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REVIEW

Tai Chi and Qigong for cancer-related symptoms and quality of life: a systematic review and meta-analysis

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Abstract

Purpose This study aims to summarize and critically evaluate the effects of Tai Chi and Qigong (TCQ) mind–body exercises on symptoms and quality of life (QOL) in cancer survivors.
Methods A systematic search in four electronic databases targeted randomized and non-randomized clinical studies evaluating TCQ for fatigue, sleep difficulty, depression, pain, and QOL in cancer patients, published through August 2016. Meta-analysis was used to estimate effect sizes (ES, Hedges' g) and publication bias for randomized controlled trials (RCTs). Methodological bias in RCTs was assessed.
Results Our search identified 22 studies, including 15 RCTs that evaluated 1283 participants in total, 75% women. RCTs evaluated breast ($n = 7$), prostate ($n = 2$), lymphoma ($n = 1$), lung (n = 1), or combined ($n = 4$) cancers. RCT comparison groups included active intervention ($n = 7$), usual care ($n = 5$), or both ($n = 3$). Duration of TCQ training ranged from 3 to 12 weeks. Methodological bias was low in 12 studies and high in 3 studies. TCQ was associated with significant improvement in fatigue (ES = − 0.53, $p < 0.001$), sleep difficulty (ES = − 0.49, $p = 0.018$), depression (ES = − 0.27, $p = 0.001$), and overall QOL (ES = 0.33, $p = 0.004$); a statistically non-significant trend was observed for pain (ES = − 0.38, $p = 0.136$). Random effects models were used for meta-analysis based on Q test and I^2 criteria. Funnel plots suggest some degree of publication bias. Findings in non-randomized studies largely paralleled meta-analysis results.
Conclusions Larger and methodologically sound trials with longer follow-up periods and appropriate comparison groups are needed before definitive conclusions can be drawn, and cancer- and symptom-specific recommendations can be made.
Implications for Cancer Survivors TCQ shows promise in addressing cancer-related symptoms and QOL in cancer survivors.

Keywords Tai Chi · Qigong · Meta-analysis · Cancer · Fatigue · Quality of life

Introduction

Improvements in the detection and treatment of cancer have resulted in an increasing number of cancer survivors, with recent estimates predicting there will be over 20 million cancer survivors living in the USA by the year 2026 [1]. However, many cancer survivors are left with long-term physical and psychosocial morbidities resulting from their cancer, its treatment, and concerns about its possible recurrence [2]. Consequently, strategies and treatment options for common cancer-related sequelae, such as fatigue, sleep disturbance, mood, pain, and quality of life (QOL), are essential.

Like many other diseases, the burden of cancer is increasingly appreciated as a complex biopsychosocial condition [2–4]. The biopsychosocial framework emphasizes that physical, psychological, and social dimensions of health, and their

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optimal care, are often highly interdependent. This perspective supports a potentially unique role for holistic mind–body therapeutic approaches that target multiple physical and psychosocial aspects of cancer symptoms, and that may offer the patient a flexible toolset for addressing their experience of the disease [5–8].

Tai Chi and Qigong are two increasingly popular mind–body interventions that have the potential to address a range of biopsychosocial factors that are part of supportive cancer care [7, 9]. Tai Chi and Qigong share a common history, which integrates elements of traditional Chinese medicine, martial arts conditioning, and lifestyle philosophy. Both incorporate elements of slow, gentle movement, awareness and regulation of breathing, as well as intentional direction of thoughts, attention, imagery, and sensation [7]. For these reasons, Tai Chi and Qigong are grouped together for this review and considered equivalent interventions, paralleling other recent reviews, and subsequently referred to as TCQ [7, 9, 10]. With respect to addressing complex constellations of symptoms, it has been hypothesized that the multi-component nature of TCQ may possess a unique potential to target and impact multiple physiological and psychological processes, thus affording an advantage over conventional single-component therapies [11–14]. The goal of this paper is to systematically review and quantitatively synthesize the state of evidence for TCQ as an intervention in supportive cancer care, to identify strengths and gaps in evidence of TCQ for cancer care, and to suggest directions for future research. Our study builds upon and extends a number of prior reviews [9, 15–17], by including a significant number of recently published clinical trials not considered in prior studies [18–23], and by specifically focusing on five clinical outcomes of key concern to cancer survivors: fatigue, sleep difficulty, mood, pain, and QOL.

Methods

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. Only data that could be extracted from final, published articles, cited in the text, were used in this systematic review and meta-analysis.

Literature search

Search methods Electronic literature searches were performed using PubMed, CINAHL, Web of Science, and Embase from inception until January 30, 2017. The search terms included multiple variations of the spelling and transliteration of Tai Chi and Qigong, and multiple cancer-related key words. Search strategies in PubMed, for example, were as follows: [cancer AND ("tai chi" or "tai chi chuan" or "tai ji quan" or "tai-ji" or "taiji" or "taijiquan") or qigong] and the database interpretation ["neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] AND ("tai chi"[All Fields] OR "tai chi chuan"[All Fields] OR "tai ji quan"[All Fields] OR "tai-ji"[All Fields] OR "taiji"[All Fields] OR "taijiquan"[All Fields]) OR ("qigong"[MeSH Terms] OR "qigong"[All Fields])]. Hand searches were performed using the bibliographies of all retrieved articles for additional references.

