

# Review complementary and integrative interventions for cancer-related cognitive changes

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## ABSTRACT

Cognitive sequelae from a diagnosis of cancer and the subsequent treatment impact survivors' quality of life and can interfere with both social relationships and employment. The search for evidence-based prevention and intervention strategies continues for both central nervous system (CNS) and non-CNS cancer-related cognitive changes. Complementary therapies in conjunction with conventional medicine are being included in integrative programs designed to maximize symptom management in cancer treatment centers providing survivorship care. The purpose of this article is to review the existing evidence for the use of complementary and integrative interventions to prevent or treat cancer-related cognitive changes and to discuss the rationale for current and future research. Search terminology

included: Complementary, alternative, and integrative medicine, cognition, cognitive function, and cancer, and yielded 20 studies that met criteria for inclusion. Preliminary results published to date indicate that some complementary therapies may be beneficial to cancer survivors experiencing cognitive concerns. A number of gaps in the literature remain primarily due to preliminary study designs, small sample sizes, lack of objective cognitive testing, and cognitive function not being a primary endpoint for much of the published work.

**Key words:** Cancer, cognition, cognitive function, complementary, integrative, interventions

## Introduction

Cognitive sequelae from a diagnosis of cancer and the subsequent treatment have a significant impact on survivors' quality of life and can interfere with both social relationships and employment.<sup>[1-3]</sup> Primary and secondary tumors of the central nervous system (CNS) long have been recognized to cause impairment in cognitive function due to both direct injury to the CNS by tumor invasion as well as from injury caused by surgery, radiation therapy, and

chemotherapy.<sup>[4]</sup> More recently, cognitive sequelae from non-CNS malignancies have been recognized and may persist as long as 20 years in a subset of individuals.<sup>[5-7]</sup> For these survivors, the level of severity and duration varies, but in many studies has been shown to be mild with only a subset of survivors having prolonged difficulties.<sup>[8]</sup> Objective neuropsychological testing indicates difficulties across a number of domains, most frequently including

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executive function, attention and concentration, short-term memory, and processing speed.<sup>[9]</sup> Survivors complain of difficulties with multi-tasking, word-finding, remembering appointments, misplacing items, reading comprehension, and aspects of driving and directions.<sup>[2,3]</sup>

A number of causal mechanisms for non-CNS cognitive sequelae have been postulated including: Inflammatory cytokine release, impairment of DNA repair mechanisms, genetic predisposition, chemotherapy-induced anemia and/or estrogen suppression, telomere shortening, cell senescence, alteration in the blood-brain barrier, and neural progenitor cell injury.<sup>[10-14]</sup> Many of these proposed mechanisms are consistent with a model of accelerated aging.<sup>[8,14]</sup> Confounding factors may include the impact of the cancer diagnosis on mood states (anxiety and depression) and the ability to direct attention.<sup>[15]</sup> Fatigue, sleep disturbance, and neuropathy also may be related to cognitive complaints.<sup>[2,16]</sup> Research to identify risk factors that may predispose some individuals to more severe and long-lasting complaints is on-going. The search for evidence-based prevention and intervention strategies continues for both CNS and non-CNS cancer-related cognitive changes. A number of pharmacologic and nonpharmacologic interventions have been studied.<sup>[17,18]</sup> Due to mixed study results and variation in study design, a standard of care for prevention or treatment of cognitive sequelae has not been established.<sup>[17]</sup> However, the National Comprehensive Cancer Network guidelines recommend regular exercise as one strategy to mitigate the cognitive impact of cancer and cancer therapy.<sup>[19]</sup>

In recent years, the investigation of complementary therapies in the United States has been supported by the development of the National Center for Complementary and Integrative Health (NCCIH), an organization within the National Institutes of Health. Complementary therapy is defined by the NCCIH as a “nonmainstream practice used together with conventional medicine” as opposed to alternative medicine which is used “in place of conventional medicine.”<sup>[20]</sup> Complementary therapies in conjunction with conventional medicine are being included in integrative programs designed to maximize symptom management in cancer treatment centers providing survivorship care. The use of complementary therapies has been demonstrated to be acceptable to individuals with cancer. Results of a recent survey of 1471 cancer survivors indicated that 66.5% reported use of complementary and alternative medicine, 43.3% of whom report use within the past year.<sup>[21]</sup> To date, preliminary work has been done to explore the use of various complementary or integrative approaches to

cognitive sequelae for cancer survivors. The purpose of this article is to review the existing evidence for the use of complementary and integrative interventions to prevent or treat cancer-related cognitive changes and to discuss the rationale for current and future research.

