Yoga for Cancer-Related Fatigue in Survivors of Hematopoietic Stem Cell Transplantation: A Mixed-Methods Feasibility Study

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Nursing)
in The University of Michigan
2019

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ACKNOWLEDGMENTS

I would like to express the deepest appreciation and gratitude to my committee chair, Professor Debra L. Barton. Without her guidance and support this dissertation would not have been possible. I would like to give special thanks to the members of my dissertation committee: Dr. Lauren P. Wallner, Dr. Mark Peterson, Dr. Cynthia Arslanian-Engoren, Dr. Moira A. Visovatti, and Dr. Sung Won Choi for their valuable guidance. They definitely provided me with the tools that I needed to successfully complete my dissertation.

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ABSTRACT

Despite its potential benefits in cancer survivorship, yoga has not been tested in cancer survivors treated with hematopoietic stem cell transplantation (HSCT). The aim of this mixed-methods study is to evaluate the feasibility of a yoga intervention offered to adult HSCT survivors with cancer-related fatigue (CRF). The secondary goals are 1) to evaluate the association of baseline CRF severity with depression, sleep disturbances, and pain; 2) to evaluate the changes in CRF, depression, sleep disturbances, pain, and physical activity from baseline to postintervention; 3) to evaluate the association of CRF change with changes in depression, sleep disturbances, and pain, and physical activity; 4) to evaluate the association of yoga adherence with self-efficacy and self-regulation skills and abilities; and 5) to explore participants' perceptions of yoga and physical activity. Twenty adult HSCT survivors were enrolled in a 6-week restorative yoga intervention, and eight of them participated in focus groups upon intervention completion.

The accrual acceptance rate was 23.2% (20/86 HSCT survivors). Twelve of the 20 participants who enrolled completed the study. Overall adherence was 45.4%. No adverse reactions attributable to yoga were reported. Of the five CRF dimensions (i.e., total CRF, physical CRF, general CRF, mental CRF, emotional CRF) evaluated at baseline, total CRF and emotional CRF correlated significantly with sleep disturbances ($r=0.52$, $P=0.02$; $r=0.57$, $P=0.01$, respectively). Baseline emotional CRF also correlated significantly with depression ($r=0.68$, $P=0.02$). Participants reported postintervention improvements in general CRF ($d=-0.75$), physical CRF ($d=-0.66$), vigor ($d=0.63$) and sleep disturbances ($d=-0.81$) (all $Ps<0.05$). Improvements in

two or more of the CRF dimensions correlated significantly with reductions in depression, sleep disturbances, and pain; correlations ranged from 0.58 to 0.86. Improvements in three CRF dimensions (general CRF, mental CRF, emotional CRF) also correlated significantly with increases in self-reported physical activity; correlations ranged from -0.58 to -0.60. Correlations between overall adherence and self-efficacy and self-regulation skills and abilities were not significant, ranging from -0.29 to 0.41. Focus group participants described a range of benefits from yoga practice, most notably stress reduction. Barriers and hurdles to practicing yoga included general time constraints, long travel distance to the intervention site, distractions during home practice, and difficult yoga poses. The most important aspects of the yoga classes from the participants' perspective were individualized instruction style and camaraderie. Participants reported three motives for physical activity engagement: maintaining and improving general wellbeing, regaining general health, and having company to exercise with. Fear of falling and/or injury was perceived by participants as the major reason for physical activity avoidance. Yoga and walking were the most commonly preferred types of physical activity by participants.

The results of this study indicate that a yoga trial in adult HSCT survivors is feasible from a safety standpoint and needs to employ strategies to improve accrual acceptance, retention, and protocol adherence rates. The reported reductions in CRF and sleep disturbances are promising and provide the foundation for hypotheses to be tested in subsequent studies. The association of CRF with depression, sleep disturbances, pain, and physical activity indicates that CRF is a multifactorial symptom partly related to concurrent symptoms and physical activity levels. The relationship between yoga adherence and self-efficacy and self-regulation skills and

abilities needs to be reevaluated with larger samples. The emergent themes from the qualitative data can be used to optimize yoga and other physical activity interventions in HSCT survivors.

CHAPTER I

INTRODUCTION

Statement of the Problem

Hematopoietic stem cell Transplantation (HSCT) is a treatment modality for several hematologic malignancies, such as leukemia, lymphoma, and multiple myeloma [1]. Approximately 20,000 people undergo HSCT in the US each year [2]. HSCT patients usually receive a high dose of chemotherapy that is also known as a preparative or conditioning regimen. This regimen eradicates a patient's bone marrow and thus it is followed by HSCT, either from the patient (autologous) or from a donor (allogeneic) [3]. During the first 100 days after transplant, patients are at high risk for life-threatening complications and non-relapse mortality [4,5]; therefore, day 100 is a milestone indicating that a patient is on the path to survivorship. Advances in HSCT technology and supportive care techniques have led to improvements in long-term survival [6]. Yet, the health-related quality of life (HRQOL) among HSCT survivors is usually compromised due to the burden of treatment side-effects and chronic symptoms, most notably cancer-related fatigue (CRF) [7,8].

The National Comprehensive Cancer Network (NCCN) defines CRF as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [9]. The physiological mechanism of CRF is not fully understood. It is hypothesized that in response to cancer and its treatments, inflammatory cytokines signal the central nervous system and generate CRF by altering neural processes [10]. Other potential mechanisms are under study

and include alterations in the hypothalamic-pituitary-adrenal axis, autonomic nervous system dysregulation, alterations in the cellular immune system, and latent viral reactivation [11]. All these potential mechanisms can make CRF a long-term problem among HSCT survivors with negative consequences on HRQOL [7,8,12]. Numerous studies have shown that CRF interferes with physical functioning and the ability to perform activities of daily living [13-15]. CRF can also be associated with other symptoms including depression, pain, and sleep disturbances [16,17].

Cancer-related fatigue is highly prevalent during the first 100 days after HSCT. In a study that evaluated CRF in 76 adult allogeneic HSCT recipients, 68 % reported CRF on the day of transplant, 90 % at day 30, and 81 % at day 100 post-transplant [12]. Studies in HSCT survivors have shown that some level of CRF may persist for years after the initial 100 days. In a study that evaluated the HRQOL in 406 adult HSCT survivors, investigators found that 56% of the participants continued to suffer from CRF for one to three years after transplant [8]. In another study measuring the prevalence of CRF in 98 adult HSCT survivors, investigators found that 35% of the participants had severe CRF persisted, without improvement for up to 15 years after transplant [7]. Recent evidence also indicates that graft versus host disease (GVHD), a potential complication after allogeneic HSCT, may worsen CRF in adult HSCT survivors, likely also due to a high inflammatory state [18]. In a survey of 263 adult HSCT survivors with moderate to severe GVHD, 84% reported any degree of CRF and 40% reported CRF that was described as quite or extremely bothersome [18]. As such, CRF is a persistent problem among adult HSCT survivors with negative consequences on HRQOL.

Yoga, an ancient therapy that combines stress-reduction techniques and physical postures, is a complementary therapy that has been proposed to improve CRF in different

populations [19,20]. Research in chronic disease populations has often emphasized the importance of self-care to improve patients' adherence to symptom management behavior [21]. As such, adherence to yoga practice in HSCT survivors may be impacted by factors related to self-care. Various definitions of self-care exist in the literature, yet it is most often conceptualized as actions to achieve and maintain maximum health [22,23]. Although the terms self-care and self-management are often used interchangeably, self-management is thought to be broader in that it addresses the management of treatments, lifestyle changes, and physical, psychosocial, and spiritual consequences of diseases [21]. The broad definition of self-management incorporating lifestyle changes and disease consequences might explain why actions to control one's symptoms are frequently subsumed in the chronic disease literature under self-care behaviors [24,25]. Given the prevalent and persistent nature of CRF, self-care of CRF (e.g., practicing regular yoga) in HSCT survivors may also involve a management approach in which survivors do not only take actions to ameliorate their CRF, but are also involved in other actions including CRF monitoring and treatment evaluation. Therefore, these actions may be better described as CRF self-care management behaviors.

Treatments for Cancer-Related Fatigue

Physical exercise has the strongest evidence for reducing CRF and is recommended by multiple clinical practice guidelines [9,26]. Furthermore, studies in adult HSCT survivors suggest promise for physical exercise as an effective treatment for CRF [27,28]; yet, integrating exercise into HSCT patients' daily lives remains very challenging. Exercise is rarely prescribed or encouraged by healthcare providers in hospitals and clinics, which might be due to the delicateness of HSCT survivors where they remain in a fragile state of physical health for several years after transplant with a high prevalence of short- and long-term complications such as

GVHD and opportunistic infections [29,30]. Additionally, there are data showing premature aging and physical frailty among HSCT survivors. In a study including 998 adult HSCT survivors (18-64 years), the prevalence of physical frailty was 8.4%, approaching that seen in the elderly population (≥ 65 years) (10%) [31]. HSCT survivors may also consider physical exercise to be risky and associated with physical injury, especially since they can experience chronic thrombocytopenia long into the survivorship period [32,33]. All of these factors contribute to a lack of integration of physical exercise into standard care for adult HSCT survivors and would suggest the need for other strategies that are perceived as easier to implement.

Alternatives to manage CRF beyond physical exercise are limited. Among these alternatives, some complementary therapies such as yoga and qigong have shown promising results for CRF [34,35]. The National Institutes of Health (NIH) defines complementary therapies as "interventions that use a variety of techniques designed to facilitate the mind's capacity to affect bodily function and symptoms" [36]. Complementary therapies include a diverse and large group of techniques administered or taught by a trained practitioner such as mindfulness, progressive muscle relaxation, and hypnosis [37].

Tai Chi and qigong are two complementary therapies evaluated for CRF with encouraging results [38,39]; yet, these therapies are strenuous and might be perceived by HSCT survivors to be associated with the same barriers as physical exercise. Other complementary therapies tested for CRF with some evidence include mindfulness-based stress reduction, psychoeducational interventions, and cognitive behavioral therapy [40-44]. However, these therapies have been tested in methodologically limited studies (e.g., low statistical power, lack of an active control group) and according to the Oncology Nursing Society, their effectiveness for CRF has not been fully established [26]. Other complementary therapies including music

therapy, massage therapy, and relaxation techniques have been evaluated for CRF in HSCT survivors with mixed results [45]. None of these therapies has been tested in rigorously designed phase II or III clinical trials [45]. In addition, most of these complementary therapies are provider-based, which may limit their use due to provider availability and thereby limit their effectiveness. As CRF might persist up to 15 years after HSCT [7], it would be helpful to establish a treatment for CRF that is patient-based and can be self-administered, which would encourage long-term use and potentially lead to a better control of CRF on the long-term.

As previously noted, yoga has been proposed to improve CRF in different populations. In women with breast cancer, two systematic reviews provide preliminary evidence that yoga may be beneficial for ameliorating CRF [19,20]. A study in prostate cancer survivors suggests promise for yoga as an effective treatment for CRF [46]. Furthermore, studies in breast cancer and heart failure patients suggest that yoga can reduce plasma levels of inflammatory markers [47-49], while other studies show an association between CRF and elevated inflammatory markers [10,50]. Therefore, it is possible that yoga interferes with the biological mechanism of CRF by reducing inflammatory activity. Moreover, a study by Komatsu, Yagasaki, Yamauchi, Yamauchi, and Takebayashi [51] evaluated the feasibility of a self-directed home yoga program in women with breast cancer and found self-directed yoga to be a safe and acceptable intervention. This implies that yoga may be safely practiced at home or in any other setting which might facilitate feasibility and practice sustainability. In addition, yoga incorporates both non-strenuous physical activity and cognitive-meditative strategies, and therefore, yoga may be appealing to adult HSCT survivors. In summary, yoga has the potential of being an efficacious, safe, and acceptable intervention for adult HSCT survivors with CRF, meaning that it can address most of the hypothesized barriers to implementing previous interventions tested for CRF.

Based on evidence supporting the use of yoga for CRF in breast cancer survivors [19,20], yoga is one option worthy of evaluation for ameliorating CRF in adult HSCT survivors. Therefore, the goal of the current single-arm, pretest–posttest study is to evaluate the feasibility of a yoga intervention offered to adult HSCT survivors with moderate to severe CRF, which will provide the pilot data needed to design and conduct a larger, adequately powered study to more fully evaluate yoga for CRF in this population. Feasibility is assessed based on four parameters: accrual acceptance, retention, protocol adherence and adverse event (e.g., fall, physical injury) rates.

In addition to evaluating feasibility, this study has five secondary aims. The first secondary aim is to evaluate the association of CRF severity at baseline with depression, sleep disturbances, and pain. Evaluating this association may contribute to an understanding of the relationships between CRF and co-occurring symptoms in adult HSCT survivors, which would be useful information needed to optimize interventions targeting CRF in this understudied population. The second secondary aim is to evaluate the potential benefits of yoga for adult HSCT survivors, which is an important first step needed to identify health problems for which yoga interventions in this population could be targeted. In addition to CRF, studies in breast cancer survivors show promising results for yoga in improving depression, sleep disturbances, pain, and physical activity [52-54]. As such, this study evaluates the changes in five outcomes (i.e., CRF, depression, sleep disturbances, pain, physical activity) from baseline to postintervention. The third secondary aim is to evaluate the association of CRF change with changes in depression, sleep disturbances, pain, and physical activity. Research on symptom co-occurrence in HSCT survivors is limited, with the majority of studies linking CRF to other cancer-related symptoms being cross-sectional [55, 56]. By testing yoga for CRF and

longitudinally evaluating CRF association with depression, sleep disturbances, and pain, the current study may provide preliminary data for future research aiming to understand the relationships between those symptoms and how interventions targeting individual symptoms can affect their complex patterns of covariation. Similarly, data demonstrating a relationship between CRF and physical activity may draw attention to CRF management as a potential approach to increase physical activity after HSCT, potentially improving HRQOL.

As previously described, research in chronic disease populations has often emphasized the importance of self-care to improve patients' adherence to symptom management behavior [21]. Self-efficacy and self-regulation skills and abilities are two variables that have been found in contemporary literature to be the most commonly associated with self-care management behaviors [57-60]. The fourth secondary aim of this study is therefore to evaluate the association between adherence to yoga practice and self-efficacy and self-regulation skills and abilities. Testing this hypothesis is extremely important to understand what might make HSCT survivors adhere to yoga practice as a symptom self-care management strategy.

Furthermore, it is worth noting that yoga participation, like any other human behavior, is a complex phenomenon that can be shaped by the physical, social, and psychological aspects of one's life, often requiring a qualitative inquiry for deeper understanding of participants' perceptions. Therefore, a qualitative inquiry may be a valuable tool for exploring HSCT survivors' perceptions of yoga in great detail, which may generate knowledge needed to inform future research in this area. It is also important to recognize that yoga incorporates a physical activity component. HSCT survivors' adherence to yoga may thus be impacted not only by their perceptions of yoga but also by their fears and motivations related to physical activity. Therefore,

the fifth secondary aim of this study is to explore adult HSCT survivors' perceptions of yoga and physical activity.

Given the absence of data regarding the safety of yoga in adult HSCT survivors, using a relatively short-term, non-intensive yoga intervention was indicated. Based on prior research showing that a yoga program at a dose of three times weekly for six weeks might be beneficial for CRF [61], participants in this study were enrolled in a six-week restorative yoga intervention. The program consisted of a weekly, 60-minute restorative yoga group class led by a certified yoga instructor along with twice-weekly home practice using a DVD. Restorative yoga was the selected type of yoga because it is well known to be less physically demanding than other yoga types [61]. Restorative yoga emphasizes supported poses and deep relaxation, and it has been safely tested in other cancer populations such as breast cancer and ovarian cancer [47,63-66].

Specific Aims

The primary aim of this study is:

- Aim 1: To evaluate the feasibility of a yoga intervention for adult HSCT survivors with CRF.

  Hypothesis: A randomized trial of yoga in adult HSCT survivors will be feasible as demonstrated by an accrual acceptance rate of at least 40%, protocol adherence rate of at least 75%, retention rate of at least 75%, and absence of yoga-related adverse events.

In addition to the aforementioned primary aim, the current study addresses the following five secondary aims:

- Aim 2: To evaluate the association of CRF severity at baseline with depression, sleep disturbances, and pain.

Hypothesis: CRF severity at baseline will be positively associated with depression, sleep disturbances, and pain.

- Aim 3: To evaluate the potential benefits of yoga for adult HSCT survivors.

  Hypothesis: CRF, depression, sleep disturbances, pain, and physical activity will significantly improve from baseline to postintervention.

- Aim 4: To evaluate the association of CRF change with changes in depression, sleep disturbances, pain, and physical activity.

  Hypothesis: Decreases in CRF from baseline to postintervention will be associated with increased physical activity and decreased depression, sleep disturbances, and pain.

- Aim 5: To evaluate the association of adherence to yoga practice with self-efficacy and self-regulation skills and abilities.

  Hypothesis: Adherence to yoga practice will be positively associated with self-efficacy and self-regulation skills and abilities.

- Aim 6: To explore adult HSCT survivors' perceptions regarding yoga and physical activity.

Literature Review

Physical exercise has the strongest evidence for reducing CRF and is recommended by multiple clinical practice guidelines [9,26]; yet, integrating exercise into adult HSCT survivors' daily lives remains very challenging. Alternatives to manage CRF beyond physical exercise are limited. However, among these alternatives, some complementary therapies (e.g., yoga, tai chi) have shown promising results for CRF [34,35,67]. Complementary therapies include a diverse and large group of techniques such as mindfulness, progressive muscle relaxation, and hypnosis [37]. Complementary therapies incorporate both non-strenuous physical activity and cognitive–

meditative strategies, and therefore, they may be appealing to HSCT survivors. Furthermore, there are preliminary data showing that some complementary therapies, such as yoga, may target one hypothesized biological mechanism of CRF, reducing inflammatory cytokines [47]. Considering the significance of CRF as a distressing problem that limits physical activity and compromises HRQOL, this integrative review aimed to provide an overview of the state of the science regarding the role of complementary therapies in reducing CRF after HSCT.

Methods

The following keywords were combined using the appropriate Boolean operators: hematopoietic stem cell transplantation, complementary therapy, and cancer-related fatigue. Furthermore, all types of complementary therapies were included in the search terms (e.g.; yoga, music therapy, hypnosis), in addition to all possible synonyms of CRF (e.g.; lack of energy, tired), hematopoietic stem cell transplantation (e.g.; bone marrow transplantation), and complementary therapies (e.g.; integrative therapies). The following databases were searched: PubMed, CINAHL, PsycINFO, Cochrane, Scopus, and Web of Science. Due to the expected low volume of literature, the search dates were not limited and all available articles were retrieved.

This integrative review was initially conducted in February 2017 and included eight articles. Periodic searches were then conducted to review current literature. The last literature search was completed in September 2018 during which a recent article by Bates et al. [68] qualified for inclusion and was added to the results. The inclusion criteria were studies published in English language and that evaluated complementary therapies in adult patients (≥ 18 years) who underwent autologous or allogeneic HSCT. Studies performed in pediatric populations were excluded. Complementary therapies involve a cognitive approach, and therefore, pediatric patients may not have the cognitive skills required to participate in these therapies. The study

design had to be randomized controlled trials (RCTs), quasi-experimental, or a single arm pretest-posttest design. Studies that included CRF as a primary or secondary outcome were included. Case studies and dissertations were excluded. Study abstracts including poster presentations and conference meetings with no available full-texts were also excluded. The quality of evidence was appraised using the Joanna Brigg Institute's Critical Appraisal Checklist [69].

Results

The search yielded 1360 articles. After the removal of duplicates, 1105 articles remained. These articles were then evaluated for meeting the inclusion criteria through reviewing titles, abstracts, and full texts. In the end, nine articles qualified for inclusion in this review. A flow diagram showing the search strategy and the number of articles retrieved, included, and excluded is presented in Figure I.1.

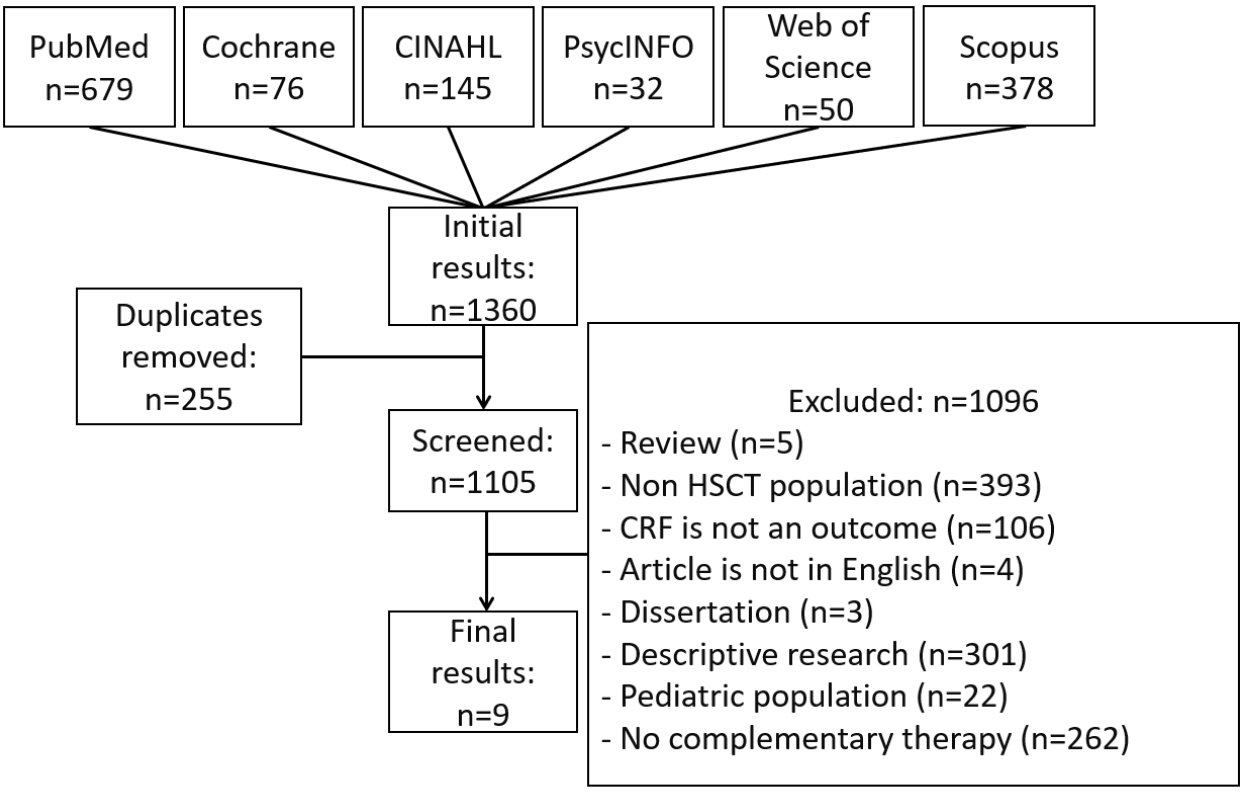

Figure I.1: Literature Review Flow Chart

The nine eligible studies evaluated the following complementary therapies among patients either hospitalized for HSCT or during survivorship: music therapy (n=5), relaxation therapy (n=2), mindfulness (n=1), and massage therapy (n=1). These studies are described according to the type of complementary therapy tested. Moreover, Appendix A (Table A.1) provides summary of the study design, measures, sample size, participants' characteristics, results, and effect sizes (ES). Appendix B (Table B.1) presents an appraisal of the included studies using the Joanna Brigg Institute's Critical Appraisal Checklist. Appendix C (Table C.1) provides information on the treatment dose and components.

Music Therapy and Cancer-Related Fatigue

A study by Cassileth, Vickers, and Magill [70] aimed to improve mood disturbances in 69 patients (age average: 52 years; females: n=37; males: n=32) hospitalized for autologous HSCT and randomized to either music therapy or usual care. Participants in the music therapy group received approximately five music sessions (20–30 min/session) starting on the day of transplant. CRF was measured using the Profile of Mood States (POMS)-fatigue subscale, administered immediately before and after each music session. The POMS scale contains five subscales: confusion, anxiety, anger, depression and CRF. Each subscale contains five items and has a possible range of 0-20 with high scores reflecting high levels of the variable [70]. The difference between groups at post-intervention was significantly in favor of the music therapy group (ES= 1.8). Furthermore, Rosenow and Silverman [71] conducted two independent studies to examine the benefits of a single, 30–45 min music session for patients hospitalized for HSCT. In the first study, Rosenow and Silverman [71] employed a single-group, pretest–posttest design and included a total of 50 HSCT recipients (age range: 22-75 years; females: n=15; males: n=35). CRF was measured using a 10-point Likert scale (0: no fatigue, 10: worst possible

fatigue), administered immediately before and after the music session, and 30–45 min after the session concluded (follow-up). Results showed significant reductions in CRF at post-intervention and follow-up, compared to baseline (ES = 0.31). The second study by Rosenow and Silverman [71] included 18 patients (age range: 31-64 years; females: n=7; males: n=11) randomized to either a single music session or waitlist control group. CRF was measured immediately before and after the session using the Brief Fatigue Inventory. The Brief Fatigue Inventory contains nine items and has demonstrated good psychometric properties (Cronbach alpha: 0.82 to 0.97) [71]. Participants in the music therapy group had a slight improvement in CRF levels after the session, whereas CRF scores slightly increased for controls. Differences within and between groups were not significant (ES = 0.11).

Another RCT by Fredenburg and Silverman [72] tested the effect of cognitive–behavioral music therapy on CRF in 11 patients (age average: 49.6 years; females: n=3; males: n=8) hospitalized for HSCT. Patients were randomly assigned to receive either a 30–45 min music session each weekday throughout hospitalization, or standard care in the HSCT unit. CRF was measured upon admission and prior to hospital discharge using the Multi-Dimensional Fatigue Inventory that includes five subscales: general CRF, physical CRF, mental CRF, emotional CRF, and vigor. The Multi-Dimensional Fatigue Inventory has demonstrated high internal consistency (Cronbach alpha: 0.7 to 0.86) [72]. In all subscales with the exception of mental CRF, the music therapy group had mean decreases from baseline to post-intervention, whereas CRF increased for controls across all subscales. Differences between groups for all the subscales missed statistical significance with effect sizes for individual subscales ranging from 0.17 to 1.02. Another study by Bates et al. [68] tested the effect of music therapy on CRF in 82 patients (age average= 58 years; female: n=37; male: n=45) hospitalized for autologous HSCT. Patients were randomly

assigned to receive either music therapy, consisting of two music therapy sessions (30 minutes/session) on the first and fifth day after HSCT, or usual care. CRF was measured at baseline and right after the second session using the POMS-fatigue subscale. Mean CRF scores increased in both groups with a greater increase in the music therapy group. Differences within and between groups were not significant (ES = 0.08).

In summary, five studies evaluated music therapy for CRF in HSCT recipients. All of them included inpatients hospitalized for transplant, two studies included only autologous HSCT recipients [68,70] and three did not report the transplant type [71,72]. The length or dose of the intervention across the four studies varied from a single music session to the more intense being a music session each weekday throughout hospitalization. The interventions were delivered in-person by a trained therapist or study investigator. Components of music therapy interventions were similar across studies in which they all used live, individualized, patient-preferred music. Guitar was used in four studies [68,71,72], and one study combined music therapy with a cognitive–behavioral approach [72]. Effect sizes were small to large (0.11–1.8) and studies that used a single music session reported smaller effect sizes than those using daily sessions. Two of the five studies reported positive results [70,71], yet none of them compared the intervention to an active control condition, thereby reducing confidence in the results. Two of the three negative trials [71,72] were grossly underpowered which likely contributed to the non-significant results. Given the very weak design of the five studies discussed, definitive conclusions about the efficacy of music therapy in reducing CRF cannot be made.

Relaxation Therapy and Cancer-Related Fatigue

Relaxation therapy is another intervention tested for CRF in HSCT recipients with mixed results. Kim and Kim [73] tested the effect of relaxation on CRF in 35 patients (age range: 20-48

years; females: n=18; males: n=17) hospitalized for allogeneic HSCT and randomized to either a relaxation program, consisting of a daily, 30-min relaxation breathing exercise for six weeks, or usual care. CRF was measured at baseline and post-intervention using the Piper Fatigue Scale that includes four subscales: behavioral/severity, affective meaning, sensory, and cognitive/mood. The Piper Fatigue Scale had demonstrated good psychometric properties (Cronbach alpha: 0.97) [73]. The music therapy group had mean decreases in all subscales from baseline to post-intervention, whereas mean CRF scores in the control group increased across all subscales. Differences between groups for all subscales were significant with effect sizes for individual subscales ranging from 1.85 to 2.26.

A pilot study by Lu et al. [74] examined the benefits of a relaxation program in 26 patients (age average: 56.6 years; females: n=13; males: n=13) hospitalized for autologous or allogeneic HSCT, stratified by the transplant type and randomized to either relaxation therapy or healing touch. Participants in the relaxation group received a daily, 20-min session of relaxation therapy for three consecutive weeks. CRF was measured at baseline and post-intervention using the POMS-fatigue subscale. The POMS has demonstrated good psychometric properties (Cronbach alpha: 0.78 to 0.91) [74]. Mean CRF scores decreased in both groups with a greater decrease in the healing touch group. Differences within and between groups were not significant (ES = 0.007).

To summarize, two studies evaluated relaxation therapy for CRF in HSCT recipients. Both studies included inpatients hospitalized for transplant, one study included only allogeneic HSCT recipients [73] and one included both autologous and allogeneic HSCT [74]. The intervention delivery and dose were different with one study using a daily session of relaxation therapy guided by a recorded cassette tape for 6 weeks [73] and the other one using a daily

relaxation session delivered by a trained graduate clinical psychology student for 3 weeks [74]. Components of relaxation therapy interventions were also different. The intervention in one study included instructions to perform relaxation breathing exercises in a supine position [73] whereas in the other study it included breathing exercises, progressive muscle relaxation, and guided imagery [74]. Both studies were underpowered and the one with positive results [73] lacked an active control group and blinding techniques, reducing confidence in the results. Given the methodological limitations of these two studies, it is difficult to draw conclusions regarding the efficacy of relaxation therapy in reducing CRF.

Mindfulness-Based Intervention and Cancer-Related Fatigue

Grossman et al. [75] evaluated the preliminary efficacy of a mindfulness-based program in improving HRQOL among HSCT survivors who were at least 6 months' post-transplant and in complete remission. The study included 62 participants (age average: 52.1 years; females: n=31; males: n=31), 32 underwent random assignment and 30 received their treatment preference. The mindfulness-based program covered stress reduction techniques and consisted of eight weekly, 2.5-h classes led by certified, experienced teachers and one all-day retreat at week six. Patients in the control group received a twice a month, 30-min psychosocial consultation by telephone. CRF was measured at baseline, post-intervention, and 3 months follow-up using the Functional Assessment of Cancer Therapy-fatigue scale. CRF was not significantly lower in the mindfulness group from baseline to post-intervention (ES = 0.01) and follow-up (ES = 0.02), compared to controls. Given the methodological flaws of this study with nearly half of the participants selecting their treatment, no conclusions regarding the benefits of mindfulness-based therapy for HSCT survivors can be made.