Eligibility criteria Randomized controlled trials (RCTs), prospective non-randomized controlled studies, and prospective non-controlled studies published in English, in which cancer was the primary disease and Tai Chi and/or Qigong were the primary interventions, were included. To strike a balance between minimizing bias and being comprehensive, meta-analyses were limited to RCTs, and tables and narrative methods were used to report on additional studies, as well as the degree to which they support or broaden findings from RCTs. Inclusion and exclusion of studies were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [24]

Assessment of risk of bias in the included studies

Three authors (ML, JN, RS) assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool updated in 2009 [25]. The tool utilizes 10 items to evaluate various sources of bias including: random sequence generation and allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other possible sources of bias (timing of outcome assessment, similarity in randomized groups at baseline, protocol compliance, and appropriate rationale for control group). Additionally, dropout rates greater than 20% for short-term and 30% for long-term follow-up studies were used to determine high risk of attrition bias [25]. All evaluated individual domains were endorsed with a "Low" (low risk of bias), "High" (high risk of bias), or "Unclear" (insufficient information provided to assess bias), following guideline criteria. Studies were rated as having an overall "low risk of bias" when at least 50% of criteria were designated as low bias. Studies with more than 50% of the individual criteria endorsed with a high bias or "unclear" were designated with an overall "high risk of bias" status [25]. All

disagreements among independent bias assessors for a given study item were resolved by team discussion.

Safety monitoring

Safety monitoring in studies was evaluated with respect to explicit mention of formal protocols for systematically monitoring adverse events, and numbers and types of adverse events reported in the study associated with the intervention [26].

Data extraction and synthesis

Data were extracted independently by two reviewers (MS, RS) in a standardized manner using an Excel spreadsheet with predefined data fields. Data relevant to study design, duration, subject population, interventions, outcome measures, and results were extracted.

Meta-analytical methods using random effects models were used to synthesize outcomes reported in 15 RCTs identified. For each outcome, data extracted included the mean and standard deviation (SD) of the pre-test and post-test values for each group, mean and SD of change scores in each group, t score or p value within group, and sample size in each group. When these data were not available, data in the form of standard errors, confidence intervals, or medians with ranges were converted into mean and SD format using previously validated statistical formulas [27, 28]. Comprehensive Meta-Analysis (CMA V 3.0) was used to estimate effect size (ES, Hedges' g) with 95% CI and publication bias (visual analysis of funnel plots). Heterogeneity was assessed by inspecting the forest plots and I^2 tests for quantifying inconsistencies among the included studies. An I^2 value higher than 50% indicates substantial heterogeneity [29]. For such outcomes, random effects models were employed. Subgroup and sensitivity analyses were also performed to examine possible sources of heterogeneity. Effect sizes based on random effects models were calculated for fatigue, mood (depression), sleep difficulty, pain, and quality of life, pooling findings from studies of patients with various types of cancer. The pooled effect size in our study was interpreted as small (ES = 0.2–0.49), medium (ES = 0.5–0.79), or large (ES = ≥ 0.8) according to Cohen's rule of thumb for effect sizes [27].

Missing data

Only data that could be extracted from final, published articles were used in this systematic review and meta-analysis. No additional data were obtained from the authors.

Results

Literature search

Figure 1 summarizes the flow of the literature search and publication selection process following PRISMA guidelines. The search returned 749 results from the 4 databases and 63 additional records through manual search. After removing duplicates, there were 475 unique papers. Titles and abstracts were then reviewed to determine whether papers met inclusion criteria, which resulted in 112 articles for in-depth, full-text review. Full-text reports were then reviewed to further specify whether publications met inclusion criteria, and a final list of 22 publications was established and subjected to the qualitative analysis, including 15 RCTs [18–23, 30–38] and 7 studies with non-randomized or no control group [39–45]. Studies by Larkey et al. [19, 33] and Fong et al. [39, 45] were represented by two papers from the same trial with separate outcomes in each publication, and three studies [20, 34, 38] compared Tai Chi/Qigong with both an active control and a no-treatment control for which each comparison was separately evaluated in analyses. A total of 15 RCTs were included in the quantitative analysis.

Study designs

Our search identified 22 studies that examined the role of TCQ in cancer care, including 15 RCTs and 7 studies with non-randomized or no control design. Key features of these studies including participant cancer type, gender, and age, and study interventions and outcomes, are summarized in Table 1.

Participant characteristics and study setting

A total of 1571 cancer patients from the 22 studies (1194 women and 377 men) were included for systematic review (Table 1). Identified studies evaluated a variety of cancer types. The majority of studies recruited patients with a single specific cancer type, mostly solid tumor with the exception of non-Hodgkin's lymphoma [18]. Breast cancer was the most prevalent cancer studied, evaluated in 10 studies (47%), followed by pooled types of breast or gynecological cancer ($n = 4$, 18%), lung or gastrointestinal ($n = 4$, 18%), prostate ($n = 3$, 13.6%), nasopharyngeal cancer ($n = 1$, 4%), and lymphoma ($n = 1$, 4%).

