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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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PHYSICAL ACTIVITY AS A THERAPEUTIC STRATEGY FOR CANCER-RELATED COGNITIVE IMPAIRMENT - A REVIEW

Anna Szot *(Corresponding Author, Email: anna.szot1201@gmail.com)*
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0002-7732-150X

Jędrzej Sztajura
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0009-8975-731X

Monika Bujak
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0008-6302-6191

Katarzyna Chowaniec-Rybka
Medical University of Silesia in Katowice, Katowice, Poland
ORCID ID: 0009-0000-1613-639X

ABSTRACT

Introduction and Purpose: After cardiovascular diseases, malignant tumors are the second most common cause of death, disability, and reduced quality of life. Cancer-related cognitive impairment (CRCI) encompasses transient or persistent cognitive dysfunction, either subjectively reported by patients or objectively confirmed through neuropsychological testing. The aim of this study is to discuss the current state of knowledge and research on the impact of non-pharmacological interventions, especially the impact of various forms of physical activity (aerobic, strength, mixed) on the cognitive functions of cancer patients during and after treatment.
Materials and Methods: A comprehensive literature search was conducted using the PubMed, BioMed Central, Scopus, and Google Scholar databases. Keywords included: physical activity, cognitive function, cancer survivors, quality of life, chemotherapy, and cancer-related cognitive impairment. References cited within selected articles were also reviewed.
Studies from the past 10 years were analyzed, applying carefully defined inclusion and exclusion criteria. This review presents the latest clinical evidence and current strategies for the management of cancer-related cognitive impairment.
Conclusions: CRCI is a prevalent condition among cancer patients, significantly impacting their quality of life and overall well-being. Cognitive dysfunction may arise from various cancer therapies, not solely chemotherapy.
The findings underscore the need for systematic monitoring of cognitive function in oncology patients, along with the integration of preventive and rehabilitative measures into comprehensive care plans. Early detection of CRCI and the implementation of cognitive rehabilitation and physical activity interventions are crucial for improving patient outcomes.

KEYWORDS

Physical Activity, Cognitive Function, Cancer Survivors, Quality of Life, Chemotherapy, Cancer-Related Cognitive Impairment

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Introduction

Malignant tumors are, after cardiovascular diseases, the second most common cause of death, disability, and reduced quality of life, according to WHO data from 2023. The treatment of malignant tumors can be divided into palliative and radical approaches. Another classification distinguishes between local treatment (surgery, radiotherapy) and systemic treatment (chemotherapy, biological therapy, hormone therapy) [1, 2].

Despite continuous advances in oncological therapies and the increasing use of organ-sparing treatments, cancer affects not only the targeted system or organ but has systemic effects on the entire body [1, 3]. Particular attention should be paid to the long-term consequences of oncological treatment and to the identification of effective strategies for their prevention or mitigation of their impact on patients' quality of life [3].

The side effects of cancer treatment depend on the chosen modality or the use of multiple modalities simultaneously (Table 1.).

Table 1. Side effects of cancer treatment depending on the treatment method used [4, 5].

Type of Treatment	Severe Side Effects	Chronic Side Effects
Chemotherapy	nausea, vomiting, fatigue, hair loss, diarrhea, anemia, muscle pain	peripheral neuropathy, organ damage, cancer-related cognitive impairment, cardiomyopathy, osteoporosis
Radiotherapy	skin damage, burn, inflammation, diarrhea (abdominal irradiation)	fibrosis, loss of tissue elasticity, scarring of organs, chronic pain, formation of secondary cancer, cancer-related cognitive impairment (irradiation of the head and neck)
Immunotherapy	flu-like symptoms, rash, joint pain	autoimmune inflammation, metabolic disorders, hormonal disorders, weight change, nerve damage, myopathy
Targeted therapy (kinase inhibitors, monoclonal antibodies)	rash, nausea, vomiting, diarrhea	recurrent skin lesions of variable severity, liver and heart dysfunction
Hormone Therapy	muscle and joint pain, hot flashes, mood changes	osteoporosis, metabolic disorders, hormonal disorders
Surgery	postoperative pain, wound infection, bleeding, wound dehiscence, limited range of motion	chronic pain, impaired healing, nerve damage

Thanks to progress in therapy, the number of people living with cancer, in remission, or completely cured has significantly increased in recent years. The neurotoxic effects of chemotherapy are mainly based on direct neurotoxicity, particularly when drugs cross the blood-brain barrier, damage it, or increase its permeability [6, 9]. Cognitive impairment may result from impaired neurogenesis, especially within the hippocampus – a structure crucial for memory and learning. Additionally, a reduction in gray matter volume and white matter microstructural integrity is observed (these changes may gradually regress, though sometimes persist for up to a decade after treatment completion). Certain chemotherapy regimens, such as those containing anthracyclines, are associated with greater neurotoxic effects.

