Open Access

OBM Integrative and Complementary Medicine

Original Research

Cognitive Impairment, Meditative Movement, and Gene Expression in Breast Cancer Survivors

Francisco V. Muñoz [‡], Linda Larkey [*]

Arizona State University, College of Nursing and Health Innovation, Pomona Valley Hospital Medical Center, Lewis Family Cancer Care Center, USA; E-Mails: fmunoz007@verizon.net; linda.larkey@asu.edu

‡ Current Affiliation: Casa Colina Centers for Health Care, Research Institute

* **Correspondence:** Linda Larkey; E-Mail: linda.larkey@asu.edu

Academic Editor: Leila Kozak

Special Issue: Integrative Therapies in Palliative Care

OBM Integrative and Complementary Medicine
2019, volume 5, issue 3
doi:10.21926/obm.icm.2003035

Received: May 20, 2020
Accepted: July 20, 2020
Published: July 27, 2020

Abstract

Breast cancer survivors (BCSs) report decrements in cognitive functioning. A Meditative Movement (MM) program (Qigong/Tai Chi Easy) combines meditation and exercise, practices known to improve cognitive function. Method: Using a single group, pre- to post-intervention assessment design, a pilot study was conducted in BCSs to test the effects of an 8-week MM intervention on cognitive functioning, sleep and mood and to explore changes on selected gene expression factors, BDNF, NF-kB1, and TP53, expected to improve with symptoms. BCSs (n=14; mean age = 61) completed the MM intervention, provided blood samples and answered questionnaires assessing cognitive function using the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG) and the Wechsler Adult Intelligence Scale (WAIS-III). Sleep and mood were assessed using the Pittsburgh Sleep Quality Index (PSQI) and Profile of Mood States

(POMS) subscales for anxiety and depression. Results: Significant improvements were noted in the FACT-COG subscales: Perceived Cognitive Impairments (p = .01), Perceived Cognitive Abilities (p = .03), Perceived Impairments on Quality of Life (p = .04), and Comments from Others (p = .04). The WAIS-III results indicated a significant improvement in Letter-Number sequencing (p-value = .01), but not for Digit Span Forward/Backwards (p-value = .60). The PSQI (p = .03) and the POMS/anxiety subscale (p = .05) showed a significant decrease. Significant changes in POMS/depression, BDNF, NF-kB1, and TP53 were not found. The intervention was shown to improve cognitive functioning, sleep quality and anxiety suggesting that MM may contribute to the recovery of a subset of persistent symptoms among BCSs.

Keywords
Cognitive impairment; Breast cancer survivors; Gene expression; Tai Chi; Qigong

1. Introduction

Approximately 78% of breast cancer survivors suffer from adverse effects of cancer treatment [1]. Decrements in cognitive functioning among BCSs is one of these adverse effects that may be due to a combination of factors such as the stress of the cancer diagnosis, treatment effects, and increased sedentary behavior, and is often referred to as chemobrain, or cancer-related cognitive impairment [1].

In addition to cognitive impairment, behavioral comorbidities such as depression, anxiety, and poor sleep quality are also prevalent in cancer survivors, affecting their quality-of-life [2-6]. Inflammation is considered a leading mechanism causing changes in neurobiology that underlie these behavioral conditions [6].

There is growing evidence for mind-body practices such as meditation/mindfulness and meditative movement as well as physical activity to improve quality of life and cognitive function in cancer patients and survivors [7-15]. Meditative Movement (MM) has been defined as practices that integrate body movement or postures, a focus on the breath, and a meditative state to cultivate deep state of relaxation [16] and offers the potential of combining both benefits of meditation and exercise for breast cancer survivors. MM combines Tai Chi movements and Qigong into a practice that has been used in research with BCSs because it is very easy to learn and guides participants quickly into a moving meditative state.

Less understood are the molecular signatures that may explain the improvements in cognitive function, anxiety, depression, and sleep quality in breast cancer patients affected by Tai Chi and/or Qigong. Although many studies have examined the effects of mind-body interventions on inflammatory markers, Bowers and Irwin [17] reviewed this body of research and noted that results are mixed and highly dependent upon clinical factors of patients at baseline. In breast cancer survivors, specifically, Janelsins et al., [18] found that the mind-body practice of Tai Chi demonstrated down-regulating effects on pro-inflammatory biomarkers.