Intervention and control group characteristics

TCQ interventions varied in their content, dosage, duration, and intensity. Of the 22 studies, Tai Chi was applied in 7 studies, Qigong in 10 studies, and Tai Chi and Qigong were explicitly combined in 4 studies. Individual TCQ sessions varied from 30 to 120 min, with session

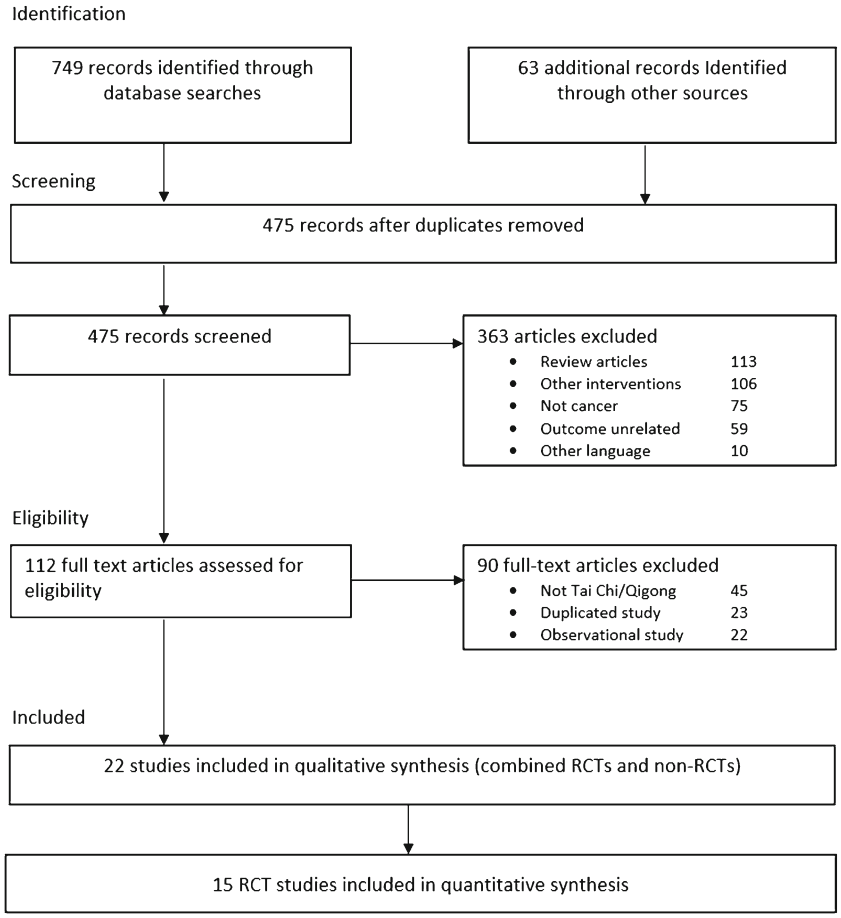


Fig. 1 Summary of the flow of our literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines

frequency ranging from one to seven times per week. Lengths of the overall training programs ranged from 3 to 24 weeks. Among the 15 RCTs, 7 studies used active control groups for comparison [19, 22, 23, 30, 31, 33, 35], including 5 studies evaluating alternative exercise [19, 22, 23, 30, 33]. Five studies utilized a waitlist control or no-treatment control for comparison [18, 21, 32, 36, 37], and three studies used a three-arm study design with both an active control and a no-treatment control [20, 34, 38].

Risk of bias assessment in RCTs

Quality of RCTs indicated an overall low risk of bias for 12 studies [18, 19, 21–23, 31–37] and an overall high risk of bias for 3 studies [20, 30, 38] (see Table 2). Among 15 RCTs, 12 studies (80%) reported a specific random sequence [18–20, 22, 23, 31–34, 36–38], but only 2 studies (13%) [18, 35] mentioned the allocation concealment process. Blinding of participants was not possible in most studies due to the features of TCQ, but two studies from one trial applied sham Qigong as an active control comparison [19, 33]. Blinding of outcome assessment was either not possible or not mentioned in 12 studies (80%) [18, 20, 21, 23, 30–32, 34–38]. No study employed intention-to-treat procedures, but seven studies had no or low numbers of dropouts [18, 19, 21, 23, 31–33], while two studies reported more than 40% dropouts at the completion of the program [36, 38]. All studies reported the timing of outcome assessments, but three studies did not report a rationale for the choice of control group [18, 21, 31]. Three studies reported significant differences at baseline on some of the study variables [18, 20, 38].

Outcome measures

Clinical symptoms evaluated included fatigue, sleep difficulty, depression, pain, and quality of life. These measures were based on multiple specific instruments and subscales described below. Many instruments, such as those that seek to assess quality of life, had been validated to measure multiple types of outcomes based on subscale scoring. Below, we focus our remaining discussion of results on meta-analyses of RCTs organized by cancer symptoms. When relevant, additional evidence from non-RCTs or uncontrolled studies are mentioned.