Massage Therapy and Cancer-Related Fatigue

Massage is another complementary therapy tested for CRF in HSCT recipients. Ahles et al. [76] examined the effect of massage therapy on symptoms of physical and psychological distress in 34 patients (age average: 41.9 years; females: n=26; males: n=8) hospitalized for autologous HSCT. Participants were randomly assigned to receive either a massage therapy, consisting of 20-min sessions of shoulder, neck, head, and facial massage, or standard care in the HSCT unit. The massage was Swedish/Esalen and delivered by a trained healing-arts specialist. Participants in the massage group received approximately three massage sessions per week during hospitalization. The immediate effects of massage were measured via a 10-point numerical scale (0: no fatigue, 10: extreme fatigue), collected prior to and 20 min following the massage sessions on day -7 (seven days before the HSCT procedure), during mid-treatment (one day before the HSCT procedure until the seventh day after procedure), and prior to hospital discharge. Both groups reported a decrease in CRF at the three assessment points with the massage group showing significantly greater reductions on day -7 ($\bar{X}$ difference: −1.94 vs. −0.47) and prior to hospital discharge ($\bar{X}$ difference: −1.71 vs. −0.33). This study lacked an active control group and blinding techniques and despite its encouraging results, it does not provide definitive evidence for massage as a treatment for CRF in HSCT recipients.

Reflection on related literature

As part of this integrative review of the literature, nine studies were identified. Three out of the nine studies included CRF as a primary outcome [71-73]. This low volume of literature indicates that the examination of complementary therapies among HSCT patients is understudied especially when looking at the wealth of literature on complementary therapies for ameliorating CRF in other cancer populations. Among all types of complementary therapies, music therapy is the most tested for CRF after HSCT, but with mixed results [68,71,72]. Other complementary

therapies tested for CRF in HSCT recipients with inconclusive evidence are relaxation therapy, mindfulness-based intervention, and massage [73-76].

The reviewed studies had major methodological limitations. One limitation is the small sample sizes and resulting low statistical power which may, in part, explain the failure to show benefit in some of the studies. Moreover, despite the positive results of four of the reviewed studies [70,71,73,76], all included 'usual care' control groups or no control at all, leaving it unclear to what extent the observed effects are based on the effects of complementary therapies rather than psychosocial factors, such as personal attention or group effects. Additionally, despite all the participants in the nine reviewed studies reporting some degree of CRF at baseline, none of the studies recruited participants based on their CRF level. A number of validated CRF measures were used with two studies using a 10-point Likert scale [71,76], which might be less rigorous than other CRF measures. Furthermore, while two of the studies blinded data collectors or investigators [70,75], none had blinded participants to the treatment allocation which might have introduced several biases. As such, there is a need for adequately powered trials with active control groups and blinding techniques to examine the effects of complementary therapies on CRF in HSCT recipients. Future trials should also use validated measures and examine immediate effects as well as longer term outcomes to ensure sustainable, clinically meaningful benefits. It is also important to recruit patients with at least moderate CRF. This will enhance statistical power by avoiding floor effect due to participants having low CRF scores at baseline.

Furthermore, this review provides support that one complementary therapy tested for CRF in other cancer populations with promising preliminary results, namely, yoga [19,20], has not been tested in an HSCT population. Furthermore, of the nine studies reviewed, only one study [75] included HSCT survivors while the remaining eight studies included patients

hospitalized for HSCT. This implies that prior research has focused on patients within the first 100 days after HSCT in which CRF is highly prevalent and can occur in up to 90% of the patients [12]. Yet, studies in HSCT have shown that CRF may persist for long after day 100 [7,8] and thus studies are needed to evaluate complementary therapies not only during the initial 100 days after transplant, but also during the extended survivorship period. Therefore, a program of research starting with a feasibility study and testing yoga for CRF in adult HSCT survivors might be an ideal next step to move the state of the science forward.

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CHAPTER II

THEORETICAL FRAMEWORK

The current study is guided by a newly synthesized middle-range theory, namely, the theory of symptom self-care management in cancer. A description of this newly synthesized theory is provided in the manuscript below.

A Cancer Specific Middle-Range Theory of Symptom Self-Care Management: A Theory Synthesis

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Abstract

Aim: This article describes the development of a middle-range theory of symptom self-care management for adults with cancer.

Background: Current evidence indicates that patients with cancer may benefit from engagement in self-care management behaviors, one of which is symptom management. A middle-range theory that explains and guides symptom self-care management in patients with cancer is lacking.

Design: This paper combines and expands prior work related to symptom management and self-care management to introduce a newly synthesized theory of symptom self-care management for adult patients with cancer. Walker and Avant's methodological approach was used to guide this theory synthesis.

Data sources: PubMed, CINAHL, and Cochrane Library databases of peer reviewed journal articles published before March 15, 2018

Implications for Nursing: The newly synthesized theory conceptualizes cancer as a chronic illness with related symptoms that persist beyond the acute phase of treatment. This theory sheds light on self-care management as an essential approach to managing cancer-related symptoms and underscores the importance of empowering and enabling patients with cancer to manage their symptoms in partnership with healthcare providers.

Conclusion: The new theory offers a comprehensive conceptualization of symptom self-care management behaviors in adults with cancer. It clarifies potential determinants and effects of cancer-related symptoms and puts forth factors that may influence patient adherence to symptom self-care management behaviors. This new theory may influence the development of symptom management interventions across the phases of the cancer self-care continuum. Research to test the new theory is warranted.

Keywords: Cancer; Nursing theory; Self-care; Symptom management

Summary Statement

Why is this research or review needed?

- Several studies documented benefits of self-care management for cancer-related symptoms. A theory that explains and guides symptom self-care management behaviors in patients with cancer does not currently exist, creating gaps in the understanding of this phenomenon.
- A new theory that encompasses key elements of symptom management and self-care management may provide a more comprehensive framework to guide the design of symptom management intervention studies for patients with cancer.

What are the key findings?

- The Theory of Symptom Self-Care Management in Cancer was synthesized through the examination of empirical evidence. Concepts within the newly synthesized theory were defined and potential relationships between concepts outlined.
- The new theory highlights the causes, dimensions, and outcomes of the symptom experience in patients with cancer.
- The new theory postulates that symptom self-care management behaviors can produce significant benefits for patients with cancer and these benefits are moderated by self-efficacy beliefs as well as self-regulation skills and abilities.

How should the findings be used to influence practice and research?

- This theory synthesis highlights the importance of involving patients with cancer in their own healthcare, with a particular focus on symptom management, providing new insights into this field of study and practice.

- The new theory informs future strategies targeted toward fostering adherence to symptom self-care management behaviors in cancer populations.
- A theoretical framework is provided in order to guide study design and intervention development for future research of cancer-related symptoms.

Introduction

Improvements in healthcare have led to increased survival in patients whose cancer has been managed as a chronic illness [1]. The five-year survival rate for the most common cancer types combined in the US increased from 50% in 1975 to 66% in 2012 [2]. Additionally, the number of people living beyond an initial cancer diagnosis in the US reached nearly 14.5 million in 2014 and is expected to increase to almost 19 million by 2024 [2]. Meanwhile, the last two decades have witnessed increased recognition of self-care as an integral aspect of living with a chronic illness, with a shift from the traditional provider-based symptom management approach to a new paradigm in which people with chronic illness are in partnership with their providers to manage symptoms [3]. This may have contributed to the development of self-care theories specific to common chronic illnesses, such as the theory of heart failure self-care [4] and the theory of diabetes self-care management [5]. These theories have been used to guide symptom management in their corresponding populations [6, 7]. However, in patients with cancer, self-care theory has not been developed in reference to symptom management.

Various definitions of self-care exist in the literature, yet it is most often conceptualized as actions to achieve and maintain maximum health [8, 9]. Although the terms self-care and self-management are often used interchangeably, self-management is thought to be broader in that it addresses the management of treatments, lifestyle changes, and physical, psychosocial, and spiritual consequences of diseases [10]. The broad definition of self-management incorporating lifestyle changes and disease consequences might explain why actions to control one's symptoms are frequently subsumed in the chronic disease literature under self-care behaviors [11, 12].

Given the prevalent and often persistent nature of cancer-related symptoms, symptom self-care in patients with cancer may also involve a management approach in which patients do not only take actions to ameliorate their symptoms, but are also involved in other actions including symptom monitoring and treatment evaluation. Therefore, these actions may be better described as symptom self-care management behaviors.

There is a growing body of research within oncology that evaluates self-care management interventions targeting symptoms (e.g., pain, fatigue) with promising results [13-15]. However, much of the research in this area is not grounded in self-care theory, but rather symptom management theory. For example, Yang, Tsai, Huang, and Lin [16] used the Theory of Unpleasant Symptoms (TOUS) to examine the effects of a home-based walking program on perceived symptom and mood states in women with breast cancer. The TOUS is a comprehensive middle-range theory that posits a number of factors influencing the symptom experience, which in turn influences patient cognitive and functional performance [17]. The TOUS also suggests that the symptom experience has a feedback loop to influencing factors, and patient performance has a feedback loop to both the symptom experience and influencing factors. Although comprehensive, the TOUS does not offer insights into the factors affecting patient adherence to symptom self-care management behaviors or take into account long-term survival or the persistent nature of cancer-related symptoms. Therefore, while it can be used to examine the symptom experience and symptom impact on patient outcomes, its application to symptom management in patients with cancer may be limited by the absence of a self-care management component. Additionally, the TOUS does not include an intervention component, making it unclear how it can be utilized to guide experimental research. Another middle-range theory commonly used to guide symptom management research is the Theory of Symptom Management

(TSM), which includes three domains that influence each other: 1) the symptom experience with three dimensions (perception, evaluation, and response); 2) symptom management strategies; and 3) symptom outcomes (i.e., quality of life, healthcare costs, self-care, morbidity, mortality, functional and emotional status) [18]. Although the TSM incorporates intervention and self-care components, its use in oncology symptom management may be limited for two reasons. First, it does not include an assessment of concurrent symptoms or take into account the interactive relationships among cancer-related symptoms. Second, self-care is depicted as a symptom outcome rather than an intervention and therefore how self-care strategies fit into the symptom management process and are evaluated is not clear.

Furthermore, self-care theories have been used to inform the design of self-care management interventions to ameliorate cancer-related symptoms. For example, Badger, Braden, and Mishel [19] examined the effectiveness of self-help classes and uncertainty-management sessions in reducing side effects in women with breast cancer, utilizing the Braden's Self-Help Model to design the study intervention. The Braden's Self-Help Model illustrates the dynamics of a learned self-help response as opposed to a learned helplessness response [20]. Similarly, Dodd and Miaskowski [21] tested the effectiveness of a self-care intervention to reduce symptom severity in patients with various cancer types. The intervention was guided by the Orem’s Self Care Deficit Theory, which proposes that people have a natural ability for self-care, and thus nursing should focus on that ability [22]. The limited use of self-care theories in cancer research to inform aspects of intervention design could be due to the lack of a symptom component in the current theories. As such, they do not describe the attributes of the symptom experience or illustrate the impact of symptom self-care management interventions on cancer patient outcomes.

None of the theories described above offer a conceptualization of symptom self-care management in patients with cancer. Although the TOUS and TSM contain important elements needed to guide symptom management research, they lack comprehensive integration of the self-care component within symptom management and of factors affecting cancer patient adherence to symptom self-care management behaviors. A new cancer specific theory that is rooted in both symptom-management and self-care management may determine the relationship of self-care management behaviors with causes and effects of cancer-related symptoms and identify factors that influence patient adherence to self-care management behaviors. Therefore, the aim of this paper is to describe the process used to synthesize a new theory of symptom self-care management for adults with cancer. Given the knowledge and skills (e.g., knowledge and literacy about symptoms, memory use) required for effective self-care management, it is unclear whether the newly synthesized theory could apply to pediatric cancer populations. It is possible that relatively mature school-aged children and adolescents with cancer, both cognitively and psychologically, can benefit from this new theory.

The development of the newly synthesized theory was guided by the methodological approach of Walker and Avant [23]. This approach organizes concepts and statements into an integrated whole, resulting in a more complex representation of the phenomenon of interest [23]. Walker and Avant describe three steps guiding theory synthesis: "1) specifying focal concepts to serve as anchors for the synthesized theory, 2) reviewing the literature to identify factors related to the focal concepts and to specify the nature of relationships, and 3) organizing concepts and statements into an integrated and efficient representation of the phenomena of interest" [23]. Concepts used in this theory synthesis were selected from the TOUS, Individual and Family

Self-Management Theory (IFSMT) [24], and Green's concept analysis of self-management behavior [25]. A description of each is presented below.

Theory of Unpleasant Symptoms

The TOUS contains three major components (influencing factors, symptom experience, and performance). There are three categories of influencing factors (situational, psychological, and physiological) that relate to one another and may interact to generate or affect the symptom experience. The TOUS proposes that symptoms can occur alone or in combination, and can interact with one another. The third and final component of the TOUS is performance, defined as the outcome of the symptom experience, which includes functional and cognitive performance. As previously noted, the TOUS puts forth that its three major components reciprocally influence each other. For example, fatigue can reduce physical activity (functional performance), which may, in turn, contribute to greater fatigue. Decreased levels of physical activity are also likely to increase depression (psychological factors) and to negatively impact job performance (situational factors) [17].

Individual and Family Self-Management Theory

The IFSMT is a middle-range theory that posits self-management is a complex phenomenon consisting of three dimensions: context, process, and outcomes. Contextual factors (i.e., condition-specific factors, physical and social environments, individual and family characteristics) influence individual and family engagement in the process of self-management. The self-management process includes knowledge and beliefs, self-regulation skills and abilities, and social facilitation. Outcomes of the self-management process are both proximal and distal. The proximal outcomes include cost of healthcare services and self-management behaviors.

Distal outcomes are partly related to the successful accomplishment of proximal outcomes, and include health status, cost of healthcare, and quality of life or perceived well-being [24].

Green's concept analysis of self-management

Green's concept analysis of self-management describes the antecedents, attributes, and consequences of self-management behaviors. The antecedents include physical, social, economic, psychological, and cultural factors, as well as collaborative and received support. Self-management behaviors are reactive actions related to a circumstantial change in health condition in order to achieve a goal (e.g., seeking counseling to help with coping with a cancer diagnosis), and to proactive actions related to problem planning, collaboration, mental support, and lifestyle (e.g., engaging in aerobic exercise to reduce one's risk of heart disease). The consequences of self-management behaviors are controlling problems, making progress toward a goal, and societal and individual benefits (e.g., increased patient satisfaction) [25].

Data Sources

Consistent with the Walker and Avant theory synthesis process, empirical literature was examined to identify potential relationships between concepts within the newly synthesized theory. A literature search was conducted using the PubMed, CINAHL, and Cochrane Library databases. The following keywords were combined using the appropriate Boolean operators: self-management, self-care, self-monitoring, symptom, self-efficacy, self-regulation, and quality of life. The search was not limited to a start date in order to capture all relevant literature. The inclusion criteria were studies published in English language and that focused on symptom management or self-care management in patients with cancer. If no relevant studies were found in patients with cancer, the inclusion criteria were extended to include studies in any other chronic disease population (e.g., heart disease, diabetes). Dissertations, case studies, and study

abstract with no available full texts were excluded. The articles were evaluated for relevancy through reviewing titles, abstracts, and full texts. Evidence for this synthesis was gathered using different research methodology, including descriptive studies, experimental research, and reviews. The new theory was initially developed in October 2015 after selecting concepts for theory synthesis and searching the literature to identify potential relationships between them. The original version of the newly synthesized theory was then revised multiple times during the time of PhD course work based on feedback from nurse scientists at the University of Michigan, Ann Arbor, and based on results of periodic searches conducted to review current literature. The last literature search was completed in March 2018 during which the new theory was last revised. The last revision aimed at enhancing the conceptualization of health-related quality of life (HRQOL) and symptom self-care management behaviors through taking into account characteristics specific to patients with cancer (e.g., long-term survival, persistent nature of cancer-related symptoms).

Discussion

Step 1 of theory synthesis: specify focal concepts

Six concepts were selected concepts for inclusion in the newly synthesized theory: 1) symptom experience; 2) influencing factors with three sub-concepts: physiological factors, psychological factors (e.g., outcome expectancy and goal congruence), and situational factors (e.g., social facilitation); 3) HRQOL with four sub-concepts (i.e., physical well-being, social/family well-being, emotional well-being, and functional well-being); 4) two types of symptom self-care management behavior, proactive and reactive; 5) self-efficacy; and 6) self-regulation skills and abilities. These six selected concepts are explained along with a rationale

for inclusion in the new theory. The definitions of the selected concepts are presented in Table II.1.

Table II.1: Conceptual Definitions

Selected concepts	Conceptual definition
Symptom experience	Each symptom is a multidimensional experience, which can be conceptualized and measured separately or in combination with other symptoms. The symptom experience has four dimensions: intensity (severity), timing (duration and frequency of occurrence), distress (discomfort), and quality. Symptoms can occur simultaneously, likely resulting in a catalyzing effect. [17]
Influencing factors	Three categories of factors (physiological factors, psychological factors, situational factors) are the antecedents that influence the occurrence, intensity, timing, distress level, and quality of the symptom experience. Examples of physiological factors include normally functioning bodily systems and disease pathology. Psychological factors include affective reaction to illness, mental state or mood, and degree of uncertainty and knowledge about the symptoms and their possible meaning. Situational factors include aspects of the social and physical environment, such as marital and family status, employment status, social support, and availability of and access to healthcare resources. These three categories may interact to influence the symptom experience. [17]
Health-related quality of life	HRQOL is a multifaceted concept that encompasses domains of an individual's life, including physical well-being, social/family well-being, emotional well-being, and functional well-being. [26]
Symptom self-care management behavior	Self-care is the capacity to take care for oneself and the performance of activities necessary to maintain, achieve, or promote optimal health, subsuming symptom management when performed by self. Symptom management refers to an individual's awareness of and response to cognitive, physiologic, or functional sensations or changes. [9]
Self-efficacy	Self-efficacy refers to an individual's perception of his or her capability to perform a specific task in order to produce a desired outcome. [27]
Self-regulation skills and abilities	Self-regulation is the process of achieving a change in health behavior. Self-regulation involves a number of skills and abilities, which include goal setting, self-monitoring, reflective thinking, decision-making, action planning, action, self-evaluation, and management of responses. [24]

Symptom experience: causes and outcomes

A concept is needed to understand the multidimensional nature of cancer-related symptoms. Therefore, the concept of symptom experience is included in the new theory. To select concepts for theory synthesis, potential causes and outcomes of the concepts should be initially selected [23]. Because the TOUS concept of influencing factors, which include physiological, psychological, and situational factors, is important for understanding the factors that give rise to or influence the symptom experience in patients with cancer, this concept was also included in the new theory. The TOUS also considers functional and cognitive performance as outcomes of the symptom experience. However, successful symptom management in patients with cancer may lead to health benefits beyond improvements in functional and cognitive performance. For instance, studies across different cancer populations found that symptoms, such as, worrying, sleep disturbance, and difficulty concentrating can affect emotional well-being [28, 29]. However, emotional well-being cannot be subsumed under functional and cognitive performance. Therefore, there is a need for a broader concept that encompasses a wider range of potential effects of cancer-related symptoms. Quality of life, an outcome of self-management behavior according to the IFMST, was initially selected as a concept for inclusion in the new theory because of its broader meaning, encompassing cognitive and functional domains. However, the concept of quality of life was replaced with HRQOL because the former may be influenced by non-health-related factors (e.g., job satisfaction, financial status). Therefore, HRQOL is conceptualized to better reflect the impact of cancer-related symptoms on an individual's life.

Many definitions exist for HRQOL in the literature, yet it is most often conceptualized to include the dimensions of physical, psychological, and social well-being [30-32]. HRQOL is also

conceptualized in the Functional Assessment of Cancer Therapy-General (FACT-G) scale to include four domains of well-being: functional, social/family, emotional, and physical [26]. The FACT-G scale is the most widely used measure of HRQOL in cancer research, having originally been validated in a sample of 545 patients with mixed cancer diagnoses, including, breast, prostate, ovarian, and colorectal cancer [33]. Currently this measure has been translated and validated for use in countries with different cultural backgrounds (e.g.; France, China, South Africa) [34-36]. Additionally, the FACT-G scale has been validated in diverse cancer populations, such as brain cancer, lung cancer, and hematopoietic stem cell transplant [37-39]. It is thus possible that conceptualizing HRQOL to include the four domains covered in the FACT-G is congruent with HRQOL as perceived by patients with cancer. Additionally, other possible dimensions of HRQOL, such as psychological and spiritual well-being, can be subsumed, at least in part, under the four domains covered in the FACT-G scale. Therefore, the four FACT-G domains may comprehensively capture the concept of HRQOL in adults with cancer. As such, it is posited in the new theory that the four domains of well-being: physical, social/family, emotional, and functional are the defining attributes of the concept of HRQOL and are, therefore, included as sub-concepts of HRQOL.

Symptom self-care management behaviors

Because cancer-related symptoms may persist for years or even decades after the completion of treatment [40, 41], a self-care management component must be incorporated in the newly synthesized theory. The IFSMT suggests that symptom management is a subset of self-management behaviors. Therefore, symptom self-management behavior was initially selected as a concept for inclusion in the new theory. However, it was replaced with symptom self-care management behavior because the latter was conceptualized to better describe symptom

management behaviors when performed by a cancer patient. Green [25] distinguishes between proactive and reactive self-management. Based on Green's theoretical perspective of self-management, the concept of symptom self-care management behavior in the new theory is classified into two types: proactive and reactive. This classification is consistent with symptom self-care management in patients with cancer, as they often may suffer from intermittent and persistent symptoms during cancer treatment and into the survivorship phase. For example, patients may use oral gargles at home to prevent chemotherapy-induced oral mucositis, which is a proactive symptom self-care management behavior or they may use an oral therapeutic mouth rinse to reduce the pain and inflammation related to existing mouth sores as a reactive self-care management behavior.

Factors influencing adherence to symptom self-care management behaviors

Adherence to symptom self-care management behaviors may be challenging because of the complexities of cancer treatments and lifestyle changes that occur after a cancer diagnosis. To date, little is known about the factors that may foster adherence to symptom self-care management behaviors in patients with cancer. According to the IFSMT, people are more likely to engage in self-management behaviors if 1) they experience social facilitation that positively supports engaging in the intended behavior; 2) they develop self-regulation skills and abilities to carry out self-management behaviors, and 3) they have knowledge about, and embrace beliefs consistent with, the recommended behavior [24]. Self-regulation involves a number of skills and abilities, which include goal setting, self-monitoring, reflective thinking, decision-making, planning, action, self-evaluation, and management of responses [24]. Knowledge and beliefs include outcome expectancy, goal congruence, and self-efficacy [24]. Self-efficacy refers to an individual's belief in his or her capacity to execute behaviors [27]. Outcome expectations are the

perceptions of potential consequences of one's actions [27]. Goal congruence refers to an individual's ability to resolve the anxiety and confusion that results from competing demands associated with goals [24].

Self-efficacy and self-regulation skills and abilities, two factors purported by the IFSMT to affect self-management, are included in the new theory. These two variables have the most supporting evidence for improving health-related behaviors [42, 43]. Chen et al. [44] found self-efficacy to be associated with self-care adherence in patients with heart failure. Furthermore, a randomized clinical trial by Olson and McAuley [45] showed significant increases in physical activity after an intervention targeting self-efficacy and self-regulation skills and abilities in patients with diabetes. It is also worth noting that the three other factors (i.e., social facilitation, outcome expectancy, and goal congruence) posited by the IFSMT to influence self-management can be subsumed under the concept of influencing factors. Outcome expectancy and goal congruence fit conceptually under psychological factors, whereas social facilitation fits conceptually under situational factors. These three factors are included as examples of influencing factors in the new theory for their potential impact on symptom self-care management behavior.

Step 2 of theory synthesis: identify related factors and relationships

We propose that the newly synthesized theory consists of four major statements that describe the relationships between the concepts within the theory: 1) Physiological, psychological and situational factors interact to give rise to or influence the symptom experience; 2) The symptom experience influences an individual's perception of HRQOL; 3) Symptom self-care management behavior influences the symptom experience with two moderators, self-efficacy and self-regulation skills and abilities, that affect the strength of this relationship; and 4)

self-efficacy and self-regulation skills and abilities interact synergistically. The proposed relationships are presented in turn with supporting evidence.

Influencing factors and symptom experience

Inspired by the TOUS, the newly synthesized theory posits that cancer-related symptoms are typically multi-factorial and are influenced by more than just physiological factors, such as cancer treatment. This proposition is supported by a secondary analysis conducted by Kim, Barsevick, and Tulman [46] that explored the predictors of symptom intensity in women with breast cancer and found that factors such as age, physical performance, and treatment modality influence the intensity of psychoneurological and gastrointestinal symptoms. Similarly, Liao et al. [47] found that in a sample of breast cancer survivors, factors including anxiety, time since diagnosis, and social support are significant predictors of changes in symptom distress across a wide range of physical and psychological symptoms. Based on this evidence, the new theory maintains the assumption from the TOUS that situational, psychological, and physiological factors influence the symptom experience.

Symptom experience and health-related quality of life

The symptom experience may affect HRQOL, as indicated by several studies [48, 49]. Chang et al. [28] assessed symptom prevalence and its relation to HRQOL in patients with various cancer types, including gastrointestinal, genitourinary, and hematologic malignancies. The number of symptoms in this study was negatively correlated with HRQOL scores [28]. These results are consistent with those of Kenne Sarenmalm, Ohlén, Odén, and Gaston-Johansson [50] that found symptoms such as lack of energy, sleep disturbances, and pain decrease HRQOL in women with recurrent breast cancer. Based on these data, the new theory suggests that the symptom experience influences a cancer patient's HRQOL.

Symptom experience and symptom self-care management behavior

Another relationship proposed by the newly synthesized theory is between symptom experience and symptom self-care management behavior. Several studies suggest that patients with cancer may benefit from self-care interventions targeting cancer-related symptoms [14, 19, 21]. A randomized controlled trial by Mock et al. [51] showed a self-paced, home-based walking exercise program to be effective in ameliorating anxiety and insomnia among women with breast cancer. Based on these data supporting the use of home-based interventions for reducing cancer-related symptoms, the new theory puts forth that proactive and reactive symptom self-care management behaviors influence the symptom experience. Proactive symptom self-care management behaviors prevent the occurrence of the symptom experience, whereas reactive symptom self-care management behaviors improve the symptom experience. Symptom improvement may be associated with a positive valence, potentially fostering adherence to reactive symptom self-care management behaviors.

Moderator variable: self-efficacy

As previously described, there are data support the hypothesis that self-efficacy enhances health-related behaviors [52, 53], but there is also evidence that self-efficacy moderates the relationship between behavioral intention and behavior [54]. A longitudinal analysis by Lippke, Wiedemann, Ziegelmann, Reuter, and Schwarzer [55] evaluating changes in physical activity in a general population found self-efficacy moderated the intention-behavior relationship. Only participants with high levels of self-efficacy acted upon their plans, whereas participants with low self-efficacy failed to translate their plans into actions [55]. It is thus possible that patients with cancer who have a strong sense of self-efficacy are more likely to engage in symptom self-care management behaviors, resulting in better symptom experience. Therefore, self-efficacy

was conceptualized in the new theory as a moderator variable that affects the strength of the relationship between symptom self-care management behavior and symptom experience. Patients with cancer who have high self-efficacy may better adhere to symptom self-care management behaviors compared to those with low self-efficacy. Better adherence to symptom self-care management behaviors may further improve the symptom experience.

Moderator variable: self-regulation skills and abilities

Ryan and Sawin [24] described self-regulation skills and abilities as integral to engaging in health behaviors. No studies were found that conceptualized self-regulation skills and abilities as a moderator of the relationship between a health-related behavior and outcome. However, it is possible that the strength of the relationship between self-care management behavior (the independent variable) and symptoms (the dependent variable) depends on the individual's level of self-regulation skills and abilities (the moderator). As previously noted, self-regulation skills and abilities include goal setting, self-monitoring, reflective thinking, decision-making, action planning, action, self-evaluation, and management of responses [24]. Self-regulation skills and abilities may therefore moderate the relationship between symptom self-care management behavior and symptom experience in various ways. For example, the importance of goal setting is underscored by research showing that goals impact task motivation and performance, and provide standards to evaluate progress [56, 57]. Thus, it is possible that patients with cancer who are goal directed become more motivated, and subsequently more likely to engage in a recommended symptom self-care management behavior. Furthermore, Schunk [58] showed that self-monitoring improves self-efficacy by enhancing a perception of progress and self-efficacy for continued progress. Therefore, it is also possible that patients with cancer monitoring their own symptoms feel more self-efficacious, leading to better adherence to symptom self-care

management behavior and better symptom control. As such, the new theory puts forth that self-regulation skills and abilities moderate the relationship between symptom experience and symptom self-care management behavior in both proactive and reactive forms. Patients with high levels of self-regulation skills and abilities are more likely to adhere to symptom self-care management behaviors compared to those with low levels of self-regulation skills and abilities. Better adherence to symptom self-care management behaviors may lead to a better control of the symptom experience.

Self-efficacy and self-regulation skills and abilities

Self-efficacy and self-regulation skills and abilities are potentially related but the relationship has not been well articulated to date. According to Bandura [59], self-efficacy is essential for effective self-regulation skills and abilities, as it influences not only the challenges people choose to undertake, but also how much effort to place and how long to persevere in the face of obstacles. This position by Bandura is supported by studies in education showing that student self-efficacy enhances academic self-regulation skills and abilities [60, 61]. However, as previously noted, one component of self-regulation skills and abilities, namely self-monitoring, was found to improve self-efficacy [58, 62]. Additionally, a general population survey by Lippke et al. [55] found a significant interaction between self-efficacy and another component of self-regulation skills and abilities (action planning), accounting for 16% of the variation in physical activity level among survey respondents [55]. As such, in addition to each being an independent moderating variable, the new theory puts forth a synergistic interaction between self-efficacy and self-regulation skills and abilities, potentially resulting in a greater moderating effect.

Step 3 of theory synthesis: construct an integrated representation

The statements described in step 2 were organized to develop the newly synthesized Theory of Symptom Self-Care Management in Cancer (Figure II.1). This theory puts forth influencing factors as antecedents that affect or generate the symptom experience in patients with cancer. Two moderators, self-efficacy and self-regulation skills and abilities, may influence cancer patient adherence to symptom self-care management behaviors in both proactive and reactive forms. The level of adherence to symptom self-care management behaviors influences the symptom experience, which in turn influences HRQOL. As mentioned earlier, the TOUS proposes reciprocal relationships between its focal concepts. The new theory maintains the relationships posited by the TOUS that the symptom experience has a reciprocal relationship to influencing factors and patient performance has a reciprocal relationship to both the symptom experience and influencing factors, with patient performance being replaced with HRQOL in the new theory. While the feedback loop between symptom experience and patient performance in the TOUS is unidirectional, the new theory suggests a bidirectional feedback loop between symptom experience and HRQOL because the latter may influence the symptom experience independent of the effect of influencing factors. The new theory also puts forth that the symptom experience has a feedback loop to reactive symptom self-care management behavior. This is because, in reactive symptom self-care management, the symptom response to treatment will inform the symptom management behavior in return. In contrast, the symptom experience does not exist in proactive symptom self-care management, and therefore, no feedback loop occurs. Lastly, influencing factors and symptom self-care management behavior may reciprocally influence each other.