For the current study, the targeted gene expression factors in this study were brain derived neurotrophic factor (BDNF), Nuclear Factor kappa B (NF-kB1) and Tumor Protein 53 (TP53). The BDNF gene regulates synaptic plasticity associated with cognitive functioning [19]. Increased levels of BDNF gene expression are associated with improved cognitive functioning [20]. Decreased levels of NF-kB1 gene expression are associated with improvements in managing chronic stress [6, 17]. Increased TP53 gene expression is associated with suppressing cancer growth [21]. There is a need for more research exploring the interactions between inflammation, cognitive functioning, and tumor suppression [6].

This pilot study examined the effects of MM on cognitive function and associated symptoms/conditions such as anxiety, depression, and sleep quality. Gene expression factors that may be associated with these changes and/or critical to recovery and future health of BCSs were explored.

Hypothesis 1: In a group of BCSs, 8 weeks of MM will significantly improve cognitive function.

Hypothesis 2: In a group of BCSs, 8 weeks of MM will significantly improve anxiety, depression, and sleep quality.

Hypothesis 3: In a group of BCSs, 8 weeks of MM will significantly affect gene expression associated with cognitive impairment, inflammation, and tumor growth.

2. Method

This was a single-group pilot study testing the effects of 8 weeks of MM practice on changes in cognitive function, anxiety, sleep quality, depression, and selected gene expression factors**.** The enrollment goal was to consent and assign forty BCSs to an eight-week MM program. Measures on cognitive functioning, associated symptoms/conditions, and gene expression data were collected before and after the 8-week MM program. This study utilized the Paired Sample t-test of SPSS [22] to report p-values from the analysis of pre- and post-MM intervention changes in the cognitive functioning, associated symptoms/conditions, and gene expression data. This study was approved by both the IRB committees at Pomona Valley Hospital Medical Center (PVHMC as the primary IRB) and at Arizona State University (ASU as the secondary IRB).

2.1 Study Population

2.1.1 Eligibility Criteria

Inclusion criteria: minimum 45 years of age; female patients diagnosed with breast cancer, stages 0–III; between six months and five years past primary treatment; ability to speak or understand English; and post-menopausal for at least one year. Exclusion criteria: Women who were unable to stand (e.g., wheelchair or walker bound); patients who were too weak or ill; patients on antibiotics; women working on night shift; and patients with anemia or uncontrolled diabetes. Pregnant women, mentally disabled persons, and prisoners were excluded.

2.1.2 Participant Recruitment

On a daily basis, the clinical trials research coordinator (CRC) at the Pomona Valley Hospital Medical Center (PVHMC) Cancer Care Center (CCC) in Pomona, CA, identified potential participants with the support of site oncologists, site oncology nurses, and the site cancer registry. Flyers were displayed at the Breast Cancer Care Center at the CCC and other affiliated breast cancer care centers in the region. The site cancer registry prepared a mailing list based on the eligibility criteria and invitations were mailed. The CRC generated a list of potential participants based on referrals from the CCC staff and from phone calls from potential participants responding to flyers and mailings.

2.1.3 Screening and Consenting

There were two options for screening and consenting potential participants. In the first option, the site PI or the CRC contacted potential participants referred by the oncology team to screen for study interest and eligibility. In the second option, potential participants responded to the mailed invitation sent by the CRC. Study eligibility and enrollment for participants recruited and screened through both options were confirmed upon review of their medical records after obtaining written consent from potential participants in accordance with Good Clinical Practice (GCP) and Health Insurance Portability and Accountability Act of 1996 (HIPAA). As CCC staff members, the CRC and site PI had access to medical records. After reception of signed Informed Consent form and medical chart review, study participants were scheduled to attend the MM classes.

2.2 Study Intervention

2.2.1 The Intervention

The MM (Qigong/Tai Chi Easy) intervention is a standardized, protocol [23] with a formal training program for practice leaders from the Institute of Integral Qigong and Tai Chi (IIQTC) and has been used in previous research with various populations [8, 24, 25]. This practice is similar to the short, simplified forms used in the majority of Tai Chi research protocols showing health benefits [26]. The protocol is taught as a series of repeated and simple-to-learn movements rather than long chains of choreographed moves that are more difficult to learn (typical of how traditional long-form Tai Chi is taught).

In this study, the MM intervention was implemented over 8 weeks with class sessions once a week at the Pomona Cancer Care Center. Each class session was approximately one hour. The participants learned gentle movements, ranging from mild to moderate levels of exertion. The participants were asked to practice the MM exercises at home, at their own pace, most days of the week, totaling at a minimum, 2 ½ to 3 hours per week and to log their MM practices in a logbook provided to them. A professionally produced DVD and manual demonstrating a core set of 10, and additional exercises for variety were given to participants to help guide their practice at home. The lead investigator, a certified Mind-Body Medicine Practitioner, and certified QG/TCE practice leader assisted the research

participants with the MM sessions. The PI and CRC provided support and guidance to the participants during the MM program.

