Cognitive Changes Associated With Cancer and Cancer Treatment: State of the Science

Diane Von Ah, PhD, RN, FAAN

The study of cognitive impairment as a late effect of cancer and its treatment has become a national research priority. The President’s Cancer Panel, the National Cancer Institute Office of Cancer Survivorship, and the National Comprehensive Cancer Network Survivorship Panel have all identified emerging chronic and late effects of cancer and its treatment, such as cognitive impairment, as top research priorities (Hewitt, Greenfield, & Stovall, 2005). The National Coalition of Cancer Survivorship, a survivor-led cancer advocacy group, also has identified cognitive impairment as a challenge facing many cancer survivors and calls for research to address this problem. The Oncology Nursing Society Research Priority Survey identified cognitive impairment as one of the most distressing and difficult symptoms to treat (LoBiondo-Wood et al., 2014). Despite the priority, research in this area is relatively limited, with many unanswered questions regarding the prevalence and impact on survivors as well as insufficient data to guide evidence-based interventions (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008; Von Ah, Jansen, Allen, Schiavone, & Wulff, 2011; Von Ah, Storey, Jansen, & Allen, 2013).

Definition of Cognitive Impairment

Cognitive impairment has been defined as those cognitive changes that negatively affect higher-order mental processes (Hess & Insel, 2007). Although no single neurocognitive signature of cancer- and cancer treatment-related effects stands out (Castellon, Silverman, & Ganz, 2005), deficits in attention, memory, speed of processing, language (word finding), and executive functioning (problem solving) appear to be most common (Anderson-Hanley, Sherman, Riggs, Abocha, & Compas, 2003; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; Vardy et al., 2008). Cognitive deficits following diagnosis and

Background: Cognitive impairment is a distressing, disruptive, and potentially debilitating symptom that can occur as a direct result of cancer or its treatment. National organizations have identified cognitive impairment as a challenge many survivors face and call for research to address this problem. Despite the priority, research is still relatively limited and questions remain unanswered about prevalence and impact on survivors, as well as coping strategies and effective treatment options available to address this potentially debilitating problem.

Objectives: The purpose of this article is to (a) analyze the prevalence and types of cognitive impairment that commonly affect survivors; (b) delineate the impact that cognitive impairment after cancer and cancer treatment has on self-esteem, social relationships, work ability, and overall quality of life among survivors; and (c) synthesize and appraise commonly used coping strategies used by survivors to address cognitive impairment and evidence-based interventions that may be incorporated into clinical practice.

Methods: A comprehensive review and synthesis of the literature was conducted.

Findings: Evidence-based interventions to address cognitive changes after cancer and cancer treatment are limited. However, emerging research has demonstrated that nonpharmacologic treatments, such as cognitive training, are likely to be effective.

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Key words: cognitive impairment; evidence-based interventions; quality of life

Digital Object Identifier: 10.1188/15.CJON.19-01AP
treatment of cancer may be subtle, yet may have a significant impact on quality of life in cancer survivors (Mehnert et al., 2007; Von Ah, Russell, Storniolo, & Carpenter, 2009).

Risk Factors

The exact etiology of cognitive deficits in cancer survivors is not fully understood and most likely is thought to be multifactorial (Bender & Thelen, 2013; Merriman, Von Ah, Miaskowski, & Aouizerat, 2013). Briefly, in cancer survivors, tumor- and/or treatment-related factors may directly or indirectly affect cognitive functioning through one or more of the following mechanisms: neurotoxic injury in the brain, microvascular injury, secondary central and/or systemic inflammatory processes, or dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in changes in endogenous hormones (estrogen and serotonin) (Merriman et al., 2013). In addition, it has been hypothesized that cancer treatment may accelerate cognitive aging by influencing aging at a cellular level, including inflammation, DNA damage, oxidative stress, telomere length, and cell senescence (Ahles, Root, & Ryan, 2012; Mandelblatt et al., 2013). Individual differences in age, education level, intelligence, menopausal status, comorbid conditions, medication usage, and genetics also may contribute to cognitive deficits in cancer survivors (Bender & Thelen, 2013). Cognitive deficits also may be compounded by other related symptoms, including fatigue, depression, and anxiety (Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005; Bender & Thelen, 2013). A summary of cancer- and treatment-related and non-cancer treatment-related factors that may influence an individual’s risk for cognitive impairment are displayed in Figure 1 (Bender & Thelen, 2013; Mandelblatt et al., 2013; National Comprehensive Cancer Network, 2013). The complexity associated with cognitive changes after cancer and cancer treatment contribute to the difficulty of understanding and effectively treating this symptom (Bender & Thelen, 2013).