Chemotherapy agents can also provoke immune responses: activation of microglia and astrocytes leads to chronic inflammation, disrupting the balance between pro-inflammatory and anti-inflammatory cytokines, and generating free radicals that damage cell membranes, proteins, DNA, and mitochondria [6, 7].

Furthermore, chemotherapy induces extensive demyelination and damages communication pathways in the brain, significantly reducing the speed of information processing and cognitive integration. Hormonal disorders contribute to cognitive dysfunction to a lesser extent [7, 9].

Cognitive disorders – **cancer-related cognitive impairment (CRCI)** – are among the most frequent and burdensome consequences of cancer treatment. They affect up to 75% of patients during active therapy and approximately 35% of patients after therapy completion. CRCI is observed predominantly in patients who have undergone chemotherapy or radiotherapy to the head and neck regions, though isolated cases have also been reported following immunotherapy [8].

CRCI encompasses both transient and persistent cognitive impairments, either subjectively reported by patients or objectively confirmed by neuropsychological assessments. Symptoms of CRCI include memory deterioration, difficulties with concentration and learning new information, slowed information processing, and impaired executive functioning [6, 8].

Importantly, CRCI is not solely a direct consequence of cancer treatment. It is also influenced by factors such as the initial diagnosis, communication of the diagnosis, stress, anxiety, depression, sociodemographic characteristics, and genetic predispositions (Table 2.) [9].

Cognitive impairment has a profound impact on daily functioning, including reduced self-confidence, challenges in maintaining social relationships, deterioration of physical condition, and difficulties with returning to work (e.g., tasks taking longer and becoming harder to perform). Consequently, CRCI negatively affects overall quality of life, which encompasses physical, psychological, environmental, social, and spiritual well-being.

Cancer changes the hierarchy of needs and requires the adaptation of existing duties and activities to the selected treatment method and its consequences [10]. Many patients experience mental disorders, and the diagnosis often causes severe anxiety, a sense of uncertainty, threat, and loss of security. It is crucial to properly communicate the diagnosis, the initial treatment plan, and the potential need for further imaging, laboratory, or genetic testing to the patient [10, 11].

At the start of cancer treatment, anxiety typically decreases, as concrete steps are taken toward curing the disease and returning to normal life. Understanding and categorizing the causes of CRCI allows for a more targeted and effective therapeutic approach [11]. Routine CRCI screening during follow-up visits is recommended for all oncology patients [9].

Before treatment, patients should be encouraged to seek psychological or psychotherapeutic support. During treatment, the introduction of physical activity, behavioral therapy, or cognitive training should be considered as non-pharmacological interventions for managing CRCI. In some cases, referral to a neurologist or psychiatrist for consultations, further diagnostics, or pharmacological treatment may also be appropriate [10, 11].

Table 2. Reasons cancer-related cognitive impairment (CRCI) [8, 9].

CANCER TREATMENT METHOD	Chemotherapy Radiotherapy Targeted therapy Immunotherapy Hormone therapy Surgical treatment
CONCOMITANT SYMPTOMS	Tiredness Anxiety Psychiatric diseases (depression, post-traumatic stress disorder) Sleep disorders Anemia Metabolic and hormonal disorders
COMORBIDITY	Cardiovascular disease Diabetes Metabolic diseases
SOCIO-DEMOGRAPHIC FACTORS	Age Education Socioeconomic status Domicile Lifestyle, BMI
GENETIC FACTORS	APOE-4 IL-1R1 COMT BDNF
BIOLOGICAL FACTORS	Activity of pro-inflammatory cytokines Increased ability to undergo apoptosis Exposure of cells to oxidative stress

The role of physical activity as a non-pharmacological method for preventing and managing cognitive impairment is based on neuromodulation and its impact on nervous system function, through:

- stimulation of neuroplasticity – the formation of new synaptic connections and neuronal pathways;
- neurogenesis;
- synthesis of neuroprotective factors such as brain-derived neurotrophic factor (BDNF), which supports neuronal growth, survival, and function;
- potential monitoring of BDNF as a biomarker and therapeutic target for mitigating CRCI symptoms;
- increased synthesis of neurotransmitters (dopamine, serotonin, norepinephrine);
- improved endothelial function and cerebral blood flow, leading to better oxygenation and nutrition of neurons [12, 13].

The aim of this study is to discuss the current state of knowledge and research regarding the impact of non-pharmacological interventions, particularly various forms of physical activity (aerobic, strength, mixed), on the cognitive functions of cancer patients during and after treatment.

Discussion

Physical activity as a non-pharmacological method for managing cognitive impairment

The most effective approach to preventing functional disorders and enhancing cognitive functions in patients undergoing cancer treatment – as well as restoring psychophysical and motor fitness – is the incorporation of various forms of physical exercise. Selecting the appropriate type of exercise based on the specific type of impairment allows for targeted improvement of patients' fitness and quality of life [12, 15].