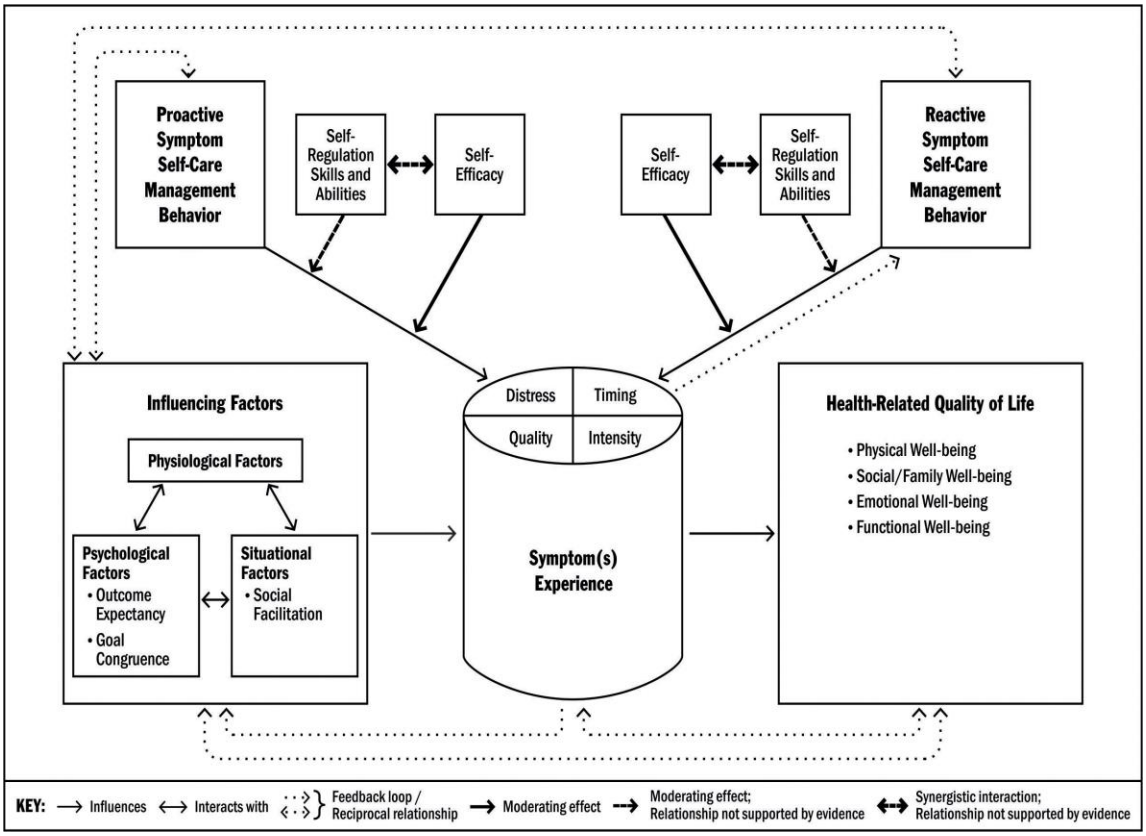

Figure II.1: Theory of Symptom Self-Care Management in Cancer

Theory testing

The next step is to empirically test and validate the newly synthesized theory. One strength of the new theory is that all of its concepts are at a level of abstractness that allows operationalization. For example, symptoms can be assessed separately using measures of individual symptoms or in combination using measures of multiple symptoms, such as, the M.D. Anderson Symptom Inventory [63]. The two moderators, self-efficacy and self-regulation skills and abilities, can be measured using valid scales, such as the Self-Efficacy for Managing Chronic Disease Scale and Index of Self-Regulation Scale [64, 65]. Symptom self-care management behavior can be measured using home diaries or practice logs specific to the treatment being tested. Factors subsumed under influencing factors can range from very concrete variables, such as demographic information, to more abstract variables, such as illness uncertainty and perceived social support that can be measured using the Mishel Uncertainty in Illness Scale and Social Support Questionnaire [66, 67]. In addition to HRQOL and its four sub-concepts (physical well-being, social/family well-being, emotional well-being, functional well-being), factors subsumed under them can be selected as outcomes of the symptom experience using the new theory. For example, exercise capacity fits conceptually under functional well-being and can be measured using the 6-minute walk test [68]. Similarly, fear of disease recurrence fits conceptually under emotional well-being and can be measured using the Fear of Progression Questionnaire [69]. A strength of the new theory is sufficiently generalized, allowing for the generation and testing of a wide range of hypotheses across various cancer populations.

Limitations

The Theory of Symptom Self-Care Management in Cancer is the first middle-range theory that explains and guides symptom self-care management in patients with cancer. It was

synthesized using Walker and Avant's methodological approach and through reviewing a substantive body of literature on self-care management and symptom management. Still, there are four limitations of this theory synthesis. First, some of the data used in this synthesis are from non-cancer populations, and whether these data are generalizable to patients with cancer is unknown. Second, the search was restricted to peer-reviewed articles published in English. Searching the gray literature or including non-English language articles could have provided a more comprehensive overview of the existing literature. Third, two of the relationships proposed (i.e., the moderating role of self-regulation skills and abilities and the synergistic interaction between self-efficacy and self-regulation skills and abilities) lack empirical support. No studies were found that tested these relationships in patients with cancer or any other patient population, although a theoretical rationale was provided. Fourth, the new theory does not address all possible connections among concepts, especially the relation of self-efficacy and other concepts in the theory.

Implications for Nursing

The newly synthesized theory may have implications for clinical practice, research and education. Oncology nurses who examine symptom management using this theory may consider developing new strategies to empower people with cancer to monitor and manage their symptoms. This may increase the likelihood of successful long-term symptom management, especially during cancer survivorship or during periods of transition from treatment to survivorship. From a research perspective, the new theory can be used to guide future studies aiming to explore the predictors of cancer-related symptoms or to examine the effect of cancer-related symptoms on HRQOL or other outcomes. The new theory can also be used to guide studies testing treatments for cancer-related symptom(s) while targeting the factors of self-

efficacy and self-regulation skills and abilities, which may improve patient adherence to symptom self-care management behaviors, potentially improving the symptom experience and subsequently HRQOL. The new theory may also influence nursing education. Inspired by this new theory, nurse educators may consider curriculum changes to put more emphasis on self-care management in patients with cancer. Additionally, the newly synthesized theory may help nursing students see the potential value of cancer patient engagement in the symptom management process.

Conclusion

Because adults with cancer are living longer, developing middle-range theories to guide self-care management in this population is indicated. This paper presented the process used to develop the Theory of Symptom Self-Care Management in Cancer. This new theory has particular value in that it goes beyond the traditional, provider-based symptom management approach in order to conceptualize cancer as a chronic illness that requires the integration of a self-care management approach into symptom management. By providing an organized theoretical perspective on the self-care management of cancer-related symptoms, the new theory holds the potential to influence cancer patient outcomes and HRQOL, as well as oncology nursing practices. Should the new theory be critiqued and tested, revision of the theory may be indicated.

Acknowledgements

The first author would like to thank members of his dissertation committee: Dr. Mark Peterson, Dr. Lauren P. Wallner, Dr. Moira A. Visovatti and Dr. Sung Won Choi for generously offering their time, support, and guidance throughout the preparation and review of this manuscript.

Author Contribution

This theoretical work was part of the doctoral dissertation of the first author, Mohamad Baydoun. The second author, Dr. Debra L. Barton, was dissertation committee chair with expertise in oncology symptom management and self-management. The third author, Dr. Cynthia Arslanian-Engoren, was committee member with expertise in nursing theory and self-care management. All authors made substantial contributions to the conception and development of the new theory. Mohamad Baydoun completed literature review and wrote the first draft of the article. Dr. Debra L. Barton and Dr. Cynthia Arslanian-Engoren revised drafts critically for important intellectual content.

Conflict of Interest

No conflict of interest has been declared by the authors.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Theory Application

To explain how the theory of symptom self-care management in cancer (TSSMC) applies to the current study and adult survivors of hematopoietic stem cell transplantation (HSCT), physiological (e.g., age, sex, cancer type, graft versus host disease status and grade), situational (e.g., marital status, employment status), and psychological factors will interact and generate the symptom experience, namely, cancer-related fatigue (CRF). Yoga is conceptualized as a reactive symptom self-care management behavior because the study targets adult HSCT survivors with preexisting moderate to severe CRF. Much of the research linking CRF to other symptoms is cross-sectional [1-4]; thus, how CRF relates to sleep disturbances, depression, and pain is not clear. Therefore, depression, sleep disturbances, and pain are conceptualized in this study as symptoms that are occurring simultaneously with CRF. Similarly, the directionality of effect between CRF and physical activity cannot be clearly determined [5,6]. It is possible that having CRF decreases the individual's interest and readiness to engage in physical activity. Prolonged physical inactivity may also decrease muscle mass and strength, thereby contributing to CRF. Therefore, physical activity may fit conceptually under influencing factors, particularly situational factors including lifestyle behaviors (e.g., diet and exercise), or under the physical wellbeing domain of health-related quality of life (HRQOL). This study targets adult HSCT survivors with moderate to severe CRF irrespective of their physical activity levels, which increases the likelihood of CRF being the initial problem that affects their physical activity. Therefore, physical activity is conceptualized in this study to fit under one domain of HRQOL in the TSSMC, namely, physical wellbeing.

The first secondary aim of this study is to evaluate the association of baseline CRF severity with depression, sleep disturbances, and pain. One relationship originally postulated by

the TOUS and maintained in the TSSMC is that symptoms can occur simultaneously, likely resulting in a catalyzing effect. It is therefore hypothesized in the current study that baseline scores for CRF will be positively associated with cooccurring symptoms (i.e., depression, pain and sleep disturbances). The second secondary aim of this study is to evaluate the potential benefits of yoga for adult HSCT survivors. The TSSMC postulates that reactive symptom self-care management behaviors influence the symptom experience, which in turn influences the four domains of HRQOL, namely, physical, social/family, emotional, and functional wellbeing. As such, it is hypothesized in the current study that after the completion of the yoga intervention (i.e., the reactive symptom self-care management behavior), adult HSCT survivors will report improvements in the symptom experience (i.e., CRF, depression, sleep disturbances, pain) and physical activity that fits conceptually under one domain of HRQOL (i.e., physical wellbeing).

With regard to the third secondary aim (i.e., to evaluate the association of CRF change with changes in depression, sleep disturbances, pain, and physical activity), the hypothesis is guided by two relationships originally postulated by the TOUS and maintained in the TSSMC. The first relationship is that symptoms can occur simultaneously, likely resulting in a catalyzing effect. The second relationship is that the symptom experience influences patient cognitive and functional performance, with patient performance being replaced with the four domains of HRQOL in the TSSMC. Based on these two relationships, it is possible that CRF and cooccurring symptoms (i.e., depression, sleep disturbances, pain) catalyze each other and that CRF impacts physical activity levels. It is therefore hypothesized in the current study that improvements in CRF from baseline to postintervention will be associated with increased physical activity and decreased depression, sleep disturbances and pain.

In regard to the fourth secondary aim (i.e., to evaluate the association of yoga adherence with self-efficacy and self-regulation skills and abilities), the TSSMC puts forth that self-efficacy and self-regulation skills and abilities moderate the benefits of symptom self-care management behaviors through impacting adherence to the behavior being studied. Therefore, adult HSCT survivors with high self-efficacy and self-regulation scores are expected to show better adherence to yoga practice than those with low self-efficacy and self-regulation scores. Better adherence to yoga practice will further decrease CRF. Since the current study is grossly underpowered to test for moderation effects, the association of yoga adherence with self-efficacy and self-regulation skills and abilities is evaluated, which may provide support for a potential moderating relationship to be investigated in a future adequately powered study. It is hypothesized in the current study that there is a positive association between yoga adherence and self-efficacy and self-regulation skills and abilities. Figure II.2 illustrates how the newly synthesized theory applies to the current study.

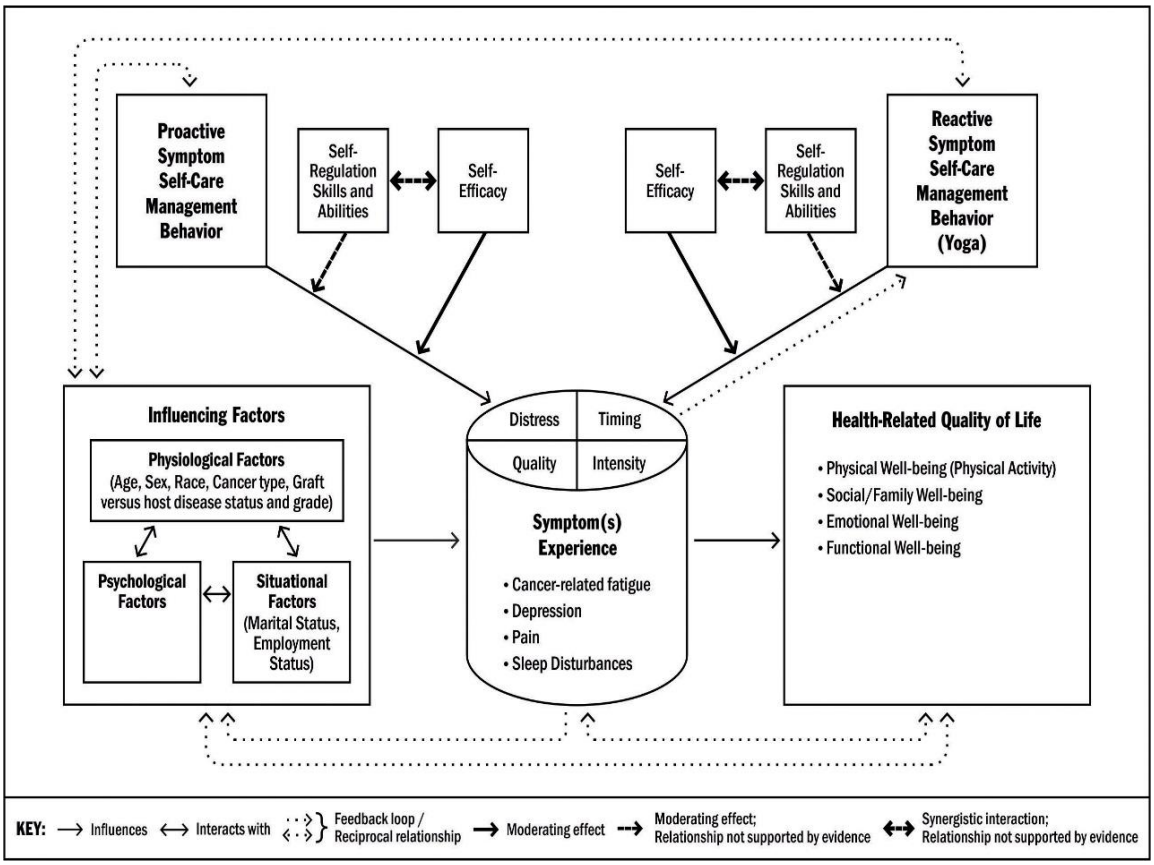

Figure II.2: Theory Application

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CHAPTER III

METHODS AND RESULTS

The methodology and results of the current mixed-methods study are presented in three manuscripts. The first manuscript, entitled "Yoga for Cancer-Related Fatigue in Survivors of Hematopoietic Stem Cell Transplantation: A Feasibility Study", addresses the primary endpoint, which is feasibility (i.e., the accrual acceptance, retention, protocol adherence, and adverse event rates), and one secondary endpoint (i.e., the association of CRF severity at baseline with depression, sleep disturbances, and pain). The second manuscript, entitled "Potential Benefits of Yoga for Hematopoietic Stem Cell Transplant Survivors with Cancer-Related Fatigue: A Feasibility Pilot Study" addresses three secondary endpoints, including 1) the potential benefits of yoga for adult HSCT survivors (i.e., changes in CRF depression, sleep disturbances, pain, and physical activity from baseline to postintervention); 2) the association of CRF change from baseline to postintervention with changes in depression, sleep disturbances, pain, and physical activity; and 3) the association of yoga adherence with self-efficacy and self-regulation skills and abilities. The third manuscript, entitled "Hematopoietic Stem Cell Transplant Survivors' Perceptions of Yoga and Physical Activity: A Focus Group Approach", addresses the qualitative endpoint, which is participants' views regarding yoga and physical activity. The measures used in this study are included in Appendix D.

Yoga for Cancer-related Fatigue in Survivors of Hematopoietic Stem Cell Transplantation: A Feasibility Study

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Abstract

Background: Cancer-related fatigue (CRF) is one of the most common symptoms experienced by cancer survivors following hematopoietic stem cell transplantation (HSCT). Yoga is a complementary approach that has supportive evidence to improve CRF in different cancer populations. However, to our knowledge, it has not been tested in an HSCT population. The primary aim of this study is to evaluate the feasibility of a yoga intervention offered to adult HSCT survivors with moderate to severe CRF. One secondary aim of this study is to evaluate the association of baseline CRF severity with depression, pain and sleep disturbances.

Methods: This feasibility study employed a single-arm, pretest–posttest design. Twenty HSCT survivors were enrolled in a 6-week restorative yoga intervention that consisted of a 1-hour once-weekly class with twice-weekly home practice using a DVD.

Results: The accrual acceptance rate was 23.2% (20/86 HSCT survivors). Twelve of the participants who initially enrolled completed the study (retention rate=60%). Overall adherence was 45.4%. No adverse reactions attributable to yoga were reported. Of the CRF dimensions (i.e., total CRF, physical CRF, general CRF, mental CRF, emotional CRF) evaluated at baseline, total CRF and emotional CRF correlated significantly with sleep disturbances ($r=0.52$, $P=0.02$; $r=0.57$, $P=0.01$, respectively). Emotional CRF also correlated significantly with depression ($r=0.68$, $P=0.02$). Correlations between the CRF dimensions and pain were not statistically significant, ranging from -0.02 to 0.29 (all $Ps>0.05$).

Conclusion: The results of this study indicate that a yoga trial in adult HSCT survivors is feasible from a safety standpoint and needs to employ strategies to improve accrual acceptance, retention, and protocol adherence rates. The association of CRF dimensions with sleep

disturbances and depression indicates that CRF tends to co-occur with other symptoms with a potential catalyzing effect.

Keywords: Cancer-related Fatigue; Hematopoietic Stem Cell Transplantation; Yoga

Introduction

Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for several malignancies, such as leukemia and lymphoma [1]. Approximately 20,000 HSCTs are performed in the US each year [2]. Improvements in healthcare and supportive care practices have led to increased survival after HSCT. The 3-year survival rate for people undergoing HSCT can range from 27% to 91% [3]. Survival rates vary depending on factors such as underlying malignancy and disease status at the time of transplant [3]. One of the most debilitating symptoms after HSCT is cancer-related fatigue (CRF) [4-8], defined by the National Comprehensive Cancer Network as a persistent, subjective sense of physical, cognitive, and emotional tiredness related to cancer or cancer treatment that is not proportional to recent activity [9]. In one study by Bevans, Mitchell, and Marden [10] including 76 adult HSCT recipients, 68 % reported CRF on the day of transplant, 90 % at day 30, and 81 % at day 100 posttransplant. Numerous studies also suggest that CRF is prevalent for up to 15 years after the initial 100 days of HSCT, prevalence rates ranging from 35% to 84% [5, 11-13].

The biological mechanism underlying CRF is unclear and is likely multifactorial. Preliminary evidence suggests a link between inflammatory markers and CRF [14, 15]. Wang et al. [16] found that serum levels of inflammatory cytokines (i.e., interleukin-6, soluble tumor necrosis factor receptor-1) were associated with increased CRF in a sample of 30 patients during the first 30 days after allogeneic HSCT. The authors suggested that increased secretion of inflammatory cytokines could occur in response to the high dose of chemotherapy received prior to HSCT, also known as a conditioning regimen [16]. However, if inflammatory activity is triggered by the conditioning regimen, why some HSCT recipients and not others experience enduring CRF during the extended survivorship period remains unknown. One factor that may

contribute to the persistent high inflammatory state and associated CRF in some HSCT survivors but not others is graft versus host disease (GVHD) [17-19]. GVHD occurs when T lymphocytes transplanted from a donor recognize the recipient's organs as foreign, initiating an immune reaction that can affect multiple organs (e.g., skin, eyes, lungs) [19]. Barak, Levi-Schaffer, Nisman, and Nagler [20] evaluated cytokine production in patients who were 5 to 12 months after allogeneic HSCT. The results showed that HSCT survivors with GVHD had higher cytokine levels (i.e., interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha) compared to those with no GVHD [20].

Another potential mechanism for CRF is reactivation of latent viruses (e.g., herpes simplex viruses, epstein barr virus) [14, 15], which is common after HSCT [21]. For example, it is estimated that 30% of allogeneic HSCT survivors and 5% of autologous HSCT survivors experience reactivation of cytomegalovirus (CMV) [22], which may contribute to CRF via triggering the immune system to produce inflammatory cytokines with antiviral effects, such as interleukin 6 [23]. Consistent with this hypothesis, Fagundes et al. [24] found that higher CMV antibody titers were associated with a greater likelihood of CRF among women with breast cancer. Another possible mechanism lies in the function of the hypothalamic–pituitary–adrenal (HPA) axis [25]. It has been hypothesized that the series of psychological stressors (e.g., anxiety about cancer diagnosis and prognosis, fear of disease progression or relapse, disruption of family and social functioning) that cancer imposes on one's life leads to recurrent activation of the HPA axis [26]. Frequent overstimulation of the HPA axis can alter cortisol circadian rhythm, triggering the production of inflammatory cytokines [27]. To our knowledge, this mechanism has not been tested in an HSCT population, with most supportive data coming from studies in women with breast or ovarian cancer [28, 29]. For example, Bower et al. [30] found that in a

sample of fatigued breast cancer survivors, elevated levels of evening cortisol and blunted cortisol responses to an experimental stressor were associated with increased levels of interleukin-6. In addition to CRF, there is preliminary evidence of an association between HPA axis dysregulation and other cancer-related symptoms, including depression, sleep disturbances, and pain [31-34]. It is therefore possible that HPA axis alteration and associated high inflammatory activity is a common mechanism for multiple symptoms, which might explain why depression, sleep disturbances, and pain, while they can occur singly, frequently cooccur with CRF [35-37].

Physical exercise, particularly aerobic exercise, has evidence for interfering with one possible mechanism that leads to CRF, HPA axis overstimulation [38-40]. However, integrating physical exercise into HSCT survivors' lives can be challenging due to several factors. First, GVHD, occurring in 27% to 72% of allogeneic HSCT survivors [17-19], has been associated with muscle wasting and weakness [41, 42], potentially making it harder to perform physical exercise. Second, it is estimated that up to 85% of HSCT survivors experience opportunistic infections of any kind (viral, bacterial, fungal) for up to 17 years after transplant [43-46]. Physical deconditioning associated with opportunistic infections may also create difficulties in making exercise a routine in this population. All of these factors contribute to a lack of integration of physical exercise into standard care for HSCT survivors and would suggest the need for other strategies that are perceived by HSCT survivors as easier to implement.

Yoga is an ancient Indian practice that has supportive evidence for improving CRF in patients with breast cancer [47-50] and prostate cancer [51]. Yoga offers a broad approach that includes bodily postures, meditation, relaxation, and deep breathing [52]. Yoga primarily aims to promote a union between body and mind by enhancing the acceptance of one's moment-to-

moment experience and engendering a sense of serenity and tranquility [52]. Preliminary data indicate that yoga interferes with one potential mechanism of CRF by reducing psychological stress and regulating cortisol circadian rhythm, resulting in lower inflammatory activity [53-55]. In addition, yoga offers a distinct advantage by combining physical activity and meditation practices, making it potentially appealing to HSCT survivors. Yoga is also person-centered and can be self-administered, which may encourage long-term use and potentially contribute to a better health-related quality of life in the long term.

Purpose

Despite the potential benefit of yoga in reducing CRF after HSCT, to our knowledge, it has not been tested in an HSCT population. The primary objective of this single-arm, pretest–posttest study is to evaluate the feasibility of a 6-week restorative yoga intervention offered to adult HSCT survivors with moderate to severe CRF. The feasibility of the yoga intervention was assessed based on the following four parameters:

1. Accrual acceptance rate (the number of participants who consented to participate as a proportion of those approached for participation). Most of the previous studies that evaluated yoga in breast cancer survivors reported accrual acceptance rates ranging from 39% to 56% [32, 33, 56-60]. Therefore, an accrual acceptance rate of at least 40% was desirable in this study.
2. Retention rate (the number of participants who completed the study as a proportion of those who enrolled in the study). Study completers were defined as those who did not drop out prior to the end of the 6-week intervention and returned at least one of the postintervention assessments. Previous yoga research in breast cancer survivors reported

study retention rates ranging from 74.5% to 91% [32,33,56-60]. A retention rate of at least 75% was therefore desirable.

3. Adherence rate (the number of yoga practice minutes performed as a proportion of the maximum prescribed). The commonly reported adherence rates in the breast cancer population for yoga interventions range from 75% to 94% [32,33,56-60]. Therefore, an overall adherence rate of at least 75% was desirable.
4. Adverse events rate. To the best of our knowledge, none of the previous studies that evaluated yoga in breast or prostate cancer survivors reported any adverse events [49-51]. Therefore, we anticipated no adverse events attributable to yoga in this study.

In addition to evaluating feasibility, one secondary aim of this study is to evaluate the association of baseline CRF severity with depression, pain and sleep disturbances. As previously noted, preliminary data indicate that CRF co-occurs with depression, pain and sleep disturbances with a potential catalyzing effect [35-37]. We therefore hypothesize in the current study a positive association of CRF severity at baseline with depression, pain and sleep disturbances. Testing this hypothesis may contribute to an understanding of the relationships between CRF and co-occurring symptoms in adult HSCT survivors, which would be useful information needed to optimize interventions targeting CRF in this understudied population. The changes in symptoms (i.e., CRF, depression, pain, sleep disturbances) from baseline to postintervention, together with the longitudinal association of CRF severity with depression, pain and sleep disturbances, will be addressed in a separate publication.

Methods

Participants and recruitment

Participants were recruited from a tertiary care, university-affiliated hospital in the midwestern United States during regularly scheduled clinic appointments. As this study targeted adult HSCT survivors with moderate to severe CRF, the following inclusion criteria were met by each participant: 1) 18 years of age or older at the time of HSCT, 2) at least 100 days after autologous or allogeneic HSCT, 3) no evidence of disease progression or recurrence after HSCT, and 4) a score of 4 or more on a 0-10 numerical scale that asked participants to rate their CRF over the past month. HSCT survivors who practiced regular yoga on their own or those considered to be at increased risk for adverse events (e.g., fall and bleeding complications, cardiopulmonary event, musculoskeletal injury, contraction of communicable infections during yoga classes) were excluded. Therefore, the following exclusion criteria were applied: 1) yoga practice in the past 30 days, 2) the use of supplemental oxygen, 3) active infection, 4) platelet level < 100000/μ, 5) absolute neutrophil count (ANC) < 1000/mm^3, and 6) limitations in physical functioning assessed by a checklist developed by Bower et al. [55] that asked participants to perform simple movements (e.g., going from a standing position to a seated positing on the floor, getting up from a seated position on the floor to a standing position, lifting each leg off the ground).

Before approaching adult HSCT survivors for participation, their eligibility was initially assessed by the first author through reviewing medical records, except for CRF score, yoga practice in the past 30 days, and physical functioning assessment. The two eligibility criteria (i.e., no evidence of disease progression or recurrence, no active infection) were also verified by the treating physician. HSCT survivors who were deemed potentially eligible based on the initial assessment were approached for participation by the treating physician, nurse practitioner, or assistant physician, and those interested in learning more about the study met with the first

author in their examination rooms. The first author explained the study and assessed participant eligibility by checking all of the eligibility criteria, including those initially verified by medical records. The recruitment goal was 20 participants, similar to the sample sizes used in previous studies evaluating the feasibility of yoga interventions in other cancer populations (e.g., breast cancer, lung cancer), which ranged from 7 to 18 participants [51,61-63]. Written informed consent was obtained from all participants. The study protocol was approved by the University of Michigan Medical School Institutional Review Board.

Yoga intervention

Studies that evaluated the effect of yoga on CRF in other populations (e.g., breast cancer, prostate cancer) with positive results have used different intervention durations, ranging from 6 to 12 weeks and from twice to three times weekly [51,53,63,64]. Given the absence of data regarding the safety of yoga after HSCT, we chose the lower end of the intervention dosage range and used a six-week, three times per week yoga intervention. To further enhance safety, we chose a gentle type of yoga that is less likely to cause any adverse events, namely, restorative yoga. Restorative yoga is well known to be less physically demanding than other yoga types [65], and it has been safely tested in other cancer populations, such as breast cancer and ovarian cancer [55,66]. Restorative yoga is based on the teachings of BKS Iyengar and consists of physical postures (asanas) and breathing control (pranayama) [67]. To maximize adherence to practicing yoga three times weekly, participants were asked to attend one restorative yoga class per week and to complete the remainder of their weekly practice at home using a 45-minute DVD. Therefore, the restorative yoga intervention consisted of six weekly yoga classes, each class 1 hour in length (total=360 minutes), with home yoga twice weekly, each home session 45

minutes in length (total=540 minutes). In other words, each participant was given a goal of completing 900 minutes of yoga practice.

Restorative yoga classes were offered at four different community-based cancer centers in southeastern Michigan. Six classes were offered each week, including one weekly evening class (6-7 pm) at each center, with one center also offering two weekly morning classes (11 am-12 pm). All classes were scheduled on weekdays. Each participant was allowed to choose a weekly class that best suited his or her schedule. The classes were taught by certified yoga instructors and conducted for 60 minutes in groups of 6 to 12 participants, including HSCT survivors participating in this study and other cancer survivors attending the community centers. The yoga classes consisted of the following poses (asanas): cross-legged (Sukhāsana), shoulder, neck, and arm stretches, moving child (Balasana), cat/cow (Marjaryasana/Bitilasana), spinal twist (Supta Jaṭhara Parivartānāsana), mountain (Tadasana), Warrior I (Virabhadrasana I), Warrior II (Virabhadrasana II), Triangle (Utthita Trikonasana), reclining hamstring (Supta Padangusthasana), and corpse (Savasana). A description of each pose is provided in Table III.1. Participants were asked to maintain regulated, deep breathing (pranayama) during poses through conscious prolongation of inhalation, breath retention, and exhalation. Props (e.g., blankets, pillows, blocks) were used to provide total support for the body and help participants perform the poses with ease and stability. The DVD for home practice was 45 minutes in length and included instructions to do the same poses performed in the classes except for three poses (i.e., Warrior I, Warrior II, Triangle) that are relatively more strenuous and may be better performed under an instructor's supervision. The DVD instead placed more emphasis on shoulder, neck and arm stretches and the corpse pose (Savasana).

