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ORIGINAL ARTICLE

Effect of medical Qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial

Byeongsang Oh · Phyllis N. Butow · Barbara A. Mullan · Stephen J. Clarke · Philip J. Beale · Nick Pavlakis · Myeong Soo Lee · David S. Rosenthal · Linda Larkey · Janette Vardy

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Abstract
Purpose Cancer patients often experience diminished cognitive function (CF) and quality of life (QOL) due to the side effects of treatment and the disease symptoms. This study evaluates the effects of medical Qigong (MQ; combination of gentle exercise and meditation) on CF, QOL, and inflammation in cancer patients.
Methods Eighty-one cancer patients recruited between October 2007 and May 2008 were randomly assigned to two groups: a control group (n=44) who received the usual health care and an intervention group (n=37) who participated in a 10-week MQ program. Self-reported CF was measured by the European Organization for Research and Treatment of Cancer (EORTC-CF) and the Functional Assessment of Cancer Therapy—Cognitive (FACT-Cog). The Functional Assessment of Cancer Therapy—General (FACT-G) was used to measure QOL. C-reactive protein (CRP) was assessed as a biomarker of inflammation.
Results The MQ group self-reported significantly improved CF (mean difference (MD)=7.78, t_{51}=−2.532, p=0.014) in the EORTC-CF and all the FACT-Cog subscales [perceived cognitive impairment (MD=4.70, t_{43}=−2.254, p=0.029), impact of perceived cognitive impairment on QOL (MD=1.64, t_{45}=−2.377, p=0.024), and perceived cognitive abilities

B. Oh · S. J. Clarke · P. J. Beale · J. Vardy
Sydney Medical School, University of Sydney,
Royal Prince Alfred Hospital & Concord
Repatriation General Hospital,
Sydney, NSW, Australia

S. J. Clarke
e-mail: stephen.clarke@sydney.edu.au

P. J. Beale
e-mail: Philip.Beale@sswahs.nsw.gov.au

J. Vardy
e-mail: janette.vardy@sydney.edu.au

B. Oh · P. N. Butow · B. A. Mullan · J. Vardy
Centre for Medical Psychology and Evidence-based Decisionmaking (CeMPED), School of Psychology,
University of Sydney,
Brennan/McCallum Building (A18),
Sydney, NSW 2006, Australia

P. N. Butow
e-mail: phyllisb@psych.usyd.edu.au

B. A. Mullan
e-mail: barbara@psych.usyd.edu.au

B. Oh (✉) · S. J. Clarke · P. J. Beale · N. Pavlakis
Department of Medical Oncology, Royal North Shore Hospital,
St Leonards 2065 NSW, Australia
e-mail: byeong.oh@sydney.edu.au

N. Pavlakis
e-mail: nick.pavlakis@sydney.edu.au

M. S. Lee
Brain Disease Research Center,
Korea Institute of Oriental Medicine,
461-24, Jeonmin-dong, Yuseong-gu,
Daejeon 305-811, South Korea
e-mail: drmslee@gmail.com

D. S. Rosenthal
Dana–Farber Cancer Institute, Harvard Medical School,
44 Binney Street, #G133,
Boston, MA 02115, USA
e-mail: drose@uhs.harvard.edu

L. Larkey
Scottsdale Healthcare Chair of Biobehavioral Oncology Research,
College of Nursing and Health Innovation,
Arizona State University,
Tempe, AZ, USA
e-mail: linda.larkey@asu.edu

(MD=3.61, t_{45}=−2.229, p=0.031)] compared to controls. The MQ group also reported significantly improved QOL (MD=12.66, t_{45}=−5.715, p<0.001) and had reduced CRP levels (MD=−0.72, t_{45}=2.092, p=0.042) compared to controls.

Conclusions Results suggest that MQ benefits cancer patients' self-reported CF, QOL, and inflammation. A larger randomized controlled trial including an objective assessment of CF is planned.

Keywords Cancer · Cognitive function · Quality of life · Inflammation · Medical Qigong

Introduction

Cognitive dysfunction in cancer survivors during and after treatment has been increasingly recognized over the past decade and is often referred to as "chemo-brain" or "chemo-fog." Up to 70% of cancer patients self-report these problems during and/or after chemotherapy treatment [1]. These symptoms can be bothersome to patients and have been shown to affect both their quality of life (QOL) and their ability to carry out normal daily activities [2–4]. Self-reported cognitive impairment has been found to be associated with fatigue, anxiety, and depression [2, 4, 5], but there is only a weak association between self-report and objective cognitive impairment on formal neuropsychological tests [1, 5–10].