## Methods

PubMed and CINAHL databases were searched using the following terminology: Complementary, alternative, and integrative medicine, cognition, cognitive function, and cancer. Due to the limited amount of published data in this area of research, criteria for inclusion in this review were articles in which outcomes of perceived cognitive function and/or objective cognitive performance were planned or reported for interventional research conducted with cancer survivors. Articles were included regardless of study design or limitations in an effort to identify all complementary intervention research conducted to date. This search yielded 11 studies<sup>[22-31]</sup> (10 completed and 1 planned) and 4 review articles.<sup>[32-35]</sup> The review articles were utilized to identify two studies not found using the search terminology.<sup>[36,37]</sup> Six additional studies<sup>[38-43]</sup> were identified from the recent Oncology Nursing Society Putting Evidence into Practice initiative<sup>[17]</sup> and one study was added due to awareness of current literature related to exercise as a potential intervention.<sup>[18,44]</sup>

## Results

Complementary and integrative therapy research for cancer-related cognitive changes conducted to date includes the investigation of a variety of diverse interventions. The articles included in this review are summarized in Table 1 and are organized into categories for nutritional supplements, mindfulness-based interventions such as meditation and physical activity with a mindfulness component, and other interventions such as haptotherapy, neurofeedback, acupuncture, and the use of restorative environments. A brief description of the various interventions and rationale for investigation is provided below.

### Nutritional supplements

#### *Ginkgo biloba*

The use of *Ginkgo biloba* to treat cognitive changes has been investigated for individuals with brain tumors with cognitive complaints following treatment with radiation<sup>[23]</sup> and for the prevention of cognitive dysfunction for women receiving adjuvant therapy for breast cancer.<sup>[24]</sup> The rationale for studying *G. biloba* is based on previous research conducted to investigate the use of the herb for individuals with

Table 1: Study Summaries

Nutritional supplements	Authors	Design and sample	Intervention description	Measures	Outcomes	Limitations
<i>G. biloba</i>	Atia <i>et al.</i> 2012 <sup>[23]</sup>	Open label, prospective, phase II, interventional n=34 patients with primary brain tumors ≥6 months after partial or whole brain radiation, no evidence of tumor progression within previous 3 months, stable or tapering steroid dose	<i>G. biloba</i> 40 mg tid PO for 24 weeks followed by 6-week washout period	Assessments at baseline, 12, 24 (end of treatment) and 30 weeks (after washout) KPS FACT-BR POMS MMSE (global cognitive function) TMT-A (attention/concentration) and B executive function) DST (attention/concentration and working memory) ROCF (immediate and delayed recall) CVLT-II F-A-S (verbal fluency)	Significant improvement noted for executive function (P=0.007), attention/concentration (P=0.002), and immediate and delayed nonverbal memory (P=0.001/0.002) at 24 weeks 68% completed 12 weeks, 56% completed 24 weeks of intervention 5 went off treatment due to toxicity (4 GI symptoms, 1 intracranial bleed)	No control group. Small sample size. High drop-out rate (44%) due to toxicity
Vitamin E	Barton <i>et al.</i> 2013 <sup>[24]</sup>  Chan <i>et al.</i> , 2004 <sup>[38]</sup>	RDBPC phase III prevention trial n=166 chemotherapy naive women with breast cancer preparing to start adjuvant chemotherapy  Nonrandomized, controlled, interventional with pre- and post-intervention assessments n=29 NPC patients with TLN (19 intervention, 10 control)	<i>G. biloba</i> 60 mg bid versus placebo initiated prior to second cycle of chemotherapy and continued 1-month post completion of chemotherapy Vitamin 3, 1000 IU PO bid for 1-year versus control	HSCS TMT-A and B PHS POMS  CMMSE (global cognitive functioning) Computerized reaction time attention test HKLLT (verbal memory) WMS-III VR (visual memory) CFT (expressive language ability) Computerized cognitive flexibility test Self-evaluation of cognitive function for 8 domains Assessments at baseline and 1-year	No differences noted between intervention and placebo arms  Improvement at 1-year for intervention group in: Global cognitive functioning P=0.035 Visual memory – P=0.007 Verbal memory – P=0.036 Executive function (P=0.04) No difference seen for attention, language, or self-evaluation	HSCS now known for large practice effect  Two instruments were developed by the authors and no information was provided on psychometrics. No randomization or blinding. Small sample size. No long-term follow-up past 1-year
Omega-3 fatty acids	Jatoi <i>et al.</i> , 2005 <sup>[42]</sup>  van der Meij <i>et al.</i> 2012 <sup>[37]</sup>	DBPC n=9 SCLC patients with complete response or minimal disease after completion of all therapy, including PCI  RDBPC n=40 patients with stage III NSCLC receiving chemotherapy	Donepezil, 5 mg/day PO for 1-month and increased to 10 mg/day if well tolerated and Vitamin E, 1000 IU/day PO versus identical placebos  Oral nutritional supplement containing EPA 2.02 g and DHA 0.92 g in 2 cans/day over 5 weeks versus an isocaloric control supplement (ensure)	MMSE Blessed dementia scale  EORTC-QoL C-30 KPS Handgrip strength PAM accelerometer	Unable to draw conclusions from this trial. Closed due to poor accrual (only 9 of 104 patients enrolled over 15 months) Median time on intervention was 42 days compared to 69 days for placebo due to anorexia, nausea, vomiting Intervention group reported better cognitive function than controls (P<0.01) and trended towards higher physical activity (P=0.05)	Eligibility criteria too narrow for enrollment  Small sample size. Cognitive function was not a primary endpoint
Mindfulness-based interventions	Milbury <i>et al.</i> 2013 <sup>[43]</sup>	RCT n=47 women with stage I-III breast cancer, 6-60 months postchemotherapy who reported cognitive impairment	Twice weekly 60 min TSM group sessions for 6 weeks versus wait-list control	Assessments at baseline, end of treatment, and 1-month later Digit span (attention and working memory) Digit symbol (visuomotor coordination, attention, processing speed) COWA (verbal fluency) RAVLT (verbal memory) FACT-COG CES-D (depression) PSQI (sleep) BFI (fatigue) MOS SF-36 (HRQoL) FACT Spiritual Well-Being Scale	TSM group demonstrated better verbal memory (P=0.06), short-term memory and processing speed (P=0.09), and reported improved cognitive function/abilities (P=0.06, 0.08) and less depression (P=0.05) 72.2% attended 75% of the sessions. 23.5% attended 100%	Small sample size. No control group. Eligibility based on self-report instead of objective tests of cognitive function. No measure of home practice during follow-up period

