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REVIEW ARTICLE

Cancer, cognitive impairment, and meditation

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Abstract

Background and objectives. Cancer-related cognitive impairment has been acknowledged as a substantial limiting factor in quality of life among cancer patients and survivors. In addition to deficits on behavioral measures, abnormalities in neurologic structure and function have been reported. In this paper, we review findings from the literature on cognitive impairment and cancer, potential interventions, meditation and cognitive function, and meditation and cancer. In addition, we offer our hypotheses on how meditation practice may help to alleviate objective and subjective cognitive function, as well as the advantages of incorporating a meditation program into the treatment of cancer patients and survivors for cancer-related cognitive deficits. *Findings.* Various factors have been hypothesized to play a role in cancer-related cognitive impairment including chemotherapy, reduced hormone levels, proinflammatory immune response, fatigue, and distress. Pharmacotherapies such as methylphenidate or modafinil have been suggested to alleviate cognitive deficits. While initial reports suggest they are effective, some pharmacotherapies have side effects and may not relieve other symptoms associated with multimodal cancer treatment including sleep disturbance, nausea and pain. Several recent studies investigating the effects of meditation programs have reported behavioral and corresponding neurophysiological modulations that may be particularly effective in alleviating cancer-related cognitive impairment. Such programs also have been shown to reduce stress, fatigue, nausea and pain, and improve mood and sleep quality. *Conclusions.* With the increasing success of cancer treatment and the ability to return to previous family, social, and work activities, symptom management and quality of life are an essential part of survivorship. We propose that meditation may help to improve cancer related cognitive dysfunction, alleviate other cancer-related sequelae, and should be fully investigated as an adjuvant to cancer treatment.

Cancer and its treatment are often associated with various physical and psychological side effects (e.g., nausea, fatigue, immune dysfunction, stress, depression, and sleep disturbance) that can range from mild to debilitating depending on several factors such as the type of cancer, stage, and treatment. Recently, reports of cognitive impairment, both objective and subjective, have increased in frequency in both cancer patients and survivors. The majority of reports have focused on women with breast cancer, although cognitive impairment has been found in patients with other types of cancer including lung cancer and malignant glioma [1]. Cancer-related cognitive dysfunction has been attributed to factors such as chemotherapy, hormone therapy (e.g., Tamoxifen or Aromatase Inhibitors), fatigue, mood disturbance (especially for subjective cognitive impairment), and cancer itself, even without evidence of metastases or a primary brain tumor diagnosis [1] (For reviews see [2–5]). Particularly in populations found to have a high long-term survival rate (e.g., breast cancer), cognitive impairment can have a substantial negative impact on quality of life. In fact, reports from the President's Cancer Panel and the National Coalition for Cancer Survivorship [6,7] indicate that both cancer patients and survivors have identified cognitive impairment as a significant factor in preventing the ability to function in family, social, and career-related activities.

As cancer-related cognitive impairment continues to gain recognition, pharmacotherapy, based on other diseases or disorders, has been indicated to help improve cognitive function [8–11]. As will be

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further discussed in subsequent sections, the use of pharmacotherapy may not be optimal in many cases as some pharmacologic treatments are unable to remediate other side effects and can be contraindicated in some patients. Further investigation of behavioral interventions would provide a valuable addition to this area of research as they may promote long-term cost effectiveness of care [12,13] and could provide social support and a sense of self efficacy (from engaging in healthy behaviors) [14] relative to pharmacotherapy alone.

Based on the incidence and concern of cancer-related cognitive impairment, the benefits of behavioral interventions that could improve cognitive function, in addition to alleviating other cancer-related sequelae, are considerable. To date, multiple studies have evaluated the efficacy of several behavioral interventions in alleviating a range of cancer-related sequelae (e.g., fatigue, mood, cognition, physical function) including exercise and diet programs, and cognitive behavioral therapies [15–17]. While most of these interventions have been found to improve certain aspects of quality of life or reduce particular symptoms, few studies have examined the effects of behavioral interventions on cognitive function in cancer. Behavioral interventions that have been associated with improved cognitive function [17], however, may not address a patient's psycho-spiritual needs which, in addition to cognitive function, are important to quality of life for many patients [18]. Furthermore, the long-term effectiveness and utilization of interventions that require guidance or administration by a professional (e.g., clinical psychologist) may be limited relative to an intervention that an individual can practice on his or her own at any time.