2.3 Measures

Basic demographic data (gender, ethnicity/race, and age) was collected at baseline. Self-report data on cognitive abilities (perceived and objective assessments), anxiety, depression, and sleep quality, and blood draws to examine gene expression, were collected pre- and post- 8-week MM program (within two weeks prior to and subsequent to the intervention).

2.3.1 Cognitive Function (CF) and Cognitive performance (CP) Tests

Cognitive function was assessed using both a self-report and an objective performance test.

Self-reported CF was assessed using the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG), 37 items, validated, including 4 subscales including perceived cognitive impairment (PCI), perceptions of effects of cognitive function on quality of life (QOL), and perceived cognitive abilities (PCA) and comments from other (OTH [27-29]

CP Tests: Two brief measures of attention/working memory from the Wechsler Adult Intelligence Scale (WAIS-III) Third Edition [30, 31] were used to assess CP: Digit Span and Letter-Number Sequencing, with reliability ratings of .90 and .82 respectively.

2.3.2 Profile of Mood States Short Form (POMS-SF)

The POMs-SF consists of 37 items, adjectives scored on a 5-point Likert scale [32]. The POMS is one of the most frequently used and validated scales in studies of psychosocial interventions with BCSs, and has been validated with Hispanics [33] and multicultural populations [34]. POMS consists of the Total Mood Disturbance (TMD) dimensions (tension-anxiety; depression-dejection; anger-hostility; confusion-bewilderment; Cronbach's alpha = .93). This pilot study reported results for the tension-anxiety and depression-dejection TMD dimensions (12 items).

2.3.3 Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI): 19 items assess sleep, including subscales for subjective sleep quality, sleep latency, sleep duration, sleep disturbance, habitual sleep efficiency, daytime dysfunction and use of sleep medications [35]. A global PSQI score >5 distinguishes good from poor sleepers with 89.6 % sensitivity and 89.5% specificity and demonstrates Cronbach's $\alpha = 0.83$ [36].

2.3.4 Process Control, Manipulations and Fidelity

Each participant received a phone call or email midweek between class attendance (whether they attended or not) to remind them to document practice time (session/minutes) and weekly record level of exertion. MM Practice Logs were provided for participants to document home practice. The midweek contact served both as process control evaluation and as a method for encouraging

adherence. Whenever a participant missed a scheduled class, she received an additional call to encourage adherence.

2.3.5 Gene Expression Data

The PAXgene Blood RNA Tube (Catalog No. 762165) was at room temperature (18-25C) and properly labeled for patient identification. The CRC collected one 2.5 ml of blood into one tube using the standard technique for BD Vacutainer® Evacuated Blood Collection Tubes.

2.3.6 After Blood Collection

The CRC inverted the PAXgene Blood RNA Tube 8 to 10 times and stored the PAXgene Blood RNA Tube upright at room temperature (18°C–25ºC) for a minimum of 2 hours and a maximum of 72 hours before processing or transferring to refrigerator (28°C) or freezer (−20°C). After 48 hours in freezer (−20°C) the blood samples were transferred and stored in a freezer (-80°C) until they were prepared for RNA sequencing. **Transport Collected Blood Samples**: Blood samples were transported to SC2 Core lab for processing and library preparation for RNA sequencing.

2.4 Retention Strategies

The PI and CRC maintained contact with the study participants by telephone, in person, or email to encourage retention in the study. In addition, to providing log-book instructions and meeting time reminders during this contact, the CRC or PI encouraged questions and sharing on how they are experiencing the research study with goal of establishing a therapeutic alliance between the research staff and the study participants. The study participants were also encouraged to initiate contact with the PI or CRC with any questions or concerns by phone, email, or in person.

2.4.1 Sample Size Justification

The enrollment goal of 40 participants followed the guidelines of Browne [37] to formulate samples sizes for pilot studies. This was the target for recruitment with an expected attrition rate of 20%. Although 27 participants were consented, only 14 completed the study. The 14 who completed the study met the standards established by Julious [38] for pilot study sample sizes. Browne and Julious [37, 38] provided sample size calculation guidelines for pilot studies designed to collect preliminary data for a clinical trial.

2.4.2 Hypothesis Testing Data Analysis Plan

This study utilized the Paired Sample t-test of the SPSS statistical program to analyze the primary outcome changes in cognitive function anxiety, depression, and sleep quality over an 8-week period. Changes in BDNF, NF-kB1, and TP53 gene expression results were analyzed using the paired sample t-test in SPSS to determine if the means of the pre- and post-MM gene expression data were significantly different.

