Original Research

Exploring Quality of Sleep, Perceived Stress and Resilience in Cancer Survivorship: A Feasibility Study of Mindfulness in Motion

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Abstract

Background: The global principles of Mindfulness-Based Stress Reduction (MBSR) have led to the creation of Mindfulness-Based Interventions (MBIs), which are interventions that retrain the mind to modify its usual stress response to increase coping and resilience. Mindfulness in Motion (MIM) is an MBI that has shown significant biologic and positive psychosocial outcomes with adult working populations, but had not previously been tested in oncology populations and their caregivers. Utilizing MIM to improve sleep quality, perceived stress,

and resilience, in both cancer survivors and caregivers through retraining their response to stress, was the aim of this study.

Methods: Participants were recruited from the survivorship arm of a large research medical center that offers free MIM classes. All class participants were invited to participate in the research that included survivors/caregivers of all stages and various types of cancer. Sleep, resilience and perceived stress were assessed pre- and post-intervention in this single arm feasibility/pilot study, with qualitative assessment of the program done upon completion. During the 8-week MIM intervention, participants (n=25) attended 1-hour group meetings once/week, and individually (via a secure password protected website) performed pre-recorded mindfulness meditations accompanied by music and gentle yoga movements daily.

Results: Significant improvements were observed in sleep quality (p<0.01), resilience (p=0.016), and perceived stress (p<0.01), with survivor/caregiver participants noting the importance of having a mixed group of survivors/caregivers in the group intervention.

Conclusions: MIM is a feasible, well-accepted intervention in a heterogeneous sample of survivors and caregivers. Psychosocial continued care such as mindfulness programing may enhance sleep quality, perceived stress, and resilience for those living with the impact of a cancer diagnosis, survivors and caregivers alike. As the numbers of survivors and caregivers expand, non-pharmaceutical programming to support this population to enhance quality of life, including sleep quality, is warranted.

Keywords

Sleep and health in cancer survivorship; sleep quality in cancer survivors; inadequate sleep in cancer survivorship; sleep as a public health issue for cancer survivors/caregivers

1. Introduction

One out of every three people in the United States will develop cancer in their lifetime, and by 2024, the number of persons living with a history of cancer is expected to have increased to over 19 million from 14.5 million in 2014 [1]. While improvements in cancer prevention efforts, early detection, and treatment advances contribute to this promising survival trend, a diagnosis of cancer continues to have a profound long-term impact on the individual and their caregivers [2]. The National Action Plan for Cancer Survivorship: Advancing Public Health Strategies defines a "cancer survivor" as a person who has been diagnosed with cancer as well as the people in their lives affected by the diagnosis, including family members, friends, and caregivers [3]. A cancer diagnosis affects many quality of life (QOL) issues for both survivor and their caregivers.

A common lifestyle change that occurs with a cancer diagnosis is the lack of sleep quality [4]. Research on sleep quality associated with a cancer diagnosis is complex but one thing is clear- interventions that improve perceived sleep quality may positively impact QOL. [5]. Good quality sleep supports many physiological and psychological processes, including a strong immune system and fortified resilience [6]. Poor sleep quality can cause internal distress to both the physical and mental state. Around 50% of survivors will experience a severe sleep disorder of some kind throughout their life after diagnosis [7, 8], which is twice as prevalent as the general population

[3]. Thus, it is important to improve perceived sleep quality in the cancer population, to enhance QOL post-diagnosis.

The support network for the survivor is also an important part of psychosocial factors that contribute to the quality of care and clinical outcomes [5]. Exploring the relationship between sleep and social support in the general population, satisfaction with social relationships was shown to be associated with a sense of meaning in life, which in turn is associated with sleep [9]. In the context of cancer survivorship and sleep, this link could have benefits for the survivor and/or the caregiver. Cultivating social support for not only the survivor, but also the caregiver could increase the hours they both sleep, thereby improving health outcomes.

