examined the risk of dementia among 6,932 elderly breast cancer patients after they had received different chemotherapy drugs, including anthracyclines (doxorubicin, mitoxantrone, daorubicin, and epirubicin), CMF, taxane (polyene taxol, paclitaxel), and others. Interestingly, no significant difference was noted between different chemotherapy drugs and the risk of dementia diagnosis (38).

The increase of pro-inflammatory cytokines levels in cancer patients post-chemotherapy is regarded as the mechanism behind CRCI. Increased levels of serum interleukin-6 (IL-6), c-reactive protein (CRP), tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), and other cytokines were associated with cognitive declines, including memory problems (39). A longitudinal study found that higher IL-6 and IL-1 concentrations were associated with increased severity in cognitive impairment, while higher IL-1 levels correlated with slower responses of patients (40). On the contrary, increased IL-4 was associated with faster response rates of breast cancer patients and fewer complaints of cognitive function, indicating it might serve as a protective factor for nerves in cancer patients (40). Also, the destruction of the blood-brain barrier, DNA

oxidative stress damage, and shortening of the neutrophils are possible hypotheses of its mechanism (17).

Radiotherapy, endocrine targeted drug treatments may also contribute to the development of CRCI (41-45). The duration of radiotherapy-induced CRCI in cancer of the non-central nervous system has been observed at months to years after treatment (46-48). However, its effect is not as severe as that caused by chemotherapy (27). After seven months of breast-conserving therapy with adjuvant breast radiotherapy, women with breast cancer displayed lower scores on the short-term verbal memory and delayed recall measures, assessed by the Wechsler Memory Scale compared to those without radiotherapy. However, this difference disappeared three years after radiotherapy (49). The short-term memory impairment after radiotherapy is estimated to correlate significantly with elevated plasma IL-6 levels (50). This investigation revealed that memory levels recovered to baseline three years after radiotherapy, along with decreased plasma interleukin IL-6 levels. IL-6 was potentially regarded as the mechanism behind CRCI induced by radiotherapy (51). A longitudinal study of breast-cancer patients demonstrated that immediate and delayed memory cognitive functions improved in patients who received adjuvant breast radiotherapy and those who did not receive radiotherapy at 18 and 36 months after diagnosis (52). In a cross-sectional study, the cognitive abilities of testicular cancer patients were assessed using neuropsychological tests three years after radiation. No significant difference in average scores was observed between patients who underwent surgery alone, and those received adjuvant radiation (53). In conclusion, radiotherapy causes a transient decline in memory function, related to IL-6 levels.

Endocrine therapy using antagonistic estrogen is commonly used to treat breast cancer patients. de Ruiter *et al.* postulated that endocrine therapy is associated with cognitive impairment in cancer patients (54). Tamoxifen, a hormone therapy combined with chemotherapy, prolonged visual, and verbal memory impairment by one year when compared to chemotherapy alone (55). The combination of tamoxifen and chemotherapy significantly reduced memory, speech fluency, visuospatial function, and processing speed than chemotherapy alone (56). A study with strict control of variables found that patients with androgen deprivation therapy mainly affected the spatial memory and language memory (57).

Endocrine therapy primarily compromises using estrogen receptor modulators and/or aromatase inhibitors. Aromatase inhibitors block the synthesis of estradiol, depriving the brain of its ability to regulate estradiol, resulting in decreased neuroplasticity and impaired cognitive function. Clinical studies have shown that selective estrogen receptor modulator therapy has adverse effects on cognitive function, particularly in elderly breast cancer patients (43). Another study found that testosterone and estradiol levels decreased significantly in prostate cancer patients after treatment with leuproverine for three months, and the related spatial memory function was significantly impaired (58). A preclinical model is used to assess the effects of endocrine therapy on androgen-blocking of the brain. It demonstrated adverse effects in the hippocampus, associated with spatial ability and the ability to memorize new events (59,60). In summary, endocrine therapy has been shown to impair memory function, including spatial and verbal memory, along with psychomotor speed function. The mechanism of impairment was linked to changes in estradiol, testosterone, and the hippocampus.