Scope of the Problem

Seventeen percent (van Dam et al., 1998) to 75% (Wieneke & Dienst, 1995) of survivors report some level of cognitive impairment (Anderson-Hanley et al., 2003; Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jansen et al., 2005; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006; van Dam et al., 1998; Wieneke & Dienst, 1995). In Von Ah, Harvison, et al. (2009), the author’s group found clinically significant memory deficits in 44% of breast cancer survivors (n = 52) who were, on average, 4.6 years (SD = 2.76) post-treatment. Five meta-analyses have also documented cognitive deficits that survivors experience, suggesting that impairments in memory, attention and concentration, speed of processing, and executive functioning are most common (Anderson-Hanley et al., 2003; Falleti et al., 2005; Jansen et al., 2005; Jim et al., 2012; Stewart et al., 2006). Although results of some prospective studies suggest cognitive impairment may attenuate over time (Jenkins et al., 2006; Tchen et al., 2005; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004), researchers have found that a substantial number of survivors continue to have objectively measured memory deficits for 5, 10, and even as long as 20 years post-treatment (Ahles et al., 2002; Jenkins et al., 2006; Koppelmans et al., 2012; Wefel et al., 2004).

In addition, researchers have explored cognitive changes associated with cancer using multiple neuroimaging techniques (Holohan, Von Ah, McDonald, & Saykin, 2013). Electrophysiologic and imaging studies reveal differences in central nervous system structure and function among survivors exposed to chemotherapy compared to baseline prechemotherapy or control participants (Brown et al., 1998; Ferguson, McDonald, Saykin, & Ahles, 2007; Inagaki et al., 2007; Kreukels et al., 2005; Saykin, Ahles, & McDonald, 2003; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Silverman et al., 2007). Results from imaging studies also have documented reduced regional volumes of gray and white matter, with studies demonstrating both short-term (Brown et al., 1998; Ferguson, McDonald, et al., 2007; Inagaki et al., 2007) and long-term effects (Saykin et al., 2005). In addition, in a review of the empirical literature, Holohan et al. (2013) identified 35 separate neuroimaging studies and noted that the majority identified structural and/or functional alterations which also were accompanied by increases in self-reported cognitive concerns, neuropsychological testing deficits, or both. Taken together, findings from these studies provide clear and convincing evidence that cognitive deficits are prevalent after cancer and cancer treatment.