Limiting physical activity due to cancer can lead to a”vicious cycle." The disease and its treatment result in decreased activity and physical fitness, leading to exercise avoidance and growing functional limitations. Reduced independence further exacerbates disability and increases the risk of disease recurrence [9, 16].

RPE – Rate of Perceived Exertion, 1RM – One Repetition Maximum

Table 3. Examples of physical training types depending on cancer type, with recommended duration and frequency [9, 15].

Type of Physical Training	Tumor	Session Duration	Frequency	Intensity	Comments
Aerobic (walking, cycling)	Breast cancer, colon cancer	30–60 min	3-5 times a week	60–80% HRmax at 12-14 RPE	Supervised or home-based
Resistance (strength exercises)	Breast cancer, colon cancer	2 sets of 8–15 repetitions	2-3 times a week	60–70% 1RM	With a trainer or supervision
Mixed (aerobic + resistance exercises)	Breast cancer, prostate cancer	45–60 min	3 times a week	Moderate intensity	Group or individual classes
Tai Chi, Yoga	Breast cancer	60 min	2-3 times a week	Light to moderate	Often in groups, with an instructor

Magnetic resonance imaging (MRI) is currently considered the most effective neuroimaging technique, enabling the acquisition of morphological, physiological, and functional information [18]. Magnetic resonance spectroscopy (MRS) allows for the assessment of metabolic and neurochemical changes induced by cancer treatment. Positron emission tomography (PET) may also be used, complementing the data obtained from MRI and MRS [20].

The majority of studies on the impact of physical exercise on cognitive function have been conducted in women with breast cancer treated with chemotherapy. It has been demonstrated that damage to cerebral vessels, associated with reduced cerebral blood flow, can persist for up to 20 years after the completion of treatment. The *I Can!* study provides evidence supporting the positive impact of physical activity, contributing to the development of recommendations for other cancer patient populations (e.g., colorectal and prostate cancer) and informing the planning of survivorship care [15, 18].

Both aerobic exercise and combined aerobic-resistance interventions have shown beneficial effects on cognitive function, as assessed by neuropsychological testing, suggesting their potential in alleviating CRCI symptoms. Positive outcomes were observed both during and after cancer therapy. Effective training sessions lasted from 10 to 60 minutes and were characterized by moderate to high intensity [9, 16]. However, improvements in processing speed and verbal memory have not been consistently confirmed [14].

It is essential to recognize the potential physical limitations in oncology patients resulting from the current disease and associated comorbidities. Intense exercise should be avoided in the presence of vomiting, fever, anemia (hematocrit <25%, hemoglobin <8 g/dL), thrombocytopenia (<5, 000/mm³), or leukopenia [12]. Physical activity should also be limited in cases of dyspnea, severe fatigue, weight loss, nausea, or bone pain, particularly when there is a risk of pathological fractures. Neurological disorders (e.g., ataxia, dizziness, peripheral sensory neuropathy) are contraindications to exercises requiring good balance and motor coordination, such as treadmill walking [9, 13].

Approximately half of oncology patients experience cachexia, and nearly 40% present with sarcopenia prior to the initiation of treatment (in lung cancer patients, the prevalence exceeds 50%) [21]. Unfortunately, both conditions are associated with poorer treatment outcomes and increased mortality. A combination of resistance and aerobic training is considered the optimal form of physical activity for this group. These interventions effectively counteract muscle atrophy, support the maintenance of lean body mass, and reduce inflammation, oxidative stress, and glucocorticoid levels [21–23].

Mindfulness-based stress reduction (MBSR) has been shown to positively influence cognitive function by reducing inflammation, regulating stress responses, and promoting neurogenesis. The integration of such therapies into supportive care programs may enhance memory, information processing, and overall quality of life in cancer survivors [24]. Yoga, which combines physical, mental, and spiritual elements, has also been found to improve cognitive function in cancer patients, particularly when practiced systematically and regularly. Similarly, traditional Chinese exercises such as tai chi and qigong, which involve synchronized movements, breath control, and meditation, have demonstrated cognitive benefits in both oncological and non-oncological populations [16, 17]. The use of specialized computer programs incorporating neurofeedback and sensory stimulation techniques also offers promising support for cognitive rehabilitation in oncology patients [19, 24].

Oncological treatments frequently disrupt the gut microbiome. Both radiotherapy and chemotherapy can lead to dysbiosis and gastrointestinal symptoms [21, 22]. Short-chain fatty acids (SCFAs), particularly butyric acid, play a crucial role in maintaining gastrointestinal health and have neuroprotective properties, as they can cross the blood–brain barrier. Physical activity promotes microbial diversity, enhances SCFA production (including butyrate), and supports the presence of beneficial bacterial strains such as *Lactobacillus johnsonii* and *L. reuteri*, which produce vitamin B12 essential for central nervous system function [21, 25]. Additionally, a diet rich in omega-3 fatty acids and antioxidant compounds has been shown to positively affect neurocognitive outcomes [22].