Results of studies investigating the incidence of objective cognitive impairment in cancer survivors are inconsistent, but most suggest that 30% of cancer patients have impairment prior to receiving chemotherapy [1, 11, 12] and 20–30% of cancer patients have ongoing cognitive impairment after completing chemotherapy [1]. The cognitive domains most commonly affected are processing speed, working memory, and executive function [1]. Several treatment factors have been associated with cognitive dysfunction across various cancer types, including chemotherapy regimen, dose, and recency of treatment [2, 7, 9, 13, 14]. In contrast to self-reported cognitive function (CF), studies have consistently shown a lack of association between objective cognitive impairment and fatigue, anxiety, depression, and QOL [2, 8, 10, 15].

The exact mechanism relating to the pathophysiology of cognitive dysfunction is not yet known, and there are no validated interventions available to combat symptoms [1]. Beyond the direct neurotoxic effects of chemotherapy, other mechanisms relating to the pathophysiology of cognitive dysfunction have been proposed, including increased inflammation [16], dysregulation of cytokines [17], lowered hemoglobin levels [18], increased blood clotting factors [5], disruption of diurnal patterns of cortisol [19], changes in sex hormones [20], or oxidative stresses [21, 22]. A study evaluating positron emission tomography scans in brain imaging suggests that impairment of CF in cancer survivors may be related to alteration of the frontal cortex, cerebrum, and ganglia by chemotherapy treatment [23]. Interventions to alleviate these conditions have not provided convincing results to recommend their use outside of a clinical trial.

Medical Qigong (MQ) is a form of Qigong specifically designed to improve the health of patients. It incorporates practice of coordinated gentle exercise and relaxation through meditation and breathing. We evaluated the efficacy of MQ on QOL, fatigue, mood status, and inflammation in a randomized controlled trial in 162 cancer patients and found significant improvement in QOL, fatigue, and mood and lower inflammatory markers in the intervention group compared to the control group [24].

To date, there have been no clinical trials evaluating the impact of MQ on CF in cancer survivors, but gentle activity has been shown to minimize or slow normal age-related declines in cognitive functioning [25, 26] and concomitant brain tissue density loss [27] and improve the CF of elderly people with cognitive impairment [28]. In addition, our parent study [24] found that MQ improved the QOL, fatigue, and mood status of cancer patients, and these variables are associated with self-reported cognitive symptoms [10].

Here, we report on the impact of MQ on self-reported CF. The primary aim was to investigate the hypothesis that MQ can improve perceived CF of cancer patients. A secondary aim was to explore the effect of MQ on inflammation, since inflammatory markers such as cytokines and C-reactive protein (CRP) have been associated with cognitive dysfunction [1] in cancer patients as well as cancer incidence, progression, and survival [29].

Methods

The participants in this study were a subset of cancer patients recruited from two major university hospitals in Sydney to the original study [24]. This was a stratified, randomized controlled trial comparing the effect of a 10-week MQ intervention to usual care controls on QOL, fatigue, mood, and inflammation in cancer patients. It was conducted between July 2006 and May 2008. The data presented here includes all patients recruited after October 2007 when the Functional Assessment of Cancer Therapy—Cognitive (FACT-Cog) questionnaire was added to the other assessments listed below to evaluate self-reported CF.

Ambulatory medical oncology patients who had a confirmed diagnosis of malignancy, had received chemotherapy

or were undergoing chemotherapy, were aged ≥18 years, and had an expected survival of more than 12 months were eligible for the trial. Patients were excluded from the study if they had a diagnosis of a major medical or psychiatric disorder, a history of epilepsy, brain metastasis, delirium, or dementia, had medical contraindications for exercise (e.g., significant orthopedic problem or cardiovascular disease), or were already practicing Qigong. Patients considered by their medical oncologist to be eligible for the study were sent an invitation letter by mail and invited to attend an information session, at which patients were screened further for eligibility. After patients gave written consent and baseline data was collected, patients were randomly assigned into the intervention and control groups and stratified by treatment at baseline (currently undergoing or completed chemotherapy treatment). The study received ethics approval from the participating hospitals.