Impact on Quality of Life and Work-Related Outcomes

Cognitive impairment can dramatically affect quality of life in survivors (Mehnert et al., 2007; Myers, 2013; Von Ah, Habermann, Carpenter, & Schneider, 2013). In a survey of 471 survivors, 62% stated that cognitive problems were disruptive to their functioning and relationships at home and at work (Hede, 2008). In qualitative interviews with 22 breast cancer survivors, cognitive impairment affected survivors’ self-confidence, self-esteem, social relationships, and perceived work ability (Von Ah, Habermann, et al., 2013). Survivors related that they often were embarrassed when they could not remember names, dates, or places and often would withdraw from social situations. In addition, many identified that dealing with cognitive changes...
after cancer and cancer treatment was most difficult when family, friends, or healthcare providers did not acknowledge or validate their concerns. Previous work by Von Ah, Russell, et al. (2009) with 135 African American (47%) and Caucasian (53%) breast cancer survivors also demonstrated that subjective cognitive impairment was related to poorer health-related quality of life, including more depressive symptoms, lower well-being, poorer physical functioning, and greater fatigue. Results from multiple studies also have shown that cognitive impairment, as demonstrated on objective neuropsychological tests, is associated with higher levels of depressive symptoms, fatigue, and anxiety (Bender et al., 2006; Cimprich, 1992, 1993; Mehner et al., 2007; Stewart et al., 2008; Wefel et al., 2004). In preliminary work conducted by Von Ah et al. (2010), which included 444 breast cancer survivors compared to 355 healthy women, the authors found that cognitive impairment on neuropsychological tests (deficits in immediate [short-term] and delayed memory, processing speed, and executive functioning) was significantly related to depressive symptoms and fatigue. Findings are supported by research results in which cognitive impairment commonly co-occurs with fatigue and depressive symptoms across the cancer trajectory (Bender et al., 2005; Bender & Thelen, 2013). In addition, many researchers have demonstrated that cognitive impairment affects perceived work ability in survivors (Calvio, Peugeot, Bruns, Todd, & Feuerstein, 2010; de Boer et al., 2008; Feuerstein, Hansen, Calvio, Johnson, & Ronquillo, 2007; Hansen, Feuerstein, Calvio, & Olsen, 2008; Pryce, 2007; Taskila, Martikainen, Hietanen, & Lindbohm, 2007; Von Ah, Habermann, et al., 2013). In a large cohort study of 1,490 employed survivors and 2,796 reference participants, survivors had significantly lower levels of perceived work ability than healthy controls (Lindbohm et al., 2012). Perceived work ability, or the capability to manage job demands (Ilmarinen & Tuomi, 2004), has been associated with job stress (Kinnunen, Parkatti, & Rasku, 1994), and several studies have confirmed that poor work ability predicts loss of work productivity, retirement intentions, long-term absence, early retirement, need for rehabilitation, and work disability (Alavinia, de Boer, van Duivenbooden, Frings-Dresen, & Burdorf, 2009; Kuoppala, Lamminpa, Vaananen-Tomppo, & Hinkka, 2011; Salonen, Arola, Nygard, Huhtala, & Koivisto, 2003; Sell et al., 2009). Overall, research has consistently documented the significant and negative impact of cancer- and cancer treatment-related cognitive impairment on survivor’s self-confidence, social relationships, quality of life, and work-related outcomes (Myers, 2013).

Coping Strategies to Address Cognitive Impairment

Although cognitive impairment after cancer and cancer treatment is a prevalent and significant problem, little research has focused on addressing these cognitive changes. Interviews with survivors provide some insight regarding how survivors live with and manage cognitive changes after cancer (Myers, 2013; Von Ah, Storey, et al., 2013). Figure 2 displays a summary of positive and potentially negative coping strategies used by survivors to address cognitive impairment. The majority of the research reviewed identified positive methods for coping with cognitive changes after cancer. In previous work (Von Ah, Storey, et al., 2013), the author’s group was able to identify and classify these positive coping strategies into five overarching and distinct categories: organizational and self-management, management of the physical environment, management of the social environment, stress and attentional fatigue-reducing methods, and engaging in mind-stimulating activities. However, the literature also reported that survivors identified potentially negative coping strategies, such as avoiding social activities, avoiding substantive social interactions, and leaving demanding employment situations (Myers, 2013). Although removal from a stressful social or work situation may be appropriate depending on the context and extent used, these avoidant strategies may not produce the long-term positive adjustment that is necessary to address cognitive changes after cancer.

Interventions for Cognitive Changes After Cancer and Its Treatment

Evidence-based interventions for cognitive impairment after cancer and cancer treatment remain limited. Researchers have explored pharmacologic and nonpharmacologic approaches to address cancer- and cancer treatment-related cognitive impairment (Von Ah et al., 2011; Von Ah, Jansen, & Allen, 2014). Table 1 displays the pharmacologic interventions trialed, including the use of donepezil, an acetylcholinesterase inhibitor often used for Alzheimer disease (Jatoi et al., 2005; Shaw et al., 2006); methylphenidate, a psychostimulant often used in children with attention deficit hyperactivity disorder (Bruera, Miller, Macmillan, & Kuehn, 1992; Butler et al., 2007; Escalante et al., 2014; Gagnon, Low, & Schreier, 2005; Gehring et al., 2012; Lower et al., 2009; Mar Fan et al., 2008; Meyers, Weitzner, Valentine, & Levin, 1998; Schwartz, Thompson, & Masood, 2002); memantine, an N-methyl-D-aspartate receptor antagonist, which has been shown to be neuroprotective in preclinical trials (Brown et al., 2013); and modafinil, a psychostimulant often used for narcolepsy (Blackhall, Petroni, Shu, Baum, & Farace, 2009; Gehring et al., 2012; Kohli et al., 2009; Lundorf, Jonsson, & Sjogren, 2009). Table 2 highlights the nonpharmacologic treatments used to address cognitive impairment, including