Table III.1: Description of Yoga Poses

Yoga Pose	Description
Cross-legged pose	• Sit in a comfortable position and cross your legs at the ankles
Shoulder Stretch	• Place your left hand on the top of your right shoulder and use your right hand to push at the left elbow
Neck Stretch	• Extend your left arm to your left side and use your right hand to reach across your left ear while slightly stretching your neck muscles
Arm Stretch	• Extend your right arm and use your left arm to twist your upper body to the left side
Moving child pose	• Take a kneeling position, place your head, arms, and torso toward the ground, and move your arms overhead while keeping the palms together
Cat/Cow pose	• Start on all fours with hands under your shoulders and knees under your hips • Inhale, arch your back, and lift your head (cat position) • Exhale, round your spine, and curl your chin (cow position)
Spinal twist pose	• Lie on your back with your knees bent and your feet flat on the floor • Shift your hips to the right and drop your right knee over the left side of your body
Mountain pose	• Take a standing position and place your feet together with ankles, hips, and knees aligned • Tuck the pelvis, lift the ribcage, and comfortably rest your neck
Warrior I pose	• Take a standing position, extend your legs in a wide stance, and lift your arms over your head • Turn your left foot to a 45-degree angle, extend your right leg out, and turn your body to the right
Warrior II pose	• Take a standing position, extend your legs in a wide stance, and lift your arms to the sides of your body • Turn your left foot to a 15-degree angle, exhale and bend your right leg to a 90-degree position
Triangle pose	• Take a standing position, extend your legs in a wide stance with the feet aligned and the back foot in a 60-degree angle towards the front, and extend your arms in a straight line parallel to the ground
Reclining hamstring pose	• Take a supine position with your legs outstretched • Stretch your right leg up toward the ceiling while pressing your left leg towards the floor
Corpse pose	• Take a supine position, close your eyes, turn your gaze inward, and extend your arms slightly away from the sides of your body

Data collection

Baseline data were collected via a questionnaire package provided to participants. Participants were given the choice to fill out the baseline questionnaire package in the clinic after providing consent or to take it home and return it using a stamped, self-addressed envelope to the study team. Participants were also given two weekly logs (home practice log and adverse event log) to be filled out by the end of each practice week. The practice log asked about frequency and length of yoga practice at home. The adverse event log asked participants to grade five items (i.e., numbness, tingling, dizziness, muscle pain, joint pain) according to the Common Terminology Criteria for Adverse Events and one additional item that allowed them to report any other adverse event they thought could be related to yoga practice. The first author called the participants by telephone once weekly during the six-week intervention period to keep track of class attendance and address any questions or concerns that arose. Upon intervention completion, the postintervention questionnaire package was mailed to the participants to fill out and return together with the two weekly logs in a stamped, self-addressed envelope.

Measures

A variety of measures were used in this study. With the exception of demographic and feasibility information, the following data were gathered at baseline and postintervention.

Demographics

The demographic information collected from participants at baseline included age, sex, race, marital status, employment status, cancer type, HSCT type, time since HSCT, and GVHD status and grade.

Feasibility

To evaluate feasibility, we maintained a log containing information on the number of HSCT survivors approached for participation and the number of those who were recruited. The number of HSCT survivors who declined or did not meet the eligibility criteria were recorded. Another log was maintained for the number of participants who dropped out during the study. These logs were used to calculate the accrual acceptance and retention rates. Data obtained from the home practice logs and weekly telephone calls were used to calculate overall adherence. Data obtained from the adverse event logs were used to calculate the adverse event rate.

Cancer-related Fatigue

CRF was assessed using two measures: The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) and the Patient-Reported Outcome Measurement Information System-Short Form (PROMIS-SF)-general CRF. The MFSI-SF includes 30 items that produce five subscales: general CRF, physical CRF, emotional CRF, mental CRF, and vigor. The MFSI-SF-total CRF score can be calculated by summing the first four subscales (MFSI-SF-general CRF, MFSI-SF-physical CRF, MFSI-SF-emotional CRF, MFSI-SF-mental CRF) and then subtracting the resulting score from the MFSI-SF-vigor subscale. The total score can range from 0 to 24 for individual subscales and from -24 to 96 for MFSI-SF-total CRF. Higher scores indicate greater CRF. Very good psychometrics have been reported for the MFSI-SF with internal consistency for individual subscales ranging from 0.87 and 0.96 [68]. The PROMIS-SF-general CRF is an 8-item scale that measures one CRF dimension (general CRF) over the past 7 days. The total score is calculated by summing the 8 items and can range from 8 to 40. Higher scores indicate greater general CRF. The PROMIS-SF-general CRF has demonstrated good psychometric properties with reliability coefficients ranging from 0.72 to 0.88 and concurrent validity ranging from 0.6 to 0.85 [69].

Depression

Depression was assessed using the PROMIS-SF-depression, which is an 8-item questionnaire that assesses depression over the past 7 days. The total score can be calculated by summing the 8 items and can range from 8 to 40. Higher scores indicate greater depression. The PROMIS-SF-depression has demonstrated good validity and reliability coefficients (Cronbach's alpha=0.91) [70].

Sleep disturbances

Sleep disturbances were assessed using the PROMIS-SF-sleep disturbances, which is an 8-item questionnaire that assesses sleep disturbances in the past 7 days. The total score can be calculated by summing the 8 items and can range from 8 to 40. Higher scores represent more sleep disturbances. The PROMIS-SF-sleep disturbance has demonstrated acceptable psychometric properties (Cronbach's alpha=0.86) [70].

Pain

Pain was measured using the Brief Pain Inventory-Short Form (BPI-SF), which is an 11-item questionnaire that assesses pain in the past 24 hours including right now. The BPI-SF includes 2 subscales: pain severity (4 items) and pain interference (7 items). The BPI-SF-pain severity subscale asks patients to rate their pain at its "worst," "least," and "average" during the past 24 hours and "right now" on 0 to 10 scales (0= "no pain", 10= "pain as bad as you can imagine"). The BPI-SF-pain interference subscale asks patients to rate how their pain interferes with their enjoyment of life, activity, walking, mood, sleep, work, and relationships with others on 0 to 10 scales (0= "does not interfere" and 10= "interferes completely"). The BPI-SF-pain severity score is obtained by calculating the mean of the 4 pain intensity items, and the BPI-pain interference score is obtained by calculating the mean of the 7 interference items [71]. The total

score can range from 0 to 10 for both the severity and interference subscales. Higher scores indicate more pain severity or interference. The BPI-SF has demonstrated good psychometric properties with high internal consistency (Cronbach's alpha=0.87) [72].

Statistical analysis

The data were analyzed using SPSS Version 22.0. Frequency distribution and descriptive statistics were generated, and recruitment, retention, protocol adherence, and adverse event rates were calculated. Assumptions of distributional normality were tested using the Shapiro-Wilk test, which is considered the most powerful normality test in studies with sample sizes smaller than 29 [73,74]. Pearson correlation coefficient was used to evaluate the association of CRF severity at baseline with depression, pain and sleep disturbances. Unpaired Student's t tests were used to compare baseline characteristics of participants who completed the study with those who dropped out. All analyses of significance were two-sided. A p value of less than 0.05 was considered statistically significant.

Results

Feasibility

Accrual acceptance

Eighty-six HSCT survivors were invited to participate in this study between December 2017 and May 2018, of whom 42 declined participation prior to eligibility assessment. The reasons these HSCT survivors gave for declining participation were a lack of interest in yoga or the study in general (n=22), long travel distance to the intervention site (community center) (n=13), general time constraints (n=5), or feeling too sick to participate (n=2). Of the 44 who expressed interest in the study and were screened for eligibility, 24 were deemed ineligible for the following reasons: not meeting the criteria of moderate to severe CRF (n=14), limitations in

physical functioning (n=7), or practicing yoga on their own during the past 30 days (n=3). Recruitment was considered complete when 20 HSCT survivors met all of the eligibility criteria and provided signed informed consent. Therefore, the accrual acceptance rate was 23.2% (20/86).

Retention

Of the 20 participants enrolled, five dropped out before starting the intervention, and three of them also did not return the baseline questionnaire package despite two reminders. Reasons for dropout included lost to follow-up (did not return phone calls), deterioration of health status (acute exacerbation of chronic sinusitis), lost interest in the study, concerns about yoga safety (participant reported balance problems and fear of falling while doing yoga), and unplanned surgery (left anterior accessory vein radiofrequency ablation) scheduled one week after joining the study. Of the remaining 15 participants who started the intervention, three dropped out prior to intervention completion for the following reasons: 1) one participant dropped out in week 2 of the intervention due to family crises and lack of time; 2) one participant dropped out in week 2 of the intervention due to health deterioration (fever and weight loss); and 3) one participant was lost to follow-up (did not return phone calls) in week 4 of the intervention. The remaining 12 participants were active in the study until intervention end and returned the postintervention questionnaire, which means that we had a retention rate of 60% (12/20). Last, with the exception of one participant, who did not return his adverse event and practice logs, home practice and adverse event data were available for all of the participants who started the intervention. A flow diagram of participant enrollment and retention is presented in Figure III.1.

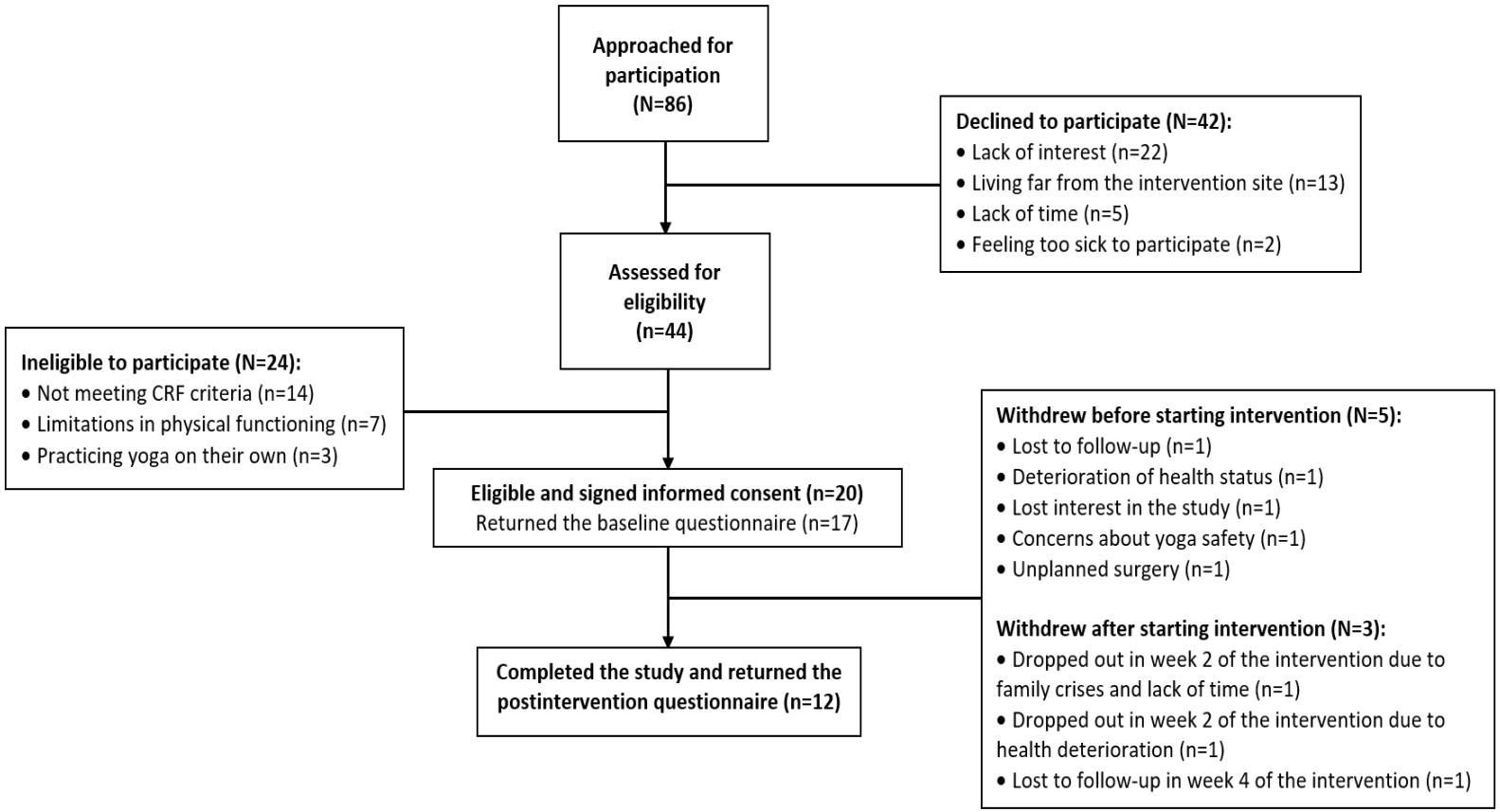

Figure III.1: Flow Diagram of Participant Recruitment, Enrollment, and Retention

Patient characteristics

Twenty HSCT survivors (13 women and 7 men) enrolled in this study. The participants ranged in age from 28 to 72 years (mean [SD], 51(12.5)). Most were Caucasian (n=17, 85%), married (n=13, 65%), and unemployed (n=7, 35%). Of the 20 participants, eight had acute myeloid leukemia (AML) (40%), three had diffuse large B-cell lymphoma (DLBCL) (15%), two had acute lymphoblastic leukemia (ALL) (10%), two had myelodysplastic syndrome (MDS) (10%), one had mixed phenotype acute leukemia (MPAL) (5%), one had myelofibrosis (5%), one had Hodgkin's lymphoma (HL) (5%), one had follicular lymphoma (FL) (5%), and one had multiple myeloma (MM) (5%). The sample consisted of 19 allogeneic HSCT survivors (95%), 13 of whom were known to have GVHD (68.4%) (grade 1-2: n=4, grade 3-4: n=3, grade unspecified: n=6), and one autologous HSCT survivor (5%). The participants were four months to 7.6 years post HSCT (mean [SD], 3.3 [2.3] years). Participant characteristics are presented in Table III.2.

Table III.2: Participant Characteristics

Characteristic	**X̄ (SD); range**
Age (years)	51 (12.5); 28-72
Characteristic	**n (%)**
Sex	
Male	7 (35%)
Female	13 (65%)
Race	
White	17 (85%)
Black	1(5%)
Asian	1(5%)
Other	1(5%)
Relationship Status	
Married	13(65%)
Partnered	1(5%)
Single	3(15%)
Missing data	3(15%)
Employment Status	
Employed	5(25%)
Unemployed	7(35%)
Retired	5(25%)
Missing data	3(15%)
Cancer type	
Acute myeloid leukemia	8 (40%)
Acute lymphoblastic leukemia	2 (10%)
Mixed phenotype acute leukemia	1 (5%)
Myelodysplastic syndrome	2 (10%)
Myelofibrosis	1 (5%)
Hodgkin's lymphoma	1 (5%)
Diffuse large B-cell lymphoma	3 (15%)
Follicular lymphoma	1 (5%)
Multiple myeloma	1 (5%)
Comorbidities (other than GVHD)	
Multiple sclerosis	1 (5%)
Arthritis	1 (5%)
Diabetes	1 (5%)
Cardiomyopathy	1 (5%)
No comorbidities	13 (65%)
Missing data	3 (15%)
Time since HSCT	
100 days to 6 months	2 (10%)
6 months to 1 year	3 (15%)
1-3 years	5 (25%)
3-5 years	5 (25%)
5-7 years	4 (20%)
7-8 years	1 (5%)
HSCT type	
Allogeneic	19 (95%)
Autologous	1 (5%)
GVHD status and staging of recipients of allogeneic HSCT (n=19)	
No GVHD	3 (15.7%)
Yes:	13 (68.4%)
Grade 1-2	4 (21%)
Grade 3-4	3 (15.7%)
Grade unspecified	6 (31.5%)
GVHD status unknown	3 (15.7 %)

HSCT: Hematopoietic stem cell transplant; GVHD: Graft versus host disease

As previously noted, eight participants dropped out of the study, five before and three after starting the intervention. Of the five participants (age average [SD]: 54.8 [10.3] years; female: n=3; male: n=2) who dropped out prior to participation, two had AML (40%), one had MDS (20%), one had DLBCL (20%), and one had myelofibrosis (20%). These participants were 4 months to 4.2 years post HSCT (mean [SD], 1.6 [1.3] years). All five of these participants received allogeneic HSCT (n=5); two had GVHD (grade 1-2) (40%), and three had an unknown GVHD status (60%). Of the three participants (average age [SD]: 60.6 [3.2] years; female: n=2; male: n=1) who dropped out after starting the intervention, two had AML (66.7%) and one had MDS (33.3%), and they were 2 to 5.9 years post HSCT (mean [SD], 4.3 [1.6] years). All three underwent allogenic HSCT (n=3) and had GVHD (grade 1 to 2: n=1; grade 3 to 4: n=1; grade unspecified: n=1). Of the remaining 12 participants (age average [SD]: 47.2 [12.8] years; female: n=8; male: n=4) who completed the study, four had AML (33.3%), two had ALL (16.6%), two had DLBCL (16.6%), one had MPAL (8.3%), one had HL (8.3%), one had FL (8.3%), and one had MM (8.3%). These participants were 7 months to 7.6 years post HSCT (mean [SD], 3.6 [2.2] years). Eleven participants underwent allogeneic HSCT (91.7%), eight of whom had GVHD (grade 1-2: n=1; grade 3-4: n=2; grade unspecified: n=5) (72.7%), and one underwent autologous HSCT (8.3%). There were no statistically significant differences in any of the baseline characteristics between the participants who completed the study (n=12) and those who dropped out (n=8).

Protocol adherence

The class participation rate for the 15 participants who started the intervention was 37.8% (2.26 classes/participant of the six classes prescribed). The average amount of home practice per participant over the 6-week intervention period for the 14 participants with home practice data

available was 292.8 minutes of the 540 minutes prescribed. Therefore, adherence to biweekly home practice was 54.2%. The overall adherence rate incorporating class and home practice for the 15 active participants was 45.4% (409.3 minutes/participant of the 900 minutes prescribed).

Adverse events

Two participants reported mild or moderate joint pain during the intervention period, but further communication with them revealed that their pain was chronic and preexisting and that it was not caused or worsened by yoga postures. Therefore, no adverse events attributable to yoga were reported by HSCT survivors in this study.

CRF association with depression, pain and sleep disturbances

To evaluate the association of baseline CRF severity with depression, pain and sleep disturbances, we included data from participants who completed the baseline assessments (n=17). The correlations between the CRF dimensions (i.e., total CRF, physical CRF, general CRF, mental CRF, emotional CRF) and the measures of depression, sleep disturbances, and pain were mostly positive, ranging from -0.02 to 0.68. Weak to moderate correlations, ranging from 0.06 to 0.68, were found between the CRF dimensions and the PROMIS-SF-sleep disturbances and PROMIS-SF-depression scales. The BPI-SF-pain severity and BPI-SF-interference subscales showed a similar pattern of correlates with the CRF dimensions as the measures of sleep disturbances and depression but at a lower magnitude; correlations ranged from -0.02 to 0.29. Furthermore, the MFSI-SF-vigor subscale correlated negatively and fairly weakly with PROMIS-SF-depression, PROMIS-SF-sleep disturbances, BPI-SF-pain severity and BPI-SF-pain interference, correlations ranged from -0.02 to -0.34. The correlations of CRF with depression, pain and sleep disturbances are presented in Table III.3.

Table III.3: Correlation Coefficients between Measures at Baseline

Outcome	PROMIS-SF-depression ($\bar{X}$= 14.7, SD=6.8)†[b]	PROMIS-SF-sleep disturbances ($\bar{X}$= 23.9, SD=6.9)†[b]	BPI-SF-pain severity ($\bar{X}$=2.4, SD=2)†[c]	BPI-SF-pain interference ($\bar{X}$=1.8, SD=1.8)†[c]
MFSI-SF-total CRF ($\bar{X}$= 35.7, SD=15.7)†[a]	0.42	*0.52**	0.12	0.29
MFSI-SF-general CRF ($\bar{X}$=13.7, SD=5)†[a]	0.26	0.34	-0.02	0.20
MFSI-SF-physical CRF ($\bar{X}$=10.7, SD=4.6)†[a]	0.06	0.42	0.16	0.28
MFSI-SF-mental CRF ($\bar{X}$=11.5, SD=5)†[a]	0.12	0.22	0.24	0.24
MFSI-SF-emotional CRF ($\bar{X}$=8.7, SD=4.7)†[a]	*0.68***	*0.57**	0.16	0.21
MFSI-SF-vigor ($\bar{X}$=9, SD=3.2)†[a]	-0.34	-0.22	-0.25	-0.02
PROMIS-SF-general CRF ($\bar{X}$=26.2, SD=5.7)†[b]	0.27	0.34	0.15	0.19

Abbreviations: CRF: Cancer-related fatigue; MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form; PROMIS-SF: Patient-Reported Outcome Measurement Information System-Short Form; BPI-SF: Brief Pain Inventory-Short Form

**Correlation is statistically significant at $\alpha < 0.05$.*

***Correlation is statistically significant at $\alpha < 0.01$.*

† Mean and standard deviation at baseline

[a]The total score can range from 0 to 24 for the individual MFSI-SF subscales and from -24 to 96 for the MFSI-SF-total CRF scale.

[b]The total score can range from 8 to 40 for the PROMIS-SF-general CRF, PROMIS-SF-depression, and PROMIS-SF-sleep disturbances scales.

[c]The total score can range from 0 to 10 for the BPI-SF-severity and BPI-SF-interference subscales.

All the correlation coefficients reported in this table are Pearson's R since scores are normally distributed.

Discussion

Feasibility

This study evaluated the feasibility of a restorative yoga intervention in adult HSCT survivors who were at least 100 days after transplant and reported moderate to severe CRF. The study failed to achieve the targeted accrual acceptance rate of at least 40% commonly reported in yoga studies in breast cancer survivors [32,33,56-60]. Our recruitment strategy may have contributed to the low accrual acceptance rate (23.2%). Given the feasibility nature of the present study, only one recruitment strategy was employed: approaching HSCT survivors during their scheduled clinic appointments. However, most HSCT survivors we met during recruitment were allogeneic HSCT survivors presenting to the clinic for GVHD management. Therefore, we had little access to other HSCT populations, including allogeneic HSCT survivors without GVHD and autologous HSCT survivors. Data increasingly suggest that HSCT survivors with GVHD experience decreases in functional capacity and physical performance that are greater than those experienced by survivors without GVHD [75,76]. GVHD pathogenesis involving a high inflammatory state can lead to physical deconditioning [42,75]. High-dose, long-term steroids used to treat GVHD can also lead to the degeneration of muscle fibers and subsequent muscle weakness and wasting that reduces exercise tolerance [77]. It is therefore possible that GVHD and associated physical and muscle deconditioning contributed to a lack of interest in yoga, feeling too sick to participate, or an unwillingness to drive long distances to the intervention site, which were the reasons HSCT survivors provided for declining participation in the current study. Another reason HSCT survivors provided for declining participation was general time constraints, which is a commonly reported reason for not participating in yoga interventions [48,57,58].

Another possible explanation for our low accrual acceptance rate lies in the immune status of HSCT survivors. The conditioning regimen that HSCT survivors typically receive prior to transplant is myeloablative and more intensive than other chemotherapy regimens received by other cancer populations [78]. Conditioning regimens can also cause severe and recurrent neutropenia beyond the nadir phase of treatment [79]. Even with normal levels of ANC ($\geq$1,500/mm^3), HSCT survivors' immunity may remain altered for several years after transplant, mainly due to immunosuppressive treatments used in GVHD management that interfere with the signaling of key inflammatory regulators (e.g., NF-κB, AP-1) needed to activate an immune response [80]. These two factors (conditioning regimen and post-HSCT immunosuppression) are unique to the HSCT population, which may contribute to a perception of vulnerability to communicable infections (e.g., influenza) that is greater among HSCT survivors than cancer survivors not treated by HSCT. This perception of vulnerability may make HSCT survivors less willing to participate in group-based yoga classes that involve sharing props and mats and being physically close to other participants due to the potential risk of contracting communicable infections.

We did not meet the targeted retention rate of at least 75% commonly reported in yoga research in women with breast cancer [32,33,56-60]. Nevertheless, our retention rate (60%) falls within the range (58% to 66%) of a few other yoga studies in breast and lung cancer survivors [31,62,81]. The reasons for the relatively low retention in our study and some studies in cancer survivors but not others are unclear, with no pattern that differentiates studies with low versus high retention rates. It is possible that the level of participation required and the characteristics of the patients included (e.g., presence of comorbidities) influenced attrition. It is also worth noting that the majority of the reasons (i.e., lost to follow-up, family crises, lack of time, loss of interest

in the study, unplanned surgery, heath deterioration) for participant dropout in the current study are also commonly reported in yoga trials in breast cancer survivors [51,53,59,81]. One participant dropped out before starting the intervention due to fear of falling while doing yoga. This reason for dropout, however, has not to our knowledge been previously reported in a yoga study. Whether the fear of falling while doing yoga reported by one participant in this study represents an individual case or a general phenomenon among HSCT survivors is an area worthy of further investigation.

Although there were no statistically significant differences in the baseline characteristics between participants who completed the study (n=12) and those who dropped out (n=8), there were some differences. Study completers were, on average, younger ($\bar{X}$=47.2 years) than those who withdrew both before ($\bar{X}$=54.8 years) and after ($\bar{X}$=60.6 years) starting the intervention. Furthermore, the five participants who withdrew prior to participation were on average 1.6 years after HSCT compared to 4.3 years for those who withdrew after starting the intervention and 3.6 years for study completers. In addition, of the 8 dropouts, five had GVHD, and three had an unknown GVHD status. On the other hand, all three patients with no GVHD diagnosis at baseline completed the study. It is therefore possible that older age, more recent HSCT (less than 18 months ago), and a diagnosis of GVHD are factors associated with increased dropout from a yoga intervention among adult HSCT survivors. No other noticeable differences were observed in the characteristics of study completers versus dropouts with regard to gender, underlying malignancy, and GVHD grade. Since our study included only one autologous HSCT survivor, no conclusions can be made regarding whether HSCT type is a factor in yoga study completion. However, given that autologous HSCT is associated with fewer complications, most importantly

GVHD [82], it is possible that autologous HSCT survivors are more likely to complete a yoga intervention than their allogeneic counterparts.

The uptake of the yoga intervention in the current study was low, with an overall adherence rate of 45.4%, which means that we did not meet the targeted protocol adherence of at least 75%. Our low adherence rate could be partly the result of the class schedule. Classes were offered only on certain days of the week, all of which were weekdays, which might have been a deterrent for participants with a full-time job. Additionally, although yoga classes were offered at four different community cancer centers, those centers were relatively close (approximately 16 miles apart). This geographic distribution might have eased class attendance for participants who lived in close proximity to the community centers, allowing them to choose the one closest to their homes. Nevertheless, travel possibly remained a burden for the majority of the participants. Inclement weather might have also contributed to low class participation, as approximately half of our sample was recruited into the study between December 2017 and February 2018. Therefore, these participants received the intervention during winter in Michigan and might have preferred not to drive during snowy weather. High inflammatory activity and muscle weakness associated with GVHD might also have contributed to low adherence. It is also worth noting that qualitative studies in breast cancer survivors suggest that CRF itself can pose a challenge to initiating and sustaining physical activity [83,84]. Therefore, the moderate to severe CRF experienced by HSCT survivors in this study may have also been a factor. Lastly, similar to previous yoga research in breast cancer and prostate cancer survivors [49-51], none of the participants in the present study reported any adverse event attributable to yoga practice. This finding is of particular importance given the fragility of HSCT survivors, which makes the administration of safe physical activity interventions in this population crucial.

In summary, of the four feasibility parameters, we met our target of no adverse events and failed to meet the targeted accrual acceptance, retention and protocol adherence rates. Given evidence of an association between GVHD and decreases in physical functioning [6,75-77], HSCT survivors without GVHD may be more willing to enroll in and commit to a yoga intervention. A future yoga trial for efficacy may therefore be feasible from accrual acceptance, retention, and protocol adherence standpoints if multiple recruitment strategies (e.g., mail out a letter to all people who underwent HSCT more than 100 days ago) are employed, which can allow access to sufficient numbers of autologous and allogeneic HSCT survivors with and without GVHD. One strategy to reduce the travel burden in a future yoga trial is offering classes at a wider variety of community settings in more distant locations. It is also important to offer classes on both weekdays and weekends and at a greater variety of times during the day. This approach may increase class participation by taking into account the competing commitments that HSCT survivors may have. Another strategy to encourage class participation is allowing HSCT survivors to bring a support person (e.g., spouse, friend) with them to the yoga classes. This strategy has been previously used in one study in prostate cancer survivors with high adherence to yoga classes (87%) [51], although the study did not demonstrate a direct link between class participation and the companion's presence. Compensating for home practice and travel to yoga classes may also contribute to better adherence.

CRF association with depression, pain and sleep disturbances

Most of the correlations between the CRF dimensions (i.e., total CRF, physical CRF, general CRF, mental CRF, emotional CRF) and the measures of depression, pain and sleep disturbances were positive, which indicates that CRF after HSCT is likely to occur in association with other cancer-related symptoms. This finding is supported by data in breast cancer survivors

suggesting that depression, pain and sleep disturbances are driven by the same underlying mechanism as CRF, elevated inflammatory markers [35-37]. Baseline scores for two CRF dimensions (i.e., total CRF, emotional CRF) correlated significantly with PROMIS-SF-sleep disturbances. This finding is consistent with a study by Gielissen et al. [13] that compared sleep disturbances in adult HSCT survivors with severe CRF to others with no or mild CRF and found more sleep disturbances among those with severe CRF. Additionally, baseline scores for emotional CRF, which is the CRF dimension to most likely be linked to depression, correlated significantly with PROMIS-SF-depression. In accord with this finding, Hann et al. [85] evaluated the factors associated with CRF in HSCT survivors and found depression was the most significant correlate with CRF, explaining 63% of the variability in CRF severity.

The correlations between the CRF dimensions and the BPI-SF-pain severity and BPI-SF-interference subscales, despite missing statistical significance, were, in large part, in the expected direction. To our knowledge, no previous studies have tested the correlation between pain and CRF in HSCT survivors. The co-occurrence of these two symptoms is, however, well documented in women with breast cancer [86,87]. For example, Bower et al. [88] found that in a large cohort of 1,957 breast cancer survivors, pain was among the three strongest correlates of CRF in addition to depression and sleep disturbances. The correlations between vigor and the measures of depression, sleep disturbances, and pain were also all in the expected direction, indicating a negative relationship. Overall, with the exception of pain showing no significant correlations with any of the CRF dimensions, our hypothesis that CRF severity at baseline would be positively associated with depression, sleep disturbances and pain is supported by the results. By supporting this hypothesis, our study provides preliminary data for future large-scale studies

aiming to understand the relationships between CRF and co-occurring symptoms in adult HSCT survivors.

Limitations and strengths

There are four limitations of this study. First, the sample was relatively homogeneous, primarily consisting of allogeneic HSCT survivors with GVHD. The study results may thus have limited generalizability to other HSCT populations, including autologous HSCT survivors and allogeneic HSCT survivors without GVHD. Second, we did not check the fidelity of intervention implementation, and therefore it is unknown to what extent the yoga instructors were consistent in intervention delivery. Third, the duration of the intervention was short compared to the longer yoga interventions (8 to 12 weeks) commonly used in yoga trials in breast and prostate cancer survivors [49-51]. It is possible that a longer intervention would have resulted in a higher attrition rate. Fourth, the study had a small sample size recruited to assess the feasibility of a yoga intervention offered to adult HSCT survivors. Therefore, it was not statistically powered to evaluate CRF association with co-occurring symptoms. One strength of the present study is that it is the first to evaluate yoga in adult HSCT survivors, providing the foundation needed to conduct and design a larger study to more fully evaluate yoga for CRF.

Implications for practice and research

This study has implications for clinical practice. None of the participants reported any adverse event attributable to yoga. Data demonstrating that restorative yoga is safe for adult HSCT survivors may be useful information for clinicians if patients ask about this type of yoga. It should be taken into account, however, that our study promoted safety, mainly through including adult HSCT survivors who were at least partially immunocompetent (ANC≥1000/mm3) and physically capable of performing yoga postures. Clinicians may need to

consider those and other factors (e.g., platelet count and risk of bleeding, lung function and breathing capacity) when weighing restorative yoga's appropriateness for individual HSCT survivors. Additionally, the results indicate that depression and sleep disturbances can be associated with CRF severity after HSCT. Clinicians aiming to optimize CRF management may therefore consider treatment options that address not only CRF but also the related symptoms that may contribute to it. This study also has implications for research. The results suggest that a future yoga trial for efficacy needs to include methods for recruiting adult HSCT survivors with greater variability in HSCT type and GVHD status. A future randomized, phase II clinical trial may also need to address the weaknesses identified in this study by including a larger sample of adult HSCT survivors, using a longer yoga intervention and checking the fidelity of intervention implementation.