Table 1 Summary of Tai Chi/Qigong studies for cancer survivors

Study	Country	Design	Type of cancer	*N* (female)	Age	Intervention	Timing of intervention	Duration (weeks)	Length, frequency (number of sessions per week)	Control	Outcome measures
Mustian 2008	USA	RCT	Breast	31 (31)	52	Tai Chi	Tx completed	12	1 h, 3×	PST	FACIT-F[a]
Oh 2008	Australia	RCT	Breast/ovary/lung	30 (24)	54	Qigong	Outpatient	8	1 h, 1–2×	UC	EORTC-QLQ
Oh 2010	Australia	RCT	Breast/lung/prostate	162 (93)	60	Qigong	Outpatient	10	1.5 h, 2×	UC	FACT-G[a], POMS[a], FACT-F[a]
Campo 2013	USA	RCT	Breast/gynecological/ colorectal/others	63 (63)	66	Tai Chi	Outpatient	12	1 h, 3×	HE	SF-36
Chen 2013	China	RCT	Breast	96 (96)	46	Qigong	During RT	5–6	1 h, 5×	NT	FACT-G[a], CES-D[a], BFI[a], PSQI
Robins 2013	USA	RCT	Breast	145 (145)	50	Tai Chi	During chemo	10	1.5 h, 1×	SG/NT	FACT-B, CES-D
Campo 2014	USA	RCT	Prostate	40 (0)	72	Qigong	Outpatient	12	1 h, 2×	SE	BSI[a], FACIT-F[a]
Loh 2014	Malaysia	RCT	Breast	197 (197)	NR	Qigong	Tx completed	8	1 h, 1×	Ex/UC	FACT-B[a], DASS, FACT-F
Larkey 2015	USA	RCT	Breast	101 (101)	59	TCQ	Outpatient	12	1 h, 2×	SQ	BDI, FSI[a], PSQI
Thongteratham 2015	Thailand	RCT	Breast	30 (30)	NR	TCQ	Tx completed	12	1 h, 4×	UC	FACT-B[a], FSI[a]
McQuade 2016	USA	RCT	Prostate	76 (0)	62	TCQ	During RT	6–8	1 h, 3×	LE/WC	EPIC, BFI, PSQI[a]
Zhang 2016	China	RCT	Lung	96 (23)	63	Tai Chi	During chemo	12	1 h, 3×	Ex	MFSI-SF[a]
Chuang 2017	Taiwan	RCT	NH lymphoma	96 (41)	60	Qigong	During chemo	3	1 h, 7×	UC	EORTC-QLQ[a], BFI[a], VSHSS[a]
Vanderbyl 2017	Canada	RCT	Lung/gastrointestinal	19 (11)	65	Qigong	During chemo	6	1 h, 3×	SE	FACT-G, HADS, pain
Larkey 2016	USA	RCT	Breast	101 (101)	59	TCQ	Outpatient	12	1 h, 2×	SQ	SF-36
Lee 2006	Taiwan	Non-RCT	Breast	67 (67)	47	Qigong	During chemo	3	1 h, 7×	UC	SDS, pain[a]
Lee 2010	Korea	NC	Gastric	33 (11)	60	Tai Chi	Outpatient	12	1 h, 1×	NC	FACT-G, CES-D
Reid-Arndt 2012	USA	NC	Breast/gynecological	29 (29)	62	Tai Chi	Tx completed	10	1 h, 2×	NC	POMS
Galantino 2013	USA	NC	Breast	12 (12)	59	Tai Chi	Tx completed	8	1 h, 2×	NC	FACT-B, FACT-F, HADS, BPI
Fong 2014/2015	Hong Kong	Non-RCT	Nasopharyngeal	52 (24)	57	Qigong	Tx completed	24	1.5 h, 3×	UC	EORTC-QLQ, MOS-sleep[a]
Huang 2016	Taiwan	Non-RCT	Breast	95 (95)	41	Qigong	During chemo	12	1 h, 3×	Ex	SF-36

RCT randomized controlled trial, *NC* no control group, *NH lymphoma* non-Hodgkin lymphoma, *NR* not reported, *TCQ* Tai Chi plus Qigong, *Tx* treatment, *RT* radiotherapy, *PST* psychosocial support, *UC* usual care, *HE* health education, *NT* no treatment, *SG* spiritual growth, *SE* stretching exercise, *Ex* exercise, *LE* light exercise, *WC* waiting control, *SQ* sham Qigong, *FACIT-F* Functional Assessment for Chronic Illness Therapy, *EORTC-QLQ* European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire, *FACT-G* Functional Assessment for Cancer Therapy–General, *POMS* Profile of Mood State, *FACT-F* Functional Assessment for Cancer Therapy–Fatigue, *SF-36* Short Form 36, *CES-D* Center for Epidemiologic Studies Depression Scale, *BFI* Brief Fatigue Inventory, *PSQI* Pittsburgh Sleep Quality Index, *BSI* Brief Symptom Inventory, *FACT-B* Functional Assessment for Cancer Therapy–Breast, *FSI* Fatigue Symptom Inventory, *EPIC* Expanded Prostate Cancer Index Composite, *DASS* Depression and Anxiety Stress Scale, *MFSI-SF* Multidimensional Fatigue Symptom Inventory-Short Form, *VSHSS* Verran and Snyder-Halpern Sleep Scale, *HADS* Hospital Anxiety and Depression Scale, *SDS* Symptom Distress Scale, *BPI* Brief Pain Inventory, *MOS-sleep* Medical Outcome Study Sleep Scale

[a] Significant between-group differences

Table 2 Quality assessment of the included studies

	Selection bias		Performance bias		Attrition bias	Reporting bias	Other bias			
Study	Random sequence	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data (ITT)	Selective reporting	Timing of outcome assessment	Similar at baseline	Compliance acceptable in all groups	Rational for control group
Mustian 2008	H	L	H	U	H	H	L	L	L	L
Oh 2008	L	U	H	U	H	L	L	L	U	L
Oh 2010	L	U	H	U	H	L	L	L	U	L
Campo 2013	L	U	H	U	L	L	L	L	L	H
Chen 2013	L	U	H	U	L	L	L	L	L	L
Robins 2013	L	H	H	U	H	H	L	H	U	L
Campo 2014	U	U	H	U	H	H	L	L	L	L
Loh 2014	L	U	H	U	H	L	L	L	U	L
Larkey 2015	L	U	L	L	L	H	L	L	L	L
Thongteratham 2015	H	U	H	U	L	L	L	L	L	H
McQuade 2016	L	U	H	U	H	H	L	H	L	L
Zhang 2016	L	U	H	H	L	L	L	L	U	L
Chuang 2017	L	L	H	H	L	L	L	H	L	H
Vanderbyl 2017	L	U	H	L	H	L	L	L	L	L
Larkey 2016	L	U	L	L	L	H	L	L	L	L

Bias was assessed as L ("low"), H ("high"), or U ("unclear"). Attrition bias scored High for those > 20% dropouts (Furlan 2009)

Fig. 2 Effects of Tai Chi/Qigong on cancer-related symptoms and quality of life. Data presented included weighted contribution, effect size (Hedges' *g*), and confidence interval of LL (lower limit) to UL (upper limit) of each study

Fatigue

Cancer related fatigue was assessed in 12 studies, including 10 RCTs [18, 20, 21, 23, 30, 32–34, 36, 37]. Fatigue was assessed using the following questionnaires: Brief Fatigue Inventory (BFI) [18, 20, 32], Fatigue Symptom Inventory (FSI) [21, 33], Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) [30, 34], Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF) [23], Functional Assessment of Cancer Therapy–Fatigue (FACT-F) [36, 46], and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) subscale for fatigue [36, 45].