Examples of Positive Coping Strategies
- Writing things down
- Using reminder cues (e.g., calendar, notes)
- Develop a routine schedule.
- Focus on one task at a time; do not rush tasks.
- Give oneself permission to make mistakes.
- Keep items and belongings in the same place.
- Surround self with supportive family and friends.
- Ask for help when necessary.
- Humor
- Seek stress-reduction activities, such as exercise, meditation, yoga.
- Obtain plenty of rest; adequate sleep
- Mind-stimulating activities: crossword puzzles, word games, sudoku

Examples of Potentially Negative Coping Strategies
- Withdrawal from social activities
- Avoiding substantive social interactions
- Leaving employment

FIGURE 2. Coping Strategies to Address Cognitive Impairment After Cancer
cognitive behavioral training (Cherrier et al., 2013; Ferguson et al., 2007, 2012; Goedendorp, Knoop, Gielissen, Verhagen, & Bleijenberg, 2014; Locke et al., 2008; McDougall, 2001; McDougall, Becker, Acee, Vaughan, & Delville, 2011; Schuur & Green, 2012; Sherrer, Meyers, & Bergloff, 1997), cognitive training (Gehring et al., 2009; Hassler et al., 2010; Kesler et al., 2013; Miotto et al., 2013; Poppelreuter, Weis, & Bartsch, 2009; Von Ah et al., 2012; Zucchella et al., 2013), electroencephalography (EEG)/neurofeedback (Alvarez, Meyer, Granoff, & Lundy, 2013), exercise (Baumann et al., 2011; Korsjens, Mesters, van der Peet, Gijsen, & van den Borne, 2006; Oh et al., 2011; Reid-Arndt, Matsuda, & Cox, 2012; Schwartz et al., 2002), ginkgo biloba (Atti et al., 2012; Barton et al., 2012), meditation (Milbury et al., 2013), mindfulness-based stress reduction (Hoffman et al., 2012), natural restorative environment (Cimprich, 1993; Cimprich & Ronis, 2003), structured rehabilitation (Rottmann et al., 2012), and vitamin E (Chan, Cheung, Law, & Chan, 2004; Jatoi et al., 2005).

The emerging empirical research has demonstrated the most support for nonpharmacologic treatments, such as cognitive training. In fact, the Oncology Nursing Society’s Putting Evidence Into Practice (PEP) resource identified cognitive training programs as likely to be effective for addressing cognitive impairment in survivors (Von Ah et al., 2014). However, additional research is needed to fully understand the benefits of interventions designed to reduce stress and improve attention, such as cognitive behavioral training, mindfulness-based stress reduction, and exercise. Research regarding pharmacologic treatments has yielded equivocal results, and those treatments need further investigation to explore their effectiveness (Von Ah et al., 2014).