As a result, interest in mind-body programs and their holistic approach to treatment continues to gain momentum as these techniques address the complex interaction among mental, physical, and spiritual outcomes [19], and can be practiced both individually and in groups. Thus far, mind-body programs have been primarily advocated as interventions to relieve stress, improve mood, reduce fatigue and improve sleep quality in cancer populations [20–22]. However, studies have reported that meditation practice has significantly improved objective cognitive function in both non-clinical [23–25] and clinical populations including children and adults with ADHD [26–28]. Furthermore, preliminary evidence suggests that meditation may have neuroprotective effects against normal aging and a genetic predisposition to develop dementia [29–31].

In this review, we propose that meditation may be particularly beneficial for patients with cancer-related cognitive impairment as it is generally non-selective and could alleviate a wide range of cancer-related sequelae, such as psychological adjustment, which could address impaired subjective and objective cognitive function. Objective cognitive function is defined here as the mental processes that are assessed independently from the patient's self-reported mental function by standardized neuropsychological measures. Subjective cognitive function is defined as the patient's perceived, self reported view of his or her mental function. Several studies have failed to find a significant association between objective and subjective cognitive function [32–35]. Furthermore, subjective, but not objective, cognitive dysfunction has been frequently associated with psychological adjustment [34–36], and some evidence suggests that perceived cognitive difficulties occur more frequently than cognitive function assessed through objective measures [37]. Given that the majority of studies on this topic examined objective cognitive function, in this review, cancer-related cognitive impairment will pertain to objective cognitive dysfunction unless otherwise specified.

Cognitive impairment and cancer

The following sections will primarily focus on women treated for breast cancer as cancer-related cognitive impairment has been the most widely studied in that population. However, cognitive dysfunction has been reported in other cancer populations who often undergo multimodal treatment and experience physical and psychological symptoms similar to breast cancer patients.

Chemotherapy-related cognitive impairment

Chemotherapy-related cognitive impairment has been the most widely reported source of cognitive deficits in cancer patients, particularly in breast cancer. However, initial evidence suggests that chemotherapy-related cognitive impairment has been observed in patients with other types of cancer (e.g., lymphoma) [4]. The deficits are often subtle, and although assessments have varied across studies, memory, attention/concentration, executive function, processing speed, and visual-spatial skills are often reported to be impaired [34,35,38–41]. While some insight into the risk factors, symptoms, and neurological mechanisms associated with chemotherapy-related cognitive impairment has been identified, the etiology is not well understood. Some chemotherapy agents may have neurotoxic characteristics including (e.g., 5-fluorouracil (5-FU)) (for review, see [1,42,43]). The hypothesized neurotoxic effects have included damage to the cerebral parenchyma, inflammatory immune response, cerebral vascular obstruction, and disruption in normal neural function, which have been attributed to abnormalities in cortical density and metabolism [2,43]. Several retrospective studies have found that cognitive impairment can occur in women while undergoing chemotherapy and persist for years after completing treatment [4]. Some women have an increased risk of developing treatment-related cognitive impairment relative to others and the risk of impairment appears to be dose dependent. That is, higher doses of chemotherapy have been associated with greater incidence of cognitive impairment [44].