Data from 10 studies were pooled for analysis; two studies [20, 34] utilized both active and no-treatment control groups. The Q value ($p < 0.001$) suggests substantial heterogeneity with I^2 of 82%. The overall effect size based on a random effects model indicates a beneficial effect of TCQ on fatigue in cancer patients (Hedges' $g = -0.53$, 95% CI −0.97 to −0.28, $p < 0.001$). A subgroup meta-analysis with a random effects model on five RCTs restricted to active control comparison groups also indicates a beneficial effect of TCQ on fatigue (Hedges' $g = -0.48$, 95% CI −0.98 to −0.14, $p = 0.009$), as did a subgroup analysis limited to seven RCTs with no-treatment control group (Hedges' $g = -0.75$, 95% CI −1.35 to −0.14, $p = 0.016$) (Fig. 2a). One non-controlled study also reported a beneficial effect of an 8-week Tai Chi program targeting fatigue in breast cancer survivors [46].

Sleep difficulty

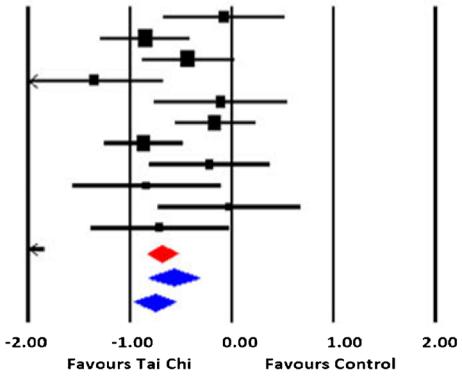
Cancer-related sleep difficulty was assessed in seven studies, including six RCTs [18, 20, 22, 32, 33, 36]. Sleep difficulty was evaluated using the following questionnaires: Pittsburgh Sleep Quality Index (PSQI) [20, 32, 33], Verran and Snyder-Halpern Sleep Scale (VSHSS) [18], EORTC-QLQ Subscale for Symptom [36, 45], and Symptom Questionnaire [22].

Data from six studies were pooled for analysis; one study [20] utilized both an active and no-treatment control group. The Q value ($p < 0.001$) suggests substantial heterogeneity with I^2 of 92%. The overall effect size based on a random effects model indicates a beneficial effect of TCQ on sleep difficulty in cancer patients (Hedges' $g = -0.49$, 95% CI −0.89 to −0.09, $p = 0.018$). A subgroup meta-analysis with a random effects model limited to the three RCTs with an active control group also support a beneficial effect of TCQ on sleep difficulty (Hedges' $g = -0.45$, 95% CI −0.87 to −0.03, $p = 0.038$). A subgroup limited to the four RCTs using a no-treatment control group showed a statistically non-significant trend in favor of Tai Chi

a

Fatigue

Study	Weight	Hedges's g	LL	UL	p
Loh2014	17.91	-0.07	-0.67	0.52	0.805
Larkey2015	25.29	-0.85	-1.30	-0.41	0.000
Zhang2016	24.54	-0.43	-0.89	0.03	0.065
Campo2014	16.54	-1.35	-1.38	-0.12	0.000
McQuade2016	15.73	-0.11	-0.77	0.54	0.736
Chen2013	15.35	-0.17	-0.56	0.23	0.415
Oh2010	15.37	-0.87	-1.26	-0.48	0.000
Loh2014	14.21	-0.22	-0.81	0.37	0.468
Thongteratham2015	13.28	-0.84	-1.57	-0.11	0.024
Oh2008	13.50	-0.02	-0.72	0.67	0.946
McQuade2016	13.62	-0.71	-1.39	-0.03	0.041
Chuang2017	14.67	-2.36	-2.87	-1.84	0.000
Overall effect		-0.53	-0.97	-0.28	0.000
Active control only		-0.48	-0.98	-0.14	0.009
No treatment control only		-0.75	-1.35	-0.14	0.016



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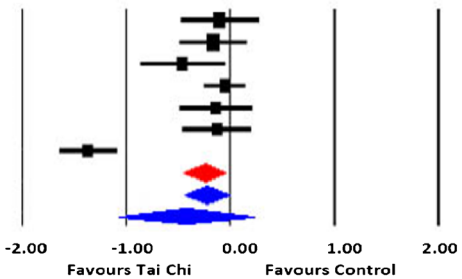
Sleep difficulty

Study	Weight	Hedges's g	LL	UL	p
Larkey2015	31.45	-0.21	-0.96	0.55	0.592
McQuade2016	41.69	-0.33	-0.99	0.33	0.324
Vanderbyl2017	26.86	-0.92	-2.02	-0.33	0.006
Chen2013	25.73	-0.10	-0.50	0.30	0.616
Oh2008	24.47	-0.28	-0.98	0.42	0.438
McQuade2016	24.65	-0.25	-0.92	0.41	0.453
Chuang2017	25.15	-2.73	-3.29	-2.18	0.000
Overall effect		-0.49	-0.89	-0.09	0.018
Active control only		-0.45	-0.87	-0.03	0.038
No treatment control only		-0.84	-2.13	0.44	0.199