Conclusion

As a first step towards testing the efficacy of yoga in reducing CRF after HSCT, this study evaluated its feasibility among adult HSCT survivors. The study indicates that a yoga trial in adult HSCT survivors is feasible from a safety standpoint and needs to employ strategies to improve accrual acceptance, retention, and protocol adherence rates. Depression and sleep disturbances may co-occur with CRF after HSCT with a potential catalyzing effect.

Acknowledgements

Special thanks are due to Dr. Dale Bixby, hematologist-oncologist, for his help with subject recruitment. Many thanks are also due to Dr. Corey Powell, Bio-statistician, for his valuable guidance in statistical analysis.

Funding Statement

This research was supported by a grant from the Oncology Nursing Society Foundation (ONSF): ONSF Dissertation Grant [17-PAF08181], awarded to the first author.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Potential Benefits of Yoga for Hematopoietic Stem Cell Transplant Survivors with Cancer-Related Fatigue: A Feasibility Pilot Study

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Abstract

Background: Despite its potential benefits in cancer survivorship, yoga has not been tested in cancer survivors treated with hematopoietic stem cell transplantation (HSCT). The primary aim of this feasibility pilot study is to evaluate the potential benefits of yoga for adult HSCT survivors with moderate to severe cancer-related fatigue (CRF). The secondary goals are 1) to evaluate the association of CRF change with changes in depression, sleep disturbances, pain, and physical activity; and 2) to evaluate the association of yoga adherence with self-efficacy and self-regulation skills and abilities.

Methods: This feasibility pilot study employed a single-arm, pretest–posttest design. Twenty adult HSCT survivors were enrolled in a 6-week restorative yoga intervention that consisted of a 1-hour once-weekly class with twice-weekly home practice using a DVD.

Results: Twenty adult HSCT survivors enrolled in this study, of whom 12 completed the yoga intervention. Participants reported postintervention improvements in two CRF dimensions, general CRF (d=-0.75) and physical CRF (d=-0.66), along with vigor (d=0.63) and sleep disturbances (d=-0.81) (all Ps<0.05). Improvements in two or more of the CRF dimensions (i.e., total CRF, general CRF, physical CRF, mental CRF, emotional CRF) correlated significantly with reductions in depression, sleep disturbances, pain severity, and pain interference; correlations ranged from 0.58 to 0.86 (all Ps<0.05). Improvements in three CRF dimensions (general CRF, mental CRF, emotional CRF) also correlated significantly with increases in self-reported physical activity; correlation coefficients ranged from -0.58 to -0.60 (all Ps<0.05). Correlations between overall adherence and self-efficacy and self-regulation skills and abilities were not statistically significant, ranging from -0.29 to 0.41.

Conclusion: The reported reductions in CRF dimensions and sleep disturbances are promising and provide the foundation for hypotheses to be tested in subsequent large clinical trials. The association of CRF dimensions with depression, sleep disturbances, pain, and physical activity indicates that CRF after HSCT is a complex and multifactorial symptom partly related to concurrent symptoms and physical activity levels. The relationship between yoga adherence and self-efficacy and self-regulation skills and abilities needs to be reevaluated with larger samples.
Keywords: Cancer-related Fatigue; Hematopoietic Stem Cell Transplantation; Self-efficacy; Self-regulation; Yoga

Introduction

Hematopoietic stem cell transplantation (HSCT) is a treatment modality for several hematologic malignancies, such as leukemia, lymphoma and multiple myeloma [1]. HSCT recipients usually receive a high dose of chemotherapy that is also known as a conditioning regimen [2]. This regimen eradicates a patient's bone marrow and thus it is followed by HSCT, either from the patient (autologous) or from a donor (allogeneic) [3]. Advances in HSCT practice have led to improved survival after HSCT, three-year survival rates ranging from 27% to 91% [4]. Yet, the health-related quality of life (HRQOL) among adult HSCT survivors is usually compromised due to the burden of treatment side-effects and chronic symptoms [5-8]. Cancer-related fatigue (CRF) is one of the most common symptoms experienced by this population, occurring in 35% to 84% of people who survive more than 100 days after HSCT [9-12].

CRF is defined by the National Comprehensive Cancer Network defines as a distressing, subjective sense of physical, emotional, and cognitive tiredness related to cancer or cancer treatment that is not proportional to recent activity [13]. The physiological mechanism of CRF is not fully understood. It is hypothesized that in response to cancer and its treatments, inflammatory cytokines signal the central nervous system and generate CRF by altering neural processes [14]. Other potential mechanisms include alterations in the hypothalamic-pituitary-adrenal axis and latent viral reactivation [15-17]. Physical exercise has evidence for reducing CRF and is recommended by multiple clinical practice guidelines [13,18]. However, adult HSCT survivors often remain in a fragile state of physical health for several years after transplant with a high prevalence of short- and long-term complications [19,20]. For example, numerous studies in allogeneic HSCT survivors report a 27% to 72% incidence of graft-versus-host disease (GVHD) [21-23], which occurs when donor's T lymphocytes initiate an immune reaction against patient

organs [23]. GVHD has been associated with physical deconditioning [24-26], potentially making it harder to perform physical exercise.

Alternatives to manage CRF beyond physical exercise are limited. Among these alternatives, yoga has preliminary evidence for improving CRF, with most supportive data coming from studies in women with breast cancer [27,28]. Yoga is an Eastern tradition that includes meditation techniques, regulated breathing and bodily postures [29]. Several studies suggest that yoga interferes with one potential mechanism of CRF by reducing inflammatory activity [30-32]. There is also preliminary evidence for yoga in improving other symptoms that frequently co-occur with CRF, including depression, sleep disturbances, and pain [33-36]. The beneficial effects of yoga on these other symptoms could be because they are driven by the same underlying mechanism as CRF, elevated inflammatory markers [37-41]. It is therefore possible that CRF reduction in HSCT survivors would be associated with improvements in concurrent symptoms (i.e., depression, sleep disturbances, pain). Alleviating CRF may also improve physical activity, as a large body of research suggests [42-44]. For example, in one study by So, Dodgson, & Tai [8] including 157 adult HSCT survivors, participants with moderate or severe CRF reported lower physical activity scores compared to those with no or mild CRF. It is therefore also possible that CRF improvement after HSCT can contribute to increases in physical activity levels.

Despite the potential of yoga as treatment for CRF, HSCT survivors may face barriers to yoga practice that hinder adherence, such as accessibility and time constraints. It is thus important to understand the factors associated with adherence to yoga to maximize its potential benefits. Self-efficacy, defined by Bandura [45] as the degree of confidence one has in the ability to perform an intended behavior, is considered one of most important factors that influence

adherence to health-related behaviors [46-48]. In one study by Desharnais, Bouillon, & Godin [49] evaluating the determinants of adherence to a physical exercise program in healthy adults, participants were classified as adherers and non-adherers based on their level of participation and number of exercise classes attended. The results showed that adherers had higher self-efficacy scores than those classified as non-adherers [49]. Additionally, according to Individual and Family Self-Management Theory (IFSMT) [50], people are more likely to adhere to health behaviors if they develop self-regulation skills and abilities (i.e., goal setting, self-monitoring, reflective thinking, decision-making, action planning, action, and self-evaluation) to carry out a recommended behavior, and this position by the IFSMT is supported by several studies [51-54]. For example, a randomized trial by Janssen, De Gucht, van Exel, and Maes [55] found improvements in exercise adherence after a motivational interviewing intervention targeting self-regulation skills and abilities in postcardiac rehabilitation patients. The Theory of Symptom Self-Care Management in Cancer [56] further posits that self-efficacy and self-regulation skills and abilities moderate the benefits of symptom self-care management behaviors by impacting adherence to the behavior being studied. Based on the theoretical works discussed and supporting evidence for self-efficacy and self-regulation skills and abilities in improving adherence to health-related behaviors [45-57], it is plausible that self-efficacy and self-regulation skills and abilities can moderate the benefits of yoga by affecting HSCT survivors' adherence to yoga practice.

Purpose

Despite the potential benefits of yoga in cancer survivorship, to our knowledge, it has not been tested in an HSCT population. The primary objective of this single-arm, pretest–posttest feasibility pilot study is to evaluate the potential benefits of yoga for adult HSCT survivors with

moderate to severe CRF, which may generate preliminary data needed to implement larger scale efficacy studies to more fully examine the benefits of yoga in this population. Based on data in breast cancer survivors showing promising results for yoga in improving CRF, depression, sleep disturbances, pain, and physical activity [32-36,58-60], we hypothesize statistically significant improvements in those outcomes from baseline to postintervention. This study also has two secondary aims. The first secondary aim is to evaluate the association of CRF change with changes in depression, sleep disturbances, pain, and physical activity. Based on previous findings in women with breast cancer showing that CRF correlates negatively with physical activity [43,44] and positively with depression, sleep disturbances, and pain [37-39], we hypothesize that improvements in CRF from baseline to postintervention will be associated with increased physical activity and decreased depression, sleep disturbances, and pain. The second secondary aim is to evaluate the association of adherence to yoga practice with self-efficacy and self-regulation skills and abilities. As previously noted, theoretical work indicates that self-efficacy and self-regulation skills and abilities moderate the benefits of yoga by impacting yoga adherence [56]. Since the current study is grossly underpowered to test for moderation effects, we evaluate the association of yoga adherence with self-efficacy and self-regulation skills and abilities, which may provide support for potential hypotheses to be investigated in future adequately powered studies. We hypothesize in the current study a positive association of three adherence measures (i.e., number of classes attended, number of minutes of home practice, overall adherence) with baseline and postintervention scores for self-efficacy and self-regulation skills and abilities. The feasibility outcomes (i.e., recruitment, retention, protocol adherence, and adverse event rates) will be fully addressed in a separate publication.

Methods

Participants and recruitment

This study was approved by the University of Michigan Medical School Institutional Review Board, and fully informed, written consent was obtained from all participants. Participants were recruited during regularly scheduled clinic appointments. This study included adults who underwent autologous or allogeneic HSCT at least 100 days previously, had no evidence of active disease, and had moderate to severe CRF. The presense of moderate to severe CRF was indicated by scores of 4 or more on a 0-10 numerical scale. Other eligibility criteria included (1) no current yoga practice (i.e., had not practiced yoga in the past 30 days), (2) no physical contraindications to restorative yoga, (3) no active infection, (4) platelet count ≥ 100000/μ, and (5) absolute neutrophil count (ANC) ≥ 1000/mm^3. These criteria were mainly designed to ensure participant safety. The recruitment goal was 20 participants.

Yoga intervention

Participants were given a goal of practicing yoga three times per week, including six weekly yoga classes, each class 60 minutes in length, with home yoga twice weekly, each home session 45 minutes in length. Therefore, each participant was given a goal of completing 900 minutes of yoga practice. To accommodate for different schedules, six classes were offered each week at four different community-based cancer centers in southeastern Michigan. One weekly evening class (6-7 pm) was offered at each center, with one center also offering two weekly morning classes (11am-12 pm). The classes were taught by certified yoga instructors. The type of yoga used in this study was restorative yoga, a gentle type of yoga that is less physically demanding than other yoga types [60-66]. Restorative yoga classes started with 10 minutes of stretching exercises to promote relaxation, followed by 40 minutes of seated, standing and supine poses (Table III.4), and closed with 10 minutes of guided relaxation and mediation. The DVD for

home practice included instructions to do the same poses performed in the classes but placed more emphasis on stretching and breathing exercises.

Table III.4: List of Yoga Poses

Yoga pose [a]
Cross-legged pose
Shoulder Stretch
Neck Stretch
Arm Stretch
Moving child pose
Cat/Cow pose
Spinal twist pose
Mountain pose
Warrior I pose
Warrior II pose
Triangle pose
Reclining hamstring pose
Corpse pose

[a] A full description of each pose is available from the first author.

Data collection

Participants completed the outcome questionnaires at baseline and postintervention (6 weeks). The baseline questionnaire package was handed to the participants in the clinic after providing consent. Adherence was assessed both through home practice log and a phone call every week by study personnel. Upon intervention completion, the postintervention questionnaire package was mailed to the participants to fill out and return together with the home practice log in a self-addressed envelope. Each participant was also given an electronic pedometer and asked to report the number of pedometer-determined steps per 24 hours twice, at baseline and postintervention, during a phone call conducted by the first author.

Measures

To assess CRF, we used the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) and the Patient-Reported Outcome Measurement Information System-Short Form (PROMIS-SF)-general CRF. The MFSI-SF is a well-validated, 30-item scale that includes five subscales (i.e., general CRF, physical CRF, emotional CRF, mental CRF, vigor) [67]. The PROMIS-SF-general CRF is an 8-item scale that measures general CRF over the past 7 days with good validity and reliability coefficients [68]. The PROMIS-SF-depression, an 8-item scale with very good psychometrics, assessed depression over the past 7 days [69]. Similarly, we used the PROMIS-SF-sleep disturbances to assess sleep disturbances in the past week. The PROMIS-SF-sleep disturbances includes 8 items and has demonstrated acceptable psychometric properties [69]. Pain was measured using the Brief Pain Inventory-Short Form (BPI-SF), an 11-item questionnaire with two subscales (pain severity and pain interference). The BPI-SF has demonstrated good reliability and validity coefficients [71].

Physical activity was assessed using two measures: a self-report questionnaire, PROMIS-SF-physical activity, and an objective measure, an electronic pedometer (Yamax SW-701 Digi-Walker Multi-Function). The PROMIS-SF-physical activity is a 12-item scale with good psychometric properties [69]. The electronic pedometer is a simple, wristwatch-sized device that has been validated previously [72]. The electronic pedometer can be placed on the belt or waistband and is triggered by vertical accelerations of the waist that occur during walking. With each step, a spring-suspended pendulum arm moves up and down, and one event is recorded. Participants in this study were asked to place the pedometer on their waistband for 24 hours to count the number of steps taken. All participants were also educated on pedometer use, including storage and handling, and were instructed to follow their usual routine and not alter it at all when wearing the pedometer. Last, self-efficacy and self-regulation were measured using the Self-Efficacy for Managing Chronic Disease Scale (SEMCD) and the Index of Self-Regulation Scale (ISR), respectively. The SEMCD is a 6-item scale that has demonstrated acceptable psychometric properties [73]. The ISR is a 9-item questionnaire with good validity and reliability coefficients [74].

Statistical analysis

We used SPSS (Version 22.0) for data analysis. Assumptions of data normality were assessed using the Shapiro-Wilk test, which is one of the most powerful normality tests in studies with sample sizes smaller than 29 [75,76]. Paired Student's t-tests (or Wilcoxon signed rank tests for nonnormally distributed scores) were used to assess changes in measures of CRF, depression, sleep disturbances, pain, and physical activity from baseline to postintervention. To evaluate the association of CRF change from baseline to postintervention with the changes in depression, sleep disturbances, pain, and physical activity, the change in each outcome measure was

calculated, and then correlations were performed using Pearson correlation coefficient (or Spearman's correlation coefficient for nonnormal data). In addition, Pearson correlation coefficient was used to evaluate the association of adherence to yoga practice with self-efficacy and self-regulation skills and abilities.We also used unpaired Student's t tests to compare baseline characteristics of participants who completed the study with those who dropped out.

Results

Eighty-six HSCT survivors were invited to participate in this study between December 2017 and May 2018, of whom 20 met all of the eligibility criteria and provided signed informed consent. Of the 20 participants enrolled, five dropped out before starting the intervention, and three of them also did not return the baseline questionnaire package despite two reminders. Of the remaining 15 participants who started the intervention, 12 completed the study and returned the postintervention questionnaire. In addition, 10 of the 12 HSCT survivors who completed the study provided the number of pedometer-assessed steps per 24 hours at postintervention. Last, with the exception of one participant, who did not return the home practice log, home practice and adverse event data were available for all of the participants who started the intervention. A flow diagram of participant enrollment and retention is presented in Figure III.2.

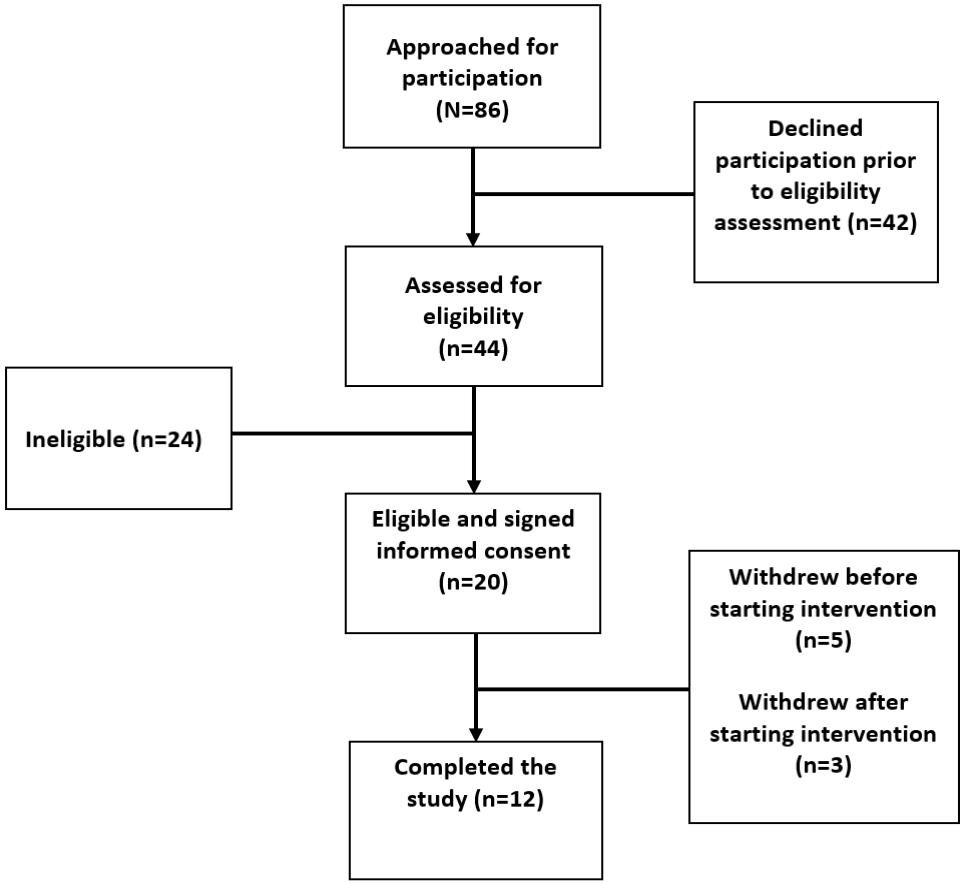

Figure III.2: Flow of Partictpants through the Study

Patient characteristics

Twenty adult HSCT survivors (13 women and 7 men) enrolled in this study. The participants' ages ranged from 28 to 72 years (mean [SD], 51(12.5)). Most were Caucasian (n=17, 85%), married (n=13, 65%), and unemployed (n=7, 35%). Of the 20 participants, eight had acute myeloid leukemia (40%), three had diffuse large B-cell lymphoma (15%), two had acute lymphoblastic leukemia (10%), two had myelodysplastic syndrome (10%), one had mixed phenotype acute leukemia (5%), one had myelofibrosis (5%), one had Hodgkin's lymphoma (5%), one had follicular lymphoma (5%), and one had multiple myeloma (5%). The sample consisted of 19 allogeneic HSCT survivors (95%), 13 of whom were known to have GVHD (68.4%) (grade 1-2: n=4, grade 3-4: n=3, grade unspecified: n=6), and one autologous HSCT survivor (5%). The participants were four months to 7.6 years post HSCT (mean [SD], 3.3 [2.3] years).

Potential benefits of yoga

Because we aim to evaluate changes in outcome measures from baseline to the end of the yoga program, this analysis included data from participants who completed both baseline and postintervention assessments (n=12 for self-report measures and n=10 for pedometer-determined steps per 24 hours). MFSI-SF-total CRF scores improved from baseline ($\bar{X}$=30.2, SD=14.5) to postintervention ($\bar{X}$=20, SD=20), but the difference did not reach statistical significance (Cohen's d=-0.5, P=0.07). All five MFSI-SF subscales (i.e., general CRF, physical CRF, mental CRF, emotional CRF, vigor) improved from baseline to postintervention, but only changes in physical CRF (Cohen's d=-0.6, P=0.04) and vigor (Cohen's d=0.6, P=0.04) were statistically significant. The participants reported statistically significant improvements in mean PROMIS-SF-general CRF, decreasing from 25.1 (SD=5.8) to 20.5 (SD=5.6) (Cohen's d=-0.7, P=0.02), and in mean PROMIS-SF-sleep disturbances, decreasing from 22.6 (SD=7.1) to 18.6 (SD=7.6)

(Cohen's d=-0.8, P=0.01). Improvements were noted in PROMIS-SF-depression (Cohen's d=-0.3, P=0.40), BPI-SF-pain severity (Cohen's d=-0.2, P=0.22), BPI-SF-pain interference (Cohen's d=-0.2, P=0.39), PROMIS-SF-physical activity (Cohen's d=0.5, P=0.10) and pedometer-determined steps per 24 hours (Cohen's d=0.6, P=0.07), but none reached statistical significance. The changes in the outcome measures from baseline to postintervention are shown in Table III.5.

Table III.5: Changes in Outcome Measures from Baseline to Postintervention

Outcome	Baseline		Postintervention		Change (post-baseline)	Cohen's d	Paired t-test (or Wilcoxon signed-rank test)	
	N	Mean (SD)	N	Mean (SD)	Mean (SD)	Effect size	t-statistic (or Z score)	P value
MFSI-SF-total CRF	12	30.2 (14.5)	12	20 (20)	-10.2 (17.9)	-0.56	1.97	0.07
MFSI-SF-general CRF	12	12 (4.7)	12	9.9 (5.1)	-2.1 (6)	-0.33	1.19	0.25
MFSI-SF-physical CRF	12	9 (4.1)	12	6.6 (4.9)	-2.4 (3.4)	-0.66	2.31	*0.04**
MFSI-SF-mental CRF	12	10.5 (4.9)	12	8 (5.4)	-2.5 (4.5)	-0.55	1.91	0.08
MFSI-SF-emotional CRF	12	7.9 (4.5)	12	6.9 (6.1)	-1 (3.2)	-0.31	0.94[a]	0.34[a]
MFSI-SF-vigor	12	9.1 (2.7)	12	11.5 (3.4)	2.4 (3.6)	0.63	-2.21	*0.04**
PROMIS-SF-general CRF	12	25.1 (5.8)	12	20.5 (5.6)	-4.6 (6.1)	-0.75	2.62	*0.02**
PROMIS-SF-depression	12	14.1 (7.4)	12	12.1 (6.9)	-2 (6.1)	-0.32	0.82[a]	0.40[a]
PROMIS-SF-sleep disturbances	12	22.6 (7.1)	12	18.6 (7.6)	-4 (4.8)	-0.81	2.83	*0.01**
BPI-SF-pain severity	12	2.6 (2.1)	12	2.1 (2.1)	-0.5 (1.3)	-0.26	1.29	0.22
BPI-SF-pain interference	12	1.8 (1.8)	12	1.5 (1.8)	-0.2 (1)	-0.26	0.87	0.39
PROMIS-SF-physical activity	12	43.5 (7.4)	12	45.3 (8.9)	1.8 (3.5)	0.51	-1.78	0.10
Pedometer-determined steps	10	3051 (1929)	10	5367.5 (3688.5)	2316.5 (3584.5)	0.64	-2.04	0.07

Abbreviations: CRF: Cancer-related fatigue; MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form; PROMIS-SF: Patient-Reported Outcome Measurement Information System-Short Form; BPI-SF: Brief Pain Inventory-Short Form

**: Difference is statistically significant at $\alpha < 0.05$.*

a: Z score and exact significance are reported from Wilcoxon signed-rank test since scores are not normally distributed.

CRF association with depression, sleep disturbances, pain, and physical activity

To evaluate the associations of CRF change with the changes in depression, sleep disturbances, and pain, we included data from participants who completed both the baseline and postintervention assessments (n=12). All of the CRF dimensions (i.e., total CRF, physical CRF, general CRF, mental CRF, emotional CRF) correlated positively with depression, sleep disturbances, and pain. Sleep disturbances showed the strongest pattern of correlations with the CRF dimensions; correlation coefficients ranged from 0.50 to 0.86. The BPI-SF-pain severity and BPI-SF-interference subscales showed a similar pattern of correlates with the CRF dimensions as the PROMIS-SF-sleep disturbances but at a lower magnitude; correlations ranged from 0.41 to 0.83. Depression showed the weakest correlations with CRF dimensions in comparison to sleep disturbances and pain; correlation coefficients ranged from 0.31 to 0.65. Furthermore, increases in the MFSI-SF-vigor subscale correlated negatively and insignificantly with decreases in PROMIS-SF-depression, PROMIS-SF-sleep disturbances, BPI-SF-pain severity and BPI-SF-pain interference, correlations ranged from -0.09 to -0.39.

The associations of CRF change with the changes in the two physical activity measures (PROMIS-SF-physical activity and pedometer-determined steps per 24 hours) were evaluated using data from participants who completed both the baseline and postintervention assessments (n=12 for PROMIS-SF-physical activity and n=10 for pedometer-determined steps per 24 hours). The CRF dimensions (i.e., total CRF, physical CRF, general CRF, mental CRF, emotional CRF) correlated negatively with the two physical activity measures and demonstrated stronger correlations with PROMIS-SF-physical activity, correlations ranging from -0.24 to -0.60, than with pedometer-determined steps per 24 hours, correlations ranging from -0.14 to -0.38.

Increases in the MFSI-SF-vigor subscale also correlated positively and insignificantly with increases in PROMIS-SF-physical activity (r=0.48) and pedometer-determined steps per 24 hours (r=0.29). The correlations between CRF change and the changes in depression, sleep disturbances, pain and physical activity are presented in Table III.6.

Table III.6: Correlation Coefficients for Changes in Outcome Measures

Outcome	PROMIS-SF-depression	PROMIS-SF-sleep disturbances	BPI-SF-pain severity	BPI-SF-pain interference	PROMIS-SF-physical activity	Pedometer-determined steps per 24 hours
MFSI-SF-total CRF	*0.59**	*0.75***	0.53	*0.61**	-0.57	-0.35[a]
MFSI-SF-general CRF	0.44	*0.72***	0.46	0.54	-0.49	-0.38[a]
MFS-ISF-physical CRF	0.31	*0.78***	0.56	0.47	*-0.58**	-0.35[a]
MFSI-SF-mental CRF	*0.61**	*0.86***	*0.68**	*0.83***	*-0.60**	-0.34[a]
MFSI-SF-emotional CRF	*0.65**	0.50	0.41	0.51	-0.24	-0.14[a]
MFSI-SF-vigor	-0.39	-0.21	-0.09	-0.19	0.48	0.29[a]
PROMIS-SF-general CRF	0.38	*0.81***	*0.58**	*0.68**	*-0.60**	-0.20[a]

Abbreviations: CRF: Cancer-related fatigue; MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form; PROMIS-SF: Patient-Reported Outcome Measurement Information System-Short Form; BPI-SF: Brief Pain Inventory-Short Form

**Correlation is statistically significant at $\alpha < 0.05$.*

***Correlation is statistically significant at $\alpha < 0.01$.*

a: Spearman's rank correlation coefficient is reported since scores are not normally distributed. All the other correlation coefficients reported in this table are Pearson's R.

Association of yoga adherence with self-efficacy and self-regulation skills and abilities

Because we aim to evaluate the association between adherence to yoga practice and self-efficacy and self-regulation skills and abilities, the five participants who withdrew from the study before starting the intervention were excluded from this analysis. Thus, 15 participants were included in the correlation analysis between protocol adherence and baseline scores for self-efficacy and self-regulation skills and abilities. Of these 15 participants, the 12 participants who returned the postintervention questionnaire package were included in the correlation analysis between protocol adherence and postintervention scores for self-efficacy and self-regulation skills and abilities. The overall adherence rate incorporating class and home practice was 45.4%. Mean SEMCD-self-efficacy was 41.2 (SD=11.3) at baseline and 44.5 (SD=9) at postintervention (total score range can range from 6 to 60). Mean ISR-self-regulation skills and abilities was 33.8 (SD=3.5) at baseline and 32.1 (SD=2.7) at postintervention (total score can range from 9 to 45). Weak to moderate correlations, ranging from -0.31 to 0.41, were found between the adherence measures (number of classes attended, number of minutes of home practice, overall adherence) and the measures of self-efficacy and self-regulations skills and abilities, and none reached statistical analysis. The correlations between the adherence measures and self-efficacy and self-regulation skills and abilities are shown in Table III.7.

Table III.7: Correlations between Protocol Adherence and Self-Efficacy and Self-Regulation

	SEMCD -self-efficacy		**ISR-self-regulation skills and abilities**	
	Baseline (n=15) $\bar{X}$ =41.2, SD=11.3	**Postintervention (n=12) $\bar{X}$=44.5, SD =9**	**Baseline (n=15) $\bar{X}$ =33.8, SD=3.5**	**Postintervention (n=12) $\bar{X}$=32.1, SD=2.7**
Number of yoga classes attended	0.16 (P=0.55)	0.19 (P=0.54)	-0.09 (P=0.74)	-0.31 (P=.031)
Total home practice time (minutes)	0.31 (P=0.27)	0.23 (P=0.45)	0.22 (P=0.43)	-0.15 (P=0.62)
Overall protocol adherence (minutes)	**0.41 (P=0.12)**	**0.29 (P=0.35)**	**0.25 (P=0.36)**	**-0.29 (P=0.35)**

Abbreviations: SEMCD: Self-efficacy for managing chronic disease scale; ISR: Index of self-regulation scale
All the correlation coefficients reported in this table are Pearson's R since scores are normally distributed.

Discussion

Potential benefits of yoga

The primary aim of this study was to evaluate the potential benefits of yoga for adult HSCT survivors. Consistent with previous findings in breast cancer survivors [27,28], participants reported statistically significant improvements in vigor (+20.8%) and two CRF dimensions, physical CRF (-26.7%) and general CRF assessed by the PROMIS-SF (-18.3%). Changes in the other CRF dimensions (i.e., total CRF, mental CRF, emotional CRF), despite missing statistical significance, were also all in the expected direction. Additionally, despite the improvement in general CRF assessed by the PROMIS-SF reaching statistical significance, general CRF measured by the MFSI-SF subscale insignificantly decreased by 17.5%. This finding could be because the PROMIS-SF-general CRF is a fully developed scale specifically designed to measure general CRF and better captured the changes in this CRF dimension. The participants also reported a 17.7% statistically significant improvement in sleep disturbances, which is a finding supported by previous results in women with breast cancer [34]. It is also worth noting that both the CRF and sleep disturbances measures showed large effect sizes, ranging from -0.55 to -0.81. These effect sizes indicate that the improvements in CRF and sleep disturbances may be clinically significant. Decreases were also noted in depression (-14.1%), pain severity (-19.2%), and pain interference (-16.6%), but none were statistically significant. This result could be attributed to the small sample size and resulting low statistical power. Another reasonable explanation for this finding is that our study targeted patients with moderate to severe CRF who happened to have low baseline scores for depression ($\bar{X}$=14.1 on an 8-40 scale), pain severity ($\bar{X}$=2.6 on a 0-10 scale) and pain interference ($\bar{X}$=2.8 on a 0-10 scale), resulting in a floor effect. Given that several studies in breast cancer survivors have supported

the use of yoga for depression and pain [35,36], it is possible that a yoga intervention targeting HSCT survivors with at least moderate depression or pain can yield positive results.