2.4.3 Missing Data

Participant responses were reviewed for missing data and participants were given an opportunity to complete overlooked questions or indicate a preference not to answer during the data collection session. All analyses were conducted on participants who completed the intervention. If post-intervention data was unavailable, missing data were not imputed. As a small pilot study to detect trends in change from pre- to post-intervention, we do not expect there to be a systematic bias introduced by the data loss of a small number of participants. One study participant did not complete her post-MM program WAIS-III measure and did not submit her MM logbook due to schedule conflicts.

2.4.4 Secondary Outcomes

Peripheral blood samples were collected before and after the 8-week MM program. The gene expression data was processed and analyzed by the bioinformatics team at the Single-Cell, Sequencing, and CyTOF Core (SC2), Children's Hospital Los Angeles (CHLA), Los Angeles. These data were analyzed using the paired sample t-test in the IBM SPSS Statistics program.

RNA sequencing: Sequencing libraries were prepared from previously purified RNA using the Illumina TruSeq Stranded mRNA Library Prep kit following the manufacturer's instructions. Sequencing was performed on a NextSeq 500 platform using 2×75bp chemistry [39].

Gene Expression data analysis: Quality control and adapter trimming was performed using trim galore (v0.4.2) with default parameters [40]. Reads were aligned to the GRCh38 reference genome and transcriptome using HISAT2, v2.1.0 [41], and transcript quantification was performed using featureCounts, v1.5.1 [42]. Differential expression analysis was performed using the 'DESeq2' R package, v1.16.1, [43] and a rank score calculated as -log10(q-val)*sign (log2 FoldChange) was used as input to the GSEA Preranked tool for pathway analysis [44].

The DESeq2 data were used to identify the gene expression changes over the 8-week MM program. DESeq2 (differential expression sequence) files are TMM (weighted trimmed mean of the log expression ratios - trimmed mean of M values) normalized count per million reads.

3. Results

Twenty-seven breast cancer survivors were consented and enrolled into the study. Fourteen completed the MM program in 8-week class cohorts ranging from 5 to 9 participants. All of the 14 study participants were female and ranged in age from 45 to 95 years old. Ten of the study participants were White, three were Latina, and one was Black.

The primary reason 13 of the 27 consented study participants dropped out of the study was schedule conflicts. Other reasons included changes in physical or emotional health related to preexisting conditions, lack of transportation, and perceived prolonged waiting time to begin MM groups after consenting. The research staff maintained contact with those who discontinued participation in case their circumstances changed until they requested no further contact with the study.

Twelve of the fourteen participants attended every weekly session at the Cancer Care Center. Two were absent more than two weekly sessions. Thirteen study participants submitted their logbooks documenting the number of minutes they practiced MM weekly. Their weekly log included their weekly 60-minute MM sessions at the Cancer Care Center. The MM logbook reported mean in minutes per week was M = 91.06, SD = 46.12.

Hypothesis One (Table 1)**: Cognitive Functioning**

Significant improvements, as predicted, were noted in the FACT-COG subscales: Perceived Cognitive Impairments (CogPCI), ($t(13) = 3.4$, $p = .01$); Perceived Cognitive Abilities (CogPCA), ($t(13) = -2.4$, $p = .03$); Perceived Impairments on Quality of Life (CogQOL), ($t(13) = 2.2$, $p = .04$); and Comments from Others (CogOth), ($t(13) = 2.3$, $p = .04$).

The significant changes for Perceived Cognitive Impairments (CogPCI) from pre-MM program, mean = 25.4 to post-MM program, mean = 17.3 indicated the BCS perceived their cognitive impairment declined. The BCS also perceived a decline in Perceived Impairments on Quality of Life (CogQOL) indicated by the significant change in pre-MM program, mean = 3.7 to post-MM program, mean = 1.8.

The positive significant changes indicated in the Perceived Cognitive Abilities (CogPCA) subscale suggested the BCSs' subjective improvement in their cognitive abilities noted in the pre-MM, mean = 16.0 significant change to post-MM, mean = 19.2. Another significant decline reported by the BCS was on the subscale, Comments from Others (CogOth), evidenced by the pre-MM program, mean = 1.5 to post-MM, mean = 0.2. This subscale reflects the BCSs' experience of what others have said to them regarding perceived cognitive decline.