Outcome measurements

Self-reported CF, QOL, and a biomarker of systemic inflammation (CRP) were measured at baseline (prior to the MQ intervention) and at the conclusion of the intervention 10 weeks later. Self-reported CF was measured with the 2-item cognitive subscale of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30 CF version 3) [30] and the 33-item Functional Assessment of Cancer Therapy—Cognitive Function (FACT-Cog version 3) [31, 32]. The FACT-Cog consists of three subscales assessing perceived cognitive impairment (PCI), perceived cognitive abilities (PCA), and impact of perceived cognitive impairments on quality of life (IPCIQL) with higher scores reflecting better CF. QOL was measured with the Functional Assessment of Cancer Therapy—General (FACT-G version 4) [33], a 27-item patient self-reported instrument designed to measure multidimensional QOL in cancer patients [34]. FACT-G consists of four subscales assessing physical well-being (PWB), emotional well-being (EWB), social well-being (SWB), and functional well-being (FWB), with higher scores reflecting better QOL. Blood was collected to measure CRP and analyzed in the biochemistry department of the participating hospitals by particle-enhanced immunological agglutination using a Roche/Hitachi analyzer.

Intervention

Patients assigned to the intervention group received the usual medical care and were invited to attend a MQ program, held in the hospital where they were treated. The MQ program was a group class, conducted over 10 weeks with two identical supervised 90-min sessions per week. Participants were required to attend at least one session per week, but were free to attend the second session as well as being encouraged to undertake home practice every day for at least half an hour. Participants were considered to have completed the MQ program if they attended a minimum of 7 out of 10 weeks.

The MQ intervention program was a modified Qigong program, developed and delivered by the first author (B.O.), an experienced MQ instructor with over 20 years experience of Qigong and training in traditional Qigong in Korea, Daoist Qigong in China, Buddhist Qigong in Australia, and mind–body medicine at the Harvard Medical School. The program was modified from traditional Qigong practice by the instructor to specifically target the needs of cancer patients to control emotions and stress as well as to improve physical function. Each session consisted of 15 min discussion of health issues, 30 min gentle stretching and body movement in standing postures to stimulate energy channels, 15 min movement in seated posture (Dao Yin exercise for face, head, neck, shoulders, waist, lower back, legs, and feet), and 30 min meditation and breathing exercises based on energy channel theory in Chinese medicine, including natural breathing, chest breathing, abdominal breathing, breathing for energy regulation, and relaxation and visualization.

To assess home practice, a diary was given to the participants to complete and return at the end of the 10-week program. Participants were advised to report or discuss any adverse effects with the MQ instructor; however, none were reported.

Participants assigned to the control group received the usual care and completed all outcome measures in the same time frame as the intervention group. Usual care was comprised of appropriate medical intervention, without the offer of additional complementary or alternative medicine resources or programs. Participants were advised to undertake normal activities but were asked to refrain from joining an outside Qigong class. The MQ intervention was offered to the control group participants after completion of the last outcome measurement, and 90% chose to participate.

Statistical analysis

Data analyses were conducted using SPSS 15. Descriptive statistics (frequency, mean, and standard deviation) were used to describe and summarize baseline data. Chi-square tests were performed to investigate differences between the complete study and dropout groups. Linear regression analyses were conducted with those who completed the intervention to examine between-group differences in the outcome variables of self-reported CF, QOL, and inflammation at week 10, after controlling for the corresponding baseline variables (age, gender, diagnosis, treatment status, and baseline data). Prior to linear regression analysis on

CRP, data were transformed logarithmically because of the non-normal distribution. Paired *t* tests and independent Student's *t* tests for both the intervention and control groups were conducted to determine within-group and between-group differences in CF, QOL, and CRP.

Results

Participants

A total of 81 patients gave written consent to participate in the substudy (50% of the original study). Participants who dropped out did not differ significantly in baseline characteristics compared to participants who remained for the entire duration of the study. Reasons for dropping out are described in the consort flow chart (Fig. 1). Fifty-four participants completed the study. Seventy percent of participants in the MQ intervention attended at least 8 out of 10 weeks of the program.

Baseline characteristics of the subsample are reported in Table 1. Sample characteristics from the parent study are reported elsewhere [24]. With the exception of ethnicity, the baseline characteristics were well balanced between the intervention and control groups. The mean age of participants was 62 years (SD=12 years), ranging from 34 to 86 years. The most common primary cancer diagnosis among participants was breast cancer (*x*%), followed by colorectal cancer (12%). There were no significant differences in measurements of self-reported CF, QOL, and inflammation biomarkers between MQ intervention and control group at baseline (Table 2).