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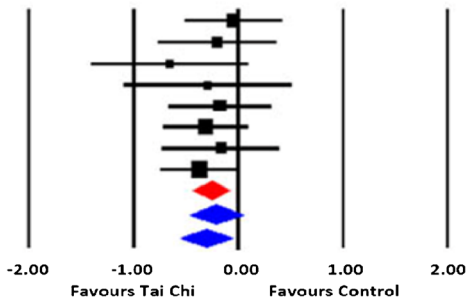
Depression

Study	Weight	Hedges's g	LL	UL	p
Larkey2015	31.60	-0.11	-0.55	0.34	0.637
Robin2013	20.07	-0.20	-0.76	0.36	0.488
Campo2014	11.76	-0.64	-1.37	0.09	0.087
Vanderbyl2017	10.32	-0.28	-1.06	0.50	0.475
Loh2014	26.24	-0.17	-0.66	0.32	0.488
Chen2013	31.55	-0.31	-0.71	0.09	0.128
Robin2013	16.14	-0.17	-0.72	0.39	0.561
Oh2010	52.31	-0.36	-0.67	-0.05	0.021
Overall effect		-0.27	-0.44	-0.11	0.001
Active control only		-0.22	-0.47	0.02	0.080
No treatment control only		-0.32	-0.54	-0.09	0.006



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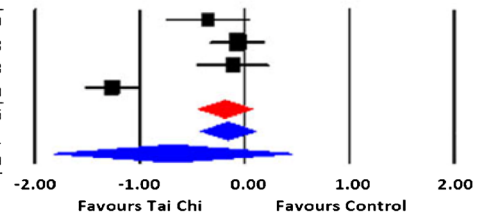
Pain

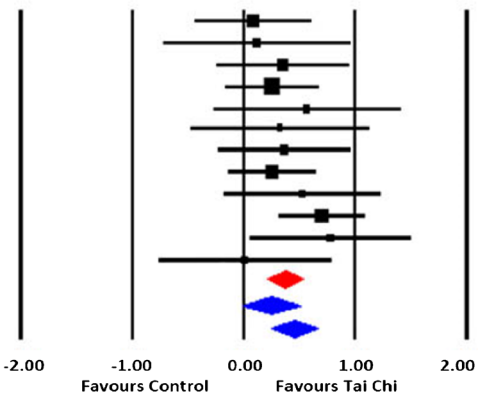
Study	Weight	Hedges's g	LL	UL	p
Vanderbyl2017	34.83	-0.69	-1.49	0.11	0.089
Campo2013	65.17	-0.14	-0.67	0.39	0.608
Oh2008	49.50	-0.22	-0.92	0.48	0.533
Chuang2017	50.50	-2.53	-3.06	-1.99	0.000
Overall effect		-0.38	-0.89	0.12	0.136
Active control only		-0.33	-0.85	0.19	0.211
No treatment control only		-1.39	-3.64	0.87	0.229



e

Quality of life

Study	Weight	Hedges's g	LL	UL	p
Campo2013	24.01	0.08	-0.45	0.61	0.760
McQuade2016	9.55	0.12	-0.72	0.95	0.785
Loh2014	18.84	0.24	-0.35	0.84	0.422
Larkey2016	38.13	0.25	-0.17	0.67	0.235
Mustian2008	9.47	0.57	-0.27	1.40	0.187
McQuade2016	11.31	0.32	-0.48	1.12	0.430
Loh2014	13.00	0.26	-0.34	0.85	0.400
Chen2013	14.48	0.25	-0.14	0.65	0.212
Oh2008	12.07	0.52	-0.19	1.23	0.149
Oh2010	14.94	0.99	0.67	1.32	0.000
Thongteratham2015	11.94	0.78	0.05	1.50	0.035
Chung2017	10.75	2.97	2.10	3.84	0.000
Vandervyl2017	11.52	0.01	-0.77	0.78	0.983
Overall effect		0.33	0.10	0.56	0.004
Active control only		0.23	-0.03	0.49	0.085
No treatment control only		0.73	0.23	1.23	0.004



(Hedges' $g = -0.84$, 95% CI −2.13 to 0.44, $p = 0.199$) (Fig. 2b). One additional non-randomized study reported that sleep difficulty score was significantly decreased in nasopharyngeal cancer survivors following a 6-month TCQ program [45].

Mood (depression)

Cancer-related depression was assessed in 11 studies, including 7 RCTs [22, 30, 32–34, 37, 38]. Depression was evaluated using the following questionnaires: Beck Depression Inventory (BDI) [33], Brief Symptom Inventory (BSI-18) [30], Center for Epidemiological Studies–Depression (CES-D) [32, 38, 42], Depression and Anxiety Stress Scale (DASS-21) [34], Hospital Anxiety and Depression Scale (HADS) [22, 46], Profile of Mood States (POMS) [37, 44], and Symptom Distress Scale (SDS) [43].