Significant improvements, as predicted, were noted in the the WAIS-III, Letter/Number sequencing results, ($t(12) = -3.2$, $p = .01$). Significant improvements were not noted in the WAIS-III, Digit Span Forward and Backward measure, ($t(12) = -0.532$, $p = .60$). One of the two objective WAIS-III assessments of cognitive performance, Letter/Number sequencing, showed significant improvement demonstrated by the pre-MM mean 10.7 increase to the post-MM mean 12.7. The WAIS-III digit span Forward/Backward assessment also demonstrated an increase in the pre-MM mean 19.2 to post-MM mean 19.7 but did not reach significance.

Table 1 Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG) Subscales.

Measure	Pre-MM mean (sd)	Post-MM mean (sd)	Pre/Post MM mean (sd) difference	P-Value
CogPCI	25.4 (14.2)	17.3 (10.5)	*-8.1 (3.7)	.01
CogPCA	16.0 (5.1)	19.2 (5.3)	3.2 (0.2)	.03
CogQOL	3.7 (3.8)	1.8 (2.2)	*-1.9 (1.6)	.04
CogOth	1.5 (2.1)	0.2 (0.4)	*-1.3 (1.7)	.04
WAIS-III Letter/Number	10.7 (3.2)	12.7 (2.8)	2.0 (0.4)	.01

sequence				
WAIS-III Digit Span Forward and Backward	19.2 (4.8)	19.7 (4.4)	0.5 (0.4)	.60

*reduction in scores indicate improvement.

Hypothesis Two (Table 2): **Sleep Quality, Anxiety, and Depression**

The Pittsburg Sleep Quality Index (PSQI) scores, evidenced significant improvement, ($t(13) = 2.5$, $p = .03$). The POMS/anxiety subscale showed a significant decrease ($t(13) = 1.9$, $p = .05$) and the POMS/depression reduction did not reach significance ($t(13) = 1.9$, $p = .08$). BCSs' poor sleep quality significantly decreased from pre-MM program, mean = 1.5 to post-MM program mean = 0.9. Their anxiety levels also significantly decreased from pre-MM program mean = 9.2 to post-MM program mean = 4.2. Depression levels also decreased, pre-MM mean = 4.1 to post-MM mean 2.0, but did not reach significance.

Table 2 The Pittsburgh Sleep Quality Index (PSQI) and Profile of Mood States (POMS).

Measure	Pre-MM mean (sd)	Post-MM mean (sd)	Pre/Post MM mean (sd) difference	P-Value
PSQI	1.5 (0.8)	0.9 (0.7)	*-0.6 (0.1)	.03
POMS Anxiety	9.2 (7.7)	4.2 (3.7)	*-5.0 (4.0)	.05
POMS Depression	4.1 (4.9)	2.0 (3.0)	*-2.1 (1.9)	.08

*reduction in scores indicate improvement.

Hypothesis Three (Table 3)**: Gene Expression Factors**

Significant changes were not found for BDNF ($t(13) = -1.1$, $p = .30$), NF-kB1 ($t(13) = -0.2$, $p = .80$), and TP53 ($t(13) = -0.52$, $p = .61$).

Table 3 Gene Expression Factors.

Measure	Pre-MM mean (sd)	Post-MM mean (sd)	Pre/Post MM mean (sd) difference	P-Value
BDNF	0.11 (0.9)	0.30 (0.7)	0.19 (0.2)	.30
NF-kB1	171.7 (25.4)	173.7 (21.6)	2.0 (3.8)	.80
TP53	12.3 (2.7)	13.1 (5.5)	0.8 (2.8)	.61

The mean (sd) differences (Table 3) in BDNF gene expression, 0.19 (-0.2); NF-kB1 gene expression, 2.0 (-3.8); and TP53 gene expression, 0.8 (2.8); all indicated an increase in RNA between pre- and post-MM intervention. Although these differences are not statistically significant.

4. Discussion

The primary outcome expected to improve in response to the intervention as cognitive function, and the assessments showed promising results on this factor, measured both with self-report and one of the objective measures. The direction of change for the FACTCog subscales all indicated a perceived significant improvement in cognitive functioning. The WAIS-III Letter/Number assessment provided significant and objective evidence to support improvement in cognitive functioning. The direction of change for the WAIS-III Digit Span Forward/Backward assessment indicated an improvement in cognitive functioning but did not reach significance.

The PSQI and POMS/anxiety subscale also provided significant and positive subjective changes in sleep quality and anxiety levels. The POMS/depression subscale evidenced positive changes but these changes did not reach significance. This lack of significance may be due to the majority of the BCSs in this study not reporting any major issues with depression.