In addition to sleep disturbances, cancer survivors and caregivers face a variety of challenges, including many practical, emotional, spiritual, social, and physical concerns [2, 10-12]. Since 60% of cancer patients are over 65 years old, there is also a need for health programs that are adapted for this age group and varying physical ability levels [10]. Since sleep quality is also typically impacted by age for non-cancer aging populations, attending to programming to support sleep quality for the aging survivor/caregiver population may be important from a public health perspective [13]. While healthcare professionals address medical treatment of the survivor, many cancer-related challenges that impact both survivor and caregiver, can be addressed utilizing integrative techniques such as Mindfulness-Based Interventions (MBIs) [3]. A diagnosis of cancer may demand increased resilience behaviors for both survivor and caregiver [14], and as recent research has highlighted, informal cancer caregivers can report even greater distress than the survivor [15], but may be less likely to seek help to address their emotional well-being [16]. The survivor/caregiver dyad is recognized as an important population to explore with mind/body interventions such as yoga to reduce fatigue and anxiety [17, 18].

Levels of acceptance of integrative techniques are increasing among healthcare professionals, and oncology patients express a high level of interest in utilizing integrative techniques [19] for themselves and their caregivers. In fact, over half of cancer survivors are consumers of integrative techniques, including relaxation, yoga, acupuncture, MBIs, and other therapies [20]. These modalities could provide non-pharmaceutical options for patients to aid them in developing strategies that may alleviate symptomology such as stress and its deleterious impact on sleep [3].

Benefits of these interventions have been increasingly well documented, and multiple studies have shown effective outcomes using MBIs in oncology patient populations [21-26]. There is existing research on mindfulness in relation to cancer, although it is often regarding mindfulness-based cognitive training (MBCT), rather than MBIs that include a focus on movement sensation [27, 28]. Studies do exist that support MBIs as beneficial for the mental and physical health of cancer patients and caregivers [23, 29], including improvement in QOL indicators and factors indicative of positive immunological and inflammatory responses [18, 21, 30]. Survivors report receiving tools making it possible for them to regulate emotions such as stress, worry, and anxiety that impact sleep, as well as decreasing rumination about their diagnosis or fear of reoccurrence [28-34].

Quality research utilizing caregivers exclusively as participants is a fairly recent phenomenon. One of the first studies demonstrated the usefulness in providing caregivers with an opportunity to share feelings of guilt, anger, and sadness, emotions that often accompany caring for a loved one with cancer, which may otherwise not be shared due to fear of judgment [33].

We developed a Mindfulness in Motion (MIM) intervention with multiple components including

mindfulness, music, community sharing, and movement (gentle seated yoga), with each component intentionally chosen for its individual contribution. This multi-component approach was designed to maximize benefits for those experiencing stressors related to a cancer diagnosis and/or sleep disturbance. Music has been found to increase well-being and relaxation, increased salivary immunoglobulin (marker related to stress), and decreased cortisol [35, 36]. For some, music may detract from meditation but for others augment it, allowing the latter group to drop into the meditative state more easily. The community aspect of the program is supported by the resulting shift from maladaptive coping strategies to experiencing a new sense of self and one's respective illness [37]. The group setting also emphasizes peer support and group learning, which was found to be especially helpful for cancer survivors [38]. Gently yoga movement was included to facilitate stress reduction rather than as a degree of measurement for movement and has been shown to improve fatigue for the cancer survivor [18].

The conceptual basis for the MIM intervention was a blend of a mindfulness program and a yoga program for cancer survivors [18, 39]. In 2002, researchers produced an operational definition of mindfulness for research investigations concerning the mediating role and mechanism of action of mindfulness [40], where two critical components were determined to be: 1) self-regulation of attention; and 2) the adoption of an orientation toward one's experiences in the present moment. MIM retains the construct of mindfulness, as originally conceived and taught by Kabat-Zinn [41], while adapting it for cancer survivors and caregivers. MIM is comparable to traditional Mindfulness Based Stress Reduction (MBSR) programs concerning the operational definition, differing in time both per day and per week committed to the intervention, the addition of music, and systematic written reflection.

The MIM intervention has shown positive psychological outcomes amongst adult working populations [42], with improvements in sleep among employees in high-stress work environments such as a Surgical Intensive Care Unit (SICU) [42, 43]. SICU personnel described their stress as being subject to an unpredictable, high-stakes stress. Comparable, cancer survivors' narratives describe their experiences as being unpredictable and out of their control. Thus, we thought that MIM may be a feasible intervention for cancer survivors and their caregivers. We hypothesized that MIM would improve sleep, enhance resilience, and decrease perceived stress. We believed it was important to conduct a pilot study to test the feasibility of MIM among cancer survivors and caregivers. Findings from this pilot study will be valuable for refining the intervention and planning for a larger randomized controlled trial of the MIM intervention.