Findings from neurophysiological studies have found a reduced P300 amplitude [45], an event-related potential (ERP) index of attention, and abnormal alpha wave activity, indicating a higher likelihood of neuropathology in women who had undergone high dose rather than low dose chemotherapy. Some neuroimaging studies have found abnormalities in white and gray matter and cortical function in breast cancer patients who had undergone chemotherapy. Gray and white matter reductions in breast cancer survivors (BCS) have been reported one year post chemotherapy relative to a group of BCS who had never received chemotherapy [46]. Silverman et al. [47,48] have found metabolic abnormalities in the prefrontal cortex associated with chemotherapy and tamoxifen treatment. As most studies reporting chemotherapy-related deficits have been retrospective, they have not accounted for possible deficits occurring prior to chemotherapy in BCS [49]. Hermelink et al. [50] and Wefel et al. [49] found that a large proportion of patients tested within each study displayed cognitive impairment prior to starting chemotherapy. It should be noted that patients assessed by Hermelink et al. [50] were tested prior to preoperative chemotherapy, initially ruling out surgery as a possible factor involved in pre-chemotherapy cognitive impairment. However, Wefel et al. [51] reported a non-significant trend suggesting that patients who underwent lumpectomy or mastectomy, or were postmenopausal, prior to chemotherapy, had a greater risk of cognitive impairment. Several factors have been attributed to pre-chemotherapy cognitive impairment including stress resulting from a cancer diagnosis [50], individual differences in pre-cancer cognitive reserve, and paraneoplastic syndromes [51].

Cognitive function and hormones

Recent findings suggest that a decrease in circulating estrogen may play a role in cancer-related cognitive deficits, as reduced estrogen and progesterone levels have been linked to attention, learning, and memory impairment [1]. BCS who received hormone therapy, but had never undergone chemotherapy, showed impaired cognitive function relative to healthy controls [52]. Other studies have reported that BCS who had received both chemotherapy and tamoxifen displayed a greater degree of cognitive dysfunction [33] and reduced metabolism in the basal ganglia [48] relative to control groups. Additional evidence supporting an association between estrogen and cognitive function in cancer was reported by Castellon et al. [53] who found that women who received radiotherapy (but no chemotherapy or hormone therapy) performed at a similar or higher level of function on several cognitive tasks relative to healthy controls matched on age, education, and IQ. The authors suggested that good cognitive performance in the BCS was associated with high premorbid endogenous estrogen levels.

It should be noted that men who undergo androgen ablation treatment may be at risk for experiencing cognitive decline. Similar to women treated for estrogen sensitive tumors, men who undergo androgen deprivation therapy for testosterone sensitive cancer (e.g., prostate cancer) may experience cognitive impairment [54], given the positive association found between testosterone and cognitive function [55]. However, additional research in this area is needed in order to further elucidate the effects of hormone deprivation therapy and cognitive function in men with cancer.

Proinflammatory cytokines, fatigue, and cognitive impairment

Bower, Ganz, and colleagues have reported clinical levels of fatigue in BCS up to 10 years following a diagnosis; furthermore, fatigue was associated with greater levels of depression, reports of attention and memory related difficulties, and increased levels of proinflammatory cytokines (e.g., IL-1β, sTNF-RII) [56]. Patients with other types of cancer often experience changes in immune function, which have been associated with psychological and physical side effects, including cognitive dysfunction. For instance, increased cytokine levels in patients with Acute Myelogenous Leukemia or Myelodysplastic Syndrome have been associated with cognitive impairment [57].

Proinflammatory cytokines can be secreted in response to psychological and physical (e.g., an immune response to a tumor or chemotherapy) stressors, and have been linked with declines in memory and planning abilities [58]. The relationship among cellular immunity, fatigue and cognitive dysfunction is complex, as cancer-related cognitive impairment may result from proinflammatory cytokines directly interfering with normal brain function, from a lack of motivation or self-efficacy due to persistent fatigue, or a combination of both factors [43,59]. Although cognitive deficits have been observed independent of mood disturbance [49], distress and fatigue have been associated with cognitive dysfunction in some cancer patients and may exacerbate perceived and actual cognitive decline during and following treatment.

