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Integrative Medicine in Cancer Survivors

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Abstract

Purpose of review—Due to medical advances and an aging population, the number of cancer survivors continues to rise. Survivors often experience late and long-term sequelae of cancer and its treatment (e.g. fatigue, pain, fear of recurrence, and stress). As a result, some patients have utilized or expressed interest in integrative medicine modalities for prevention of recurrence, optimizing health, enhancing quality of life, and managing symptoms. The purpose of this review is to focus on research published during the past year that informs our understanding of the utility of integrative medicine for cancer survivors.

Recent findings—Physical activity, diet, dietary supplements, mind-body modalities, acupuncture, and massage therapy all may play a role in the management of the physical (e.g. fatigue and pain) and emotional (e.g. anxiety and fear) issues faced by cancer survivors.

Summary—Integrative medicine therapies are appealing to and utilized by many cancer survivors and may reduce symptom burden. Clinicians who provide cancer survivorship care may improve patient care by understanding the evidence for and against their use.

Keywords

Integrative medicine; Complementary alternative medicine; Cancer; Survivorship

Introduction

The number of cancer survivors in the United States is expected to grow to nearly 19 million by 2024 [1]. Survivors sometimes experience the physical, social, and emotional effects of cancer and its treatments for years afterwards. Long-term symptoms can include fatigue, pain, neuropathy, lymphedema, difficulty sleeping, weight gain, cognitive dysfunction, sexual dysfunction, and fear of recurrence [2].

Integrative medicine promotes the physical, emotional, and spiritual health of a person by incorporating multiple evidence informed modalities alongside conventional therapy. The

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National Center for Complementary and Integrative Health (NCCIH) developed a five domain concept: 1) manipulative & body-based methods, 2) mind-body medicine, 3) alternative medical systems, 4) energy therapies, 5) biologically based therapies (Figure 1). According to the Society for Integrative Oncology, specific modalities include physical activity, diet, dietary supplements, mind-body modalities, acupuncture, and massage therapy [3]. Cancer survivors often use integrative medicine to address long-term adverse effects and symptoms [2]. In fact, many times oncology patients utilize integrative modalities without the knowledge of their providers [4].

This manuscript aims to highlight studies published during 2016 that either offer novel ideas for integrative medicine or include findings that may substantially change or reinforce current practice.

Physical Activity

Many cancer survivors experience changes in body composition (e.g., loss of muscle strength, cachexia, weight gain) that impact physical function and quality of life [5,6]. Sedentary lifestyle may contribute to the consequences of cancer treatment [7,8]. American Cancer Society (ACS) guidelines recommend 150 minutes per week of aerobic exercise and two strength training sessions per week [9]. Several recent studies have demonstrated the benefit of physical activity for cancer survivors, most notably for quality of life. IM exercises such as tai chi may motivate cancer survivors to live a more active lifestyle even when conventional approaches (e.g., biking, treadmill) are too challenging.

In pancreatic cancer survivors, telephone surveys of patients with stage 1 or 2 disease shortly after surgery identified few patient-reported barriers to participating in exercise programs. Many of these patients voiced an opinion that exercise would be better facilitated if they were aware of and educated about such programs shortly after diagnosis [10].

The Iowa Women's Health Study (conducted from 1986 to 2004) surveyed 14,357 women aged 55–69, more than 2 years removed from a cancer diagnosis, who were no longer receiving cancer-specific treatment. Only those still alive for more than one year after survey completion were included in the final analysis. Baseline and follow-up surveys assessed the frequency of both moderate and vigorous activity but did not assess duration of activity. The study demonstrated that inactive cancer survivors (i.e., those active less than once per week) were significantly more likely to report poor quality of life controlling for age, comorbidity, body mass index (BMI), and diet [11].

A cross-sectional study of 145 colorectal cancer survivors also found that greater sedentary time was associated with lower physical functioning, higher fatigue scores, and lower quality of life and lower role functioning [12,13]. Similarly, in 98 prostate cancer survivors, there was a trend toward an association between sedentary lifestyle and poorer quality of life [14].