Furthermore, insignificant improvements were noted in the two measures of physical activity, mean PROMIS-SF-physical activity scores increased by 3.9% and mean pedometer-determined steps per 24 hours by 43.1%. Given this considerable improvement in the average steps per day together with preliminary data in breast cancer survivors showing that yoga improves physical activity [77,78], the non-significant improvement in pedometer scores is likely a function of low statistical power. The substantial difference in the improvement between the two measures (+3.9% versus +43.1%) could be attributed to two factors. First, the electronic pedometer is an objective measure that might have better captured the changes in physical activity levels compared to the self-report measure, PROMIS-SF-physical activity. Second, fewer participants provided pedometer-determined steps per 24 hours at postintervention than those who returned the PROMIS-SF-physical activity (10 versus 12), making it possible that those who used the pedometer at postintervention were the most physically active. In addition, both measures of physical activity showed large effect sizes (0.51 for PROMIS-SF-physical activity and 0.64 for pedometer-determined steps per 24 hours), which increases the likelihood of physical activity improvement being clinically significant. To summarize, our hypothesis of improvement in the outcome measures from baseline to postintervention is partially supported by our results, with changes in physical CRF, general CRF, vigor and sleep disturbances reaching statistical significance, thus providing the pilot data needed for subsequent, rigorously designed clinical trials.

CRF association with depression, sleep disturbances, pain, and physical activity

The first secondary aim of this study was to evaluate the association of CRF change with changes in depression, sleep disturbances, pain, and physical activity. Improvements in two or more of the CRF dimensions (i.e., total CRF, general CRF, physical CRF, mental CRF, emotional CRF) correlated significantly with reductions in depression, sleep disturbances, pain severity and interference. This finding is consistent with data in breast cancer survivors showing that CRF occurs simultaneously with other symptoms rather than in isolation [38,39], which is attributed to a potentially common biological mechanism, elevated inflammatory activity [40,41]. However, much of the research linking CRF to other symptoms is cross-sectional [79,80]; therefore, how CRF relates to sleep disturbances, depression, and pain is not clear. Given the relatively high scores for sleep disturbances at baseline ($\bar{X}$=22.6 on an 8-40 scale) together with the strong pattern of correlations found between sleep disturbances and the CRF dimensions, correlations ranging from 0.50 to 0.86, it is plausible that sleep mediated, at least partly, the effects of yoga on CRF in this study. In other words, yoga resulted in better sleep, which decreased CRF. Nevertheless, the possibility of a reciprocal relationship cannot be ruled out, as improvements in CRF may have ameliorated sleep disturbances in a feedback loop. Pain severity and interference demonstrated a similar pattern of correlation with the CRF dimensions as sleep disturbances but at a lower magnitude; correlations ranged from 0.41 to 0.83. Preliminary data suggest that the relationship between pain and CRF can be mediated by sleep disturbances, in which pain causes trouble sleeping, and the latter intensifies CRF [81]. It is therefore possible that yoga decreased pain interference with sleep, which ameliorated CRF in this study. This possibility is supported by the finding that mental CRF, which is the CRF dimension to most likely be linked to sleep disturbances, had the highest correlations among all the CRF dimensions with pain severity (r=0.68) and interference (r=0.83).

In regard to the relationship between depression and CRF, it has been hypothesized that depression can be a driving mechanism for CRF through inflammatory pathways [82]. Consistent with this hypothesis, previous studies indicate that CRF can occur independent from depression [83,84]; however, depression, when it occurs, usually coexists with CRF [85,86]. Given the relatively low depression scores at baseline ($\bar{X}$=14.1 on an 8-40 scale) along with depression improvement showing the weakest correlates with the CRF dimensions in comparison to sleep disturbances and pain, correlations ranging from 0.31 to 0.65, depression was likely not a confounding factor for CRF in this sample of HSCT survivors. Another noticeable finding is that the correlations between vigor and the measures of depression, sleep disturbances, and pain were in the expected direction, indicating a negative relationship. The magnitude of the correlations was low, however, with correlations ranging from -0.09 to -0.39. This finding could be because vigor represents a subjective feeling of physical strength and is therefore conceptually different from the CRF dimensions, potentially affecting the mechanisms through which it relates to other symptoms. For instance, better sleeping may contribute to less physical CRF during the day, increasing vigor levels. Improvement in depression may also reduce emotional CRF, potentially contributing to better vigor. The examples provided indicate that vigor is likely a more distal variable in the relationship with depression, sleep disturbances, and pain compared to the CRF dimensions, which may explain the lower correlations noted for vigor.

Although the directionality of effect cannot be determined, research suggests that physical activity can be impacted by CRF [43,44]. Correlations between CRF dimensions and physical activity measures in this study were in the expected direction, indicating a negative relationship. The CRF dimensions also demonstrated stronger correlations with PROMIS-SF-physical activity, correlations ranging from -0.24 to -0.60, than with pedometer-determined steps

per 24 hours, correlation coefficients ranging from -0.14 to -0.38. Additionally, three CRF dimensions (i.e., physical CRF, mental CRF, general CRF assessed by the PROMIS-SF) correlated significantly with PROMIS-SF-physical activity compared to no significant correlation with pedometer-determined steps per 24 hours. One plausible explanation for this finding is that CRF reduction after yoga was more likely to influence participants' perceived physical activity assessed by PROMIS-SF-physical activity than actual physical activity assessed by electronic pedometer. Correlations between the vigor and physical activity measures were also in the expected direction, indicating a direct relationship. Vigor also had a higher correlation with PROMIS-SF-physical activity (r=0.48) than with pedometer-determined steps per 24 hours (r=0.29), possibly also due to vigor affecting participants' perception of physical activity levels more than actual physical activity.

In summary, with the exception of pedometer-determined steps per day showing no significant correlations with any of the CRF dimensions, our hypothesis that improvement in CRF would be associated with increases in physical activity and decreases in depression, sleep disturbances and pain is supported by our results. By supporting this hypothesis, our study provides preliminary data for subsequent large studies aiming to understand the causal links between CRF and co-occurring symptoms or physical activity in adult HSCT survivors, which would be useful information needed to design more effective interventions targeting cancer-related symptoms or physical activity after HSCT.

Association of yoga adherence with self-efficacy and self-regulation skills and abilities

The second secondary aim was to evaluate the association of yoga adherence with self-efficacy and self-regulation skills and abilities. Overall adherence incorporating class and home

practice correlated insignificantly with both self-efficacy and self-regulation skills and abilities, which is a finding that is inconsistent with numerous studies in various populations (e.g., heart failure, diabetes, chronic kidney disease) showing that self-efficacy and self-regulation skills and abilities improve health-related behaviors [46-49,53,54]. However, all of those studies were adequately powered, with sample sizes ranging from 81 to 244; therefore, our insignificant results may be due to low statistical power. Nevertheless, most of the correlations in this analysis were positive, indicating that self-efficacy and self-regulation skills and abilities may enhance yoga adherence. Juxtaposed with this finding, baseline scores for self-regulation skills and abilities correlated negatively with the number of classes attended, yet the correlation was negligible (r=-0.09); thus, it is less likely that this result reflects a genuine inverse relationship.

We also found that postintervention scores for self-regulation skills and abilities correlated negatively and weakly with the number of classes attended (r=-0.31), total home practice time (r=-0.15), and overall adherence (r=-0.29). Given that data showing self-regulation skills and abilities positively impact health-related behaviors [51-55], the current negative correlations are likely due to the very small sample size used in the postintervention analysis (n=12), potentially resulting in a low variability in self-regulation skills and abilities scores (extremely small standard deviation of 2.7) and consequently spurious negative relationships. Additionally, some of the HSCT survivors reported difficulty understanding the items of the ISR-self-regulation skills and abilities questionnaire, which raises questions about the consistency in participants' interpretation of the meaning of the questions and response options across the two time points (baseline and postintervention). Another potential contributing factor to these negative correlations lies in the low adherence rate to the yoga intervention (45.4%). It is possible that the participants at baseline had high expectations regarding their self-regulation

skills and abilities needed to adhere to the recommended yoga intervention. However, when their actual adherence conflicted with their expectations, participants might have experienced frustration that influenced their self-assessment of self-regulation skills and abilities at postintervention. Consistent with this possibility, ISR-self-regulation skills and abilities slightly decreased from baseline ($\bar{X}$=33.8) to postintervention ($\bar{X}$=32.1). It is also worth noting that, to our knowledge, all of the previous longitudinal studies demonstrating a relationship between health behaviors and self-regulation skills and abilities assessed the latter at baseline only, arguing that baseline scores are predictive of future adherence behaviors [53,54]. Therefore, how self-regulation skills and abilities can be impacted by one's adherence to the behavior being studied is not clear. To summarize, our results failed to support our hypothesis of an association between yoga adherence and self-efficacy and self-regulation skills and abilities. This hypothesis should be reevaluated in a large-scale yoga trial to draw firmer conclusions regarding the potential role of self-efficacy and self-regulation skills and abilities in influencing yoga adherence.

Limitations

There are numerous limitations of this study. First, the study was not statistically powered to evaluate yoga benefits, CRF association with co-occurring symptoms and physical activity, and the relationship between yoga adherence and self-efficacy and self-regulation skills and abilities. Second, the study employed a single-arm design with several potential biases. For example, with the absence of a control group, the possibility of a maturation effect in which the outcomes measured naturally improved with the passage of time since HSCT cannot be ruled out. However, given that our sample included patients at variable time points after HSCT, 4 months to 7.6 years, along with prior research showing persistent symptoms (i.e., CRF, sleep

disturbances) for up to 10 years after HSCT [8,12,87], the likelihood of a maturation effect is minimal. Another potential bias stems from the absence of an active control group, making it unknown to what extent the observed improvements were due to yoga or to nonspecific effects such as social interaction occurring during yoga classes. The lack of an active control condition also did not allow us to blind participants to the treatment allocation, and participants might have had positive expectations regarding yoga efficacy. Third, the study was designed to capture the short-term effects of yoga by employing one postintervention assessment immediately after the end of the intervention. It is therefore unknown to what extent the observed benefits would be sustained over the longer term. Fourth, the duration of the intervention was short compared to the longer yoga interventions (8 to 12 weeks) commonly used in yoga trials in breast and prostate cancer survivors [27,28,61]. It is possible that a longer intervention would have yielded greater benefits. Fifth, the sample was relatively homogeneous, primarily consisting of allogeneic HSCT survivors with GVHD. The study results may thus have limited generalizability to other HSCT populations, including autologous HSCT survivors and allogeneic HSCT survivors without GVHD.

Implications for research and clinical practice

The present study has implications for research. To the best of our knowledge, this is the first study to evaluate the potential benefits of yoga for adult HSCT survivors, providing the foundation needed to conduct larger, adequately powered yoga trials in this population. Second, research on symptom co-occurrence in HSCT survivors is limited, with the majority of studies linking CRF to other behavioral disturbances being cross-sectional [7,10-12]. By testing yoga for CRF and longitudinally evaluating CRF association with depression, sleep disturbances, and pain, our study provides preliminary data for future research aiming to understand the

relationships between those symptoms and how interventions targeting individual symptoms can affect their complex patterns of covariation. Third, evidence suggests that poor physical activity can be a great obstacle to HSCT survivors' HRQOL [6,8]. Physical activity can also be very affected by CRF [43,44]. In this regard, this study draws attention to yoga as a potential approach to increase physical activity by mitigating CRF, potentially improving HRQOL. The present study also sheds light on a potential association between yoga adherence and the variables of self-efficacy and self-regulation skills and abilities, informing future studies aimed at increasing adherence to health-related behaviors in adult HSCT survivors. This study also has implications for clinical practice. The results suggest that CRF after HSCT may be influenced by pain and impaired sleep. Clinicians may therefore recommend interventions targeting pain and sleep disturbances as a potential approach to reduce CRF in adult HSCT survivors.

Conclusion

The current study indicates that yoga appears to have some potential benefits for adult HSCT survivors, especially with regard to CRF and sleep disturbances. The results also suggest that CRF reduction after HSCT can be associated with improvements in other cancer-related symptoms (i.e., depression, pain) and self-reported physical activity. The study failed to demonstrate a relationship between yoga adherence and self-efficacy and self-regulation skills and abilities, indicating a need to retest this association with a larger sample of adult HSCT survivors.

Acknowledgements

Special thanks are due to Dr. Dale Bixby, hematologist-oncologist, for his help with subject recruitment. Many thanks are also due to Dr. Corey Powell, Bio-statistician, for his valuable guidance in statistical analysis.

Funding Statement

This research was supported by a grant from the Oncology Nursing Society Foundation (ONSF): ONSF Dissertation Grant [17-PAF08181], awarded to the first author.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Hematopoietic Stem Cell Transplant Survivors' Perceptions of Yoga and Physical Activity: A Focus Group Approach

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Abstract

Background: Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for several hematologic malignancies but has potential negative consequences for health-related quality of life. Several modalities of physical activity, most notably yoga, have shown potential benefits for side effects of cancer treatments in non HSCT populations. Exploring perceptions of yoga and physical activity in HSCT survivors is relevant and timely as research extends to this population.

Objective: The purpose of this study is to explore HSCT survivors' perceptions of yoga and physical activity.

Methods: A qualitative descriptive study was conducted as part of a single-arm feasibility study. Eight adult HSCT survivors participated in focus groups following a six-week restorative yoga intervention that consisted of a 1-hour once-weekly group class with twice-weekly home practice using a DVD. Data were transcribed verbatim and analyzed using the Krueger method.

Results: Participants described a range of psychological (improved stress, sleep, body awareness and understanding), physical (improved muscular strength, body flexibility and range of motion), and physiological (improved breathing, energy, pain, and blood pressure) benefits from yoga practice. Barriers and hurdles to practicing yoga included general time constraints, travel distance to the intervention site, distractions and interruptions during home practice, and difficult yoga poses. Important aspects of the yoga classes from the participants' perspective were individualized instruction style, camaraderie, shared understanding of the cancer experience among class participants, and the feeling of not being judged by others when unable to perform certain poses. Participants reported three motives for physical activity engagement: maintaining and improving general wellbeing, regaining general health, and having company to exercise

with. Fear of falling and/or injury and concerns about contracting communicable infections might, on the other hand, be reasons for physical activity avoidance after HSCT. Yoga and walking were the most commonly preferred types of physical activity by participants.

Conclusion: The results of this qualitative study provide insights into HSCT survivors' perceptions of yoga, including their perceived benefits from and barriers to yoga and experiences with participating in a yoga program, laying the foundation needed to develop and examine yoga interventions for this population. The results also contribute to an understanding of HSCT survivors' fears, motivations, and preferences regarding physical activity, informing future strategies targeted to increasing HSCT survivors' adherence to physical activity interventions.

Keywords: Health-related quality of life; hematopoietic stem cell transplant; physical activity; yoga

Introduction

Hematopoietic stem cell transplantation (HSCT) is a standard treatment for several malignancies, such as leukemia and lymphoma [1]. It involves replacing patient stem cells by new ones either collected in advance from the patient (autologous) or from a donor (allogeneic) [1]. During the first 100 days after transplant, non-relapse mortality from infectious complications are common, occurring in about 5% of autologous HSCT recipients and 22% of allogeneic HSCT recipients [2,3]. Therefore, day 100 is a milestone indicating that a patient is on the path to survivorship. Advances in HSCT supportive care practices have led to improvements in long-term survival after HSCT [4]. Depending on several factors, such as the disease and remission status at the time of transplant, the 3-year survival rate for patients undergoing HSCT can range from 27% to 91% [5]. Yet, the health-related quality of life (HRQOL) among HSCT survivors is often compromised, and associated with cancer-related symptoms (e.g., pain, anxiety, sleep disturbances) [6-9]. Additionally, several studies in allogeneic HSCT survivors report a 27% to 72% incidence of graft-versus-host disease (GVHD) [10-12], which occurs when donor's T lymphocytes initiate an immune response against patient organs [12]. GVHD has been associated with decreased physical functioning, further impairing HRQOL [13,14].

Increasing attention has been given to interventions targeted to helping patients maintain reasonable HRQOL after HSCT. For example, the documented benefits of aerobic exercise programs that are designed specifically for HSCT survivors include improvements in cancer-related fatigue (CRF) [15-17], physical activity [18], and muscular strength and endurance [19,20]. However, complications such as GVHD, prolonged thrombocytopenia, organ toxicity, and late opportunistic infections are common after HSCT [21-23] and may reduce tolerability

for aerobic exercise in this population. One type of physical activity has not received attention for the enhancement of HRQOL after HSCT, namely, yoga.

Yoga is an ancient Indian practice that has been gaining popularity in the Western world. Yoga promotes a union between body and mind by incorporating both nonstrenuous physical exercise (i.e., bodily postures, stretching) and cognitive strategies (e.g., relaxation, meditation) [24]. Preliminary evidence from studies in women with breast cancer suggests that yoga can improve HRQOL [25], physical functioning [25], cognitive functioning [26], CRF [27,28], depression [29], sleep disturbances [30], and pain [31]. In addition, yoga offers a distinct advantage by combining physical activity and meditation practices, making it potentially appealing to HSCT survivors. Yoga is also person-centered and can be self-administered, which may encourage long-term use and potentially contribute to a better HRQOL in the long term. Given the potential benefits of yoga in cancer survivorship, we recently completed a single-arm study evaluating the feasibility of a yoga intervention offered to 20 adult HSCT survivors, aiming to inform a future randomized trial for efficacy. This feasibility study was specifically targeted at one of the most common and distressing symptoms after HSCT, namely, CRF [32,33].

Yoga participation, like any other human behavior, is a complex phenomenon that can be shaped by the physical, social, and psychological aspects of one's life, often requiring a qualitative inquiry for deeper understanding of participants' perceptions. Therefore, a qualitative inquiry may be a valuable tool for exploring HSCT survivors' perceptions of yoga in great detail, which may generate knowledge needed to inform future research in this area. For example, exploring HSCT survivors' perceived benefits from yoga can provide insights into yoga benefits beyond those that can be assessed through conventional instruments, potentially identifying

health problems for which yoga interventions in this population could be targeted. Additionally, exploring HSCT survivors' experiences with yoga class participation can help future researchers tailor their yoga interventions to suit the needs and expectations of HSCT survivors. Qualitative research can also offer in-depth understanding of the barriers and hurdles to performing yoga that HSCT survivors can face and that can limit the effectiveness of yoga. It is also important to recognize that yoga incorporates a physical activity component. Therefore, HSCT survivors' adherence to yoga can be affected not only by their perceptions of yoga but also by any fears or concerns they have about physical activity and their motivations for physical activity. Surprisingly, to our knowledge, research on HSCT survivors' perceptions of physical activity does not currently exist, creating gaps in the relevant literature. HSCT survivors' fears, concerns and motivations regarding physical activity need to be identified to be able to address them in future strategies aiming to improve adherence to yoga or other physical activity interventions after HSCT. Moreover, to the best of our knowledge, no prior work has explored HSCT survivors' physical activity preferences. It is thus unknown whether yoga is the most appealing modality of physical activity in this understudied population. Knowledge of the types of physical activities that HSCT survivors would prefer is crucial for designing effective physical activity interventions and may improve accrual acceptance and adherence.

Purpose

The purpose of this qualitative descriptive study is to explore adult HSCT survivors' perceptions of yoga and physical activity, particularly their perceived benefits from and barriers and hurdles to performing yoga, their experiences with participation in yoga classes, their fears, concerns and motivations regarding physical activity, and their physical activity preferences. Focus groups are the selected methodology because they allow a large amount of information

representing multiple perspectives to be gathered efficiently [34]. Focus groups also capitalize on the interaction between participants, which can generate richer and deeper information than can be collected through one-to-one interviews [34]. These features of focus group methodology make it particularly well suited to provide an in-depth understanding of HSCT survivors' views on yoga and physical activity.

Methods

Recruitment

This qualitative study was embedded in a single-arm study evaluating the feasibility of a yoga intervention offered to adult HSCT survivors with moderate to severe CRF. Participants were recruited by the first author from a tertiary care, university-affiliated hospital in the midwestern United States during regularly scheduled clinic appointments. Participants were first asked to participate in a 6-week yoga intervention and then in focus groups upon the completion of the intervention. Inclusion criteria included autologous or allogeneic HSCT survivors, 18 years of age or older at the time of HSCT, at least 100 days after HSCT, no evidence of active disease, and a score of 4 or more on a 0-10 numerical scale that asked participants to rate their CRF over the past 30 days. Exclusion criteria included current yoga practice, active infection, the use of supplemental oxygen, platelet count < 100000/μ, absolute neutrophil count (ANC) < $1000/mm^3$, and limitations in physical functioning. Participants provided written informed consent for the qualitative component of the study at the time of recruitment for the yoga intervention. The study was approved by the University of Michigan Medical School Institutional Review Board.

Yoga intervention

The participants were enrolled in a 6-week restorative yoga intervention that consisted of a 1-hour once-weekly class with twice-weekly home practice. Restorative yoga classes were offered at four different community-based cancer centers in southeastern Michigan. Six classes were offered each week, including one weekly evening class at each center, with one center also offering two weekly morning classes. Each participant chose a weekly class that best suited his or her schedule. The classes were taught by certified yoga instructors and conducted in groups of 6 to 12 participants, including HSCT survivors participating in this study and other cancer survivors attending the community centers. The classes consisted of shoulder, neck, and arm stretches, as well as restorative yoga poses. The poses were done in a standing (i.e., mountain pose, warrior I pose, warrior II pose, triangle pose), lying (i.e., spinal twist pose, reclining hamstring pose, corpse pose), or seated (i.e., cross-legged pose, moving child pose, cat/cow pose) position. Participants were asked to maintain regulated, deep breathing during poses. To aid with home practice, participants were given a yoga DVD that included instructions to do the same poses performed in the classes except for three poses (i.e., Warrior I, Warrior II, Triangle) that are more strenuous and can be better performed under an instructor's supervision.

Focus groups

The focus group sessions were held at a research office where there is privacy and a relaxing environment. The first author facilitated all the sessions. Before each session, the participants were encouraged to interact with one another and to state their opinions freely even if they differed from what others had said. The sessions were audio-recorded and conducted using a pre-established set of questions (see Table III.8). The sessions lasted approximately one hour. The participants were mailed a thank you note and a $40 gift card within two weeks of focus group participation to compensate them for their time and travel.

Table III.8: Focus Group Questions

- What were the benefits you received from practicing yoga?
- Can you please describe some of the barriers and hurdles to practicing yoga?
- Can you please describe your experiences with participation in yoga classes?
- What motivates you to do physical activity?
- What fears or concerns do you have about physical activity?
- Are there other types of physical activity you would like more than yoga?

Data analysis

The data were transcribed verbatim and analyzed using the Krueger method [36]. The first author (MB) and an experienced qualitative researcher (ML) independently analyzed the data using the same steps of the Krueger method, and each developed a code list. The researcher started by reading all the transcripts several times to become familiar with the data and to remind himself of the whole scope of the discussions. Next, the researcher sorted the data into coding categories, starting with selecting a question to analyze and assigning a code that described the first response to the question. Then, the researcher examined the second response; if the second response was a similar answer, he gave it the same code. If the second response was different, the researcher gave it another code that best described it. The researcher constantly compared the participants' responses and made decisions such as combining, separating, and creating codes. This process continued with all the responses to the questions until all were categorized and the data were exhausted. Finally, the emerged coding categories were arranged across the focus group questions, as the participants at times provided answers to questions asked earlier or to questions that had not yet been asked. Four focus groups were conducted, and data saturation was achieved after the fourth group during which no new themes were evident in the findings. The unit of analysis was data from the four focus group sessions, and the results reflected the collective experiences of the study participants.

A number of strategies were used to enhance methodological rigor. Credibility was enhanced through a "self-reflexivity" diary maintained by the group facilitator during the data collection and analysis. The group facilitator used this diary to document his own expectations about the participants' responses, thereby minimizing their influence on the results. Confirmability was achieved through participant feedback. At the end of each session, the

facilitator provided an ending summary and asked the participants for affirmation. Then, the results were revised as directed by the participants, and the session was considered complete if all the participants agreed that the summary provided accurately reflected their point of view. Validity and verifiability of the results were established through interrater reliability agreement assessment. After they independently analyzed the data, the facilitator and the experienced researcher discussed any disagreements and reconciled the differences, and then they independently recoded the data while using the finalized coding list to compare the agreement on the coding used. In the end, interrater reliability was calculated using the formulation of Miles and Huberman [37] (number of agreements divided by total number of agreements and disagreements) and was 100%. Both MB and ML agreed that the final results were verifiable.

Results

Participants

Eight HSCT survivors (7 women and 1 man) participated in four focus groups (2 participants/session) after completing a six-week yoga intervention. The participants' ages ranged from 28 to 72 years (mean [SD], 48.3 [14.2] years). Of the eight participants, six were married (75%), one was living with a partner (12.5%) and one was single (12.5%). In addition, of the 8 participants, three were unemployed (37.5%), two were employed (25%), two were retired (25%), and one was on long-term sick leave (12.5%). The majority (7 participants) were allogeneic HSCT survivors (87.5%), five of whom had GVHD (71.4%) (grade 1-2: n=1; grade 3-4: n=2; grade unspecified: n=2). One participant underwent autologous HSCT (12.5%). Of the 8 participants, four had leukemia (50%), 3 had lymphoma (37.5%), and 1 had multiple myeloma (12.5%). The participants were 7 months to 7.6 years post HSCT (mean [SD], 4.1 [2.6] years). Participant characteristics are presented in Table III.9.

Table III.9: Characteristics of Focus Group Participants

Group	N	Age (years) Mean (SD)	Gender	Ethnicity	Underlying disease	HSCT type	Time since HSCT (years) Mean (SD)	GVHD status and grade
1	2	32 (4)	Female (n=2)	Caucasian (n=1) West Asian (n=1)	HL (n=1) DLBCL (n=1)	Allogeneic (n=2)	5.1 (1.6)	GVHD (grade 3-4) (n=1) GVHD (grade unspecified) (n=1)
2	2	43.5 (9.5)	Female (n=2)	Caucasian (n=1) Black (n=1)	ALL (n=2)	Allogeneic (n=2)	4.8 (2.9)	No GVHD (n=1) GVHD (grade 3-4) (n=1)
3	2	55.5 (8.5)	Female (n=1) Male (n=1)	Caucasian (n=2)	AML (n=1) MM (n=1)	Autologous (n=1) Allogeneic (n=1)	2.6 (1.5)	Not applicable (n=1) GVHD (grade 1-2) (n=1)
4	2	62.5 (9.5)	Female (n=2)	Caucasian (n=2)	MPAL (n=1) DLBCL (n=1)	Allogeneic (n=2)	3.8 (3.2)	No GVHD (n=1) GVHD (grade unspecified) (n=1)

Abbreviations: HL: Hodgkin lymphoma; DLBCL: Diffuse large B-cell lymphoma; ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; MPAL: Mixed phenotype acute leukemia; MM: Multiple Myeloma; HSCT: Hematopoietic stem cell transplantation; GVHD: Graft-versus-host disease

Emerged themes

Twenty-nine themes emerged from the data. A summary of the focus group questions and emerged themes is presented in Table III.10.

Table III.10: Summary of Focus Group Themes

Focus group questions	Emerged themes
Perceived benefits of yoga	Improved stress/calmness Increased body awareness and understanding Improved sleep Improved body flexibility/range of motion Improved breathing Reduced pain Increased muscular strength Increased energy Lowered blood pressure
Barriers and hurdles to practicing yoga	General time constraints Long travel distance to the intervention site Distractions and interruptions during home practice Difficult poses
Experiences with yoga class participation	Individualized yoga instructions Camaraderie Shared understanding of the cancer experience Nonjudgmental atmosphere
Fears and concerns about physical activity	Fear of fall/injury Fear of contracting communicable infections
Motives for physical activity	Maintaining and improving general wellbeing Regaining general health Having company
Physical activity preferences	Yoga Walking Running Biking Hiking Dancing Weight lifting

Perceived benefits of yoga

The participants were first asked to describe their perceived benefits of performing yoga, and they described nine benefits that can be classified into three categories: psychological (improved stress, sleep, body awareness and understanding), physical (improved muscular strength, body flexibility and range of motion), and physiological (improved breathing, energy, pain, and blood pressure) benefits.

Psychological benefits

Stress reduction and calmness were the overarching and direct benefits of yoga reported by all of the focus group participants. One participant said, *"Personally through practicing yoga, one, I'm finding reduced stress levels."* Another participant shared that the benefits she experienced from doing yoga were *"stress reduction in general"* and *"being calm."* The participants also discussed how yoga took them "*out of all the stress of right now*" by narrowing their focus to just their breathing, which engendered a sense of calmness that pushed "*away all the other thoughts."* As one participant expressed, "*the benefits to me are that it calms my brain. It allows it to stop thinking about everything*." A second participant stated that yoga helped her to be *"calm"* and *"present"* and took her *"away from everything else in"* her "*life."* A third participant stated, *"I have this big weight on my chest...Then, I just feel it* [the weight] *the whole time or feel it when I sit down and start doing it* [yoga]. *Eventually that goes away, so it's that release of that weight."* Some of the participants also indicated that they could maintain those feelings of stress relief and calmness throughout the day. As one participant shared, "*It* [yoga] *gives you peace, and then you can go carry out the rest of your day and you've got a good start*

to your day." Another stated that "*once I've done it* [yoga] *for a few times, it's easier to remember when you're in a stressful situation, like driving or whatever, to just sit back, stay calm, take a deep breath and just, you know, just let up a little bit on the go, go, go part of my life."* A third participant described similar feelings: *"The class that I go to, pretty much they say the only requirement is to relax. If you can't do these poses, sit and just focus on that deep belly breathing and the present. I think that translates in every area of your life to just have that calmness."* Three participants associated yoga practice with greater body awareness, and two of them indicated that yoga made them *"mindful"* of their bodies and *"aware of where"* they were "*in space and being."* A third commented that yoga increased both her body awareness and understanding: *"It* [yoga] *has been good for creating more, I can't think of the word, understanding of my body, of knowing my own body's limits and understanding that there's more that I can do that I didn't necessarily know that I could."* In addition, two participants reported that yoga helped them "*sleep better",* and one of them attributed her sleep disturbances to negative, uncontrolled thoughts: *"I wake up in the night, which always happens. Then, sometimes I can't go back to sleep. Part of what happens is I start thinking about what if I get kidney disease? I wonder about the impossible things. I'm just programmed to dread."* Later in the course of the discussion, the same participant said that yoga improved her sleep by quieting *"the chatter of voices"* in her head.