In recent years, targeted drugs have been recognized as novel cancer treatments (61). Studies have found sunitinib aided in the reversal of cognitive impairment, including memory loss and word retrieval difficulty (62). A longitudinal study found that 31% of renal cancer patients treated with antiangiogenic tyrosine kinase inhibitors displayed a decline in cognitive function compared to baseline performance. This was more pronounced with executive function and episodic memory, suggesting that targeted drugs may elicit a direct neurotoxic effect (63). However, the mechanism behind targeted drug-induced CRCI is still unclear. Investigations have established that vascular endothelial growth factor (VEGF) plays a vital role in this process, and VEGF inhibitors may affect cognitive function by acting on neurogenesis, brain blood flow and the regulation of long-term potential (64,65).

Additionally, immune dysregulation and cytokine release may also be underlying mechanisms (66). Interestingly, everolimus has been found to delay aging and reduce the risk of Alzheimer's disease in preclinical trials (67). A study found that everolimus increased hippocampal neurogenesis and synaptogenesis to improve cognitive function and prevent cognitive decline (68). Different targeted drugs show various effects on cognitive function, with the underlying mechanism associated with changes in VEGF, immune function, and level of cytokines. The emergence of novel targeted drugs highlights the need for further investigations to elucidate their effects on CRCI development.

Individual factors

Anxiety, depression, fatigue, insomnia

Some biological and psychological variables, including anxiety, depression, and insomnia, may aid in showing the likelihood of cognitive impairment in some patients. Emotional problems, including depression and anxiety, induce cognitive impairment, with a significant and linear correlation observed between emotional problems and cognitive impairment, including attention deficiency (69,70). People with cancer are more likely to experience symptoms of depression and anxiety compared to healthy individuals (71,72). Studies have found an inverse correlation between affective problems and cognitive function (73). Anxiety and depression also show a synergistic effect on executive function in cancer patients. Individuals diagnosed with the combination of depression and anxiety disorders display poorer performance with tasks on executive function than individuals with depression or anxiety disorder alone (74). However, the correlation between the subjective and objective evaluation of cognitive function is weak. Additional studies have revealed a significant correlation between subjective assessments of cognitive function problems and affective problems (75,76).

Insomnia has been shown to contribute to the severity of cognitive impairment in cancer patients (77,78). A study analyzing the relationship between insomnia disorders and cognitive function in breast cancer patients found patients with mild, moderate, and severe insomnia scored lower on cognitive assessments when compared with cancer patients without sleeping disorders. Additionally, a direct correlation was noted between insomnia severity and cognitive impairment (78). These findings highlighted the need for systematic evaluation of areas other than cognition, including emotional states and sleep quality.

Genes

Genetic factors, apolipoprotein E (APOE), catechol-O-methyltransferase (COMT), and brain-derived neurotrophic factor (BDNF), increase the risk of CRCI. The subtype of apolipoprotein E (APOE), APOE 4, is the leading risk factor for Alzheimer's disease (79). A systematic review revealed three longitude studies and one cross-sectional study, which indicated the APOE 4 alleles was a risk factor for CRCI (80-83). The study found patients with the ApoE 4 alleles were more susceptible to neurotoxicity from chemotherapy than those without this gene, displaying significantly lower scores on language learning and memory, visual memory, spatial memory, and executive function (17,82). Another investigation revealed that testicular cancer patients with APOE 4 were found to be less cognitively competent after chemotherapy than those without this gene. There was no association noted established between APOE 4 and structural brain changes (83). While another six studies reported a correlation between APOE 4 and brain changes, these were reported to be non-significant (84-89).