(Continued)

Table 1: (Continued)

Nutritional supplements	Authors	Design and sample	Intervention description	Measures	Outcomes	Limitations
	Speca <i>et al.</i> , 2000 <sup>[30]</sup>	RCT n=90 patients with a history of any type of cancer (86 women, 23 men; 38 with breast cancer)	7 weekly 90 min mindfulness meditation-based stress reduction program sessions versus wait-list control	Assessments pre- and post-intervention POMS SOSI	Intervention group demonstrated less mood disturbance (including confusion, $P<0.05$ ) and symptoms of stress (including cognitive disorganization, $P<0.01$ ) than controls	Small sample size. Cognition was not a primary outcome. No objective cognitive testing
	Hoffman <i>et al.</i> , 2012 <sup>[41]</sup>	RCT n=229 women with breast cancer after completion of surgery, chemotherapy, and radiation therapy	8-week MBSR program (2.25 h weekly and one 6 h session in week 6) versus wait-list control	Assessments at baseline (T1), 8 weeks (T2), and 12 weeks (T3) POMS FACT-Breast FACT-Endocrine symptoms WHO-5 (mood, QoL, well-being)	MBSR group demonstrated main effect improvement for all measures. Improvement noted for POMS confusion subscale at T2 ( $P=0.002$ )	Cognition was not a primary outcome. No objective cognitive testing
MBMT	Lesiuk, 2015 <sup>[45]</sup>	Nonrandomized longitudinal n=15 women with stage I-III breast cancer receiving adjuvant chemotherapy	MBMT-60 min/week for 4 weeks	Assessments of attention at baseline (T1) and conclusion of intervention (T2) Assessment of mood states at baseline and at the conclusion of each session CPT-II POMS-BF	Attention was improved at T2 ( $P=0.022$ ) as was mood ( $P<0.001$ ), with particular decrease in fatigue ( $P<0.001$ )	No randomization or control. Small sample size
Mindfulness-based exercise						
Yoga	Galandino, <i>et al.</i> , 2012 <sup>[26]</sup>	Case series n=4 women with stage II breast cancer prior to chemotherapy	Iyengar-inspired yoga program twice a week for 12 weeks	Assessments at baseline, 6 and 12 weeks during chemotherapy, and 1 and 3 months after chemotherapy Functional reach test (balance) Sit and reach test (flexibility) POMS FACT-breast (QoL) PCQ (subjective cognitive function) Cogstate (objective cognitive function)	Improvement trends noted for objective tests of cognitive function (speed, accuracy, and reduced errors) Participants did not report differences in perceived cognitive function	Unable to recruit desired sample size (sample size goal not reported). Results limited to case series of four women who were representative of different aspects of the sample
	Derry <i>et al.</i> , 2014 <sup>[44]</sup>	Secondary analysis of cognitive outcomes for RCT n=200 breast cancer survivors within 2 months to 3 years of completion of treatment with the exception of anti-estrogen therapy	Hatha yoga intervention twice a week for 12 weeks versus wait-list control	Assessments at baseline, postintervention and 3-month follow-up BCPT cognitive problems scale MOS SF-36 MFSI-SF CES-D LPS-stimulated IL-6, IL-1 $\beta$ , TNF- $\alpha$	Intervention group reported less cognitive complaints at 3 months ( $P=0.003$ ) after controlling for distress, fatigue, and sleep disturbance. Dose response noted for participants with frequent yoga practice ( $P<0.001$ ) Inflammatory cytokine levels were not predictive of cognitive complaints	Objective cognitive function not assessed
	Vadiraja <i>et al.</i> , 2009 <sup>[31]</sup>	RCT n=85 women with stage II/III breast cancer receiving adjuvant radiation therapy	Daily 60 min yoga sessions (at least 3 per week in-person with instructor) for 6 weeks versus supportive counseling (15 min every 10 days by trained social worker)	Assessments at baseline and 6 weeks EORTC-QoL C30 (HRQoL) PANAS	Yoga group demonstrated improvement in cognitive functioning dimension for the EORTC-QoL C30 ( $P=0.03$ )	Small sample size Cognition not a primary endpoint No assessment of objective cognitive function