The Better Exercise Adherence after Treatment for Cancer (BEAT Cancer) intervention entails three months of supervised exercise and face-to-face stress management and behavior modification. A randomized controlled trial (RCT) revealed that BEAT Cancer improved quality of life, lower extremity function, and satisfaction with life in breast cancer survivors.

Improvement in fatigue based on the SF-36 vitality scale was also noted [15]. The intervention benefit was larger in those with lower baseline scores and less support at home [16].

Another formal exercise intervention recently studied was the LIVESTRONG at the YMCA exercise program. Ninety-five survivors were randomized to a 12-week, twice-weekly exercise program involving 90 minute sessions that included a warmup, aerobic exercise, resistance training, and a cool-down period. This group had improved quality of life (measured by the Functional Assessment of Cancer Therapy-General, FACT-G) but no difference in cancer-related fatigue compared to 91 survivors randomized to a 12-week waiting list [17].

The benefits of resistance training are of particular interest in cancer survivors. One RCT found 16 weeks of resistance training 3 days per week resulted in significant improvement of fatigue and quality of life, as measured by the FACIT and FACT-G scales respectively, to levels in the general population [18]. Further research will be needed to determine if these improvements in fatigue and quality of life are sustained. Despite historic concerns that strength training and weight lifting might exacerbate lymphedema, a recent study of breast cancer survivors demonstrated no increase during six months of moderate to high intensity resistance training [19]. Of note, this study did not include a control group, so uncertainty remains, particularly for those at highest risk of lymphedema.

Diet

The ACS published guidelines for cancer survivors that recommend increased fruit, vegetable, and whole grain consumption and minimal consumption of red and processed meats [20]. Prior epidemiologic studies of diet have identified improved survival after cancer with increased intake of fruits and vegetables [21,22], while a whole-food, plant-based diet has been shown to decrease systemic inflammation in newly diagnosed cancer patients [23]. Still, high levels of non-adherence to healthy diet patterns have been found across all ethnic groups in cancer survivors [24,25]. Recent studies have examined and demonstrated the feasibility of nutritional interventions with a goal of changing health behavior.

A culinary group intervention that focused on simultaneously providing emotional support and culinary education involved 10 weekly 2-hour sessions of structured dietary education, “hands-on” cooking sessions, and group discussion led by both a mental health professional and dietician. The intervention group (n=96) had significant improvement in health-related quality of life and positive affect (using the validated Positive and Negative Affect Schedule 20-item scale) compared to the waitlist control group (n=88) [26]. Incorporating such an intervention in survivorship care could be feasible and effective.

Another novel intervention is Growing Hope, a multifaceted, garden-based intervention in which survivors receive education and are provided access to an urban garden. After four weeks, Growing Hope was feasible, well-accepted, and efficacious in a small cohort of patients as it increased consumption of fruits and vegetables, decreased consumption of added sugars and red/processed meat, and demonstrated positive trends in non-HDL

cholesterol ($p=.050$) and fasting blood glucose ($p=.043$) [27]. Larger studies are warranted for effectiveness and potential for clinical practice.

The effect of diet on cancer-related fatigue in breast cancer survivors was considered in a small trial that investigated the effects of the Fatigue Reduction Diet, high in fruits, vegetables, whole grains, and omega-3 fatty acids. Individualized counseling was incorporated. When compared to an attention control ($n=15$) that received equal counseling time with no dietary education, the intervention group ($n=15$) reported improved fatigue and sleep after 3 months [28]. Though small, this study used an appropriately matched attention control group and supported the feasibility of incorporating this fatigue reduction diet in larger studies.

Dietary Supplements

Most dietary supplements (e.g., essential oils, herbs, minerals and vitamins) are not recommended in national guidelines for cancer survivorship despite being of great interest to patients [29].

Vitamin D has been thought to boost the immune system and reduce inflammation. Lower quality of life has been noted in patients with vitamin D deficiency [30,31]. In an observational study of postoperative esophageal cancer patients, 49 patients who took 200–400 IU daily over one year were compared to 254 non-users. Better quality of life and disease-free survival were detected in the vitamin D group, but there was no significant difference in overall survival identified [32]. Different distributions of confounders between the groups make these data inconclusive but intriguing.