Data from seven RCTs were pooled for meta-analysis; two studies [34, 38] utilized both an active control and a no-treatment control group. The Q value ($p = 0.40$) suggests non-significant heterogeneity with I^2 of 4%. Although the Q value confirms consistency on depression among included studies, we decided to apply random effect model to be consistent with other variables that showed statistical heterogeneity [47]. The overall effect size based on a random-effects model favors TCQ on depression in cancer patients (Hedges' $g = -0.27$, 95% CI −0.44 to −0.11, $p = 0.001$). A subgroup meta-analysis limited to five RCTs using an active control group showed a statistically non-significant trend toward TCQ improving depression (Hedges' $g = -0.22$, 95% CI −0.47 to 0.02, $p = 0.080$). A subgroup meta-analysis limited to the three RCTs with a no-treatment control group showed a statistically positive effect of TCQ (Hedges' $g = -0.32$, 95% CI −0.54 to −0.09, $p = 0.006$) (Fig. 2c). One additional non-controlled study [46] also reported a beneficial effect of TCQ on anxiety and depression in breast cancer survivors following an 8-week Tai Chi program.

Pain

Cancer-related pain was assessed in seven studies, including four RCTs [18, 22, 31, 36]. Pain was evaluated using the following questionnaires: EORTC-QLQ Subscale for Symptom [18, 36, 45], Medical Outcomes Study Short-Form Health Survey (SF-36) Subscale for Pain [31], Brief Pain Inventory (BPI) [46], and Symptom Questionnaire/Checklist [22, 43].

Data from four RCTs were pooled for analysis. The Q value ($p < 0.001$) suggests substantial heterogeneity with I^2 of 94%. The overall effect size based on a random-effects model indicated a statistically non-significant trend in favor of TCQ on cancer-related pain (Hedges' $g = -0.38$, 95% CI −0.89 to 0.12, $p = 0.136$). Subgroup meta-analyses limited to RCTs using active control groups (Hedges' $g = -0.33$, 95% CI −0.85 to 0.19, $p = 0.211$) and no-treatment control groups (Hedges' $g = -1.39$, 95% CI −3.64 to 0.87, $p = 0.229$) showed similar trends. Since the number of studies included for cancer-related pain was too small to conduct a random-effect model (less than 5) [47], we conducted fixed-effects model after excluding a single outlier study [18]. This sensitivity analysis based on a fixed-effects model revealed a similar non-significant trend in favor of TCQ (Hedges' $g = -0.28$, 95% CI −0.66 to 0.09, $p = 0.137$, $I^2 = 0$) (Fig. 2d). Two additional non-controlled studies in breast cancer also reported positive effects of TCQ on pain [43, 46].

Quality of life

Quality of life (QOL) was assessed in 16 studies, including 12 RCTs [18–22, 31, 32, 34–38]. QOL was evaluated using the following questionnaires: EORTC-QLQ [18, 37, 45], FACIT-F [35], FACT-General [22, 32, 37, 42], FACT-Breast [21, 34, 38, 46], SF-36 [19, 31, 41], and Expanded Prostate Cancer Index Composite (EPIC) [20].

Data from 11 RCTs were pooled for analysis; two studies [20, 34] utilized both an active and a no-treatment control group. The Q value ($p < 0.001$) suggests substantial heterogeneity with I^2 of 73%. The overall effect size based on random-effects model favors TCQ on QOL in cancer patients (Hedges' $g = 0.33$, 95% CI 0.10 to 0.56, $p = 0.004$). A subgroup analysis limited to the five RCTs with an active control group indicated a statistically non-significant trend in favor of TCQ on QOL (Hedges' $g = 0.23$, 95% CI −0.03 to 0.49, $p = 0.085$) [19, 20, 31, 34, 35]. A subgroup analysis limited to the eight RCTs utilizing a no-treatment control indicated a statistically significant benefit of TCQ (Hedges' $g = 0.73$, 95% CI 0.23 to 1.23, $p = 0.004$) (Fig. 2e) [18, 20–22, 32, 34, 36, 37]. Non-controlled studies add mixed evidence, with one study reporting improvements in QOL in breast cancer survivors [46], but a second study reporting no improvement in QOL in nasopharyngeal cancer survivors [39].

Reports of safety and adverse events

Of the 14 randomized trials (15 papers), only one study [22] explicitly reported use of a formal protocol for monitoring adverse events. Four trials [18, 22, 32, 33] reported that there were no intervention-related adverse events. The remaining 10 trials did not include any mention of adverse events.

Discussion

Tai Chi and Qigong for cancer care

Exercise is increasingly recommended for cancer survivors [48], but optimal forms and regimens for addressing different

symptoms across different cancer populations have yet to be identified. Tai Chi and Qigong, which both integrate musculoskeletal conditioning along with training in multiple cognitive skills and breath regulation, and which are typically delivered in groups that provide psychosocial support, show great promise for addressing the constellation of physical and psychological morbidities faced by cancer survivors. However, few evidence-based syntheses are available to inform TCQ's integration into cancer care. Extending prior meta-analyses and systematic reviews by including six RCTs [18–23] not considered in earlier reviews, our findings support that TCQ may be effective in reducing multiple symptoms commonly experienced by cancer survivors. Statistically significant and clinically meaningful medium effect sizes in favor of TCQ were observed for symptoms of fatigue and sleep difficulty. Smaller but statistically significant effect sizes were also observed for QOL and depression, and a non-significant trend in favor of TCQ was observed for pain. Of note, for fatigue and sleep difficulty, significant effect sizes persisted even when comparisons were limited to active controls, a much more rigorous test of effectiveness than simply usual care or waitlist. This finding suggests that the benefits of TCQ are likely not solely due to attention or psychosocial support factors, but instead, are the result of mind–body exercise-specific activities. Finally, although the evaluation of TCQ's safety within the majority of trials included was not systematically assessed or reported, there were no serious adverse events cited in any study. This finding, along with other more comprehensive reviews of adverse events reported in clinical trials, suggests that TCQ is likely to be safe for cancer survivors [26].