(Continued)

Table 1: (Continued)

Nutritional supplements	Authors	Design and sample	Intervention description	Measures	Outcomes	Limitations
Tai Chi	Reid-Arndt <i>et al.</i> 2012 <sup>[29]</sup>	Nonrandomized prospective <i>n</i> =23 women with history of any type of cancer (breast, ovarian, endometrial, NHL, CLL) at least 12 months after completion of therapy (surgery –65%, radiation –61%, chemotherapy – 100%)	10-week Tai Chi course (1 h sessions, twice a week)	Assessments at baseline and within 1-month after intervention RAVLT (memory) TMT-B and stroop test (executive function) COWA (language) WAIS-III digit span and digit symbol and TMT-A (attention) MASQ IES-R POMS short form	Improvements noted for immediate and delayed memory, verbal fluency, attention, and executive functioning ( <i>P</i> <0.05) as well as self-reported verbal ( <i>P</i> =0.01) and visual memory ( <i>P</i> <0.05)	Small sample size No control
Qigong	Oh <i>et al.</i> , 2012 <sup>[28]</sup>	RCT <i>n</i> =81 patients with history of any type of cancer who had received/were receiving chemotherapy. Subset of patients participating in a parent study once cognitive outcome added	90 min Qigong sessions twice a week for 10 weeks and daily home practice (30 min) versus usual care	Assessments at baseline and conclusion of 10 week EORTC-QoL-C30 (2 cognitive items) FACT-COG FACT-General (QoL) CRP levels	Qigong group demonstrated self-reported cognitive improvements on both the EORTC items and FACT-COG ( <i>P</i> =0.05) after controlling for baseline scores. CRP levels were lower in the Qigong group ( <i>P</i> =0.042) but not associated with self-reported cognitive function	Cognitive function not a primary outcome for the parent study No assessment of objective cognitive function No blinding of participants
Other						
Haptotherapy	van den Berg <i>et al.</i> 2006 <sup>[33]</sup>	Semi-experimental intervention trial with matched controls <i>n</i> =57 patients with any type of cancer (31 — intervention, 26-controls) adults recruited prior to receiving chemotherapy	Five 45-min haptotherapy sessions over the course of chemotherapy versus usual care	Assessments at baseline and completion of intervention EORTC-QoL C30 POMS HDI evaluation of psychosocial care	Haptotherapy group scored higher on EORTC cognitive items (OR=5.18, reliability interval 1.07-23.02)	No randomization. Small sample size. Cognition was not primary outcome. No assessment of objective cognitive function
Neurofeedback	Alvarez <i>et al.</i> 2013 <sup>[24]</sup>	Prospective, wait-list controlled <i>n</i> =23 women with breast cancer 6-60-months postchemotherapy with self-reported cognitive impairment	10 weeks of wait-list control followed by 10 weeks of neurofeedback administered over 33 min	Assessments at baseline, weeks 1, 5, and 10 prior to neurofeedback initiation; then at weeks 4, 7 and 10 during neurofeedback; and 4 weeks later FACT-COG FACT-Fatigue PSQI BSI	Improvements noted on all self-reported cognitive measures across time following the intervention ( <i>P</i> <0.001). Participants' scores did not differ from normative populations on 3 function of 4 of the FACT-COG subscales	Small sample size. No randomization. No assessment of objective cognitive function
	de Ruiter <i>et al.</i> 2012 <sup>[24]</sup>	RDBPC <i>n</i> =70 pediatric brain tumor survivors (ages 8-18) with caregiver reported cognitive complaints and 35 sibling controls	Neurofeedback (33 min sessions) twice a week for 15 weeks	Assessments at baseline (T0), postintervention (T1), and 6 months later (T3) Qeeq ANT (attention and processing speed) Visual sequencing task and age appropriate Wechsler digit span (memory) WISC-III/WAIS-III (intellectual functioning) Stop signal task (inhibition) Tracking and pursuit task (visuomotor integration) SDQ child, parent, and teacher versions (social/emotional functioning) SPPC and SPPA (self-esteem) Kidscreen 27 (HRQoL) CIS (fatigue) SDSC (sleep) SWAN (attention) BRIEF parent and teacher version (executive function)	Planned study published in 2012. Results not yet published	

(Continued)

Table 1: (Continued)