Another study (by interview at diagnosis and then annually for two years) of vitamin D supplementation in patients with stage II colorectal cancer found improved 24-month quality of life (by FACT-C) in vitamin D users ($n=95$) compared to non-users ($n=358$) [33]. However, there was considerable heterogeneity between the two groups in terms of age, gender, education, income and smoking. No significant association was found between vitamin D use and risk of recurrent or all-cause mortality.

Vitamin D supplementation has also been studied in the context of aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) in breast cancer patients. A randomized, blinded trial assessed the efficacy and safety of vitamin D 4000 IU daily ($n=57$) to usual care of 600 IU vitamin D daily ($n=56$) for 6 months. AIMSS was scored using the breast cancer prevention symptom scales-MS subscale. The scores were similar in the two groups (2.3 vs. 2.4) with no significant difference in score change after 6 months (2.0 vs. 1.9) [34]. These small studies of Vitamin D supplementation in cancer survivors should be seen only as hypothesis-generating given the confounding factors and that prior large RCTs have shown harm instead of benefit of single-substance supplementation [35]. The focus of dietary counseling for cancer survivors should be more holistic and encourage survivors to follow a whole-food, plant based diet.

Mind-body Modalities

Survivors are at risk for anxiety and depression due to disease-related stressors (e.g., fear of recurrence, symptom burden, lifestyle alterations, financial strain). Psychological symptoms can occur alongside physical symptoms and affect quality of life [36,37]. The ACTION study, a longitudinal study performed in eight countries of Southeast Asia, found a substantially high prevalence of psychological distress using the Hospital Anxiety and Depression Scale in patients with a poor socioeconomic status [38]. A recent cross-sectional study of hematologic cancer survivors in Australia showed that, compared to the general population, up to a quarter of survivors report above normal levels of anxiety/depression and one fifth report above normal levels of stress based on the validated Depression Anxiety and Stress Scale 21-item version [39]. Mind-body modalities (meditation, yoga, tai chi, hypnosis, relaxation techniques, and music therapy) are often used for the reduction of anxiety, mood disturbance, and chronic pain [3].

Mindfulness-Based Stress Reduction (MBSR) is a commonly employed form of mind-body therapy utilizing group yoga, meditation exercises, and discussions on stress and coping with trained instructors to create greater awareness of the mind and body interaction. This is thought to reduce unconscious thoughts that negatively impact various aspects of health (emotional, spiritual, and physical) [40]. A pilot study has documented frontal lobe regulation of emotional awareness using functional magnetic resonance imaging (fMRI) when comparing the effects of 4 weeks of MBSR training to a control group using stress reduction reading [41].

A large clinical trial found that 12-week MBSR (n=152) improved anxiety, fear of recurrence, and fatigue compared to usual care (n=147) in breast cancer survivors. Differences in depression, pain and quality of life were not statistically significant. This was a large, methodologic RCT that found significant impacts on multiple symptoms for survivors at both 6 and 12 weeks [42].

The MINDSET trial compared 8 weekly sessions of MBSR (gentle yoga, meditation exercises, and discussion on mindfulness) to 12 weekly sessions of Supportive Expressive Group Therapy (SET). Improvements in mood disturbance, stress symptoms, and social support (measured by a validated 19-item survey that measures the availability of companionship, assistance, and other types of support) were seen in the mindfulness group (n=69) compared to the SET group (n=70). Quality of life was not impacted [43].

A smaller RCT compared MBSR to psychoeducational support (PES) in breast (n=60) and colorectal cancer (n=11) survivors to evaluate effects on cancer-related fatigue. MBSR consisted of 8 weekly 2 hour sessions of guided training on mindfulness meditation practices tailored to fatigued survivor needs. PES consisted of 8 weekly group discussions on cancer-related fatigue with tips and strategies. Though results were not statistically significant between groups, SF-36 vitality score changes within both groups were significant from start to end. The MBSR group changed from 30.54 to 52.21 post-intervention, and in the PES group, the score changed from 33.33 to 43.57 post-intervention. Improvements in Fatigue Symptom Inventory scores in fatigue interference and fatigue severity were also observed in

both groups [44]. The presence of improvement in each group supports the value of further research into both MBSR and PES for clinical practice.