2. Materials and Methods

2.1 Sample

Cancer survivors and caregivers were recruited to a pilot feasibility study of the MIM program via the cancer hospital's survivorship programming office. Individuals had the option of attending the free MIM program or to attend the program and participate in the research (pre and post surveys). The facilitator of the eight weekly sessions was blinded to which program participants were also participating in the research. Reasons for refusal participate in the research surveys was collected in addition to basic demographic characteristics (e.g. age, gender, race, ethnicity, marital status, education, etc.). All study participants provided signed informed consent. The study was

approved by the Institutional Review Board of The Ohio State University

2.2 Procedures

2.2.1 Recruitment

Cancer survivors and caregivers were recruited via posted flyers throughout the cancer hospital, and in primary care physicians' offices within the healthcare system.

2.2.2 Intervention

Mindfulness in Motion (MIM) was developed by the first author (MK) from a previous mindfulness-based intervention [44] to preserve the concept of mindfulness as originally established by Kabat-Zinn [45]. MIM upholds the Kabat-Zinn protocol by its incorporation of didactic education, breathing, relaxation, body scans, and gentle yoga movement as means of facilitating a meditative state. MIM differs from traditional MBSR by reducing the time per day (meditations of 20 minutes versus 45-60 minutes) and decreasing the length of didactic meetings to one hour per week versus 2.5-3 hours per week. In addition, MIM includes relaxing background music and emphasizes gentle chair/standing yoga movement. The protocol has been described in detail elsewhere [43].

For the current study, the MIM program was further modified for cancer survivors by incorporating more cancer-specific questions in self-reflection activities (Table 1), and emphasizing relaxation and mindful yoga as a way to set the stage for considering various perspectives. It is a participatory educational approach for learning a practical strategy for increasing quality of sleep that was hypothesized to potentially also impact resilience and perceived stress for cancer survivors/caregivers.

All weekly group sessions were conducted at a Comprehensive Breast Cancer Center that hosts survivorship programs. This report includes the MIM delivered in two 8-week groups during March through May and September through October 2014. Participants received a detailed workbook to aid in both classroom experiences as well as continued practice outside of the structured sessions. In addition, downloadable MIM 20-minute practices (via an online portal) that mimicked the weekly group experience were provided to all participants. MIM workbooks contained an overview of the intervention and key concepts. Each week had a section that included self-reflection questions, a log for home mindfulness practice, and supplemental readings pertaining to each week's theme. Access to written and audio materials was through the online portal. Participants were able to stream materials via the internet or download them permanently to personal devices, making the practices accessible beyond the 8-week program.

Table 1 Mindfulness in Motion weekly themes, self-reflection activities, and additions for cancer survivors/caregiver.

Week	Theme	Self-reflection activity	Additions for cancer survivorship
1	**Willingness towards daily practice**	Identifying meaning: Exploring the greatest stresses and pleasures in life	Has a cancer diagnosis impacted what gives you the most meaning in life? Have your stresses changed or remained the same since living with cancer?
2	**Cultivating mindful sleep**	Worry and anxiety: What keeps you up at night?	How much time out of your day is spent thinking about cancer? Does worrying about cancer, its impact on you or your loved one impact your quality of sleep?
3	**Vision of self; Supported by breath**	Vision of self: Knowing who we are and how others see us, and knowing where we want to go	How has living with cancer impacted your vision of yourself and/or how you view your loved ones?
4	**Mindful eating and yoga**	Mindful eating: Eating diary	Added information about diets to reduce cancer risk
5	**Movement through balance**	Exploring commonalities from when you felt unbalanced vs. balanced	What can keep you feeling balanced through a cancer diagnosis and treatment?
6	**Awareness of sensation**	Exploring commonalities in sensations perceived as pleasant vs. unpleasant	Has cancer impacted the way you perceive sensations/your awareness of sensations? Can you let go of thoughts and concentrate on sensations before bed to help you fall asleep?
7	**Clarity and release**	Recognizing the biggest stressor in your life right now; perceptions vs. reality; changeable vs. unchangeable	How can we change a reaction to an unchangeable situation (like a cancer diagnosis) in order to decrease the suffering it causes?
8	**Staying grounded and moving forward**	Reflecting on how mindfulness has affected you thus far and how will you continue to practice mindfulness	Has mindfulness helped deal with the presence of cancer in your life?