### Nursing Implications and Need for Future Research

Oncology nurses are in a prime position to address cognitive changes after cancer and cancer treatment. Nurses need to recognize the cancer- and non-cancer-related factors that may place a survivor at higher risk for cognitive changes. In addition, nurses must fully
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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Findings</th>
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<tr>
<td><strong>Cognitive-Behavioral Training</strong></td>
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<tr>
<td>Cherrier et al., 2013</td>
<td>Seven one-hour sessions for seven weeks</td>
<td>Improvement in perceived cognitive function</td>
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<tr>
<td>Ferguson, McDonald, et al., 2007</td>
<td>Memory Attention Adaptation Training (MAAT), 30–50 minutes for four months</td>
<td>Improvement over time in perceived cognitive functioning, verbal memory, attention, and executive psychomotor functioning</td>
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<tr>
<td>Ferguson et al., 2012</td>
<td>MAAT training</td>
<td>Improvement in verbal memory</td>
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<tr>
<td>Goedendorp et al., 2014</td>
<td>Individualized training (5–26 sessions, $\bar{x} = 12.5$, SD = 4.7) focused on reducing fatigue</td>
<td>Improvement in perceived concentration; no improvement on neuropsychological assessment</td>
</tr>
<tr>
<td>Locke et al., 2008</td>
<td>Six sessions of cognitive rehab and six sessions of problem-solving therapy for two weeks</td>
<td>Improvement in mood; unable to obtain follow-up on objective cognitive functioning</td>
</tr>
<tr>
<td>McDougall, 2001</td>
<td>75 minutes, eight sessions for four weeks with MT and self-efficacy</td>
<td>Improvement in perceived cognitive functioning; memory efficacy, and metamemory; no improvement in memory performance</td>
</tr>
<tr>
<td>McDougall et al., 2011</td>
<td>30 minutes per week for eight weeks of MT with four, two-hour booster sessions</td>
<td>Improvement in perceived cognitive functioning and visual memory</td>
</tr>
<tr>
<td>Schuurs &amp; Green, 2012</td>
<td>Two hours per week for four weeks; includes psychoeducation and problem-solving approaches</td>
<td>Improvement in immediate (short-term) and delayed memory, visuospatial skills, and language and attention; these were sustained at three months postintervention except for language and attention.</td>
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**Cognitive Training**

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<tr>
<td>Gehring et al., 2009</td>
<td>Two hours per week for six weeks of cognitive training</td>
<td>Improvement in perceived cognitive function immediately and at six months postintervention; improvement in attention and memory at six months postintervention only</td>
</tr>
<tr>
<td>Hassler et al., 2010</td>
<td>90 minutes per week for 10 weeks of CT</td>
<td>Improvement in learning, perception, concentration, attention, memory, retentiveness, and verbal memory</td>
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<tr>
<td>Kesler et al., 2013</td>
<td>48 executive function training sessions for 12 weeks</td>
<td>Improvement in cognitive flexibility, verbal fluency, and processing speed</td>
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<tr>
<td>Miotto et al., 2013</td>
<td>Minimum of five 30-minute sessions of semantic organizational strategies</td>
<td>Improvement in verbal recall and increased activation</td>
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<tr>
<td>Poppelreuter et al., 2009</td>
<td>Two intervention groups: four one-hour sessions of (a) attention and memory training in person or (b) attention and memory per computer compared to control</td>
<td>No intervention effects</td>
</tr>
<tr>
<td>Von Ah et al., 2012</td>
<td>10 one-hour sessions for 6–8 weeks; two groups (MT or ST compared to control)</td>
<td>Improvement in perceived cognitive function both groups; MT had improvement in immediate and delayed memory, ST had improvement in immediate and delayed memory as well as processing speed.</td>
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<tr>
<td>Zucchella et al., 2013</td>
<td>16 one-hour sessions for four weeks</td>
<td>Improvement in visual attention and verbal memory</td>
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**EEG/Neurofeedback**

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<th>Study</th>
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<tr>
<td>Alvarez et al., 2013</td>
<td>20-session neurofeedback regimen</td>
<td>Improvement in perceived cognitive function</td>
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**Exercise Programs: Combined or Alone**

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<tr>
<td>Baumann et al., 2011</td>
<td>60 minutes of resistance training two times per week for 12 weeks</td>
<td>Improvement in attention and working memory; no improvement in verbal memory; no baseline control group</td>
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<tr>
<td>Korstjens et al., 2006</td>
<td>Two-hour sessions two times per week for 12 weeks of physical fitness, plus seven two-hour psycho-education sessions</td>
<td>Improvement in perceived cognitive function</td>
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*Interventions that combine pharmacologic and nonpharmacologic approaches
CT—cognitive training; EEG—electroencephalography; MBSR—mindfulness-based stress reduction; MT—memory training; ST—speed-of-process training