Clinical hypnotherapy involves a therapist inducing relaxation in a patient to bring on a suggestive state of consciousness then directing the person's attention to specific thoughts [3]. The effect of hypnosis on hot flashes in breast cancer survivors has been well elucidated in prior studies [45]. This has led to the recommendation in guidelines by The North American Menopause Society (NAMS) to include clinical hypnosis as non-hormonal treatment of menopause-associated vasomotor symptoms [46]. More recent studies have looked at the role of hypnosis for other cancer-related sequelae, specifically when combined with cognitive behavioral therapy (CBT).

A small RCT found an improvement in cancer-related pain, fatigue and sleep disturbances compared to an educational control when patients underwent four sessions of the Valencia model of waking hypnosis, a psychotherapy-type process to promote suggestion, combined with CBT. These gains were noted to be stable at 3 month follow-up [47]. Another small RCT identified reduced anxiety in early stage breast cancer survivors who underwent 15 sessions of a multiple-component structured group intervention that combined support with CBT and hypnosis components compared to a single-component group intervention based on support [48].

Meditative Movement forms of exercise (qigong, tai chi, yoga) are mind-body practices that use body posture and movement, focused breathing, and meditation in order to activate self-healing through endogenous mechanisms from the body/mind integration. These practices usually require low to moderate aerobic exertion, but are often scalable to all levels of physical ability [49]. Prior studies of these techniques suggest a potential benefit of Meditative Movement on cancer-specific quality of life, but the number of studies is limited, significant heterogeneity in methodology is present, and many have been performed in countries where yoga is more readily practiced as part of the culture [50,51].

A recent trial looked at the effect of a 12-week qigong/tai chi easy class (n=42) in breast cancer patients compared to a sham control group (n=45) involving gentle movements but no focus on breathing or mind. Interestingly, improvements were noted in both groups on standardized physical and mental health scales as well as subscales focusing on cognitive function effect on quality of life [52].

In another study, 12 weeks of DVD-guided yoga was compared to strengthening exercises in breast cancer survivors with fatigue. The yoga group (n=18) received a DVD that contained introduction to yoga philosophy with sections on relaxed breathing, warm-up, gentle yoga, seated sun salutation, standing yoga, chair stretches and guided relaxation. The strengthening group (n=16) received a DVD with various exercises and resistance bands. Both were determined feasible and demonstrated improvements in cancer-related fatigue and quality of life [53]. Though the study was small, it provides encouraging preliminary evidence for this approach.

A secondary analysis of the effect of yoga on cancer-related cognitive impairment compared 4 weeks of the Yoga for Cancer Survivors (YOCAS) program (breathing exercises, gentle

Hatha and restorative yoga postures, and meditation) to standard care. The yoga group (n=177) experienced a significant reduction in memory problems compared to the standard care group (n=179), based on scores on the MD Anderson Symptom Inventory [54]. Future trials should be specifically designed to assess the impact of yoga on cognitive function in survivors.

Acupuncture/Acupressure

Acupuncture is a therapeutic technique involving needle, pressure or electrical stimulation and the unique Chinese medicine concept of Qi (or vital energy) to utilize interactions of the peripheral and central nervous system with muscle fascia for physical or mental benefits. There are several forms including simple acupuncture, moxibustion, electroacupuncture, warm acupuncture, and point injection, among others. Acupressure involves pressure applied by fingers or a device to acupoints as opposed to needle or electrical stimulation [3]. Acupuncture has been investigated in the treatment of cancer-related pain that is insufficiently controlled by analgesics, as well as for cancer-related insomnia and breast-cancer related hot flashes [55,56,57].

A recent multicenter RCT looking at hot flashes in breast cancer survivors, the AcCliMaT study, compared 105 patients assigned to acupuncture plus self-care (increased fruit/vegetables, reduced caffeine/alcohol, exercise) versus 85 assigned to self-care alone. It found a significantly lower hot flash score (11.3) in the acupuncture group after 12 weeks of therapy compared to the control group (22.7). At 3- and 6-month follow-ups, statistically significant improvements in hot flash scores persisted (−7.9 and −8.8 respectively). Secondary findings of fewer climacteric symptoms and better quality of life were also statistically significant [58]. This demonstrated effect of acupuncture in a larger more methodical trial generates optimism for its utility for symptom palliation in breast cancer survivors.