2.3 Measures

The baseline survey was given prior to the first group session and the post intervention survey was given after the last session. The baseline survey included: a) Demographic characteristics; b) the Pittsburgh Sleep Quality Index (PSQI, 19 items); c) Connors-Davidson Resilience Scale 10 (CD-RISC 10, 10 items); and d) the Perceived Stress Scale (PSS, 10 items). The post-intervention survey included the same measures and asked participants to rate the usefulness of each component of the MIM program.

Demographic characteristics included age, gender, race, ethnicity, marital status, education, and household income. Survivors provided information about their cancer diagnosis, stage at diagnosis, and cancer treatment(s).

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) [46]. This is a 19 item scale that measures sleep quality and disturbances (dysfunction). For the baseline survey, sleep was measured for the previous month and it was measured for the previous 8 weeks for the post-intervention survey. The index has good diagnostic sensitivity and specificity (a score of 6 or above yields a diagnostic sensitivity of 89.6% and a specificity of 86.5%) in distinguishing good versus poor sleep. The scale yields a total score (range 0 to 21), referred to as the global PSQI score, which was used in this study.

Resilience was measured with the Connor-Davidson Resilience Scale 10 (CD-RISC 10) [47]. Resilience corresponds to the ability to maintain good functioning in the face of stress or trauma. CD-RISC scores have been shown to increase after treatments designed to improve resilience [48]. The 10-items version of the CD-RISC (score range 0 to 40) has been validated with good reliability (alpha value of 0.85) and validity to differentiate individuals functioning well after adversity from those who are not [47].

Perceived stress was measured with the Perceived Stress Scale (PSS) [45]. Participants rated their responses to 10 statements about their feelings and thoughts during the past month (baseline) and 8 weeks (post-intervention) on a 5-point Likert-type scale ranging from "never" to "very often" (score range 0 to 40). The PSS measures the degree to which situations in life are appraised as stressful. Items are designed to evaluate how overloaded, unpredictable, and uncontrollable one finds one's life. Cohen reported internal consistency scores of .84, .85, and .86 [49].

2.4 Program Evaluation

The post-intervention survey included questions about how useful participants found specific components of the program, the convenience of the location, time, and duration of the program, participants' favorite and least favorite aspects of the program, and qualitative takeaways from the program. The program evaluation was inspired by Jon Kabat-Zinn [50], and developed by the study principle investigators (MK) to assess participant satisfaction and to inform further intervention refinement for the cancer survivor/caregiver population.

2.5 Statistics

A paired t-test was used to compare the pre- and post-intervention scores on the global PSQI, CD-RISC 10, and PSS. Associations of type of participants (cancer survivor, caregiver, or both) with

the changes in CD-RISC 10, PSQI, and PSS from baseline to post-intervention were evaluated using one-way analysis of variance (ANOVA). The Bowker's test was also used, as individual items in the PSQI were treated as the categorical data to assess differences in the proportion of patients in agreement with the individual items (sleep duration, sleep disturbance, sleep latency, daytime dysfunction, habitual sleep efficiency, sleep quality, and use of sleeping medication) before and after the intervention.