Physical benefits

Four participants linked the muscle stretching that yoga involves with improvements in body flexibility, and they reported feeling *"stretchy"* and *"more lucid physically"* after doing

yoga. As one participant expressed, *"I have a lot of tightness, muscle tightness and everything, and yoga I think really helped to stretch that out. I'm not as tight as I was before."* The participants also explained that *"stretching the muscles"* and *"increasing flexibility"* had enhanced their range of motion. One participant commented, *"I wasn't able to twist to this degree, and now I can, so it* [yoga] *just helps me work back towards where I was before."* Similarly, another participant reported noticing *"benefits"* in terms of "*being willing and able to get down on the floor to pick up something or to scrub up a spot."* Three participants also reported improvements in muscular strength while attributing their muscle wasting to long-term steroids used to treat GVHD. These participants described yoga as *"a good way"* to *"build back"* their muscles after *"being on steroids and the muscle weakness*." As one participant explained, *"I was on steroids for four or five years, and steroids eat away at your muscles and you become very weak. That's what the yoga helps with."*

Physiological benefits

Three participants reported improvements in their breathing, describing it as being *"full"*, *"deep"* and *"regular enough"* while doing yoga. For example, one participant said that yoga allowed her *"lungs to expand and taking it* [the breath] *all the way in."* This participant further explained, *"I can see it* [the breath] *going in, and then I can think, 'Oh, my cells, they're nourished.'"* Similarly, a second participant said that yoga allowed her to use *"all of"* her *"lungs instead of just part of them"* and added that yoga improved her *"breathing issues"* caused by lung GVHD. In her own words, *"I have some GVHD in my lungs, and I think yoga is something that I can do that strengthens me. I suppose it helps me with my breathing."* Two participants

reported decreased pain as a result of yoga practice. One participant with *"arthritis"* shared that she was *"not waking up in the middle of the night in* [joint] *pain anymore"* after the yoga intervention. A second participant reported that yoga mitigated headaches caused by tension in the *"neck"* and *"shoulders"* and added that *"I wake up with headaches a lot 'cause I'm so tense. In that manner, it* [yoga] *has helped a lot."* Two participants also reported *"more energy"* after doing yoga, and one of them emphasized this point while sharing her experience with performing yoga in the morning: *"It* [yoga] *got me started in the morning to where I got things done during the day. I didn't sit around and relax all morning long like I would normally do."* Lastly, one participant with hypertension reported improved "*blood pressure"* since joining the study and gave "*yoga credit*" for that.

Barriers and hurdles to practicing yoga

Next, the participants were asked to describe the barriers and hurdles to practicing yoga. Four themes emerged from the data: general time constraints, long travel distance to the intervention site, distractions and interruptions during home practice, and difficult yoga poses. General time constraints were the most significant barrier to yoga practice as reported by six participants. One participant explained that time constraints due to family responsibilities interfered with her participation: "*I gotta finish this, and I'll do it* [yoga]. *By that time, I have to go pick up my son or something, and then there's the rest of life happening*." A third participant said that she was "*just doing stuff at the last possible minute*" during the intervention period and was "*always stressed which would be a good time to do yoga*." Another shared*, "it's kind of hard for me to find a whole hour in the day to commit to it* [yoga]*."* In the words of another

participant*, "I'm a disciplined person. I do my homework* [referring to yoga], *but I have a busy life, really busy life."* Another barrier to yoga practice reported by five participants was that the community centers were relatively distant from their homes, which reduced their ability to attend all of the yoga classes prescribed. As one participant shared, *"I guess distance is a barrier, although I want to do it* [attend the yoga class]*."* Similarly, another participant said that she skipped certain classes because there was a *"20 to 30 minute drive getting there* [to the community center] *and back, an hour drive all together."* A third commented, *"It* [attending a yoga class] *turned into a three-hour thing, well no, two-hour thing, going there* [to the community center]*, doing yoga, coming back home."*

Distractions and interruptions during home practice were hurdles to yoga practice from the perspective of five focus group participants. These participants indicated that they were unable to perform some of their home sessions effectively due to distractions or interruptions caused by pets, family members, or the home environment. One participant explained, "*one of the times my cat crawled up on my lap and fell asleep as I was breathing. They* [DVD instructions] *were like, Okay, let's change positions. Touch your toes. I'm like, No. I can't do that*." The same participant mentioned that she was mentally distracted by the home environment, as it reminded her of "*the to-do list of things*", and she explained, *"my brain at home says here's the five things that you should be doing at home like cuddling, watching the cat, or cuddling with the cat, watching TV."* A second participant said that she was distracted a few times by noises made by her *"kids"* when they *"didn't go to school."* Another shared that she experienced interruptions from her husband: *"If I tend to do it* [yoga] *when my husband's*

home, then he's trying to talk to me through it, which I tell him to just leave the room. I got to do my class first. My husband likes to talk." Two participants also reported lack of strength that lead to difficulties in doing certain yoga poses, and one of them attributed her lack of strength to her "*pretty severe myopathy"* after *"many, many years of* [taking] *prednisone."* This participant further explained, *"some of the poses require some upper body strength that I don't possess yet. I think some of the poses are a little difficult, but the great thing about yoga is if you can't hold the pose, then you just start again."* Another participant shared that she was once challenged by a pose but modified it using props: *"I couldn't put my hands flat on the mat, so I used the blocks to grip onto."* Despite those two participants reporting difficult poses, there was a general perception among all eight participants of the gentleness of the yoga poses, describing them as "*basic"* and *"doable"* and adding that there were *"always modifications"* that they could apply to make the poses more convenient. As one participant explained, *"if there is something* [pose] *that's hard, it can be adapted to not be as hard if that's what you want to do, so that's helpful."* Another shared, *"There's a certain hardness to it* [yoga]*, but it's all easy."*

Experiences with yoga class participation

The participants were then asked to describe their experiences with participation in yoga classes. Four themes emerged from the data: individualized yoga instructions, camaraderie, shared understanding of the cancer experience, and nonjudgmental atmosphere. Overall, the eight participants held positive views about the yoga instructors and described them as "*really good*", *"energetic"*, and "*very knowledgeable*." The participants also explained that the instructors guided them *"in a very sensitive and intelligent way"* to perform the poses while

being attentive to the physical capabilities of individual participants and modifying the poses to the ability level of each one. As this participant said, "*they* [the instructors] *always offer like you can do this pose, and here's four different ways to modify it. If you can't move in this particular way, this might be the better way to do this pose*." In the words of another participant, *"She* [the instructor] *definitely caters it to each person. If you can't sit cross legged, then you can sit on a chair."* The participants also explained that the instructors made sure they were doing the poses correctly and helped them change the poses as needed. As one participant stated, "*they* [the instructors] *can point it out that I'm using the wrong muscles or something else. It might be more straining doing it the way that I'm doing it versus the way that I should be doing it*." Another participant associated the individualized instruction style with a sense of safety: *"The instructor has got her eye out for me that I don't start doing something that she thinks I might hurt myself."*

Furthermore, six focus group participants indicated that they enjoyed the camaraderie that yoga classes offered. These participants explained that *"the socializing part"* and the conversations that occurred before and after classes fostered a positive experience. One participant shared, *"the instructors are generally very nice and remember who you are. When you pop in, they're like, 'Hi. Good to see you again.'"* Another shared, *"I feel totally comfortable there* [community center]. *It just feels inviting, and it feels it's a good place to go. I enjoy it."* A third participant stated, "*other people that weren't new* [in the yoga class] *when I came greeted me and told me why they were there. So, it was kinda nice that, you know, everybody just kinda talked and shared."* One participant also highlighted the encouragement that occurred among class participants: *"I liked the camaraderie, the encouraging from*

everybody. Everybody encouraged everybody else." Another commented that *"having other people there* [in the yoga classes] *too"* made *"it a lot more fun."* Three participants also indicated that interacting with cancer survivors had engendered a sense of shared understanding of the cancer experience. As one participant explained, "*It was a bunch of other cancer survivors, so you could relate. Everybody could relate. We were all suffering basically from the same things. I like it."* A second participant described similar feelings, *"It just felt very comfortable. Everyone* [in the yoga class] *knows that we're all struggling in some way."* A third participant stated*, "you feel like there's a kind of an empathy there* [in the yoga classes] *among even people you don't know."* Two participants also mentioned that they felt no one judged their ability to perform the yoga poses. As one participant expressed, "*I was never sitting there* [in the yoga class] *like someone's gonna judge me because I'm unable to do this thing* [yoga pose]*."* Similarly, a second participant said that she *"liked"* the classes because there was *"no judgment",* adding that *"you* [can] *go* [to the class]*, and you do what you can, and that's all."* This participant also added that she felt no need *"to be prefect"* when doing yoga because they were all cancer survivors with *"similar ability levels."*

Fears and concerns about physical activity

The participants were asked to describe their fears and concerns about physical activity. Of the eight participants, six expressed fears of falling and/or injury during physical activity, and two of them also reported concerns about contracting communicable infections during group-based activities. Two participants did not have any fears or concerns with respect to physical activity. The participants indicated that they *"can't always trust"* their *"body"* during physical

"exercise", which makes them *"terrified of falling"* or being physically *"hurt."* As a result, they tended to avoid or limit activities they perceived as potentially physically harmful, such as *"push-ups"* and *"Tough Mudder."* One participant said, *"I've had a bike, but I haven't ridden it since my transplant cuz I'm afraid of falling off."* Another participant described similar feelings: *"I walk on the treadmill, and I'm thinking, 'Is this gonna hurt my hip or other joints at some point?' I don't run anymore."* A third participant expressed fear of walking her dog: *"she* [the dog] *can pull me over. I can feel it, feel really unsteady on my feet when she pulls really hard to lunge at another dog. And it's like, uh, yeah, I still have apprehension about doing it* [walking the dog]*."* Some participants also expressed worry about the negative consequences if they were to fall and become injured, thinking the consequences could be *"very bad"* or *"dangerous."* As one participant explained, *"if I fell and actually broke a hip or a wrist, those consequences would be enormous for me because it would take weeks and weeks to recover."* Another stated that *"my number one fear about falling is that I would lose, in the recuperation, what I've gained."* Concerns about contracting communicable infections, mainly airborne, was another factor that could limit participation in physical activities from the participants' perspective. The participants explained that they practiced caution during outdoor activities that require being close to other people, especially during the *"flu season."* One participant expressed worry about *"germs"* during *"social outing things"*, which caused her to watch what she was "*doing, eating,* [and] *touching."* This participant further explained that *"sick people do not stay home, so we have to be vigilant about going out."* Similarly, another participant said that she had to *"be careful around sick people"* and provided an example from the yoga classes, "*I think last week,*

there was a woman, like, one person away from me, she was coughing. And I thought, 'is she covering her mouth?'. You know, we're sitting there doing yoga, and we're supposing to be calm, but, you know, it freaks me out to be close to someone who's coughing."

Motives for physical activity

Next, the participants were asked to describe their motives for physical activity. Three themes emerged from the data and can be divided into two categories: intrapersonal (maintaining and improving general wellbeing, regaining general health) and interpersonal (having company to exercise with) motives.

Intrapersonal motivators

The general perception among the eight participants was that their physical activity engagement derived from a desire to maintain or improve their general wellbeing. The first response from all the participants when they were asked this question was to *"get better*" or *"feel better in general."* When the participants were asked to provide more in-depth and detailed answers, they described how physical activity could maintain or improve specific aspects of their general wellbeing, including physical (i.e., improving and maintaining physical strength, maintaining physical fitness, and managing CRF), psychological (i.e., improving mood and anxiety), emotional (i.e., feeling happy and cheered up), social (i.e., being nice to others), and functional (i.e., increasing energy, functioning and productivity) wellbeing. Some participants noted that they engaged in physical activity to improve their physical strength. As one participant said, *"I do it* [physical activity] *so I'll feel stronger and better."* Another stated, *"I want to improve. I wanna make myself better, and I wanna make myself stronger."* A third indicated that

physical activity is important for physical strength maintenance: *"I like strength, being able to pick stuff up and do things in the yard, and as I get older, I need to keep the body strong."* Other participants shared that they engaged in physical activities so that they could consume high caloric food and maintain physical fitness. For example, one participant said that she exercised so that she *"can have ice cream."* Similarly, another shared that she *"would be way overweight*" without exercising. In addition, one participant pointed out that physical activity helped her manage her CRF: *"I fight fatigue a lot, but if I don't do these things* [physical exercise]*, I will feel more tired."* Two participants also indicated that physical exercise could improve their psychological wellbeing, and one of them specifically said that exercise could *"brighten"* her *"mood."* Another participant shared that exercise was an *"anxiety release"* for her. Some participants also linked physical exercise with positive emotions. As one participant said, *"it's about feeling better. I mean, after exercising I'm glad. I don't know."* Another participant associated physical exercise with both emotional and social wellbeing: "*It cheers me up to do it* [exercise]*, that I'm probably nicer to the people around me. I think I would be grumpy if I didn't exercise."* Other participants indicated that physical activity could improve their functional wellbeing. As one participant commented, *"I feel better and more productive when I am physically activ*e." Similarly, another participant said that physical activity helped her *"function better"* and increased her *"energy."* Another motive for physical activity engagement reported by two participants was regaining their general health. One participant expressed a desire to become *"healthy again"* when discussing her motives for physical activity. A second participant

described similar feelings: *"I was healthy, I was able to hold on. Then since being sick and trying to come back, whatever, I just wanna get back there. I wanna get back to being healthy."*

Interpersonal motives

Four participants indicated that having company can motivate them to engage in physical activities, and they perceived doing activities with others as an opportunity *"to catch up with people"* and *"to socialize"*, making those activities *"interesting"* and *"fun."* One participant said, *"Sometimes my partner just asks, 'Hey, do you wanna go walk around the mall?' I'll be like, 'Yeah, sure.'"* Another added, "*If there's somebody else that, like my neighbor, I would go run with. That would be great."* The same participant shared that a companion usually motivated her to increase her exercise duration: *"We also motivate each other to go farther or whatever. Even if I would go out, but only go out for 30 minutes, whatever, then she'd be like, 'Let's keep going'".* A third participant implied that having a companion may also enhance a sense of commitment to exercise and specifically said that she could find a *"million excuses of, like, what's got be done"* other than to go walking, so she was more likely to go walking with a companion because she would know *"that person is relying on"* her *"to be there"*.

Physical activity preferences

Lastly, the participants were asked about other modalities of physical activity that they preferred more than yoga. However, the participants responded to this question by listing activities that they preferred in addition to yoga and not more than yoga, indicating that they did not have a strong preference for any physical activity type over yoga. One participant responded, *"I don't really have anything that I prefer over yoga. I do walking too"*, while another said, "*I*

like walking, but that's probably lower or the same as yoga." A third participant commented, *"I think that yoga seems to be just my speed. I enjoy it, and I also do walking."* A fourth shared, *"I would say that I probably enjoy yoga as much as I enjoy running."* Other statements made by the participants also indicated that yoga appealed to them. As one participant said, *"I will continue to do yoga at home beyond the length of the study. I enjoy it."* A second participant stated, *"Yoga is pretty good for me. I don't think I would be doing anything too high impact."* Nevertheless, each participant identified one to three types of activities that he or she preferred in addition to yoga. Of those other activities, the vast majority mentioned *"walking"* (7 participants), followed by *"running"* (2 participants), *"biking"* (2 participants), *"hiking"* (1 participant), *"dancing"* (1 participant), and "*weight lifting"* (1 participant).

The participants identified different reasons why walking appealed to them, one of which was that walking is a convenient exercise. For example, one participant said that walking is an exercise that *"you can just do"* compared to yoga, which involves multiple steps such as *"put the DVD in"* and *"get the two blankets"*. Another reason shared by a second participant was that walking was a low-intensity exercise for her: *"I just wanna be able to bike and walk a longer distance. Unfortunately, I cannot jog or do a lot of high-impact activities."* A third said that she liked the "*the fresh air and the change of scenery"* that walking provides. The reasons participants provided to explain why running, biking, and hiking appealed to them were mainly associated with these being outdoor activities. The participants reported that those activities gave them *"a chance to be in nature"*, as they enjoyed the *"connectedness to the earth and the sun*" or "*being outdoors"* or *"in the woods."* Running was also appealing to one participant because it

"winds" her *"anxiety quicker and faster"* than other physical activity types. Additionally, weight lifting appealed to one participant because it was *"more strenuous"* than other exercises. One participant also enjoyed dancing because it connected her to the person she was before HSCT, as she knows that she *"can never be that person again."* Despite the fact that the participants identified several activities other than yoga that appealed to them, there was a general perception among them that yoga is *"different"* and offers unique advantages, as it is gentler and incorporates stretching and meditative techniques. As one participant said, *"I like the breathing and the concentrating and the calm of yoga, where walking's a little more intensive, and, you know, that would be the plus for yoga."* In the words of another participant, *"there's something, there's some peacefulness and calming and stretchiness that comes with yoga that feels right for my body. It feels like it's something my body needs and should have; all bodies should have. I firmly believe that."*

Discussion

Perceived benefits of yoga

Consistent with the results of qualitative research in breast cancer survivors [38-40], participants reported various health benefits from yoga practice including stress reduction and calmness. It is well documented that one stress-response mechanism is frequent overstimulation of the hypothalamic pituitary adrenal axis, resulting in disrupted diurnal cortisol rhythm [41-44]. Data also increasingly suggest that cortisol alteration influences the onset and severity of a range of cancer-related symptoms, most notably CRF, depression, sleep disturbances, and pain [45-47]. It is therefore possible that stress reduction and associated cortisol regulation contributed to other

yoga benefits reported by some of the participants, including improvements in sleep and pain. Other mechanisms might have also contributed to better sleep and pain relief beyond stress reduction. For instance, the mitigation of arthritis-related pain reported by one participant could be in part the result of yoga postures involving moving the joints through a range of motion. The relief of headaches resulting from tension in the shoulder and neck muscles reported by another could also be attributed to the stretching poses that target the shoulder and neck muscles. In addition, preliminary data suggest that yoga increases two biological markers (gamma-aminobutyric acid and melatonin) involved in sleep-regulating mechanisms [48,49], potentially contributing to better sleep. Another possible mechanism underlying sleep improvement is the reduction of pain-related sleep disturbances. One participant in this study indicated that yoga decreased pain occurring at night, and later in the course of the discussion, she reported better sleep. All of these potential mechanisms indicate that yoga is promising for the treatment of sleep disturbances and pain after HSCT. Given that studies in HSCT survivors have reported a 42% to 69% incidence of sleep disturbances [50-52] and 32% to 41% incidence of chronic pain [52,53], the positive effects of yoga on sleep and pain reported by the focus group participants should be treated as hypotheses to be tested in subsequent clinical trials.

Some of the HSCT survivors reported the benefit of improved breathing. This benefit is likely to be part of the stress-relieving mechanism that yoga cultivates. Yoga involves mindful and deep breathing that focuses one's attention only on the present moment [54], which may in turn improve stress by directing the mind away from any negative thoughts that impose suffering, sadness, or anger [55,56]. The breathing component of yoga may also confer benefits

beyond stress reduction. While the typical targets of GVHD are skin and liver [57], several studies in allogeneic HSCT survivors report a 2% to 20% incidence of lung GVHD [58-60], which manifests as bronchiolitis that causes shortness of breath and increased breathing effort [60]. Data also increasingly suggest that the breathing symptoms of lung GVHD are chronic, as a certain level of GVHD-induced lung damage is irreversible [60]. Yoga breathing exercises (pranayama) involving repetitive deep and regulated breathing may increase lung expansion and diaphragm strength and subsequently strengthen breathing capacity, which may mitigate lung GVHD symptoms. More research may thus be warranted to continue to evaluate yoga in adult HSCT survivors with lung GVHD.

Another yoga benefit experienced by half of the participants was enhanced body flexibility and range of motion. Decreased body flexibility after HSCT can be attributed, in large part, to GVHD effects on body muscles and joints. It is well documented that high-dose, long-term steroids used to combat GVHD can lead to degeneration of muscle fibers and connective tissues surrounding the bones, resulting in muscle soreness that limits range of motion [61,62]. GVHD treatment has also been associated with avascular necrosis [63], a condition that occurs in approximately 10% of allogeneic HSCT survivors and is characterized by a decreased blood supply to the joints, including hips, ankles and shoulders, contributing to joint stiffness and reduced range of motion of the joints involved [64]. Studies in general populations have shown that yoga improves general body flexibility, attributing this improvement to the stretching poses of yoga that increase the length of both muscle and connective tissues and loosen stiff joints [65-67]. These data from general populations coupled with the improvements in body flexibility and

range of motion reported by the HSCT survivors in the current study provide the foundation needed for future research in this area. Furthermore, the focus group participants reported increased muscular strength, which can be the result of the limb extension and muscle contraction that some yoga poses involve. Muscle weakness in allogenic HSCT survivors is primarily due to steroid use for GVHD treatment [61,62]. Another contributing mechanism lies in the fact that GVHD pathogenesis involves systemic inflammation [68], potentially contributing to physical deconditioning. An expected response to physical deconditioning is to reduce physical activity. Over time, the latter may diminish muscle strength. To our knowledge, the only intervention with documented benefits for muscular weakness in allogeneic HSCT survivors with GVHD is aerobic exercise [19,20]. This study therefore sheds light on yoga as another potential treatment option, one that is less intense than aerobic exercise, for GVHD-induced myopathy.

Barriers and hurdles to practicing yoga

The participants explained that general time constraints were the main barrier to yoga practice, which is a finding supported by previous studies in breast cancer survivors and healthy adults [38,67]. One factor that might have contributed to this finding is that classes were offered at only two times (11am-12pm, 6pm-7pm) and on weekdays, so the class schedules might have conflicted with the participants' family and work responsibilities. Thus, future yoga trials may need to consider offering classes on both weekdays and weekends and at a greater variety of times during the day. This approach may increase class participation by taking into account the competing commitments that HSCT survivors may have. Another barrier to yoga practice

identified by the participants was the long travel distance to the intervention sites (community centers). The distance barrier has also been reported by women with breast cancer participating in a yoga intervention [38]. Although yoga classes in the present study were offered at four separate community centers, the centers were relatively close (approximately 16 miles apart). This geographic distribution might have eased participation for the HSCT survivors who lived in close proximity to the community centers, allowing them to choose the one closest to their homes. Still, travel apparently remained a burden for the majority of the participants. Future researchers may therefore consider partnering with other facilities to offer yoga classes at more and farther locations, which may reduce the travel burden and increase class participation.

One hurdle to yoga practice, specifically home yoga, identified by the HSCT survivors was distractions and interruptions caused by family members, housemates, or pets. To our knowledge, this finding has not been reported in previous yoga studies in any cancer population, possibly because the majority of the qualitative studies addressing yoga in cancer survivors have focused on class-based yoga interventions. This finding is, however, supported by studies in other populations (i.e., people living with human immunodeficiency virus, patients with osteoarthritis), which have identified space and distractions as issues with home yoga [69,70]. One general population study by Muntean, Neustaedter, & Hennessy [71] noted that the following strategies are helpful to avoid distractions and interruptions while performing yoga at home: choosing a quiet and calm room, selecting a time for practice during which distractions are less likely to occur, turning off phones and electronic devices, and asking family members or housemates for privacy and to avoid coming into the room where yoga is being practiced. These

strategies can be employed in future yoga research with HSCT survivors to minimize distractions and help HSCT survivors focus on their practice. Although yoga classes offer distinct advantages (i.e., instructor-led, group-based) over home yoga, the latter may be more attractive to HSCT survivors who cannot travel or afford yoga classes or those who simply feel more comfortable doing yoga in a private location. Implementing and evaluating strategies that aid HSCT survivors with home practice are thus crucial and represent an area worthy of further investigation.

Experiences with yoga class participation

Statements made by the participants indicated that the instruction style contributed to positive experiences. Specifically, the individualized feedback provided by the instructor was perceived to be beneficial, as it helped the participants perform the postures efficiently and safely. This finding extends previous research results in breast cancer survivors showing the instructor's ability to provide feedback to each participant allowed them to reach their maximum capacity without harm [40]. Future yoga interventions may therefore benefit from instructor training that focuses on the complications and functional impairments that HSCT survivors commonly experience and the importance of modifying poses based on individual participants' physical capabilities. If HSCT survivors feel the yoga instructor has a genuine concern for their safety and wellbeing, this may enhance continued participation and reduce dropouts. Consistent with this hypothesis, a longitudinal qualitative study by Brunet and St-Aubin [72] explored breast cancer survivors' motivation to stay in a group-based exercise program and found that the instructor's attributes, such as providing personalized instructions and developing a caring climate, were determinants of whether the survivors continued participating.

Camaraderie was another important aspect of the yoga from the participants' perspective. This finding is supported by previous research in breast cancer survivors noting social cohesion occurring during yoga classes [39]. Prior research in breast cancer survivors also suggests that the social dimension of yoga classes has beneficial effects on participants' mood states and general wellbeing [40]. It is worth noting that classes in the present study were offered in community settings, which might have facilitated group interaction by providing a suitable atmosphere for participants to socialize before and after classes. Nevertheless, yoga studies in women with breast cancer note social interaction during classes held at facility-based sites [38,40]. Furthermore, in accord with previous findings in breast cancer survivors [39], some of the focus group participants noted a sense of shared understanding of the cancer experience among class participants. This finding is of particular importance given that HSCT survivors are unique in their treatments (e.g., conditioning regimen) and complications (e.g., GVHD), which are usually not understood by the general public. This lack of understanding might create a sense of isolation among HSCT survivors and would suggest a need for social support networks that allow them to share their experiences with similar others. While support groups might be the optimal platform to share information and seek help, research in other populations (i.e., breast cancer, colorectal cancer) suggests that a cancer survivor participation in support groups might be limited by doubts about their utility and perceptions of support groups as depressing [73-75]. Group-based yoga interventions may therefore be an alternative opportunity for HSCT survivors to naturally express their feelings and problems and actively help each other feel better.

Fears and concerns about physical activity

The focus group participants cited fear of fall/injury as a factor that can limit or prevent them from performing routine daily activities (e.g., walking the dog) and physical exercises (e.g., biking). This finding is in line with previous qualitative studies in other cancer populations (i.e., breast cancer, head and neck cancer) [76-78]. Of note, research demonstrates that most patients reduce physical activity after HSCT [79], attributing that reduction to several factors such as GVHD [14], CRF [8], depressive symptoms [80], and disrupted family relationships [81]. However, this study indicates that the decreases in physical activity levels among HSCT survivors could be partly the result of fear of fall/injury. Future research in this population should thus seek to explore this phenomenon in more detail and to examine strategies to temper it. As a result of the fear of fall/injury, HSCT survivors may become less physically active, which has been shown in other populations (e.g., older adults, patients with chronic obstructive pulmonary disease) to reduce physical work capacity and over time lead to a decreased ability to tolerate activities of daily living [82,83]. It is important to recognize, however, that HSCT survivors can experience physical limitations due to GVHD and other comorbidities (e.g., neuropathy) [84-86], and their fear of fall/injury can therefore be legitimate. Nevertheless, HSCT survivors need not respond to their fears by activity avoidance. Addressing their fears may be accomplished through strategies to help HSCT survivors increase and sustain physical activity within the constraints of their capabilities, which may in turn build confidence in their ability to exercise and help them lead physically active lifestyles within safe boundaries.

Motives for physical activity

Consistent with previous finings in breast cancer survivors [87] and people with diabetes [88], the overall perception among the participants was that their motivation for physical activity derived from an interpersonal motive, which was to maintain and improve their general wellbeing. The participants also provided examples of how physical activity improved specific aspects of their wellbeing, including physical, psychological, emotional, social, and functional wellbeing. In addition, one interpersonal motive for physical activity reported by half of the participants was having a companion to exercise with. This finding is supported by reports from previous studies in other populations (i.e., patients with head and neck cancer, older adults) that having an exercise companion is associated with an increased likelihood of physical activity participation [77,89,90]. This increased likelihood is due to the enjoyment associated with the companion's presence, which encourages people to put more effort into overcoming perceived exercise barriers [90]. Having an exercise companion may therefore increase adherence to physical activity interventions in HSCT survivors. For example, it may be valuable to allow HSCT survivors to bring a friend or family member with them to yoga classes, which may promote enjoyment and continued class participation.

Physical activity preferences

Participants did not have strong preferences for any physical activity type over yoga. This finding suggests that yoga appealed to them, which supports the feasibility of future yoga interventions in adult HSCT survivors. The majority of the participants also identified walking as a convenient, low-intensity exercise that they could do in addition to yoga. Walking has also been found to be one of the most commonly preferred types of physical activity in different

populations, such as women with breast cancer [78] and patients with low back pain [91]. It is also worth noting that walking-based exercise programs have been previously tested in several populations (e.g., prostate cancer, lung cancer) with positive effects on various health outcomes, such as physical functioning [92], anxiety [93], depression [93], CRF [94] and sleep disturbances [95]. Additionally, the two published studies on walking-based exercise programs in HSCT survivors demonstrate the benefits of improved physical activity [96], anxiety and depression [97]. In this study, we provide support that walking may be the most common type of physical activity after HSCT. Accordingly, attention should be paid to increasing the evidence base for walking-based exercise programs in this population.

Limitations and strengths

This study has two limitations. First, despite multiple attendance reminders and extensive efforts to schedule focus group sessions at dates and times that were convenient for three or four participants, only two HSCT survivors participated in each session. This scheduling issue mainly occurred because the HSCT survivors had completely different schedules, and it was very difficult to come to agreement on a date and time that worked for more than two participants. A larger number of participants in each group might have enhanced group dynamics and generated richer data. Second, the sample was relatively homogenous, primarily consisting of allogeneic HSCT survivors whose perceptions of yoga and physical activity were likely influenced by GVHD effects. As such, the results may have limited transferability to autologous HSCT survivors. The majority of our sample participants were also women. Male HSCT survivors

might hold different views on yoga and physical activity, and different themes might therefore have emerged if the sample included more men.

One strength of the present study is that it adds to the relevant literature through implications for research and clinical practice. To the best of our knowledge, this study is the first to seek an understanding of HSCT perceptions of yoga, providing insights into the development and examination of yoga interventions after HSCT. To our knowledge, this study is also the first to explore HSCT survivors' fears, motivations and preferences regarding physical activity, informing future strategies aimed at increasing adherence to physical activity programs in this population. This study may also inform clinical practice. Overall, the participants expressed positive views of yoga and associated yoga practice with positive outcomes. Thus, although no evidence for any of the potential yoga benefits in HSCT survivorship currently exists, clinicians may include yoga when discussing physical activity options with adult HSCT survivors. Walking is another form of physical activity that appears to be appealing to HSCT survivors and may be incorporated into their care.

Conclusion

Although a fair amount of literature exploring patient perceptions of yoga and physical activity in cancer survivorship is available, no attention has been paid to understanding the experiences of yoga or physical activity among cancer patients treated with HSCT. Therefore, this study explored adult HSCT survivors' perceptions of yoga and physical activity. The emergent themes discussed in this paper identify several avenues for future researchers and can be used to optimize yoga and other physical activity interventions designed specifically for adult

HSCT survivors. As our sample was predominantly women who had undergone allogeneic HSCT and had GVHD, replicating this study with a sample with a more equitable gender representation and with greater variability in HSCT type may be indicated.

Acknowledgements

Special thanks are due to Dr. Dale Bixby for his help with subject recruitment.

Funding Statement

This research was supported by a grant from the Oncology Nursing Society Foundation (ONSF): ONSF Dissertation Grant [17-PAF08181], awarded to the first author.

Conflict of Interest

The authors declare that they have no conflict of interest.

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CHAPTER IV

DISCUSSION

Cancer-related fatigue (CRF) is one of the most common symptoms in patients with cancer [1]. Several studies of adult cancer survivors treated with hematopoietic stem cell transplantation (HSCT) reported a CRF prevalence ranging from 35% to 84% [2-4]. Despite its preliminary evidence for improving CRF, yoga has not been tested in an HSCT population. Feasibility studies estimate key parameters (e.g., recruitment, retention) needed to design and conduct planned randomized clinical trials. As such, a study evaluating the feasibility of yoga in adult HSCT survivors and preceding a planned trial for efficacy was indicated to move the state of the science forward.