Pharmacotherapy for cancer-related cognitive impairment

As cancer-related cognitive dysfunction continues to receive recognition, pharmacotherapy has been indicated based on the use of pharmacologic treatment in other diseases or disorders with similar symptoms or etiologies [60]. Erythropoiten has been indicated to improve cognitive impairment by increasing metabolic activity; although, the use of erythropoiten in non-anemic patients is not recommended [60]. Antidepressants may be indicated for patients who are experiencing mood disturbances and report subjective cognitive impairment. However, such treatment would be limited to patients who meet clinical criteria for a mood disorder. Methylphenidate (Ritalin) has been indicated as treatment for both impaired cognitive function and fatigue [61]. Some side effects, however, are also associated with methylphenidate including hypertension, angina, glaucoma, and in some cases, addiction [60,62]. Furthermore, two recent studies have failed to find improved cognitive function and fatigue in double-blind placebo controlled trials testing methylphenidate in cancer patients [63,64].

Modafinil (Provigil) has been indicated recently to alleviate fatigue and cognitive impairment and has been found to be effective with minimal side effects [65]. Kohli and colleagues found enhanced performance in memory and attention in women who had previously undergone chemotherapy for breast cancer. Initial findings also suggest that modafinil can alleviate fatigue [66,67]. While initial evidence suggests a link between improved cognitive function and pharmacotherapy [8,61], it should be noted that pharmacotherapy alone cannot alleviate other symptoms (e.g., distress, sleep disturbances) and lacks benefits often derived from behavioral-based interventions such as self-efficacy, control, and physical activity. Moreover, behavioral-based interventions may provide lifelong coping tools to help decrease distress, improve quality of life, impart a sense of empowerment, and promote long-term cost effectiveness [13,68].

Summary

Cancer-related cognitive deficits can occur in the form of objective or subjective impairment. Findings from several studies suggest that objective and subjective cognitive function are not associated, and that subjective, but not objective cognitive function is often associated with mood. Cancer-related objective cognitive impairment (in the absence of a primary brain tumor or metastases) is typically subtle, affecting higher order cognitive function (e.g., working memory, executive function) and the corresponding cortical and subcortical regions thought to subserve these processes. While most research in this area has been conducted with BCS who have undergone chemotherapy, recent studies have examined other populations, particularly patients who receive similar treatment regimens (e.g., hormone deprivation therapy). Within the literature, chemotherapy is consistently cited as a factor involved in cancer-related cognitive impairment. The underlying mechanisms of chemotherapy-related cognitive impairment are still debated within the literature and are beyond the scope of this paper (see [2] for a recent review). However, the evidence suggests that chemotherapy-related cognitive deficits can occur independently of mood disturbance. Several studies have found a positive association between hormone function and cognitive function in men and women, further suggesting that hormone deprivation therapy may play a role in cancer-related cognitive impairment. A pro-inflammatory immune response is also likely a contributing factor. In summary, several factors can contribute to cancer-related cognitive impairment, potentially aggravating other symptoms and decreasing quality of life. Given the diffuse nature of cancer-related cognitive impairment, we propose that an effective intervention will take all of these factors into account.

Meditation

The combination of various adverse effects associated with cancer therapy can create difficulty in returning to previous roles and activities during and following treatment and decrease quality of life. A mind-body practice such as meditation, offers a potentially effective intervention, alone or in combination with other therapy to alleviate both objective and subjective cognitive dysfunction in addition to other treatment-related side effects. Meditation has been described as “a wakeful hypometabolic physiologic state” in which the practitioner is extremely relaxed, yet alert and focused [69]. Although meditation methods can vary, many types of meditation share common features including the focused, controlled regulation of breathing and control over thoughts and feelings that come to mind. Given the continuous attention-based processes involved in initiating and maintaining a meditative state, meditation has been proposed to be an attentional training exercise [70,71].