The research design for the GME study was based on the intent to perform a pilot study and examine a trend for effects of the intervention on gene expression and symptom changes. Regarding the enrolled participants failing to initiate, we have further explained that conducting this study in a small cancer center, recruitment was slow, thus often extending the time from consent to a new class group start date. This is now discussed in the limitation section.

Limitations. The MM suggested time goal for the study participants was between 2.5 and 3 hours per week. The MM logbooks showed a mean of 1.5 MM hours per week for the study participants. Lower than projected time engagement in the intervention may have attenuated results across all of the assessments. Increasing the amount of engagement time between the research team and the study participants using phone calls, texts or other types of encouragement may increase the MM practice hours per week. The consented participants who did not begin the study may have perceived too long a wait time for the MM groups to begin. The wait time often resulted in loss of interest or change in other circumstances. For these consented participants, consistent communication from the research team may have maintained their engagement with the study until the MM groups were started.

Despite the small number of study participants, the results of this study parallel the results of larger studies conducted on the effects of meditation, exercise, and mind-body practices such as Yoga or Tai Chi/Qigong on the cognitive functioning, anxiety and quality of life factors for BCS [7-15, 45]. The absence of significant change in the means for pre- and post- intervention BDNF, TP53 and NF-kB1 gene expression may indicate that there is no effect of the intervention, that the intervention dose was insufficient, or that the sample size was too small. Another study that examined NF-kB gene expression in response to a 12-week MM intervention, Tai Chi Chih (TCC), but with higher dose (2 hours/week), reported less increase in NF-kB gene expression compared to control, but also not reaching significance [46]. Differences between the two studies may due to type of study participants (older adults vs. BCSs), and length and dose of intervention.

Given such a small sample size, we did not examine potential associations of the biomarkers assessed with the improvements in cognitive functioning and quality of life factors. In larger studies in the future, it would be important to examine these relationships as possible mediators of

symptomatic change. Rather than a focus on the target genes themselves, an analysis of the biological pathways of cognitive functioning, tumor suppression, and pro-inflammation may yield more insight on potential effects of the MM program on the molecular signatures and gene expression within the study participants.

Further, while many studies of MM in cancer patients or survivors have examined (and found) reductions in inflammatory cytokines, very few have assessed the gene expression pathways to that inflammation, and none, to our knowledge, have explored BDNF specifically. Although significance changes were not found, these novel targets were worth exploring, and in fact, show promise for studies that are better powered for significance testing.

5. Conclusion

This pilot study tested the effects of the MM program on changes in cognitive functioning and associated symptoms/conditions such as anxiety, depression, and sleep quality. This study also utilized gene expression factors to improve understanding of the biological mechanisms potentially associated with these changes. The patient self-reported data indicated the MM program was perceived as improving cognitive functioning, in support of other study results. This perception was further supported by an objective cognitive performance measure showing significant improvements on one of the two assessments. The patient self-reported data also indicated the MM program was perceived as improving anxiety and sleep quality. The gene expression data did not evidence significant results to support association with positive changes in cognitive performance, anxiety, and sleep quality. The major limitation of this study is the underpowered sample size that does not allow for the definitive testing of the hypotheses. This study provided preliminary data for a future powered randomized control trial to study psycho-behavioral outcomes and associated genomic expression factors.

Acknowledgements

This project was supported by a grant from the National Cancer Institute (1R01CA182901- 01A1).