Other related genes include COMT, DNA repair genes, oxidative stress genes, genes associated with breast cancer phenotypes, and GNB3 genes. COMT regulate dopamine levels in the frontal cortex, which is mediated executive and memory functions. A study found COMT gene polymorphisms were related with higher risk of CRCI in breast cancer survivors after chemotherapy (87). Research has found that patients carry e BDNF Met allele are at lower risk of CRCI, especially in terms of speech fluency and multitasking (90). Other genetic polymorphisms, such as those related to the folic acid pathway, estrogen receptor alpha genetic polymorphism, and DNA methyltransferase 1 polymorphism are also related to cognitive function (91,92). CRCI was not found to be associated with the genes coding IL-6, TNF, IL-1β, and brain-derived neurotrophic factor (BDNF). Except for APOE 4, genetic risk factors were not widely investigated (93). In general, the evidence is limited for possible genetic risk factors for CRCI, but we can reach a consensus that genetic factors are associated with cognitive impairment in cancer patients after treatment.

Risk factors for children

Some might wonder whether risk factors for children is different from that for adults. Risk factors for adult CRCI include cognitive reserve, age, genetic factors, and ethnicity, while risk factors for children include genetic factors, female sex, younger age at diagnosis, chemotherapy dose, and both dose and field size for radiation. Studies have shown 25% and 33% of children have cognitive impairment due to the chemotherapy (94). Boys shows better performance than girls in the aspect of cognitive function (95), and children who have the chemotherapy at younger ages have the worse performance (96). Research has shown that higher dose of chemotherapy, the severer cognitive deficits when the child grow up. One study on the survivors of childhood acute lymphoblastic leukemia showed worsened deficits in attention, as well as executive function and processing speed that higher doses of methotrexate (97).

CRCI interventions

Drug therapy

CRCI interventions have always been a topic of interest in researchers. Some believe stimulants, including methylphenidate and modafinil, play a significant role in treating CRCI. In 2019, a systematic review of six randomized controlled trials was conducted, where methylphenidate was administered in 244 cases across three trials while 146 cases received modafinil in the remaining three studies. The effects of their treatments on cognitive function and quality of life were assessed in all participants. Improvements in the cognitive function were observed in two studies using modafinil and one using methylphenidate. The underlying mechanism behind stimulants refers to neural signal processing by increasing synaptic concentrations of dopamine and norepinephrine in the brain's prefrontal cortex (98-100).

Cotinine is the primary metabolite of nicotine. A study that examined the effects of cotinine on cognition and depression-like behavior in rats treated with CMF suggested it may contribute to CRCI recovery. The investigation also revealed that cotinine could alleviate the cognitive function side effects caused by chemotherapy (101).

Antidepressants have been shown to contribute to the treatment of CRCI. Studies have demonstrated that fluoxetine ameliorated memory impairment is caused by methotrexate chemotherapy and reversed neurogenic disorders in mice (102,103). The study revealed that 5-fu, a widely used chemotherapy drug, significantly reduced the number of proliferating cells in the dentate gyrus. The administration of fluoxetine, in combination with 5-fu, prevented the reduction of the number of proliferating cells in the sub-granular area of the dentate gyrus. Additionally, recipients of the combination therapy outperformed those who received monotherapy concerning hippocampal-dependent spatial working memory tests. These studies found that 5-fu exerted a negative effect on both cell proliferation and hippocampal-dependent working memory, while fluoxetine contributed to reversing these defects (104). A study on fluvoxamine found fluvoxamine ameliorated the taxol-induced neurotoxicity by partially inducing sigma-1 receptors, providing new evidence for the role of antidepressants in improving the chemical brain (105).