With regard to alleviating cancer-related cognitive deficits, we advocate practices that require initial and sustained mental effort on the part of the practitioner, as opposed to practices that are designed to merely clear or empty the mind. Such effortful practices would include focused meditation, in which the practitioner focuses on a single object or thought, and mindfulness or insight meditation, which trains the practitioner to attend to the whole of their experience without the sense of subject and object. Based on formulations put forward by Lutz and colleagues [72], focused meditation requires the ability to initiate and focus attention on an intended object over a prolonged period, inhibit potential distractions, and subsequently reengage the focused meditative state. Mindfulness or insight meditation practices are different in that they require the constant monitoring of the practitioner's experience as a whole, but like focused meditation, requires the ability to disengage from a distracting entity (e.g., a thought, sound, etc.) (see Table I). Based on findings that will be discussed in subsequent sections, several studies suggest that meditation engages and modulates neural circuits that subserve the higher order cognitive processes that are often impaired in cancer-related cognitive deficits. Importantly, although the previously discussed meditation practices require considerable mental effort from the practitioner, they simultaneously promote relaxation and a sense of well-being as the practitioner becomes more familiar with the techniques. The following sub-sections specifically focus on the effects of meditation on cognitive function, given the main objective of this review. Other benefits of meditation practice in cancer populations are briefly discussed in subsequent sections, but for more, comprehensive reviews of meditation in cancer see [20–22].

Table I

Key Features of Meditation
• Active, yet relaxed mental state • Concentration • Regulated breathing to connect the mind with the body • Disengage from distractions • Focused meditation: focus on a specific object such as a sound, word, or thought • Mindfulness or insight meditation: attend to the whole of experience without a sense of subject and object

Behavioral and neurophysiological modulations in cognitive function associated with meditation

Several meditation studies have reported enhanced performance on various cognitive tasks measuring sustained attention and cognitive flexibility and control [23–25,73,74]. Studies investigating the cortical and subcortical modulations associated with meditation are consistent with these findings as meditation has been associated with significantly increased cortical thickness in prefrontal, temporal, and parietal regions [75]. Furthermore, meditation practice has been associated with increased activity in neural circuits thought to subserve sustained attention and cognitive control [23].

Several recent studies using experimental paradigms designed to assess aspects of attention and cognitive control have reported significant modulations associated with mindfulness-based meditation practice. For example, Jha et al. [24] found differences among naïve participants who underwent an 8-week mindfulness meditation course and a similar control group with no meditation training in a conflict monitoring task which measures aspects of attention and cognitive control [76]. While neither group showed differences at baseline, the meditation group showed significantly better performance than the control group when tested after the course [24].

Electrophysiological studies have found neurophysiological modulations associated with meditation practice [77,78]. Lutz et al. [78] investigated neural synchrony using electroencephalography (EEG), an index of higher-order cognition such as attention or working memory, in expert meditators and controls during both resting and meditative states. Compared to controls, expert meditators showed greater neural synchrony over frontal-parietal regions during baseline states, which further increased during a meditative state over frontolateral and posterior regions. Slagter et al. [25] directly assessed the behavioral effects and neurophysiological effects of meditation practice on the resource allocation of attention. After three months of meditation practice, participants in the meditation group demonstrated significant differences in performance relative to the control group as they obtained significant increases in accuracy to detect a target with corresponding reductions in the ERP, P3b, which reflects an increase in attentional resources.

In a recent fMRI study, Brefczynski-Lewis [23] and colleagues reported interesting findings for novice, intermediate and expert meditators. Relative to novice meditators, intermediate meditators showed significantly greater activation in areas that have been linked with attentional processing including frontal-parietal, cerebellar, temporal and parahippocampal regions. However, an inverted u-shaped function was found when comparing all three groups as expert meditators obtained significantly less activation than intermediate meditators in the attention-related regions of interest. The authors proposed that meditation engages attentional neural systems, but at a highly advanced level, mental control and the ability to maintain a meditative state becomes less effortful as indicated by lower levels of activation in the expert group.

Meditation and subjective cognitive function

As discussed previously, several studies have failed to find an association between subjective and objective cognitive impairment; rather, subjective cognitive impairment may occur more often and has been associated with mood disturbance. Specific aspects and mediating factors (e.g., sleep disturbances, hormone levels) involved in the association between mood and perceived cognitive function have not been reported in detail. However, several studies evaluating the effects of a meditation based intervention have reported improvements in aspects of mood and stress [79,80], which may play a mediating role in improved subjective cognitive function. Future studies exploring the association between psychological adjustment and perceived cognitive function would be helpful in tailoring meditation programs to address both characterizations of cognitive impairment.