Nutritional supplements	Authors	Design and sample	Intervention description	Measures	Outcomes	Limitations
Acupuncture	Johnston et al., 2011 <sup>[27]</sup>	RCT n=12 (5-intervention, 7 control) women treated for breast cancer with complaints of fatigue (scores >4 on BFI)	Four weekly 50-min education sessions to improve self-care (exercise, nutrition, stress management) and eight 50-min acupuncture sessions versus usual care	Assessments at baseline and following completion of the intervention BFI FACT-COG	Intervention group reported reduction in fatigue (ES=1.85) but no reduction of cognitive complaints	Unable to achieve desired sample of n=80. Cognition was secondary endpoint
Restorative environment	Cimprich, 1993 <sup>[39]</sup>	RCT n=32 women newly diagnosed with stage I/II breast cancer	Participation in restorative activities for 20-30 min at least 3 times a week for 3 months versus usual care	Assessments at 3, 18, 60, and 90 days after primary surgery for breast cancer Digit span Symbol digit Letter cancellation Necker cube pattern control (TAS score = capacity to direct attention) AFI VAMS	Intervention group demonstrated improvement in TAS over the 4 time points. Significant improvement was noted between 3 and 90 day assessments (P=0.01). Both groups demonstrated improvements in AFI over time. The intervention group improvement was more consistent across time points	Specific data not collected re: Control group participation in restorative activities
	Cimprich and Ronis, 2003 <sup>[40]</sup>	RCT n=157 women newly diagnosed with breast cancer prior to surgery	Exposure to a natural environment for 120 min/week until 19 days postsurgery	Assessments at approximately 17 days presurgery (T1) and 19 days postsurgery (T2) Digit span forward Digit span backward TMT-A and B Necker cube pattern control (TAS score = capacity to direct attention) SDS	The intervention group demonstrated better TAS scores at T2 (P=0.03). Baseline TAS scores and group significantly contribute to the regression model for TAS at T2 (P<0.001 and 0.01 respectively)	26 women (older and less educated) were lost to follow-up at T2. Lack of diversity in sample (majority Caucasian and well-educated)

G. biloba: Ginkgo biloba, AFI: Attentional function index, ANT-Attention network task, BFI: Brief fatigue inventory, BCPT: Breast cancer prevention trial, BRIEF: Behavior rating inventory of executive functioning, BSI: Brief symptom inventory, CES-D: Center for epidemiologic studies depression scale, CFT: Category fluency test, CIS: Checklist individual strength, CMMSE: Cantonese mini-mental status examination, COWA: Controlled oral word association, CPT-II: Conners' continuous performance test II, CRP: C-reactive protein, CVLT-II: California verbal learning test part II, DBPC: Double blind, placebo controlled, DHA: Docosahexaenoic acid, DST: Digit span test, ROCF: Modified Rey Osterrieth complex figure, EPA: Eicosapentaenoic acid, EORTC-QoL C30: European organization for research in the treatment of cancer-quality of life, ES: Effect size, FACT: Functional assessment of cancer therapy-brain, FACT-COG: Functional assessment of cancer therapy-cognition, GI: Gastrointestinal, HDI: Helen downsing institute, HKLLT: Hong kong list learning test, HRQoL: Health-related quality of life, IES-R: Impact of event scale-revised, KPS: Karnofsky performance scale, LPS-stimulated IL-6, IL-1β, TNF-α: Lipopolysaccharide-stimulated production of interleukin 6, interleukin 1 beta, tumor necrosis factor alpha, MASQ: Multiple abilities self-report questionnaire, MFSI-SF: Multidimensional fatigue symptom inventory-short form, mg: Milligrams, MMSE: Mini-mental status exam, MOS SF-36: Medical outcomes study short form 36, NHL: Non-hodgkin lymphoma, NPC: Nasopharyngeal cancer, NSCLC: Nonsmall cell lung cancer, PAM: Physical activity monitor, PANAS: Positive and negative affect schedule, PCQ: Perceived cognition questionnaire, bid: Twice daily, HSCS: High sensitivity cognitive screen, PO: Per os (oral), POMS: Profile of mood states, POMS-BF: Profile of mood states-brief form, PSQI: Pittsburgh sleep quality index, RAVLT: Rey auditory verbal learning test, RCT: Randomized controlled trial, RDBPC: Randomized double blind placebo controlled, SCLC: Small cell lung cancer, IU: International units, SDQ: Strengths and difficulties questionnaires, SDS: Sleep disturbance scale for children, SOSI: Symptoms of stress inventory, SPPC/SPPA: Self-Perception profile for children/adolescents, SWAN: Strengths and weaknesses of ADHD-symptoms and normal-behavior, tid: Three times a day, TAS: Total attention score, TMT: Trail making tests, TLN: Temporal lobe radionecrosis, TSM: Tibetan sound meditation, VAMS: Visual analogue mood scale, WMS-III VPR: Visual reproduction subset of the wechsler memory Scale-III, qEEG: Quantitative electroencephalography, WAIS-III: Wechsler adult intelligence scale for children-III, OR: Odds ratio, MBSR: Mindfulness-Based stress reduction, WHO: World health organization, QoL: Quality of life, MBMT: Mindfulness-based music therapy

Alzheimer's disease and dementia. Results have been mixed, but *G. biloba* is thought to demonstrate antioxidant activity, increase cerebral blood flow, improve glucose utilization, and stimulate hippocampal choline uptake. Attia *et al.* reported that 24 weeks of therapy with 40 mg of *G. biloba* 3 times a day was associated with improvements on objective tests of executive function, attention, concentration, and verbal memory for 34 patients treated with radiation therapy for brain tumors.<sup>[23]</sup> Attia *et al.* noted a high drop-out rate for participants in the intervention arm. In contrast, Barton *et al.* found no significant results for the use of *G. biloba* 60 mg twice a day during chemotherapy for breast cancer versus placebo ( $n = 166$ ) for the prevention of cognitive changes.