Donepezil, an acetylcholinesterase inhibitor used to treat Alzheimer's disease, is regarded as a neurotransmitter modulator and has received considerable attention from CRCI investigators. Animal model studies and clinical trials confirmed donepezil was effective in improving cognitive function in cancer patients (106-108). In one study, breast cancer patients with CRCI symptoms were administered donepezil for 24 weeks, at doses of 5 mg daily for the first four weeks, which increased to 10 mg daily for the subsequent 20 weeks, post-chemotherapy. The donepezil group showed a significant improvement in memory compared with the placebo group, suggesting a considerable effect on the hippocampal memory system (108). Another study found donepezil improved hippocampal-dependent memories, including spatial memory (106).

The central oxidative stress response is another suspected mechanism hypothesized for chemotherapy-induced CRCI (17). Studies have shown that antioxidant therapy before and during chemotherapy can prevent oxidative stress and cognitive dysfunction caused by chemotherapy. Treatment with the antioxidant zinc sulfate (ZnSO4) before chemotherapy can prevent short-term memory impairment caused by carmustine. Further, carmustine caused hippocampal cell death and inflammation, which were also reduced in rats treated with ZnSO4 (109). Konat *et al.* studied the effects of cyclophosphamide and adriamycin on memory in rats. The investigation revealed that the combination of cyclophosphamide and doxorubicin impaired memory function. However, no short-term memory impairment was found when the rats were administered the antioxidant n-acetylcysteine during chemotherapy (110).

Animal studies have shown that acute cisplatin treatment reduces dendritic branching and spinal density, along with the induction of mitochondrial degradation. When compared with the control group, rats receiving long-term cisplatin showed poor performance in conditional situational fear, situational object discrimination, and new object recognition tasks. N-acetylcysteine therapy can prevent free radical production, improve apoptotic cell death and loss of dendritic spines, as well as partially reverse cisplatin-induced cognitive impairment (111).

A series of studies found that cognitive impairment in cancer patients was associated with persistent neuroinflammation (112,113). A study on mice reported that a lower-dose of the anesthetic propofol slowed cognitive impairment caused by the chemotherapeutic drug cisplatin (114).

Propofol has also been reported to play a neuroprotective role by inhibiting inflammatory activity. It reduced oxidative stress and prevented an increase in neuronal mitochondrial swelling in animal models of nerve injuries, including ischemic stroke and traumatic brain injury (115).

Previous studies have shown that cisplatin-induced cognitive dysfunction is associated with damage to the synaptic mitochondria of the brain and abnormalities in the mitochondria of the peripheral nervous system (113). Therefore, propofol may reduce cisplatin-induced memory impairment by inhibiting neuroinflammation, reducing oxidation, and preventing mitochondrial damage.

Silver leaf, a Chinese herbal medicine, is used to prevent cognitive decline in elderly individuals. It has been found to have a curative effect on cognitive function (116). A study found the ginkgo Biloba extract 761, a standardized extract compound of ginkgo Biloba, has similarities to antioxidants regarding function. It protects the brain from oxidative stress damage and apoptosis, regulates cerebral blood flow, and interacts with catecholamine to effectively improve executive ability, selective attention, and memory function for verbal and non-verbal material in cancer survivors (117). In conclusion, the stimulants (methylphenidate and modafinil), metabolites of nicotine(cotinine), antidepressants (fluoxetine and fluvoxamine), dementia drugs (donepezil), antioxidants (ZnSO4, n-acetyl cysteine, propofol and Chinese herbal of the silver leaf) have been shown to contribute to the prevention of cognitive impairment of patients with cancer.

Psychotherapy

In 2019, Fernandes *et al.* conducted a systematic review and revealed the beneficial effects of rehabilitation training in cognitive function improvement, including memory, attention, executive function, and processing speed (118). Two types of cognitive rehabilitation training have been identified: computer and strategy training. Computer training refers to the performance of cognitive training tasks using a computer. Strategy training refers to cognitive behavior training and behavior-oriented practice. The training, which aims to rehabilitate impaired cognitive and compensation functions through psychological education and training, consists of 20 minutes to 2-hour sessions over 4–12 weeks in the group and individual settings (119,120). Most studies applying cognitive rehabilitation after breast cancer indicated that profound improvement in cognitive tests and quality of life. The areas consist of executive functioning, working memory, attention, memory, processing speed, and visual-spatial skills were found to be improved due to the intervention (121,122). One study selected quantitative EEG biomarker and found that cognitive rehabilitation contributed to increased global brain activity. In the view of participants, the cognitive rehabilitation intervention was helpful to compensate for memory problems (123). Additionally, this intervention is also helpful in treating emotional problems, such as the anxiety and depression (124).