The conceptualization of the study variables was guided by the theory of symptom self-care management in cancer (TSSMC) [5]. Depression, sleep disturbances, and pain were conceptualized as symptoms that were occurring simultaneously with CRF. Given the strong pattern of association between CRF change and changes in sleep disturbances and pain together with emerged themes indicating preexisting sleep problems and pain among the focus group participants, sleep disturbances and pain might have been contributing to CRF. Therefore, the conceptualization of sleep disturbances and pain as "symptoms experience" in this study does not rule out the possibility of these two symptoms acting as influencing factors. Sleep disturbances fit conceptually under psychological factors. Pain has both physical and emotional components and can be the result of several pathophysiological mechanisms [6]; therefore, it may fit conceptually under physiological factors. Furthermore, the absence of emergent themes

pertinent to depression along with depression change showing the weakest correlates with CRF improvement suggest that depression was unlikely to be a driving mechanism for CRF. Therefore, the results support the conceptualization of depression in this study as a symptom cooccurring with CRF but not generating it. It is also important to recognize that CRF improvement after yoga might have engendered a sense of well-being among the HSCT survivors, contributing to decreases in depression, sleep disturbances, and pain. These three symptoms could therefore also be subsumed under the domains of health-related quality of life (HRQOL) that can be influenced by the symptom experience according to the TSSMC. Sleep disturbances and depression fit conceptually under emotional wellbeing, whereas pain may fit conceptually under physical or emotional wellbeing. Overall, the results indicate that adult HSCT survivors can experience multiple symptoms simultaneously rather than CRF in isolation, with a potential for one or more concurrent symptoms to act as an antecedent (influencing factors) and/or consequence (HRQOL) of CRF (symptom experience).

Physical activity was conceptualized to fit under one domain of HRQOL in the TSSMC, namely, physical wellbeing. The TSSMC suggests that the symptom experience influences HRQOL. This suggestion leads to the assumption that CRF improvement following yoga might have improved physical activity levels among the HSCT survivors. Nevertheless, the directionality of the relationship cannot be determined, and improvements in physical activity following yoga might have also ameliorated CRF. The TSSMC postulates that reactive symptom self-care management behaviors reciprocally impact the influencing factors, which in turn affects the symptom experience. It is therefore possible that physical activity has also acted as a

situational factor, encompassing lifestyle behaviors (e.g., diet and exercise), that influenced the symptom experience (CRF). Either way, the significant association between three CRF dimensions (i.e., general CRF, physical CRF, emotional CRF) and self-reported physical activity found in this study indicates that a yoga intervention targeting CRF may have the potential to improve one important domain of HRQOL after HSCT (i.e., physical well-being). On the other hand, the study found no association between CRF and physical activity assessed by pedometer scores. The considerable improvement in pedometer-determined steps per 24 hours by 43% is thus likely to be in large part directly the result of yoga practice (i.e., the reactive symptom of self-care management behavior) and independent of CRF (i.e., the symptom experience). Therefore, it is possible that symptom self-care management behaviors can directly influence the four domains of HRQOL (i.e., physical, social/family, emotional, and functional well-being) in the TSSMC, providing insights into a new potential relationship among concepts in this newly synthesized theory. Given the small sample size and resulting low statistical power, together with the absence of a comparison group and several resulting biases, no firm conclusions from this study can be made regarding whether a revision of the TSSMC is currently indicated. Further studies are warranted to refute, substantiate, or refine the relationships purported by the TSSMC.

Major Research Findings and Directions for Future Research

The study results support the safety of restorative yoga in adult HSCT survivors. The findings also indicate that restorative yoga appears to improve CRF and sleep disturbances after HSCT. The unmet hypotheses regarding the three feasibility parameters (accrual acceptance, retention, and protocol adherence rates) and changes in pain, depression, and physical activity

from baseline to postintervention were based on studies in women with breast cancer. It should be recognized, however, that although yoga has recently emerged as a reasonably feasible intervention to mitigate cancer side effects and improve physical activity in breast cancer survivors [7], there is no guarantee that yoga will have similar feasibility or yield the same benefits in adult HSCT survivors who receive completely different treatments (i.e., conditioning regimen) and experience unique complications, most notably graft versus host diseases (GVHD) [8]. Therefore, despite interpreting the current study results based on previous research findings in women with breast cancer, the feasibility and benefits of yoga may need to be considered in each cancer population separately.

This study makes a unique contribution to the literature as the first to evaluate the correlation between CRF and pain in adult HSCT survivors. Cancer-related pain is highly prevalent in adult HSCT survivors [9] and is one of the symptoms that commonly cooccur with CRF in women in breast cancer [10]. Therefore, the lack of association found between CRF and pain at baseline should not underrate the possibility of the latter being a perpetuating factor for persistent CRF after HSCT. The significant association found between CRF and pain when evaluated longitudinally supports this possibility. The results also support previous studies showing that sleep disturbances due to pain may contribute to CRF [11, 12]. Future research in adult HSCT survivors should, therefore, examine whether pain treatment improves insomnia and, in turn, mitigates CRF.

Although the directionality of relationships is not always clear between CRF, sleep disturbances and depression, there is considerable evidence that interventions targeting sleep

disturbances or depression can ameliorate CRF [13, 14]. However, most supportive evidence comes from studies in women with breast cancer, and as previously indicated, findings in other cancer populations may not be readily generalizable to HSCT survivors. This study's findings showing improvements in sleep and depression associated with CRF reduction are important and contribute to the field. Nevertheless, research on symptom relationships in HSCT survivors is still in its very early stages, and additional research is needed to support the hypothesis that insomnia and depression are precipitating mechanisms for CRF after HSCT.

Decreased physical activity is commonly reported in adult HSCT survivors [15, 16], but little is known about the relationship between physical activity and CRF in this population beyond a small number of studies showing a cross-sectional association [2, 17, 18]. The current study, therefore, adds to the literature through evaluating this relationship longitudinally and extending a growing body of research in other populations (e.g., breast cancer, prostate cancer) suggesting bidirectional influences between CRF and physical activity [19, 20]. However, what remains unknown in all cancer populations is how CRF relates to physical activity and a cancer survivor's ability to perform everyday activities. Further longitudinal studies may thus be warranted to explore the mechanism underlying this relationship and to assess whether its magnitude can vary depending on patient characteristics (e.g., type and intensity of cancer treatment). Future research can also build upon our results to examine potential mediating and moderating processes (e.g., GVHD, inflammatory cytokines, psychological distress) that may affect the strength of the relationship between CRF and physical activity.

The current study found positive but not significant correlations between self-efficacy and yoga adherence. Originally evaluated in patients with diabetes and chronic kidney disease, the positive impact of self-efficacy beliefs on adherence to health-related behaviors has been well documented in the literature [21, 22]. Given that, to our knowledge, this was the first study to evaluate the relationship between self-efficacy and a health-related behavior (yoga) in a cancer population, the positive correlations are reassuring. Furthermore, unlike previous studies in various populations (e.g., asthma) [23, 24], the present study failed to demonstrate that self-regulation skills and abilities are related to the health-behavior being studied (yoga). It should be noted, however, that the vast majority of previous studies in this area have evaluated interventions (e.g., self-monitoring instructions, positive reinforcement of health-related behaviors) targeting self-regulation skills and abilities to improve participants' adherence to the behavior under study, and participants' self-regulation skills and abilities were assessed in relation to that particular behavior. However, self-regulation skills and abilities in this study were measured in a broader context, encompassing assessment of self-regulation patterns involved in maintaining health and managing illness. Future yoga studies may thus benefit from enhancing the conceptualization and operationalization of self-regulation skills and abilities by narrowing their scope to yoga practice, which may yield results that are consistent with the literature.

This study was also the first to explore adult HSCT survivors' perceptions regarding yoga and physical activity, thereby generating multiple new research hypotheses and questions for future examination. The most frequent barriers to class attendance (i.e., long travel distance to the intervention site, general time constraints) may not be easily remedied in future studies.

Some studies suggest that home-based yoga interventions may be a practical approach to address the challenges associated with class participation [25, 26]. However, this and previous studies in breast cancer survivors indicate social interaction during classes may increase personal motivation to do yoga [27-29]. Findings from this study also suggest that home practice is associated with limitations (e.g., distracting environment). Whether home- or class-based yoga is more appropriate for adult HSCT survivors is an outstanding issue and represents an area worthy of investigation.

The most frequent motivations, fears, and preferences regarding physical activity reported in this study are consistent with previously published studies in breast cancer survivors [30, 31]. This consistency is noteworthy given that previous studies included samples selected for the main purpose of exploring participant perceptions of physical activity. The qualitative component of this study, however, included adult HSCT survivors who accepted enrollment and actively participated in a yoga intervention, thereby they were also more apt to express positive views regarding physical activity. A more ambitious qualitative study may thus be needed to enhance our understanding of adult HSCT survivors' perceptions of physical activity using a more representative sample of this population. The current qualitative work also provides the foundation for future studies aiming to understand adult HSCT survivors' perceptions of access for physical activity programs and their perceived barriers, risks, and the personal, social, and environmental factors that influence regular physical activity. Given increasing evidence supporting physical activity benefits in HSCT survivorship [32], exploring HSCT survivors'

perceptions of physical activity in greater detail is warranted to inform the development of effective physical activity interventions after HSCT.

Implications for the Design of a Future Study

This study informs the design of a future randomized, active-control study testing yoga efficacy in reducing CRF after HSCT. Given that yoga is a multicomponent activity, a validated placebo yoga intervention does not currently exist. However, several yoga studies have assigned controls to low-intensity stretching exercise or progressive muscle relaxation [33-35]. Both the meditative and physical components of yoga may be a pathway through which yoga impacts CRF [36, 37]. Therefore, the subsequent phase II study can randomize participants to yoga or nonmeditative muscle relaxation to control for the group format of yoga classes and other nonspecific effects (e.g., attention, expectations of efficacy). The present study suggests that the intervention in the planned study should be delivered at different sites (e.g., community centers) and by different providers (i.e., restorative yoga teacher, muscle relaxation instructor) to increase the intervention uptake. As such, a manual should be used in the future trial to provide uniform intervention delivery across the intervention sites and to check whether the intervention deliverers adhere to the procedures included in the manual. The intervention manual can also allow the replication of findings by other investigators and facilitate intervention dissemination.

The current study's findings indicate that the subsequent clinical trial should employ multiple recruitment strategies to improve accrual acceptance, retention, and protocol adherence rates. In addition to approaching adult HSCT survivors during their scheduled clinic appointments, the planned study may benefit from handing out recruitment flyers and brochures

to adult HSCT survivors presenting for other services (e.g., physical therapy, laboratory tests), which may allow access to survivors with greater variability in HSCT type and GVHD status. Another essential recruitment method is mailing out a letter to all potentially eligible adult HSCT survivors, which can allow access to survivors who do not have a regular clinic appointment or other healthcare visits scheduled during the recruitment period. The phase II study should also consider measuring inflammatory cytokines and cortisol levels to explore the biological mechanisms underlying the potential benefits of yoga and to assess whether these mechanisms are consistent with those hypothesized in women with breast cancer (e.g., affecting the activity of the hypothalamus-pituitary-adrenal axis) [1]. Finally, the effect sizes obtained for CRF measures in this study can be used for estimating the sample size in the future trial.

Implications for Practice and Policy

Given the promising results of this study, health care providers (HCPs) may discuss the potential benefits of yoga with adult HSCT survivors. HCPs can also encourage adult HSCT survivors to try various types of gentle yoga (e.g., restorative yoga) to find a yoga type that works best for them. If there is any noticeable CRF improvement, HCPs may consider publishing single case studies, which may enhance our understanding of how and whether yoga mitigates CRF after HSCT. The current study's findings suggest that HCPs may consider treating sleep disturbances and pain in adult HSCT survivors with concurrent CRF to improve or prevent worsening of CRF, which may increase the likelihood of successful long-term CRF management. HCPs may also recommend treatments for CRF to improve adult HSCT survivors' ability to engage in activities of daily living. Additionally, influenced by the qualitative findings, HCPs

providing education for adult HSCT survivors may put more emphasis on methods to prevent falling, injury, and communicable infections without decreasing physical activity. The qualitative results also indicate that individual preferences of adult HSCT survivors should be considered by policy stakeholders in developing community- and facility-based physical activity programs to enhance the likelihood of long-term success.

Strengths and Limitations

One major strength of this study is employing a mixed-methods design, which offered important information that could have been inaccessible by a solely quantitative approach. For example, the focus group participants reported several hurdles to yoga practice that may explain the low protocol adherence rate. As seen in Appendix E (Table E.1: Joint Display of Quantitative and Qualitative Data), both the quantitative and qualitative findings suggest sleep improvements among the study participants. The qualitative data also provide important insights into the potential mechanisms leading to improvements in sleep (e.g., reduction of pain-related sleep disturbances) and pain (e.g., increased joint flexibility). Data identifying possible underlying mechanisms driving yoga benefits are crucial for building hypotheses and guiding symptom-targeted yoga interventions for adult HSCT survivors. Although CRF and energy are not conceptually congruent, the improvements in energy reported by some of the focus group participants also support the decreases in CRF dimensions captured quantitatively. Several other yoga benefits emerged from the focus group data but were not quantitatively evaluated, identifying additional health problems that could be targeted by yoga in adult HSCT survivors.

In addition to several methodological flaws, one limitation of this study is related to external validity. The feasibility parameters (e.g., protocol adherence) were, in large part, influenced by the geographic proximity to the community centers. However, the availability and accessibility of community-based yoga classes can vary widely across regions, which may limit the generalizability of our findings. At a broader level, the cross-cultural generalizability of the results (e.g., participants' perceptions of yoga, accrual acceptance rate) is unknown when considering how yoga maybe perceived differently in non-Western cultures. For example, yoga in Indian philosophy is rooted in spiritual components, such as self-discipline and detachment from the human senses, whereas Western yoga focuses primarily on physical components [38].

Conclusion

This mixed-methods study was the first to evaluate yoga in adult HSCT survivors. The quantitative data provided important information regarding the feasibility and potential benefits of yoga for this population. Furthermore, the qualitative data provided an exploration and in-depth understanding of adult HSCT survivors' perceptions of yoga and physical activity. The field is now ready for and requires a large-scale, adequately powered, controlled trial to examine the efficacy of yoga in reducing CRF after HSCT.

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APPENDICES

Appendix A: Table A.1: Evidence Summary

Complementary therapy	Study	Design	Control group	Sample size and population	CRF Measure	Assessment timepoints	Results
Music therapy	Cassileth, Vickers, & Magill (2003)	RCT	Usual care	69 patients hospitalized for autologous HSCT; Age (mean) = 52 years; Female (n=37), Male (n=32)	Profile of Mood States – fatigue subscale	Immediately before and after music therapy with patients receiving approximately five music sessions (≈10 data points)	CRF decreased in the intervention group and increased CRF among controls. The difference between groups was significant (ES=1.8).
	Rosenow & Silverman (2014)	Pretest-posttest single group	Not applicable	50 patients hospitalized for HSCT; Age (range)= 22-75 years; Female (n=15), Male (n=35)	10-point Likert scale	Immediately before and after a single music session, and 30-45 minutes after the session concluded (3 data points)	Significant reductions in CRF right after the music session and at 30-45 minutes follow-up compared to baseline (ES=0.31).
	Rosenow & Silverman (2014)	RCT	Usual care	18 patients hospitalized for HSCT; Age (range) = 31-64 years; Female (n=7), Male (n=11)	Brief Fatigue Inventory	Immediately before and after a single music session (2 data points)	CRF decreased in the intervention group and increased among controls, but there were no significant differences within or between groups (ES=0.11).
	Fredenburg & Silverman (2014)	RCT	Usual care	11 patients hospitalized for HSCT; Age (mean) = 49.6 years; Female (n=3), Male (n=8)	Multi-Dimensional Fatigue Inventory	Baseline (upon admission) and post-intervention (prior to hospital discharge) (2 data points)	In all CRF subscales with the exception of mental CRF, the intervention group reported reductions in CRF scores, whereas CRF increased across all subscales for controls. Differences between groups were not significant. General CRF (ES=0.31), physical CRF (ES=0.17), reduced activity (ES=0.31), reduced motivation (ES=1.02), mental CRF (ES=0.33)
	Bates et al. (2017)	RCT	Usual care	82 patients hospitalized for autologous HSCT; Age (mean)= 58 years; Female (n=37); Male (n=45)	Profile of Mood States – Fatigue subscale	Baseline and post-intervention (right after the second music session on the fifth day after HSCT) (2 data points)	CRF increased in both groups from baseline to post-intervention and follow-up with a greater increase in the intervention group, but there were no significant differences between groups at post-intervention (ES=0.08) compared to baseline.

Relaxation therapy	Kim & Kim (2005)	RCT	Usual care	35 patients hospitalized for allogeneic HSCT; Age (range) = 20-48 years; Female (n=18), Male (n=17)	Piper Fatigue Scale	Baseline and 6 weeks later at post-intervention (2 data points)	CRF decreased in the intervention group and increased among controls with significant differences between groups across all CRF subscales. Behavioral/severity (ES=2.26), affective meaning (ES=1.86), sensory (ES=2.2), cognitive/mood (ES=1.85)
	Lu, Hart, Lutgendorf, Oh, & Silverman (2015)	RCT	Healing touch	26 patients (autologous: n=15, allogeneic: n=11) hospitalized for HSCT; Age (mean)= 56.6 years; Female (n=13), Male (n=13)	Profile of Mood States – Fatigue subscale	Baseline and 3 weeks later at post-intervention (2 data points)	CRF decreased in both groups with a greater decrease in the control group, but there were no significant differences within or between groups (ES=0.007).
Mindfulness-based intervention	Grossman et al. (2015)	RCT	Psychosocial telephone consultation	62 HSCT survivors (autologous: n=19, allogeneic: n=43) at least 6 months after transplant; Age (mean) = 52.1 years; Female (n=31), Male (n=31)	Functional Assessment of Cancer Therapy – Fatigue	Baseline, 8 weeks later at post-intervention, and 3 months follow-up (3 data points)	CRF decreased in both groups from baseline to post-intervention and follow-up with a greater decrease in the intervention group, but there were no significant differences between groups at post-intervention (ES=0.01) and follow-up (ES=0.02) compared to baseline.
Massage therapy	Ahles et al. (1999)	RCT	Usual care	34 patients hospitalized for autologous HSCT; Age (mean) = 41.9 years; Female (n=26), Male (n=8)	10-point Visual Analog Scale	Before and 20 minutes after massage therapy on day -7, during mid-treatment (day -1 until day 7), and prior to hospital discharge (6 data points)	The intervention group reported significantly lower CRF after massage therapy on day -7 (mean difference "massage group" = -1.94, mean difference "control group" = -0.47) and prior to hospital discharge (mean difference "massage group" = -1.71; mean difference "control group" = -0.33) but not during mid-treatment compared to the control group.

Appendix B: Table B.1: Literature Appraisal

Study	Randomization	Groups similar at baseline	Participants blinded	Therapist blinded	Outcome assessor blinded	Concealment to treatment allocation	Treatment groups treated identically	Complete follow-up (no attrition)	Intention to treat analysis	Outcomes measured in the same way for treatment groups	Reliable measures
Cassileth, Vickers, & Magill (2003)	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Yes
Rosenow & Silverman (2014)	No	Not applicable (single arm)	No	No	No	Not applicable	Not applicable	No	No	Not applicable	Unclear
Rosenow & Silverman (2014)	Yes	Groups were not compared at baseline	No	No	No	No	No	No	No	Yes	Unclear
Fredenburg & Silverman (2014)	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes
Bates et al. (2017)	Yes	Yes	No	No	No	No	No	No	No	Unclear	Yes
Kim & Kim (2005)	Yes	Yes	No	No	No	No	No	No	No	Unclear	Yes
Lu, Hart, Lutgendorf, Oh, & Silverman (2015)	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes

Grossman et al. (2015)	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	Yes
Ahles et al. 1999	Yes	Yes	No	No	No	No	No	No	No	Unclear	Yes

Appendix C: Table C.1: Intervention Description

Complementary therapy	Study	Description	Dose
Music therapy	Cassileth, Vickers, & Magill (2003)	Live, individualized music delivered by a trained therapist who determined the frequency of music sessions according to clinical need. The therapist discussed music preferences and clinical problems with patients to determine the appropriate content of the music sessions.	Approximately 5 sessions during hospitalization (20-30 minutes/ session)
	Rosenow & Silverman (2014)	The researcher played patient-preferred live music utilizing the iso-principle, matching music qualities to the patient's current behavioral state while encouraging verbal interaction between songs. The researcher used an acoustic guitar	Single session (30-45 minutes)
	Rosenow & Silverman (2014)	The researcher played patient-preferred live music utilizing the iso-principle, matching music qualities to the patient's current behavioral state while encouraging verbal interaction between songs. The researcher used an acoustic guitar.	Single session (45 minutes)
	Fredenburg & Silverman (2014)	The intervention represented an integration of patient-preferred live music and cognitive behavioral therapy. The cognitive behavioral approach was added to enhance both immediate and long-term music therapy effects during and after patient hospitalization. Sessions were delivered by a study investigator who completed a psychiatric music therapy course. Acoustic guitar was used during the sessions.	Each weekday throughout hospitalization (30-45 minutes/session)
	Bates et al. (2017)	Live, individualized music delivered by a board-certified music therapist. Songs were chosen by the patient and sung by the music therapist. The patient was encouraged to make as many choices as possible. The music therapist used an acoustic guitar.	Two sessions (30 minutes/session)
Relaxation therapy	Kim & Kim (2005)	Relaxation breathing exercise guided by a recorded cassette tape. The tape was 30 minutes in length and included instructions to perform breathing exercises in a supine position.	Daily session for six weeks (30 minutes/session)
	Lu, Hart, Lutgendorf, Oh, & Silverman (2015)	During the first week, participants were guided through passive progressive muscle relaxation. In the second week, a personalized guided imagery meditation was used. In the third week, the participants chose the relaxation technique they used. Sessions were delivered by a trained graduate clinical psychology student.	Daily session for three weeks (20 minutes/ session)
	Grossman et al. (2015)	The mindfulness-based program was based upon concepts of stress reduction techniques that propose that mindfulness may positively affect acceptance of intractable health-related	8-weeks mindfulness-based program including

Mindfulness-based intervention		changes, appreciation of available life experiences, realistic sense of control and accuracy of perception. The mindfulness classes were led by experienced, certified teachers.	weekly, 2.5-hours classes and one all-day retreat at week six.
Massage therapy	Ahles et al. (1999)	The massage techniques ("Swedish/Esalen" massage) were a combination of effleurage and petrissage to the shoulders, neck, face, and scalp. The effleurage consisted of smooth, long, rhythmical strokes up either side of the spine and out across the shoulders, with both hands working simultaneously. The petrissage consisted of gentle kneading. Massage was performed by a trained healing-arts specialist.	An average of 3 sessions per week during hospitalization (20 minutes/session)

Appendix D: Study Measures

D.1. Multidimensional Fatigue Symptom Inventory-Short Form

MFSI-SF

Below is a list of statements that describe how people sometimes feel. Please read each item carefully, then circle the one number next to each item which best describes **how true each statement has been for you in the past 7 days.**

		Not at all	A little	Moderately	Quite a bit	Extremely
1.	I have trouble remembering things	0	1	2	3	4
2.	My muscles ache	0	1	2	3	4
3.	I feel upset	0	1	2	3	4
4.	My legs feel weak	0	1	2	3	4
5.	I feel cheerful	0	1	2	3	4
6.	My head feels heavy	0	1	2	3	4
7.	I feel lively	0	1	2	3	4
8.	I feel nervous	0	1	2	3	4
9.	I feel relaxed	0	1	2	3	4
10.	I feel pooped	0	1	2	3	4
11.	I am confused	0	1	2	3	4
12.	I am worn out	0	1	2	3	4
13.	I feel sad	0	1	2	3	4
14.	I feel fatigued	0	1	2	3	4
15.	I have trouble paying attention	0	1	2	3	4
16.	My arms feel weak	0	1	2	3	4
17.	I feel sluggish	0	1	2	3	4
18.	I feel run down	0	1	2	3	4
19.	I ache all over	0	1	2	3	4
20.	I am unable to concentrate	0	1	2	3	4
21.	I feel depressed	0	1	2	3	4
22.	I feel refreshed	0	1	2	3	4
23.	I feel tense	0	1	2	3	4
24.	I feel energetic	0	1	2	3	4
25.	I make more mistakes than usual	0	1	2	3	4
26.	My body feels heavy all over	0	1	2	3	4
27.	I am forgetful	0	1	2	3	4
28.	I feel tired	0	1	2	3	4
29.	I feel calm	0	1	2	3	4
30.	I am distressed	0	1	2	3	4

D.2. Patient Reported Outcome Measurement Information System-Short Form- Cancer-Related Fatigue

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7 1	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3 2	I have trouble <u>starting</u> things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41 3	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40 4	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35 5	How much were you bothered by your fatigue on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49 6	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
FATIMP3 7	How often did you have to push yourself to get things done because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16 8	How often did you have trouble finishing things because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.3. Patient Reported Outcome Measurement Information System-Short Form-Depression

Emotional Distress – Depression – Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDDEP04 1	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06 2	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29 3	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41 4	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP22 5	I felt like a failure	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP36 6	I felt unhappy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP05 7	I felt that I had nothing to look forward to .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP09 8	I felt that nothing could cheer me up.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

D.4. Patient Reported Outcome Measurement Information System-Short Form- Sleep Disturbances

Sleep Disturbance – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Very poor	Poor	Fair	Good	Very good
Sleep1091	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep1162	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep203	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep444	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep1085	My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep726	I tried hard to get to sleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep677	I worried about not being able to fall asleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep1158	I was satisfied with my sleep.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

D.5. Patient Reported Outcome Measurement Information System-Short Form-Physical Activity

Please respond to each item by marking one box per row.

The following questions ask about your ability to stand and move with and without support. "Support" means using items such as canes, walking sticks walkers and leg braces, or other people.		Yes	No			
PF_Screener 2	Can you walk 25 feet on a level surface (with or without support)?	☐	☐			
		Yes→ Participant receives all items No→ Participant skips PFC6 to PFB5 and proceeds to PFA55				
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFC6	Are you able to walk a block on flat ground?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC29	Are you able to walk up and down two steps?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA39	Are you able to run at a fast pace for two miles?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA25	Are you able to do yard work like raking leaves, weeding, or pushing a lawn mower?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFB7	Does your health now limit you in doing strenuous activities such as backpacking, skiing, playing tennis, bicycling or jogging?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB5	Does your health now limit you in hiking a couple of miles on uneven surfaces, including hills?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA55	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC53	Are you able to get in and out of bed?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA9	Are you able to bend down and pick up clothing from the floor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PF_23	Are you able to reach and get down an object (such as a can of soup) from above your head?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFC35	Does your health now limit you in doing eight hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

D.6. Brief Pain Inventory-Short Form

Brief Pain Inventory—*Short Form*

Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours.

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Please rate your pain by circling the one number that best describes your pain on the **average**.

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Please rate your pain by circling the one number that tells how much pain you have **right now**.

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely interferes

B. Mood

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely interferes

C. Walking ability

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely interferes

D. Normal work (includes both work outside the home and housework)

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely interferes

E. Relations with other people

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely interferes

F. Sleep

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely interferes

G. Enjoyment of life

Does not interfere	0	1	2	3	4	5	6	7	8	9	10	Completely interferes

D.7. Self-Efficacy for Managing Chronic Disease Scale

Self-Efficacy for Managing Chronic Disease 6-Item Scale

We would like to know how confident you are in doing certain activities. For each of the following questions, please choose the number that corresponds to your confidence that you can do the tasks regularly at the present time.

1. How confident are you that you can keep the fatigue caused by your disease from interfering with the things you want to do?

2. How confident are you that you can keep the physical discomfort or pain of your disease from interfering with the things you want to do?

3. How confident are you that you can keep the emotional distress caused by your disease from interfering with the things you want to do?

4. How confident are you that you can keep any other symptoms or health problems you have from interfering with the things you want to do?

5. How confident are you that you can do the different tasks and activities needed to manage your health condition so as to reduce you need to see a doctor?

6. How confident are you that you can do things other than just taking medication to reduce how much you illness affects your everyday life?

not at all confident | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | totally confident

D.8. Index of Self-Regulation Scale

Index of Self-Regulation

We are interested in your thoughts about how you take care of yourself. Please answer the following questions by responding Strongly Disagree, Disagree, Undecided, Agree, or Strongly Agree.

I think of the benefits of changing the ways that I take care of myself	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree (We are interested in your thoughts about how you take care of yourself. Please answer the following questions.)
I remind myself of the good that I am doing by changing the ways that I take care of myself	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree
I remind myself of the importance of changing the ways that I take care of myself	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree
I keep track of how I am doing in changing the ways that I take care of myself	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree
I watch of signs of progress as I change the ways that I take care of myself	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree
I monitor myself to see if I am meeting my goals	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree
I have learned new habits that help me take care of myself	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree
I have learned to approach old situations in new ways	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree
I have learned to make changes that I can live with.	◯ Strongly Disagree ◯ Disagree ◯ Undecided ◯ Agree ◯ Strongly Agree

Appendix E: Table E.1: Joint Display of Quantitative and Qualitative Data

Outcome/theme	Change in outcome measure	Participant experience (selected excerpts)
Cancer-related fatigue	↓ in MFSI-SF-total CRF (Cohen's d=-0.56, P=0.07) and MFSI-SF-general CRF (Cohen's d=-0.33, P=0.25)	No theme related to CRF emerged from the focus group data.
Sleep disturbances	↓ in PROMIS-SF-sleep disturbances (Cohen's d=-0.81, P=0.01)	*"I can say it* [yoga] *helps me sleep better too now."*
Pain	↓ in BPI-SF-pain severity (Cohen's d=-0.26, P=0.22) and BPI-SF-pain interference (Cohen's d=-0.26, P=0.39)	*"I am not waking up in the middle of the night in* [joint] *pain anymore."* *"I wake up with headaches a lot 'cause I'm so tense. In that manner, it* [yoga] *has helped a lot."*
Depression	↓ in PROMIS-SF-depression (Cohen's d=-0.32, P=0.40)	No theme related to depression emerged from the focus group data.
Physical activity	↑ in PROMIS-SF-physical activity (Cohen's d=0.51, P=0.10) and pedometer-determined steps per 24 hours (Cohen's d=0.64, P=0.07)	No theme related to physical activity improvement emerged from the focus group data.
Muscular strength	Not assessed quantitatively	*"I was on steroids for four or five years, and steroids eat away at your muscles and you become very weak. That's what the yoga helps with."*
Stress and calmness	Not assessed quantitatively	*"Personally, through practicing yoga, one, I'm finding reduced stress levels."* *"once I've done it* [yoga] *for a few times, it's easier to remember when you're in a stressful situation, like driving or whatever, to just sit back, stay calm, take a deep breath and just, you know, just let up a little bit on the go, go, go part of my life."*
Body awareness and understanding	Not assessed quantitatively	*"It* [yoga] *has been good for creating more, I can't think of the word, understanding of my body, of knowing my own body's limits and understanding that there's more that I can do that I didn't necessarily know that I could."*
Breathing	Not assessed quantitatively	*"I can see it* [the breath] *going in, and then I can think, 'Oh, my cells, they're nourished.'"* *"I have some GVHD in my lungs, and I think yoga is something that I can do that strengthens me."*
body flexibility and range of motion	Not assessed quantitatively	*"I'm more lucid physically."* *"I wasn't able to twist to this degree, and now I can, so it* [yoga] *just helps me work back towards where I was before."*

Energy	Not assessed quantitatively	*"I suppose after I do yoga I have more energy to get through the day."*
Blood pressure	Not assessed quantitatively	*"My blood pressure has been really good…I think my blood pressure is better."*