3. Results

3.1 Study Participation

Forty-five cancer survivors and caregivers signed up for the MIM class (Figure 1). Previous mindfulness-based interventions have used participants attending at least 75% of sessions [51, 52] to be included in the analysis. Among the 45 individuals, 37 consented to the study (six did not consent and two never attended). Among individuals who consented to the study, six withdrew from the study and six attended less than six sessions. Reasons for withdrawing or not attending sessions included infection, illness, work conflict, emergencies, and not liking group sessions. This report focuses on the 25 (67.6%) individuals who consented and attended at least six of the eight sessions.
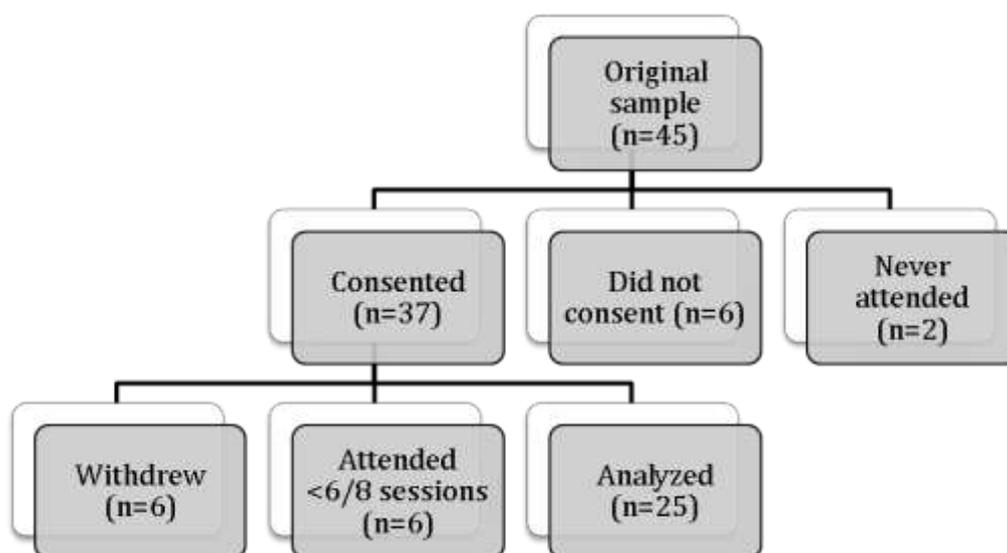
Figure 1 Study participation and completion flow diagram.

3.2 Sample Characteristics

Demographic characteristics of the participants are listed in Table 2. Participants included survivors of breast (n=7), endometrial (n=3), cervical (n=2), ovarian (n=2), leukemia (n=2), lymphoma (n=1), prostate (n=1), and skin (n=1) cancer. One cancer survivor declined to share their cancer diagnosis. Survivors completed various treatments including chemotherapy, surgery, radiation, hormone therapy, anti-hormones, targeted drug therapy, and stem cell blood transplant. Half of the participants reported more than one treatment type. The participants also included five caregivers without a cancer diagnosis.

Table 2 Demographic characteristics of cancer survivors (n=20) and caregivers (n=5).

Survivors and Caregivers (n=25)	
Age (years)	n (%)
Mean (SD)	54.6 (13)
Range	21 - 72
Gender	
Female	22 (88)
Male	3 (12)
Race	
White	21 (84)
African-American	4 (16)
Marital Status	
Married	14 (56)
Single, Divorced, Widowed	11 (44)
Education	
Some college	2 (8)
Bachelor's	7 (28)
Graduate degree	8 (32)
Master's	4 (16)
Doctorate	4 (16)
Household Income	
<$50,000	5 (20)
$50,000-100,000	6 (24)
>100,000	7 (28)
Refused	7 (28)
Survivors Only (n=20)	
Time (in years) since diagnosis	n (%)
Mean (SD)	4.3 (6.1)
Range	0.1 – 21.1
Cancer Stage	
0	2 (10)
1	2 (10)
2	3 (15)
3	3 (15)
4	3 (15)
Not known	7 (35)

3.3 Outcomes

Participants reported significant increases in global sleep quality (p<0.01) and resilience over the course of the 8-week intervention (p=0.016), with significant decreases in perceived stress (p<0.01) (Table 3).

Table 3 Comparison of sleep quality, resilience, and perceived stress from pre-intervention and post-intervention surveys (n=25).

Measurement	Pre Mean	Post Mean	Change (post-pre)			p-value
			Mean	Std Dev	95% CI	
PSQI global score	8.64	6.28	-2.36	3.30	(-3.72, -1.00)	0.002
CD-RISC 10	27.96	30.60	2.64	5.11	(0.53, 4.75)	0.016
PSS	17.20	13.56	-3.64	4.82	(-5.63, -1.65)	0.001
PSQI=Pittsburgh Sleep Quality Index (score: 0 to 21); CD-RISC 10=Connor-Davidson Resilience (score: 0 to 40); PSS=Perceived Stress Scale (score: 0 to 40)						

Whether a participant was a cancer survivor or caregiver did not significantly affect the change of global PSQI (p=0.21), CD-RISC 10 (p=0.67), and PSS (p=0.38) scores from pre- to post-intervention. However, cancer survivors reported greater changes in PSS and CD-RISC 10 scores while caregivers experienced greater changes in the global PSQI score as compared to survivors themselves (Table 4).