(Continued on the next page)
assess each survivor for this late and long-term effect of treatment. Survivors often will express concerns regarding memory lapses (remembering names, dates, and places), inability to concentrate, and difficulty following instructions or completing tasks. These concerns should be fully assessed and referred to other healthcare professionals (e.g., neuropsychologist, psychiatrist) for evaluation if they disrupt everyday functioning (Jansen, 2013). At a minimum, nurses should acknowledge the survivors’ cognitive concerns because research has suggested that the acknowledgement alone can reduce distress. In addition, nurses should thoroughly assess and treat other symptoms that commonly co-occur with cognitive impairment, such as depression and anxiety. Addressing these other co-related symptoms may also help ameliorate the perception of cognitive impairment. Nurses should be aware of and refer survivors with concerns to reputable resources, such as the PEP resource for cognitive impairment (www.ons.org/practice-resources/pep/cognitive-impairment). This site is routinely updated with the most relevant empirical research in this area.

Based on the current research, cognitive training has shown to be useful in addressing cognitive impairment and has been identified as likely to be effective in improving cognitive impairment in cancer survivors (Von Ah et al., 2014). More research is needed, however, to fully identify effective interventions that are feasible and cost effective. Much of the current research is still limited by the research design (e.g., lack of randomized, controlled trials; lack of an attention control comparison group; laboratory versus home-based programs), small sample sizes,

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<td><strong>Exercise Programs: Combined or Alone (Continued)</strong></td>
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<tr>
<td>Oh et al., 2011</td>
<td>90 minutes per week for 10 weeks of medical qigong</td>
<td>Improvement in perceived cognitive function</td>
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<tr>
<td>Reid-Arndt et al., 2012</td>
<td>60 minutes of tai chi two times per week for 10 weeks</td>
<td>Improvement in perceived cognitive function, immediate and delayed memory, verbal fluency, attention, and executive functioning; no control</td>
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<tr>
<td>Schwartz et al., 2002a</td>
<td>15–20 minutes of aerobic exercise four days per week with MPH</td>
<td>Improvement in perceived cognitive function (mental health)</td>
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<td><strong>Ginkgo biloba</strong></td>
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<td>Attia et al., 2012</td>
<td>120 mg per day for 24 weeks; six-week washout</td>
<td>Improvement in executive function, nonverbal memory attention, and concentration; no control group for practice effects</td>
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<tr>
<td>Barton et al., 2012</td>
<td>120 mg per day</td>
<td>No treatment effect</td>
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<td><strong>Meditation</strong></td>
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<tr>
<td>Milbury et al., 2013</td>
<td>Tibetan sound meditation for six weeks</td>
<td>Improvement in perceived cognitive function, verbal memory, and processing speed immediately post-intervention; no improvement six months later</td>
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<td><strong>MBSR</strong></td>
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<tr>
<td>Hoffmann et al., 2012</td>
<td>Eight-week program of MBSR</td>
<td>Improvement in perceived cognitive function–confusion</td>
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<td><strong>Natural Restorative Environment</strong></td>
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<tr>
<td>Cimprich, 1993</td>
<td>60–90 minutes per week of walking gardening</td>
<td>Improvement in attentional fatigue</td>
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<tr>
<td>Cimprich &amp; Ronis, 2003</td>
<td>120 minutes per week of exposure to the natural environment</td>
<td>Improvement in capacity to direct attention</td>
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<td><strong>Structured Rehabilitation</strong></td>
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<td>Rottmann et al., 2012</td>
<td>Six-day residential course</td>
<td>Improvement in perceived cognitive function</td>
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<td><strong>Vitamin E</strong></td>
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<tr>
<td>Chan et al., 2004</td>
<td>Vitamin E 2,000 IU per day</td>
<td>Improvement in global cognitive functioning, verbal and visual memory, and executive functioning; no improvement in attention</td>
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<tr>
<td>Jatoi et al., 2005a</td>
<td>Vitamin E 1,000 IU per day and donepezil for four weeks</td>
<td>No treatment effect</td>
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*February 2015  •  Volume 19, Number 1  •  Clinical Journal of Oncology Nursing*
limited sample diversity (mostly conducted in brain tumor or breast cancer survivors with well-educated and Caucasian participants), and lack of assessment using standardized neuropsychological tests. Research in this area is vital to fully address cancer- and cancer treatment–related cognitive impairment, which has been shown to be a prevalent, bothersome, and potentially debilitating symptom.

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