#### Vitamin E

The anti-oxidant properties of Vitamin E have attracted researchers investigating interventions for cognitive dysfunction resulting from temporal lobe radionecrosis<sup>[38]</sup> and for studying the potential for combined effects with the cholinesterase inhibitor, donepezil.<sup>[42]</sup> Chan *et al.* found that 1000 international units of Vitamin E per day for a year improved results of the objective tests for global cognitive functioning, attention, verbal memory, language ability, and cognitive flexibility for patients with nasopharyngeal cancer who developed temporal lobe necrosis as a result of radiation therapy.<sup>[46]</sup> Jatoi *et al.* attempted to study Vitamin E in combination with donepezil as a treatment to prevent cognitive impairment for patients with small cell lung cancer following completion of therapy. However, due to narrow inclusion criteria, they were unable to successfully recruit participants and closed the trial after 15 months and a sample size of nine.

#### Omega-3 fatty acids

Omega-3 fatty acids (also referred to as n-3 polyunsaturated fatty acids) are purported to reduce the production of inflammatory cytokines. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are obtained from fish oil and have been investigated as treatment for cognitive impairment. A recent meta-analysis indicated positive results for adults with cognitive impairment without dementia.<sup>[47]</sup> One study has been published in which EPA and DHA were evaluated in patients with nonsmall cell lung cancer receiving chemoradiotherapy.<sup>[37]</sup> In this small study, the intervention group did report better cognitive function than controls, although cognition was not a primary endpoint for the study and no objective cognitive testing was done.

### Mindfulness-based interventions

Mindfulness has been operationally defined by a two-component model.<sup>[48]</sup> The first component of the model

consists of developing skills to sustain attention (typically by focusing on the breath via meditation techniques) on the current experience and developing flexibility for switching focus to keep attention anchored in the current experience. The second component involves cultivating an orientation of curiosity and acceptance to the current experience. Bishop *et al.* summarize the definition of mindfulness as "the self-regulation of attention, which involves sustained attention, attention switching, and the inhibition of elaborative processing."<sup>[48]</sup> Mindfulness also involves gaining insights into ones' thoughts and feelings in order to adopt a decentered perspective and cope with challenges.<sup>[48]</sup>

#### Meditation

Rationale for the investigation of meditation and other mindfulness-based techniques is related to evidence linked to the reduction of anxiety, depression, and the stress response as well as enhancing the immune system.<sup>[30,33,41,43]</sup> Results of meditation studies conducted in children and adults with attention deficit-hyperactive disorder demonstrated positive results for improving cognitive function and laid the foundation for investigation in the cancer population.<sup>[33]</sup> Several mechanisms for improved cognitive function have been proposed, including increased activity in neural circuitry associated with attention; prefrontal, temporal, and parietal cortical thickening; and decreases in stress-induced cortisol levels.<sup>[33]</sup> Meditation has been postulated to have neuroprotective effects and may reduce age-related cognitive decline.<sup>[32]</sup> Meditation, including foci on breathing regulation and control of thoughts and feelings, is postulated as a type of attentional training exercise and has been explored as an intervention for a number of cancer-related symptoms such as anxiety, depression, and fatigue.<sup>[30,33,41]</sup> Three randomized, controlled trials have been published in which meditation has been investigated as a potential intervention for cognitive complaints following treatment for breast<sup>[41,43]</sup> or other types of cancer.<sup>[30]</sup> Only one of these studies was designed with performance on objective tests of cognitive function as a primary outcome.<sup>[43]</sup> Milbury *et al.* found significant improvements for verbal memory, short-term memory, and processing speed following a 6-week intervention of Tibetan sound meditation for a small sample of breast cancer survivors with posttreatment cognitive complaints. Results from the other two studies demonstrated improvements in subjective cognitive function for larger samples following mindfulness-based meditation/stress reduction programs.<sup>[30,41]</sup>

#### Mindfulness-based music therapy

Lesiuk recently published results from a small study conducted to assess the impact of 4 weeks of mindfulness-

based music therapy for women with breast cancer receiving adjuvant chemotherapy.<sup>[45]</sup> Music stimuli was identified as a good alternative source for mindfulness focus versus the more traditional focus on the breath. Participants improved on the objective tests of attention following the intervention. Due to the small sample size and lack of a control group, the conclusions that can be drawn from this study are limited.