Meditation, including breathing relaxation, also contributes to recovery from CRCI. Studies have shown that meditation relieves stress and pain, reduces fatigue, slows cognitive decline, and improves the quality of life (22). Some meditation relaxation exercises reduce stress, which directly or indirectly strengthens the immune system and regulates cytokines (125). Studies have confirmed mindfulness-based stress-reduction courses aid in the cognitive rehabilitation of cancer patients (126,127).

Physical therapy

Exercise therapies, including aerobic exercise, resistance training, balance training, yoga, qigong, tai chi, are believed to be effective in ameliorating CRCI and improving patients' quality of life (128-132). Aerobic exercise leads to an increase in the expression of neurotrophic and nerve protection factors, including BDNF and VEGF. An increased level of these factors is related explicitly to the hippocampus neurogenesis, which is crucial for spatial memory. Additionally, many studies have shown that exercise induces neurogenesis, increases the hippocampus volume, and improves hippocampus-dependent cognitive function (133-135). In a study of sedentary breast-cancer survivors, the group of individuals who participated in a 12-week exercise program showed improved processing speed and reduced cognitive impaired symptoms within two years of diagnosis compared to the control group (136). Recently, treatment programs use high-intensity endurance training with set intervals and assign an exercise physiotherapist to each breast-cancer patient to closely monitor the amount of daily exercise. Studies have suggested that these types of programs significantly improve cognitive ability by affecting markers, including TNF-α, IL-6, IL-1, CRP, BDNF, and VEGF (137).

Electroencephalogram (EEG) biofeedback, otherwise known as neural feedback, have also been incorporated into treatment programs for breast cancer patients at 6 to 60 months post-chemotherapy. This program consisted of a total of 20 sessions over ten weeks and was found to mitigate fatigue, sleep disorders, and emotional problems. Also, improvements were shown in cognitive function performance. Furthermore, all participants completed the

program, which suggests the EEG biofeedback treatment is a safe and effective form of CRCI therapy (138).

A prospective cohort study of post-chemotherapy cancer patients found patients treated with acupuncture scores higher on a neurocognitive assessment and outperformed the control group concerning cognitive function after adjusting for age, menopause, cancer stage, and a dose of a chemotherapy regimen. Magnetic resonance spectroscopy analysis revealed that the relative concentration of n-acetyl aspartic acid in the left hippocampus, an area associated with impaired working memory, was significantly reduced in the group treated with acupuncture. The findings of the study led to the proposal that acupuncture improved CRCI through reducing demyelination and neuronal activity in the white matter of the hippocampus (139). In summary, exercise, EEG biofeedback therapy, and acupuncture can improve memory, processing speed, and other cognitive functions.

Currently, drug treatment is regarded as a rapid, effective, and resource-efficient way to treat CRCI. However, the side effects associated with drug therapy still poses to be a disadvantage. Psychological therapy and physical therapy are less likely to have side effects but display less efficacy compared to drug therapy (125).

Summary and prospect

CRCI is a significant problem for cancer survivors and originates from cancer itself, surgery, chemotherapy, radiotherapy, endocrine treatments, and targeted drug treatments. Individual factors, including genetic makeup and emotional state, also contribute to CRCI development. Specifically, chemotherapy is associated with memory impairment, attention, psychomotor speed, and executive functions. The severity of cognitive impairment was directly correlated with the chemotherapy dose. However, the long-term effects of different chemotherapy methods on cognitive function did not differ significantly different. Radiotherapy, endocrine therapy, and targeted drugs can also cause cognitive decline. However, side effects are often temporary for radiotherapy, controversial for chemotherapy, and unclear for endocrine and targeted drug therapy, which all require further examination.