Author Contributions

Dr. Munoz conducted the study, analyzed, and interpreted results while taking the lead in writing the manuscript. Dr. Larkey provided study oversight, expertise for MM intervention, and editorship for manuscript. Both authors provided critical analysis as they shaped the research and manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Lambert, M, Ouimet LA, Wan C, Stewart A, Collins B, Vitoroulis I, et al. Cancer-related cognitive impairment in breast cancer survivors: An examination of conceptual and statistical cognitive domains using principal component analysis. Oncol Rev. 2018; 12: 371. doi: 10.4081/oncol.2018.371. eCollection 2018 Jul 4.
2. Mosher CE, Duhamel KN. An examination of distress, sleep, and fatigue in metastatic breast cancer patients. Psychooncology. 2012; 21: 100-107. doi: 10.1002/pon.1873.Epub 2010 Nov 24.
3. Lockefeer JP, De Vries J. What is the relationship between trait anxiety and depressive symptoms, fatigue, and low sleep quality following breast cancer surgery. Psychooncology. 2013; 22: 1127-1133. doi: 10.1002/pon.3115. Epub 2012 Jun 13.
4. Fontes F, Severo M, Goncalves M, Pereira S, Lunet N. Trajectories of sleep quality during the first three years after breast cancer diagnosis. Sleep Med. 2017; 34: 193-199. doi: 10.1016/j.sleep.2017.03.022. Epub 2017 Apr 4.
5. McCall M. Yoga intervention may improve health-related quality of life (HRQL), fatigue, depression, anxiety and sleep in patients with breast cancer. Evid Based Nurs. 2018; 21: 9. doi: 10.1136/eb-2017-102673. Epub 2017 Nov 25.
6. Santos JC, Pyter LM. Neuroimmunology of behavioral comorbidities associated with cancer and cancer treatments. Front Immunol. 2018; 9: 1195. doi: 10.3389/fimmu.2018.01195.
7. Greenlee H, Balneaves LG, Carlson LE, et al. Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer. J Natl Cancer Inst Monogr. 2014; 2014: 346-358. doi: 10.1093/jncimonographs/lgu041
8. Larkey LK, Roe D, Smith LL, Millstine D. Exploratory outcome assessment of Qigong/Tai Chi Easy on breast cancer survivors. Complement Ther Med. 2016; 29: 196-203. doi: 10.1016/j.ctim.2016.10.006.
9. Greenlee H, Dupont-Reyes MJ, Balneaves LG, et al. Clinical guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. CA Cancer J Clin. 2017; 67: 194-232. doi: 10.3322/caac.21397.
10. Treanor CJ, McMenamin UC, O'Neill RF, et al. Non-pharmacological interventions for cognitive impairment due to systemic cancer treatment. Cochrane Database Syst Rev. 2016: CD011325. doi: 10.1002/14651858CD011325.pub2.
11. Carlson LE, Tamagawa R, Stephen J, Drysdale E, Zhong L, Speca M. Randomized-controlled trial of mindfulness-based cancer recovery versus supportive expressive group therapy among distressed breast cancer survivors (MINDSET): Long-term follow-up results. Psychooncology. 2016; 25: 705-709. doi: 10.1002/pon.4150.
12. Gentry AL, Erickson KI, Sereika SM, et al. Protocol for exercise program in cancer and cognition (EPICC): A randomized controlled trial of the effects of aerobic exercise on cognitive function in postmenopausal women with breast cancer receiving aromatase inhibitor therapy. Contemp Clin Trials. 2018; 67: 109-115. doi: 10.1016/j.cct.2018.02.012.

13. Hartman SJ, Nelson SH, Myers E, et al. Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory & motion study. Cancer. 2018; 124: 192-202. doi: 10.1002/cncr.30987.
14. Lyman GH, Greenlee H, Bohlke K, et al. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. J Clin Oncol. 2018: JCO2018792721. doi: 10.1200/JCO.2018.79.2721.
15. Park HS, Kim CJ, Kwak HB, No MH, Heo JW, Kim TW. Physical exercise prevents cognitive impairment by enhancing hippocampal neuroplasticity and mitochondrial function in doxorubicin-induced chemobrain. Neuropharmacology. 2018; 133: 451-461. doi: 10.1016/j.neuropharm.2018.02.013.
16. Larkey LK, Jahnke R, Etnier J, Gonzalez J. Meditative movement as a category of exercise: Implications for research. J Phys Act Health. 2009; 6: 230-238.
17. Bower J, Irwin M. Mind-body therapies and control of inflammatory biology: A descriptive review. Brain Behav Immun. 2016; 51: 1-11. doi: 10.1016/j.bbi.2015.06.012.
18. Janelsins MC, Davis PG, Wideman L, et al. Effects of Tai Chi chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. Clin Breast Cancer. 2011; 11: 161-170.
19. Xu B. BDNF (I)rising from exercise. Cell Metab. 2013; 18: 612-614. doi:10.1016/j.cmet.2013.10.008
20. Lange M, Joly F, Vardy J, et al. Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors. Ann Oncol. 2019; 30: 1925-1940. doi: 10.1093/annonc/mdz410.
21. Brenner DR, Brockton NT, Kotsoppoulos J, et al. Breast cancer survival among young women: A review of the role of modifiable lifestyle factors. Cancer Causes Control. 2016; 27: 459-472. doi: 10.1007/s10552-016-0726-5.
22. IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.
23. Jahnke R, Larkey LK, Rogers CE. Dissemination and benefits of an accessible Tai-Chi-Qigong (TCQG) program for older adults. Geriatr Nurs. 2010; 31: 272-280. doi: 10.1016/j.gerinurse.2010.04.012
24. Smith LL, Larkey L, Blackstone R, Celaya M. Feasibility of a meditative movement intervention for bariatric patients. Appl Nurs Res. 2014; 27: 231-236. doi: 10.1016/j.apnr.2014.02.009.
25. Larkey LK, Roe D, Weihs K, Jahnke RA, Lopez AM, Guillen J, et al. Randomized controlled trial of Qigong/Tai Chi Easy on cancer-related fatigue in breast cancer survivors. Ann Behav Med. 2014; 49: 165-176. doi:10.1007/s12160-014-9645-4.
26. Jahnke R, Larkey LK, Rogers C, Etnier J, Lin F. A comprehensive review of health benefits of Qigong and Tai Chi. Am J Health Promot. 2010; 24: 1-25.
27. Jacobs SR, Jacobsen PB, Booth-Jones M, Wagner LI, Anasetti C. Evaluation of the functional assessment of cancer therapy cognitive scale with hematopoietic stem cell transplant patients. J Pain Symptom Manage. 2007; 33: 13-23.
28. Cheung YT, Lim SR, Shwe M, Tan YP, Chan A. Psychometric properties and measurement equivalence of the English and Chinese versions of the functional assessment of cancer therapy-