Warm acupuncture was studied for breast cancer-related lymphedema in a trial that compared 1 month of warm acupuncture in 15 patients (30 minutes, 6 acupoints, 3 needles topped by 3-cm moxa stick) to a diosmin 900 mg tid control in 15 patients. In addition to improving objective measures of lymphedema at the acupoints, acupuncture appeared to improve quality of life according to the European Organization for Research and Treatment of Cancer's QLQ-30 questionnaire [59]. Continued study of the optimal regimen of warm acupuncture for treating lymphedema is warranted.

Another trial compared the effectiveness of two types of self-administered acupressure to usual care in treating cancer-related fatigue in breast cancer survivors. In the acupressure group that utilized relaxing acupoints, 66.2% of women reached normal fatigue levels at week six compared to 60.9% in the acupressure group that utilized stimulating acupoints, and 31.3% in the usual care group ($p < .001$). Also of note, only the self-administered relaxing acupressure group demonstrated a significant improvement in sleep and quality of life, with a sustained effect seen 4 weeks after therapy [60]. Self-administered relaxing acupressure may be a cost-effective way to reduce fatigue in breast cancer survivors.

Massage

Many cancer survivors have explored massage therapy for relief from physical pain and its functional sequelae (e.g. anxiety, depression, insomnia, and fatigue). When past studies compared massage therapy to an active comparator such as attention, reading group, or caring presence, pooled studies have favored massage therapy for pain, cancer-related fatigue, and anxiety. However, these studies have a high level of heterogeneity, insufficient reporting of data, and inconsistent methodologies (i.e. blinding, allocation concealment), making it challenging to make a strong recommendation for the use of massage therapy in this setting [61, 62].

A recent RCT (n=40) compared Anma therapy, a particular type of Japanese massage, to no therapy in gynecologic cancer survivors. A reduction in subjective severity of physical complaints was observed after one 40 minute massage, and this was sustained with continuous weekly sessions for eight weeks [63]. Future studies should assess the efficacy in survivors of other cancers, and should ideally include a larger sample and longer follow-up.

Conclusion

The study of integrative medicine therapies in cancer survivorship continues to be of great importance. The number of cancer survivors will continue to increase over the next decade, resulting in a substantial demand for interventions to address their physical and psychological needs. There have been many studies published over the last year that have addressed the feasibility, safety, and efficacy of integrative medicine modalities, including some novel techniques. However, a common theme seems to be the small size and heterogeneous methodologies of many of these studies. Larger randomized controlled trials are required to definitively identify which integrative medicine techniques are truly beneficial in the setting of cancer survivorship. Such studies should focus on elucidating the optimal candidates and uses for these therapies so they can be most effectively implemented in clinical practice. It is important to remember when counseling cancer survivors that combinations of health-related interventions (diet, exercise, stress reduction, social support) will lead to the greatest benefit on cancer outcomes, and integrative medicine is invaluable to help promote and support positive, holistic health-related behavior change [64].

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Key points

- Cancer survivors can experience the physical, social, and emotional effects of cancer and its treatments such as fatigue, pain, neuropathy, lymphedema, difficulty sleeping, weight gain, cognitive dysfunction, sexual dysfunction, psychological distress and fear of recurrence.
- Integrative medicine promotes the physical, emotional, and spiritual health of a person by incorporating complementary therapies (physical activity, diet, dietary supplements, mind-body modalities, acupuncture, and massage therapy) with conventional therapy.
- Recent studies have demonstrated effectiveness of various integrative medicine modalities though there were noted limitations in the methodologies and sample sizes.
- The association of physical activity with improved quality of life was shown in a number of recent studies.
- Due to anticipated demand for symptomatic interventions, more robust randomized controlled trials are required to definitively identify which integrative medicine techniques are beneficial in the cancer survivorship setting.

The 5 Domains of Complementary and Alternative Medicine

Figure 1.
The 5 Domains of Complementary and Alternative Medicine. Put together from NCCIH.