Meditation, illness, and cancer

In addition to improved cognitive function, other positive outcomes have included reductions in anxiety and pain, and improvement in psychological well-being and quality of life [81,82]. The findings suggest that meditation may be a particularly effective intervention for the psychological and physical sequelae associated with a cancer diagnosis and treatment, especially since the number of cancer patients who seek complementary therapies in addition to standard care continue to increase. Earlier studies have investigated the efficacy of meditation, particularly MBSR, for patients with cancer. In a mixed cancer population, MBSR was found to reduce levels of depression and stress relative to a control group [82]. Carlson et al. [80] examined the benefits of MBSR in an outpatient oncology population and found the program was effective in decreasing mood disturbance and stress symptoms. Importantly, the effect was maintained up to one year later [80].

While several studies have investigated the effects of meditation practice on sleep disturbances, distress, immune function, cortisol levels, and fatigue during cancer treatment and survival, no randomized trial has examined the effects of meditation on cognitive function, as assessed by standardized neuropsychological tests, in cancer patients. Although it has not been used as an intervention for cognitive dysfunction in cancer patients, meditation has been reported as an effective cognitive-based intervention in children and adults with ADHD and individuals potentially at risk for developing dementia [26,27,30].

The proposed effects of meditation on cancer-related cognitive impairment and other side effects

As discussed previously, cancer-related cognitive impairment often includes deficits in attention, memory, and executive function. Based on the behavioral and neurophysiological findings, we propose that meditation may act as a mental training activity that could improve cognitive function within these domains. We further propose that since meditation practice provides training in objectively acknowledging and releasing other thoughts or feelings that come to mind, cancer patients may have decreased intrusive thoughts and be better able to cope with negative thoughts, feelings, or emotions, which may improve perceived cognitive function. In correspondence to the neural correlates of meditation that have been associated with reduced levels of anxiety and reactivity to acute pain and improved immune response, Davidson and others [83] have suggested that meditation helps to reset the frontal systems that regulate emotional responses and sense of self. As immune-based inflammatory processes may also influence cognition and treatment-related symptoms, a meditation-based practice could be beneficial as it has been associated with regulation and positive changes in immune function [77,80,84]. In addition, meditation programs have been associated with stress reduction and improved sleep quality, which may help to regulate stress-induced cortisol levels [79,80,84], and play a mediating role in improving subjective cognitive function. Based on these findings, we hypothesize that meditation practice would be an effective intervention to help alleviate self-reported and objective cognitive decline that can result from cancer and its treatment, as well as other common sequelae including disturbances in affect and sleep, fatigue, nausea, pain and declines in quality of life. It should be noted that some of the previous meditation findings should be interpreted with caution given that these studies often lacked strict methodology, making it difficult to interpret and generalize the results [85]. Future studies using a more rigorous design, such as a randomized controlled trial, are necessary to strengthen the credibility of the findings and interpretations attributed to meditation, particularly in cancer populations.

As many forms of meditation do not require physical activity, thus posing little danger to the patient, meditation practice may be feasible at any treatment stage. There are various forms of meditation and patients should be exposed to different practices until they find one that suits them. The mode of administration of a meditation program (e.g., in class) and other feasibility issues should be taken into account when considering the population and stage of treatment for whom the program is designed. Patients undergoing active treatment typically have limited time and inconsistent schedules in order to accommodate work and other responsibilities, which could affect their ability to participate in structured intervention classes. Perhaps a program with few in-class sessions, with the majority of training online or through another medium such as an auditory CD, may increase feasibility in this group. In contrast, patients outside of treatment may have more flexibility in their schedules, which could increase the feasibility of regular class attendance.

As objective and subjective cognitive function continues to gain recognition as a critical aspect of quality of life in cancer patients and survivors, it is important to develop effective interventions as well as examine the mechanisms underlying their efficacy. Emerging research suggests that meditation practice is associated with a considerable number of benefits and has helped to elucidate the complex relationship between mental and physical health. Given that meditation practice has been associated with improved cognitive function in non-cancer populations and has been shown to alleviate several cancer-related sequelae, further examination of the association between meditation practice and cognitive function is warranted in both cancer patients and survivors.

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