### Mindfulness-based exercise

As with meditation, several forms of exercise include a mindfulness-based component. Exercise and physical activity are of great interest as potential interventions for cancer-related cognitive complaints due to the proposed mechanism of decreasing markers of inflammation associated with cognitive dysfunction and increasing levels of brain-derived neurotrophic factor and hippocampal volume.<sup>[18,49,50]</sup> Likewise, exercise combined with the potential added benefit of mindfulness may potentiate the benefits of either intervention alone as the two interventions may work through different mechanistic pathways.<sup>[44]</sup>

Yoga, Tai Chi, and Qigong share many similarities in that each combines physical movements or postures with breathing techniques and meditation with the goal of improving health and well-being.<sup>[51]</sup> Yoga practices originate in India and Tibet. Qigong, of which Tai Chi is one form, originates in China. These mind-body practices have been studied as strategies for stress reduction and symptom management in a number of populations and are sometimes referred to as meditative-movement therapies.<sup>[52]</sup>

#### Yoga

Results of three studies designed to investigate the potential benefits of yoga for cancer-related cognitive complaints in women with breast cancer have been published to date.<sup>[26,31,44]</sup> These studies include a case series for women taking part in an Iyengar-inspired yoga program, a secondary analysis of a randomized controlled trial of a hatha yoga program following the completion of breast cancer treatment and a randomized controlled trial of an integrated yoga program with a supportive counseling component delivered throughout treatment with radiation therapy. Galantino *et al.* reported improvement trends for tests of objective cognitive function and no difference in perceived cognitive function following the Iyengar-inspired yoga program.<sup>[26]</sup> However, they were unable to recruit to their desired sample size and limited their publication of results to four women. Derry *et al.* and Vadiraja *et al.* did not assess objective cognitive function.<sup>[31,44]</sup> Results from both studies demonstrated improvements in subjective cognitive function and a dose-response was noted for the hatha yoga

program. Markers of inflammatory cytokine levels did decrease for participants who took part in the hatha yoga program, however an association was not demonstrated with subjective cognitive function.<sup>[44]</sup> Cognitive function was not a primary endpoint for the investigation of the integrated yoga program.<sup>[31]</sup>

#### Tai Chi

One small study was conducted to evaluate a 10-week Tai Chi course for women with any type of cancer at least 12 months following the completion of all cancer therapy.<sup>[29]</sup> Improvements in objective tests of cognitive function were demonstrated 1 month after the intervention. The Yang form of Tai Chi was employed and is considered to be a moderate intensity form of exercise designed not to exceed 50% of participants' oxygen intake. The small sample size and lack of a control group limit the conclusions that can be drawn from these encouraging results.

#### Qigong

Oh *et al.* studied the effects of 10 weeks of Qigong for individuals with any type of cancer exposed to, or receiving, chemotherapy.<sup>[28]</sup> Improvement in subjective cognitive function was demonstrated at the completion of the intervention. No association between subjective cognitive function and a marker of inflammation (C-reactive protein) was demonstrated. The study design did not include objective tests of cognitive function.

### Other

#### Haptotherapy

Haptotherapy is a complementary therapy combining touch, counseling, and talking to achieve relaxation and facilitate getting in touch with one's feelings.<sup>[53]</sup> This intervention is based on haptonomy in which thoughts, feelings, and words are combined into what is referred to as psycho-tactile contact.<sup>[53]</sup> This form of complementary therapy is practiced primarily in the Netherlands and much of the source material is written in the Dutch language.<sup>[54]</sup> One study has been published in English in which haptotherapy was investigated as an intervention for perceived well-being in patients receiving chemotherapy.<sup>[36]</sup> The intervention involved five sessions over the course of treatment for a very small sample. Subjective cognitive function improved for the intervention group. The interpretation of results is limited by the lack of randomization and the small sample size. Cognition was not a primary outcome for the study.

#### Neurofeedback

Neurofeedback (also referred to as electroencephalographic [EEG] — biofeedback) involves the presentation of real-



time feedback to individuals regarding their brain waves as measured by EEG electrodes placed on the scalp.<sup>[22,25]</sup> One type of neurofeedback provides the individual with positive reinforcement when a desired brain wave is produced. Reinforcement may be visual or auditory such as seeing a move or hearing music.<sup>[25]</sup> Results from studies in which neurofeedback was associated with improved cognitive function for attentional-deficit hyperactivity disorder and traumatic brain injury provided a framework for investigating neurofeedback in the oncology population.<sup>[22,25]</sup> Proposed mechanisms for neurofeedback include enhancement of neuroplasticity and training of the brain to shift away from pathological brain wave patterns through positive reinforcement not unlike operant conditioning.<sup>[22,25]</sup> Description of a planned neurofeedback trial for children treated for primary brain tumors was published in 2012.<sup>[25]</sup> More recently, Alvarez *et al.* reported results of a 10-week neurofeedback intervention for women with breast cancer between 6 and 60 months of completing chemotherapy who report cognitive impairment. This method of neurofeedback differs from that used by de Rooter *et al.* in that rather than providing positive feedback for specific brain waves, the participant's brain is allowed to utilize the feedback (brief interruptions in recorded music) to enable self-organization.<sup>[22,25]</sup> Alvarez *et al.* noted improvements for all self-reported cognitive measures across all study time points. The participants served as their own controls and the sample size was small.