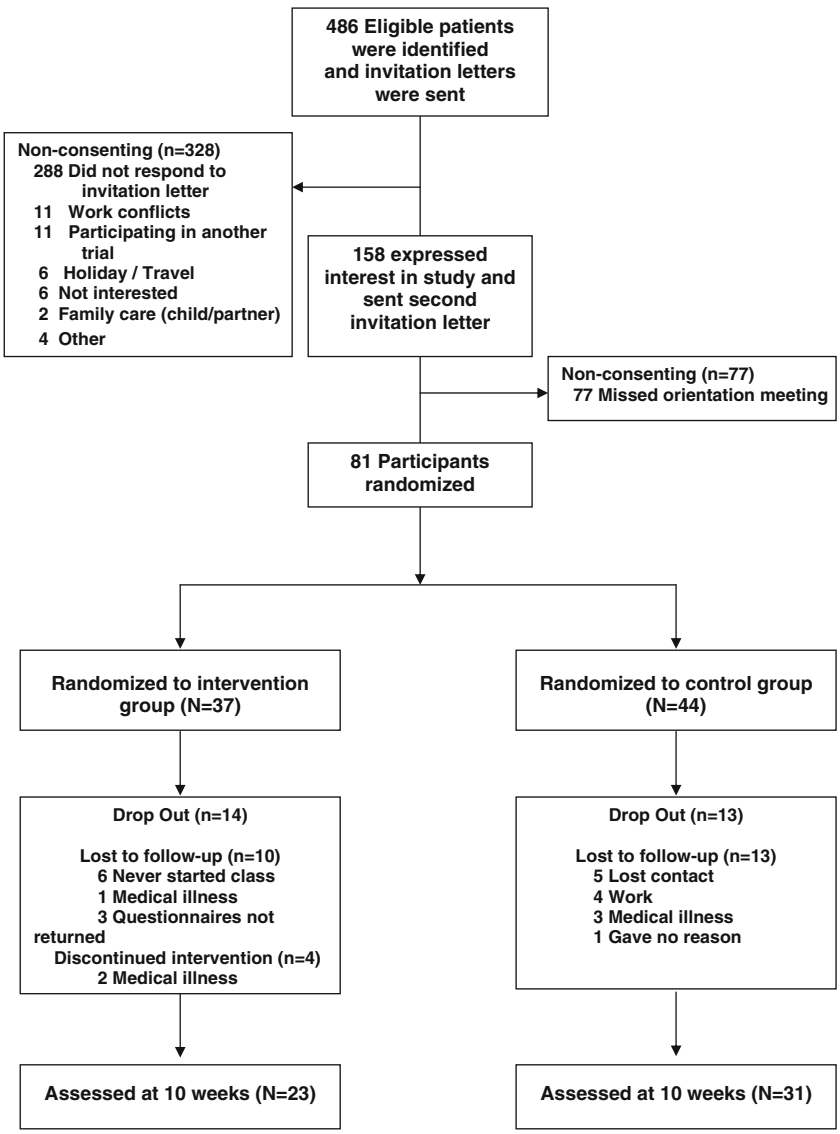

Fig. 1 Recruitment (October 2007–May 2008)

Table 1 Demographic characteristics of participants at baseline

	Intervention (n=37)	Control (n=44)
Mean age (SD)	64.6 (12.3)	61.1(11.0)
Gender (%)		
Female	18 (50.0)	20 (50.0)
Male	18 (50.0)	20 (50.0)
Marital status (%)		
Currently married or de facto relationship	24 (66.7)	29 (72.5)
Never married	5 (13.9)	5 (12.5)
Separated/divorced	3 (8.3)	4 (10.0)
Widowed	4 (11.1)	2 (5.0)
Ethnicity (%)		
Caucasian	28 (82.4)	23 (57.5)
Asian	4 (11.8)	9 (22.5)
Indigenous Australian	0 (0.0)	1 (2.5)
Other	7 (5.9)	7 (17.5)
Educational level (%)		
≥Secondary	20 (52.8)	25 (52.5)
≤Tertiary	17 (47.2)	19 (47.5)
Primary cancer diagnosis (%)		
Breast cancer	12 (32.4)	13 (30.2)
Lung cancer	4 (10.8)	3 (6.9)
Prostate cancer	3 (8.1)	5 (11.6)
Colorectal cancer	8 (21.6)	11 (25.7)
Gastric cancer	2 (5.4)	6 (13.9)
Other	8 (21.6)	5 (11.6)
Cancer treatment		
Adjuvant	16 (45.7)	26 (60.4)
Metastatic	19 (54.3)	17 (39.6)
Completion of chemotherapy treatment (%)		
Completed	23 (65.7)	25 (61.0)
In progress	12 (34.3)	16 (39.0)