Finally, the regulation of glucose and insulin metabolism is crucial, as carbohydrate metabolism disorders (e.g., prediabetes, type 2 diabetes) and obesity are recognized risk factors for cognitive impairment, including Alzheimer's disease. Leptin also plays a significant role by influencing metabolism and neurodegenerative processes [21, 22, 26].

The impact of other therapies on cognitive functions in cancer patients

Certain hormonal therapies, such as aromatase inhibitors, tamoxifen, and androgen deprivation therapy (ADT), may impair cognitive functions, particularly in the domains of working memory, attention, executive functions, vocabulary, and speech. These effects are not always confirmed by objective neuropsychological testing but are frequently reported subjectively by patients. The degree of impairment may depend on the type of hormonal therapy, the duration of follow-up, and individual patient predispositions [20, 27]. Hormonal therapy for breast cancer is associated with endothelial damage of cerebral vessels. Tamoxifen, an estrogen receptor antagonist, promotes the release of vasodilatory substances from the endothelium and exhibits antihypertensive effects. However, inhibition of estrogen activity leads to increased vascular tone, reduced cerebral blood flow, and a heightened risk of cardiovascular events. Studies assessing the impact of hormonal therapy on cognitive function are inconclusive, primarily due to the concurrent administration of chemotherapy in many patients [27, 28].

Pharmacological Interventions

In recent years, research has mainly focused on non-pharmacological interventions for CRCI. Pharmacotherapy in this field remains limited and relatively underexplored. Thus far, psychostimulants have been the primary agents studied, including dopamine and norepinephrine reuptake inhibitors (e.g., methylphenidate), modafinil, cholinesterase inhibitors (e.g., donepezil), and NMDA receptor antagonists (e.g., memantine) [19, 29]. Improvements in attention, alertness, and psychomotor speed have been demonstrated, particularly with the use of methylphenidate and modafinil. Donepezil has been shown to reduce inflammation, stimulate neurogenesis, and support memory by positively influencing hippocampal function [29, 30].

Memantine, on the other hand, may reduce neuronal excitotoxicity induced by radiotherapy, suggesting its potential role in patients undergoing such treatments [30].

Animal studies have also demonstrated promising results with the use of antidepressants (e.g., fluoxetine), nicotine derivatives, and zinc sulfate (owing to its antioxidant properties) in the prevention and treatment of cognitive impairment following cancer therapy [30, 31]. Moreover, the administration of melatonin at a dose of 20 mg/day has been evaluated in women with breast cancer undergoing adjuvant chemotherapy, with findings indicating significant improvements in attention, executive functions, auditory processing, and verbal fluency.

Ongoing research aims to develop novel neuroprotective and anti-inflammatory strategies that could provide new therapeutic avenues for CRCI and serve as effective complements to non-pharmacological interventions [19, 30].

Despite the growing interest in CRCI, awareness of this phenomenon among healthcare professionals and patients remains insufficient [32]. Low recognition of CRCI symptoms may lead to delayed diagnosis and intervention. Promoting interdisciplinary collaboration among oncologists, neurologists, clinical psychologists, physiotherapists, and cognitive rehabilitation specialists is therefore crucial [33, 34]. The development and implementation of standardized management protocols, grounded in current scientific evidence and guidelines, would enable more systematic diagnosis and treatment of CRCI. Furthermore, patient education campaigns are needed to raise awareness about the potential cognitive consequences of cancer treatment and the available support and rehabilitation options [33, 35].

Conclusions

Physical activity and cognitive rehabilitation currently represent the most effective strategies for preventing and managing cognitive impairment in cancer patients. Although the benefits of psychological and behavioral therapies are less clearly defined, existing studies indicate short-term improvements in cognitive performance. A major challenge remains the standardization of diagnostic tools for CRCI, which are predominantly based on subjective reports from patients or their families.

Moreover, it is difficult to isolate the effects of specific therapies on cognitive function, as many other factors can influence the development of CRCI. Significant efforts are now underway to integrate the recognition and management of CRCI into health policy and clinical practice. Key goals include a better understanding of the neurobiological mechanisms underlying CRCI and the development of novel assessment and rehabilitation methods.

Physiotherapists and other rehabilitation specialists should recognize CRCI as a common side effect of oncological treatment and should adapt therapy plans to address the cognitive needs of patients. Cognitive function should be systematically monitored, and preventive and rehabilitative strategies should be integrated into comprehensive oncology care programs.

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All authors contributed to the article.
All authors have read and agreed with the published version of the manuscript.

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