cognitive in Asian patients with breast cancer. Value Health. 2013; 16: 1001-1013. doi: 10.1016/j.jval.2013.06.017.

29. Van Dyk K, Crespi CM, Petersen L, Ganz PA. Identifying cancer-related cognitive impairment using the fact-cog perceived cognitive impairment. JNCI Cancer Spectrum. 2020; 4: pkz099. doi:10.1093/jncics/pkz099.
30. Wechsler D. WAIS-III administration and scoring manual. 3rd ed. Psychological Corp; 1997. p. 217.
31. Lozano-Lozano M, Martin-Martin L, Galiano-Castillo N, et al. Integral strategy to supportive care in breast cancer survivors through occupational therapy and a m-health system: Design of a randomized clinical trial. BMC Med Inform Decis Mak. 2016; 16: 150. doi: 10.1186/s12911-016-0394-0.
32. Curran SL, Andrykowski MA, Studts JL. Short form of the profile of mood states (POMS-SF): Psychometric information. Psychol Assess. 1995; 7: 80.
33. Perczek R, Carver CS, Price AA, Pozo-Kaderman C. Coping, mood, and aspects of personality in Spanish translation and evidence of convergence with English versions. J Pers Assess. 2000; 74: 63-87.
34. Annesi JJ. Behaviorally supported exercise predicts weight loss in obese adults through improvements in mood, self-efficacy, and self-regulation, rather than by caloric expenditure. Perm J. 2011; 15: 23.
35. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res. 1998; 45: 5-13. Doi: 10.1016/s0022-3999(97)00298-5.
36. Buysse D, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28: 193-213.
37. Browne RH. On the use of a pilot sample for sample size determination. Stat Med. 1995; 14: 1933-1940
38. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceut Stat. 2005; 4: 287-291.
39. Illumina. Studying gene expression using RNA sequencing. 2018. Retrieved from: https://www.illumina.com/techniques/sequencing/rna-sequencing.html.
40. FelixKrueger/TrimGalore. Trim Galore is a wrapper around Cutadapt and FastQC to consistently apply adapter and quality trimming to FastQ files, with extra functionality for RRBS data. 2018. Retrieved from: https://github.com/FelixKrueger/TrimGalore.
41. Kim D, Langmead B, Salzberg S. HISAT: A fast spliced aligner with low memory requirements. Nat Methods. 2015; 12, 357-360. doi: 10.1038/nmeth.3317
42. Liao Y, Smyth GK, Shi W. FeatureCounts: An efficient general purpose program for assigning sequence reads to genomic features. Bioinformatics. 2014; 30: 923-930. doi: 10.1093/bioinformatics/btt656.
43. Love M, Huber W, Anders S. Moderated estimation of fold changes and dispersion for RNA-seq data with DESeq. Genome Biol. 2014; 15: 550. doi: 10.1186/s13059-014-0550-8.
44. Subramanian A, Tamayo P, Mootha V, et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression files. PNAS. 2005; 102: 15545-15550. doi: 10.1073/pnas.0506580102.

45. Wayne PM, Lee MS, Novakowski J, et al. Tai Chi and Qigong for cancer-related symptoms and quality of life: A systematic review and meta-analysis. J Cancer Surviv. 2018; 12: 256-267. doi: 10.1007/s11764-017-0665-5.
46. Black DS, Irwin MR, Olmstead R, Ji E, Crabb Breen E, Motivala SJ. Tai chi meditation effects on nuclear factor-κB signaling in lonely older adults: A randomized controlled trial. Psychother Psychosom. 2014 ;83: 315–317. doi.org/10.1159/000359956