#### Acupuncture

Acupuncture involves the insertion of wire-thin needles into particular locations (acupoints) along specific meridians (channels in the body that transport energy).<sup>[55]</sup> Rationale for the investigation of acupuncture involves neurofunctional modulation of the CNS to increase neuroplasticity after injury and increase cerebellar circulation.<sup>[34]</sup> A combination of patient education and acupuncture was investigated for the relief of cancer-related fatigue.<sup>[27]</sup> No differences in subjective cognitive function, the secondary endpoint, were demonstrated.

#### Restorative environment

One of the earliest complementary therapies investigated for improving cancer-related cognitive complaints was exposure to a restorative environment (such as spending time in a park or garden, observing wildlife, or participating in activities of the arts such as music or painting).<sup>[39,40]</sup> Cimprich and Ronis postulated that exposure to activities that engage fascination and have restorative properties would decrease or prevent attentional fatigue associated with cancer and cancer therapy. Positive results were

published from two studies in which improvements were demonstrated for objective cognitive function following the intervention.<sup>[39,40]</sup>

## Discussion

The investigation of complementary and integrative therapies as interventions for cancer and cancer-related cognitive changes is a relatively nascent field of research. Cimprich's early work in restorative environments for women receiving surgery for breast cancer dates back to 1993, however her follow-up study was not conducted until 2003 and no further work with this intervention has been published. All other studies included in this review have been published since 2003 and no more than three studies have been published for each intervention. Small sample sizes, heterogeneity of tumor types, and variations in study designs limit the conclusions that can be drawn.

Most of the work (nine studies) has been conducted in the area of mindfulness-based interventions. A number of gaps in the literature remain primarily due to preliminary study designs, small sample sizes, lack of objective cognitive testing, and cognitive function not being a primary endpoint for much of the published work. Of the mindfulness-based studies, five were related to mindfulness-based exercise. Three of these studies were randomized, controlled trials, although one involved secondary analysis for a cognitive endpoint added to a larger trial. The results from these three studies investigating yoga, tai chi, and qigong were positive for self-reported cognitive function. The small tai chi study results also were positive for objective cognitive function. Four studies were designed to investigate the types of meditation (Tibetan sound - 1, mindfulness meditation-based stress reduction - 2, and mindfulness-based music therapy - 1). Although results all were positive, only one study design included cognitive function as a primary outcome and included objective cognitive testing.

To date, the bulk of the research conducted in the area of cancer and cancer treatment-related cognitive changes has been with breast cancer survivors. The studies reviewed here are no exception as 11 of 20 are specific to breast cancer. Of note, two studies were focused on primary brain tumors and three involved survivors of any type of cancer.

Study designs vary as to whether both subjective (self-report) and objective (neuropsychological testing) measures are included. Some have postulated that subjective and objective instruments actually measure different constructs of cognitive function with subjective tests being influenced by mood states such as anxiety and depression.<sup>[56,57]</sup> This

hypothesis is supported by the frequent lack of correlation between subjective and objective tests. Survivors' perception of cognitive changes has been documented to precede physiological changes in activation and structural changes assessed by neuroimaging.<sup>[58]</sup> Neuropsychological testing requires specialized training and can be time-consuming from both a resource and survivor burden perspective. However, documentation of objective cognitive changes has been considered necessary for verifying impairment and may be required for survivors' seeking medical disability. Recent work by Von Ah *et al.* indicated that the perceived cognitive abilities subscale of the Functional Assessment Cancer Therapy-cognition may be clinically relevant and useful as an assessment tool in clinical practice outside the constraints of a clinical trial.<sup>[3]</sup> Eight of the 20 studies reviewed here were designed to assess both subjective and cognitive functions. The majority (11 studies) included the self-report measures alone.

The sheer volume of available neuropsychological measures complicates comparing results across trials. Recently, the International Cancer and Cognition Task Force published recommendations for core measures to be included in prospective trials.<sup>[58]</sup> These measures are specific to the cognitive domains of executive function, memory, and processing speed and are believed to be more appropriate for capturing the subtlety of cognitive changes for this patient population than global cognitive measures.<sup>[58]</sup>

## Conclusions and Recommendations for Future Research

The study results published to date indicate that some complementary therapies may be beneficial to cancer survivors experiencing cognitive concerns. Further work is needed to ascertain the mechanisms behind mindfulness-based interventions. However, the preliminary results discussed here indicate some promise in the use of mindfulness-based interventions for cancer and cancer treatment-related cognitive complaints. Larger, randomized controlled trials are needed to establish effect sizes for specific types of mindfulness-based interventions. Comparisons between nonmindfulness-based exercise, mindfulness-based exercise, and meditation would be of interest to ascertain potential differences in mechanisms and efficacy. Likewise, further work is needed to determine the most efficacious timing, duration, and intensity of the interventions. Study populations need to continue to be expanded beyond breast cancer as the phenomenon of cancer and cancer treatment-related cognitive changes is not restricted to breast cancer survivors. Additional

prospective trials designed to measure both subjective and objective cognitive functions following complementary and integrative interventions to minimize cognitive changes still are needed to inform evidence-based practice changes.

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### Conflicts of interest

There are no conflicts of interest.

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