Table 4 Comparison of sleep quality, resilience, and perceived stress from pre-intervention and post-intervention surveys for survivors (n=20) and caregivers (n=5).

	N	Global PSQI (post-pre)		CD-RISC 10 (post-pre)		PSS (post-pre)	
		Mean	Std Dev	Mean	Std Dev	Mean	Std Dev
Survivor	20	-2.00	3.45	3.16	5.54	-4.00	4.76
Caregiver	5	-4.40	1.82	1.20	3.56	-3.60	5.08
Global PSQI=Pittsburgh Sleep Quality Index (score: 0 to 21); CD-RISC 10=Connor-Davidson Resilience (score: 0 to 40); PSS=Perceived Stress Scale (score: 0 to 40)							

3.4 Acceptability and Benefit of the Intervention

Participants rating of the various components of the MIM program as very useful are shown in Figure 2. The majority of participants found the various program components positive. The group dynamics, the duration and frequency of the sessions, and breathing awareness were the most useful components reported by the participants.
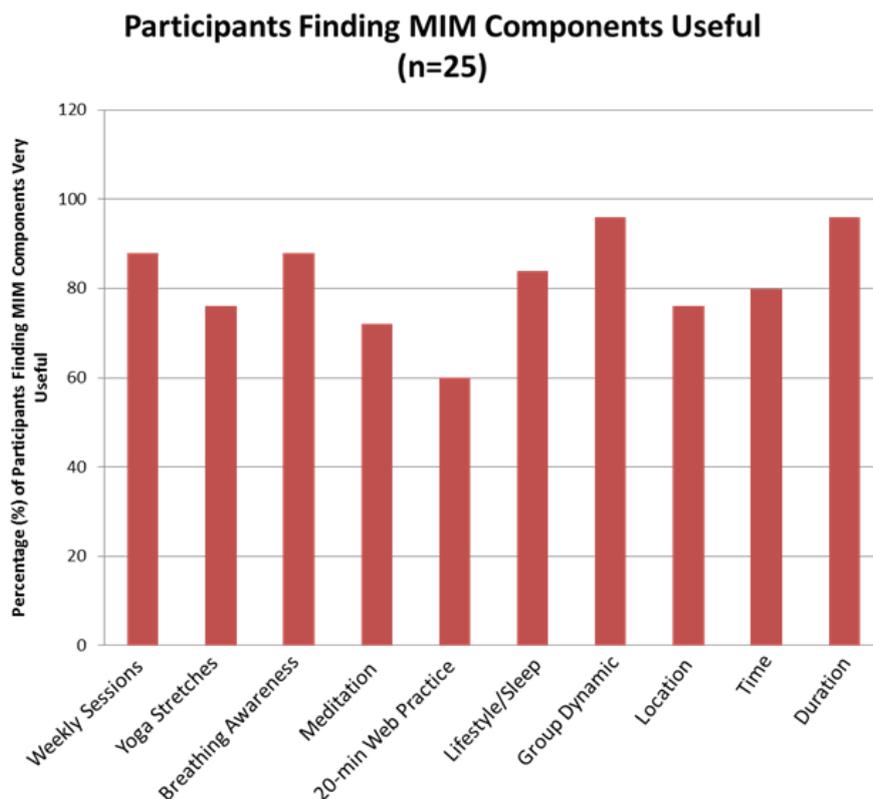
Figure 2 Participants' rating of program components.

Participants provided answers to open-ended questions pertaining to their satisfaction and specific takeaways from the program. In response to the question about new strategies they have learned, participant stated:

"To put my worries aside and give myself the restful night I deserved."

"To be more compassionate and kinder to myself."

"To be 'in the day' and not worry that my daughter's cancer might come back."

Participants described their biggest take away lesson about dealing with cancer as:

"Other caregivers were similar to me and couldn't sleep, worrying about their spouse"

"Every thought changes the way my body feels. Thoughts create physical changes that create health or illness."

"Hearing the comments from others helped me acknowledge negative thoughts, concerns, problems and let them go, so I could fall asleep faster."