Numbers vary due to missing data; n<10, collapsed for chi-square test

Table 2 Baseline outcome measurement of participants

Variables	Mean (SD)	
	Intervention (n=37)	Control (n=44)
CF measured by EORTC QLQ-C30	77.5 (21.2)	71.7 (26.9)
CF measured by FACT-Cog		
PCI	54.3 (16.1)	50.5 (19.2)
IPCIQL	12.6 (3.6)	11.3 (5.0)
PCA	19.5 (7.5)	18.6 (7.4)
QOL measured by FACT-G[a]		
PWB	21.3 (5.4)	21.9 (4.4)
SWB	23.5 (7.6)	23.7 (7.0)
EWB	18.2 (4.0)	17.7 (4.5)
FWB	18.2 (5.3)	17.8 (6.3)
Global QOL	81.8 (17.3)	81.2 (17.6)
Inflammation[a]		
CRP (mg/L)	1.1 (1.3)	1.0 (1.0)

Higher scores reflect better CF and QOL

[a] Lower figures reflect lower inflammation/logarithmic transformations that were used in the model

Effect of the intervention on cognitive function, quality of life, and inflammation

Between-group score changes in self-reported CF, QOL, and CRP are summarized in Table 3. Participants in the MQ group reported significant improvements in the CF scale of EORTC QLQ-C30 and all the domains of CF of the FACT-Cog compared to those in the usual care group at 10 weeks follow-up, after controlling for baseline scores. Participants in the MQ group also reported greater improvements in QOL than those in the usual care group at 10 week follow-up, after controlling for baseline scores (FACT-G, $t_{45}=-5.715$, $p<0.001$, MD=12.66) . QOL subdomain analyses showed that changes in scores were significantly larger for all subdomains of QOL in the intervention compared to the control group. Participants in the MQ group had significantly lower CRP levels, ($t_{45}=2.092$, $p=0.042$, MD=−0.72) than the control group at week 10, but no significant association was found between self-reported CF and CRP at baseline or post-intervention.

Discussion

This is the first randomized clinical trial to demonstrate that MQ improves self-reported CF of cancer survivors who have received chemotherapy. Measurement of self-reported CF with both the EORTC-CF and the FACT-Cog showed significant differences between the MQ group and usual care group at 10 weeks, after adjusting for baseline variables (age, gender, diagnosis, treatment status, and baseline data). In addition to significant differences between groups, the difference in change in perceived CF score in the pre-intervention and post-intervention analysis showed that the cognitive scores of the MQ group improved significantly, while the control groups' scores did not change.

The mechanisms and component part(s) of MQ (breathing method, meditation, and gentle exercise) responsible for these changes cannot be clearly delineated from the current study's research design. Both meditation and gentle exercise have been shown to improve psychosocial well-being. For example, patients practicing meditation have demonstrated greater gains in psychological well-being [35], whereas patients involved in gentle exercise have demonstrated more notable changes in physical functioning [36]. Hence, to clarify the extent to which each component part in MQ contributes to the positive effects found in the current study, a four-arm trial consisting of meditation, physical activity, MQ, and control groups is needed. Such research would significantly contribute to developing optimal cancer care.

Table 3 Effects of MQ within-group and between-group differences (complete case analysis)