Depression and anxiety problems often accompany cancer, which may cause cognitive disorders. Further longitudinal studies are needed to confirm the mechanism behind the effect of antidepressants on CRCI and the mediating role of emotional problems. Other antidepressants, including vortioxetine, escitalopram, and Zoloft, along with venlafaxine and duloxetine, have not yet been examined and require further investigations.

At present, the relationship between ApoE 4 and CRCI is still unclear. Furthermore, the contribution of specific genes to CRCI, including COMT, DNA repair genes, are not widely investigated. Current literature does not supply robust conclusions about the role of genetic factors in CRCI development. This highlights the requirement for a comprehensive genetic study across a large population to investigate the effect of genetic variations and its contribution to CRCI development. The underlying mechanism is still controversial and requires further research with more robust and systematic experimental designs across large patient populations. The beneficial effect of anti-dementia drugs for CRCI, donepezil, has been confirmed by animal experiments and clinical trials. Moreover, memantine, an n-methyl-d-aspartic acid receptor antagonist, is an anti-dementia drug that improves glutamate neurotransmission. It is useful for the treatment of many dementia types, including Alzheimer's disease and Lewy body dementia. Currently, memantine is found to be effective in improving cognitive function in patients with central-nervous-system cancer. However, clinical studies investigating its efficacy in non-CNS cancer patients have not been performed, highlighting a need for this area to be studied (140).

Additionally, there is no consensus on the relationship between CRCI and dementia. A large retrospective study involving 18,360 patients found that CRCI increased the risk of Alzheimer's disease (141). However, a recent study found a negative association between Alzheimer's disease and cancer. This study reported a lower risk of developing Alzheimer's disease in cancer patients compared to healthy people. Also, Alzheimer's patients displayed a lower risk of developing cancer, which might be explained by cancer prevents neurodegeneration (142). In general, the relationships among ApoE 4, anti-dementia drugs, dementia, and CRCI should be confirmed in future studies. Additionally, brain function modifications need to be examined to explore the mechanism behind the changes.

Preclinical studies suggest that antioxidants improved cognitive impairment. The effects of antioxidants ZnSO4, n-acetylcysteine, and propofol on CRCI need to be confirmed by clinical trials with longitudinal design across large patient samples.

Traditional Chinese medicine ginkgo and physical therapy acupuncture may help treat CRCI in cancer

patients. However, the sample sizes of these trials were small. Also, the number of prospective studies was limiting. A prospective clinical design with large patient samples is needed, along with the identification of underlying mechanisms requiring future studies. Furthermore, the anti-dementia drug, fufanghaishe, has been proven to be effective in treating Alzheimer's disease (143). In this regard, the efficacy and pathological mechanism of fufanghaishe may also be a potential avenue of future research in treating CRCI.

Psychological therapy, including cognitive rehabilitation training and meditation, can alleviate CRCI. The effects of other psychotherapy methods, including music therapy and painting, on CRCI requires further investigations.

Exercise, EEG biofeedback therapy, and acupuncture were found to have a positive effect on CRCI. Other physical therapy methods should also be examined.

Repeated transcranial magnetic stimulation (rTMS) is applied by passing unattenuated repeated stimulation of a magnetic signal and stimulates the nerves in the cortex through the skull. Studies have found that rTMS contributes to improving work executive function and objective memory function in people diagnosed with depression. High-frequency rTMS improves working memory, cognitive flexibility, and verbal fluency in the same patient population (144). At present, no research of rTMS has been conducted on the cognitive function of cancer patients, which still has yet to be verified by subsequent studies.

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