4. Discussion

The current study assessed cancer survivors and caregivers sleep quality, resilience, and perceived stress before and after an 8-week MIM program. The intervention significantly increased global sleep quality, resilience, and decreased perceived stress among participants. In addition, the majority of participants found the components of the intervention very useful and were satisfied with the program. These findings support MIM as a feasible, well-accepted intervention for cancer survivors and their caregivers. Our study is consistent with previous research in which abbreviated MBIs successfully provided an acceptable mindfulness intervention for cancer survivors and their

caregivers [28, 53, 54]. Furthermore, our study is also consistent with research that shows that mindfulness for cancer survivors is correlated with greater sleep efficiency and less sleep disturbance compared to that of survivors receiving normal care [55] and the more often a participant practices mindful mediation, the better sleep quality they experience [24].

Participants reported that they benefited most from the group dynamics of the program as well as from the information provided. Other researchers have speculated as to how the group intervention component resulted in positive changes, but it is of complex nature and unclear at this point [24]. Psychosocial support is central to reducing cancer-related distress as evidenced by Greene, who found MBIs to be particularly effective for worry [56] which could be a major inhibitor of sleep quality.

The MIM intervention was accepted by participants. This is reflected predominantly in the qualitative comments and the perceived usefulness of each aspect of the program; all aspects were rated at least an 8.3 out of 10, with 10 being "very useful." In addition, survivors most wanted more lifestyle information during weekly sessions. This indicates that cancer survivors are open to learning more about living resiliently with cancer and could benefit from a program that provides this information (including quality of sleep information) in a clinical setting. Moreover, research has shown mindfulness interventions are effective in not only managing symptom burden but also in affecting various health behaviors, including eating and smoking [57]. This demonstrates that an intervention like MIM could be doubly effective for cancer survivors by providing an avenue for health behavior change to a group that is open, and ripe, to make such changes. MIM could be replicated in any cancer center delivering treatment, and our intention is to video the didactic and experiential segments of the group educational hour so that trained facilitators could lead the community building within the weekly MIM meetings.

4.1 Study Limitations.

A limitation of this study was the high attrition rate (44%), which, as shown in feedback from participants, could largely be attributed to many of the stressors and healthcare obstacles unique to cancer that survivors experience. The few number of caregivers was also a major limitation, as with only five caregivers it was not possible to see the real difference of impact of the MIM programming on survivors as compared to caregivers. The online portal showed that 23/25 participants accessed the portal to download the daily practices but we did have the capability to track adherence to practice via the website. Other studies show that that total time spent practicing home meditations best predicted study outcome measures [58], thus it would have been very informative to track adherence to online homework practices. This reveals the importance of daily practice and demonstrates a need, in future research, to examine the frequency of daily practice outside of the in-person group intervention.

As with any pilot or feasibility study, there are inherent limitations including using a small convenience sample from one geographic location, having few male participants, and there was no control group. This suggests that participants had a high level of motivation and openness to new techniques and may not reflect the general cancer survivor population. Single-arm studies limit causal inferences about the effect of interventions, however, the data showed that the majority of participants reported the program components as very useful and there were significant improvements in sleep quality and resilience, with decreased perceived stress.

4.2 Conclusion.

In conclusion, the findings correlate with and expand upon known data pertaining to MBIs and sleep quality to enhance QOL in cancer survivors and caregivers. They align with the current clinical practice guidelines from the National Cancer Institute which give MBSR a Grade A for effectiveness – meaning "there is high certainty that the net benefit is substantial" – and that practitioners should inform patients and caregivers of these types of programs [59]. We were able to determine the components of the program that participants found most useful, and participants completed pre and post-intervention surveys. Study strengths include a focus on a population with needs to improve sleep quality and resilience, as well as reducing their perceived stress. MIM represents an example of a feasible MBI that is shorter in weekly meeting duration (as compared to MBSR), in addition to recommended daily individual practice. Randomized controlled trials comparing MIM with usual care, and MIM with the longer MBSR, is needed to establish the "value added" towards resilient cancer survivorship and overall sleep quality garnered via MIM for both survivors and caregivers in the clinical oncology setting.

Author Contributions

MDK conceived and designed the intervention and the experiment, and wrote the manuscript, EW, OG and MH acquired the data, in addition to helping draft and revise the manuscript, MK significantly helped in manuscript revision, and LW analyzed the data.

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Competing Interests

The authors have declared that no competing interests exist.

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