Variables	Within-group (week 10–week 0)		Between-group (intervention and control)			
	Mean difference from baseline (95% CI), independent samples *t* test		Mean difference between groups (95% CI), independent samples *t* test	Regression statistics		
	MQ group (n=23)	Control group (n=31)		*t* value	*df*	*p* values
CF measured by EORTC QLQ-C30	7.25 (0.79 to 13.70)	−0.54 (−5.89 to 4.81)	7.78 (−0.35 to 15.92)	−2.532	51	0.014
CF measured by FACT-Cog						
Impact of perceived cognitive impairment	3.00 (−1.92 to 7.92)	−1.70 (−4.33 to 0.93)	4.70 (−0.30 to 9.71)	−2.254	43	0.029
IPCIQL	0.71 (−0.11 to 1.54)	−0.93 (−2.56 to 0.71)	1.64 (−0.31 to 3.59)	−2.377	45	0.024
PCA	1.25 (−0.59 to 3.09)	−2.36 (−5.11 to 0.40)	3.61 (0.07 to 7.14)	−2.229	45	0.031
QOL measured by FACT-G[a]						
PWB	2.36 (0.84 to 3.87)	−0.72 (−1.70 to 0.27)	3.07 (1.38 to 4.76)	−3.944	51	<0.001
SWB	2.90 (1.81 to 7.06)	−1.53 (−3.29 to 0.23)	4.43 (1.81 to 7.06)	−3.961	48	<0.001
EWB	1.36 (0.29 to 2.44)	−0.90 (−2.32 to 0.53)	2.26 (0.41 to 4.11)	−3.677	48	0.012
FWB	2.52 (1.10 to 3.94)	−0.83 (−1.91 to 0.26)	3.35 (1.64 to 5.06)	−4.430	49	<0.001
Total QOL	8.41 (5.82 to 11.00)	−4.25 (−7.82 to 0.67)	12.66 (8.00 to 17.32)	−5.715	45	<0.001
Inflammation biomarker[b]						
CRP (mg/L)[c]	−0.28 (−0.72 to 0.17)	0.44 (−0.48 to 0.92)	−0.72 (−1.37 to −0.07)	2.092	45	0.042

[a] Higher scores reflect positive effect of intervention

[b] Lower scores reflect positive effect of intervention

[c] Logarithmic transformations were used in the model

Due to a lack of robust validation of instruments to measure self-reported CF in cancer patients, we selected two questionnaires commonly used, the EORTC-CF and FACT-Cog [30, 31], and found similar results in both. As discussed above, numerous cognitive studies in cancer patients have found that self-reported CF is associated with psychological distress and QOL [15]. Hence, it is possible that at least some of the improvement in self-reported CF in the MQ group may be due to improvement in subjects' QOL, fatigue, and/or mood from participating in the intervention.

Another significant finding from this study was the positive effects of MQ on inflammation as measured by the CRP. There is increasing evidence that CRP is predictive for cancer recurrence and survival [29, 37]. In the general population, CRP has also been found to be associated with CF [38]. One of the main hypotheses for the etiology of cognitive impairment in cancer survivors is dysregulation of the immune system with elevation of cytokine levels secondary to the cancer and/or the chemotherapy [10, 17, 22]. It has been proposed that the increased cytokine release may interact with DNA damage to create a cycle of chronic inflammation [22]. A number of studies have suggested that MQ leads to improved immune function [39, 40] and reduced inflammation. We did not find a significant association between CRP and self-reported CF; however, this could be reassessed in a larger study.

Although our results are promising, several limitations of the current study should be noted. Firstly, CF was not the primary endpoint of the original study. The study only measured self-reported CF (EORTC-CF and FACT-Cog), and as outlined above, this can have a poor correlation with objective CF. However, patients are concerned about perceived impairment even if they score within normal limits on neuropsychological tests and reports of cognitive dysfunction have been related to diminished QOL. Therefore, improving self-reported CF is important to patients, even if it has a limited association with objective measures. Future studies should evaluate the impact of MQ on CF with a combination of neuropsychological tests, neuroimaging, and subjective self-report outcome measurement.

A further limitation was that blinding the participants to their treatment allocation was not possible due to the nature of the intervention. The inclusion of a control group was nonetheless important to compare changes between those who did and did not receive a MQ intervention and to control for changes in self-reported CF that may occur over time without an intervention. We acknowledge that it is possible that some of the benefits reported from the MQ intervention may be due to experimental bias and confounding factors (e.g., extra care vs. non-extra care), participants' expectancy (placebo effects), and social interactions due to being a member of a group. To control for this in a future study, a third group, non-therapeutic but with the same amount of contact time could be offered, although this would present logistical issues. It would also be interesting to investigate any relationship between the MQ dosage level (including home practice) and efficacy. We attempted to do this in the current substudy with the participants' home diary, but unfortunately, at the end of 10 weeks, <50% of participants returned the diary.

Finally, the study population is heterogeneous both in relation to tumor type and staging. A future study will be conducted in a more homogenous patient population, who have completed adjuvant treatment and have no evidence of disease recurrence.

Conclusions

Improving chemotherapy-related CF and QOL of cancer patients is important for patients as well as clinicians. The results from this study suggest that MQ may have a positive influence on self-reported CF and QOL of cancer patients. It also appears that MQ has the potential to decrease the level of inflammation experienced by cancer patients. A further study with larger sample size and including an objective neuropsychological test is needed to validate results and identify the mechanisms by which MQ achieved the positive results.

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Conflict of interest All authors declare that they have no conflict of interest.

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