The overall conclusions of our study largely parallel conclusions reported in other recent reviews, but in addition to including updated evidence, the methods employed in our study differed in important ways. First, a number of prior reviews have been limited to qualitative synthesis and have not also included quantitative meta-analytical methods [7, 11, 49–51]. For studies that did include meta-analysis, two studies published in 2014 focused only on breast cancer and included outcomes not evaluated in our study [15, 16]. Pan and colleagues [16] included nine published trials (four based on the same data set) and concluded there is no significant effects of Tai Chi on the symptoms we evaluated, but this review did not include three more recently published studies of breast cancer [19, 21, 52]. However, this study reported improvements in outcomes of grip strength and upper extremity function which were not evaluated in our study. Yan and colleagues' meta-analyses [15] were limited to five Tai Chi trials published as of 2012 and reported improvements in emotional well-being, but not in other domains of quality of life. Zeng and colleagues' meta-analyses [9] included 13 RCTs evaluating both Tai Chi and Qigong, only 5 of which overlapped with those included in our study. They also reported clinically meaningful and statistically significant benefits to cancer-specific quality of life following TCQ training, with smaller effects on depression and anxiety. Finally, one 2016 review [17] including meta-analytic methods employed broader inclusion criteria, synthesizing results from multiple mind–body modalities, including acupuncture, massage, and music therapy, in addition to Tai Chi and Qigong. All previous meta-analyses [9, 16, 49, 51] shared common methodological concerns—including the small number of RCTs on specific cancer-related outcomes, the moderate to high risk of bias, and the heterogeneity of outcome measures—that limit conclusions that could be drawn.

It has been suggested that the broad, multi-symptom benefits of TCQ may result from its multi-component mind–body approach [12, 13, 53]. Klein and colleagues [7] outline multiple potentially therapeutic training components commonly delivered in TCQ programs targeting cancer patients—including low-impact exercise, breath regulation, mindfulness and meditation, self-massage, relaxation techniques, and "energy cultivation" practices based on principles of traditional Chinese medicine—each of which could potentially impact multiple cancer-relevant outcomes. In fact, indirect evidence from controlled trials evaluating individual therapeutic elements of TCQ such as moderate physical exercise [19, 41], mindfulness meditation [54–56], breath regulation [57], imagery/visualization [58], and psychosocial support [59, 60] demonstrates that each of these elements individually can all impact relevant clinical outcomes. Mechanistic exploration of how multi-component practices like TCQ, in comparison to more unimodal interventions (e.g., exercise, meditation), impact individual as well as constellations of symptoms [11] represents a rich area for further research.

Our study which was limited to the effects of TCQ on cancer-related symptom management did not address two important and related questions: Does TCQ impact biological processes that may impact prevention or progression of cancer, and is there any evidence that long-term practice of TCQ changes risks of cancer-related death? Regarding the first question, a growing number of experimental and clinical studies suggest that TCQ and related mind–body training may possibly lead to a downregulation of inflammatory processes (e.g., nuclear factor kappa B pathway) that have been associated with cancer progression, but studies to date are too limited in number and quality to draw strong conclusions [61]. Regarding longer-term effects on cancer-related mortality, no randomized trials have evaluated this question. However, data from the Shanghai Men's Health Study which includes mortality rates for 61,477 men followed from 2002 to 2009 reported that men who reported practicing Tai Chi or Qigong had a hazard ratio of 0.78 (CIs 0.066 to 0.91) for cancer-related death compared to sedentary men [62]. This finding parallels the general observation that higher physical activity is associated with reduced cancer-related mortality rates [55].

An important methodological decision in this study was to use random-effects models for meta-analyses. Our decision was based on a number of factors and follows established guidelines [29, 47]. First, we began with the statistical assumption that the sample of studies we evaluated showed heterogeneity since study populations across studies varied with respect to different types of cancer. This assumption is also supported by I^2 and Q statistics that indicated more than 50% between-study heterogeneity in effect size. Second, it has been suggested that random models can be used when >5 studies are included in analyses. As this was not the case in some subgroup analyses, we chose a fixed-effect model approach when I^2 was less than 50%. While not reported in our results, exploratory analyses of effect sizes for all outcomes based on random models were found to be either equal to or larger than the fixed-effect results we reported, with only minor qualitative differences in statistical significance.

Limitations and suggestions for future research

There are a number of limitations to this study. First, the analysis was limited to papers published in the English language. Including studies in other languages may better represent the evidence and could make the conclusions drawn more generalizable to other cultures. Second, because of the heterogeneity of outcomes reported in these studies, the meta-analysis was by necessity limited to the most common outcome measures. Until there are more studies that use the same outcomes, it will be difficult to robustly evaluate TCQ and the various domains that it can impact. In addition to better reporting of key design features (e.g., blinding, randomization, adverse event reporting), future studies should report features specifically relevant to TCQ studies (e.g., details, rationale, and validity of training protocols). This will enable future reviews to better evaluate protocol-specific effects. Third, our analyses pooled results from studies with a wide range of training exposure, with intervention spanning 3 to 24 weeks with additional variations related to frequency and length of weekly classes. Future individual studies and pooled meta-analyses should evaluate the impact of dosing and explore optimal durations, frequencies, and intensities of protocol delivery. Fourth, the pooling of studies that was done for meta-analysis does not capture the diversity and complexity of participants across studies, and thus limits the inferences that can be drawn regarding the benefits of TCQ to specific populations. That being said, the largest group by cancer type was breast cancer, while most other randomized controlled trials included a variety of cancer types. Future reviews should further stratify results based on type of cancer, age, or other demographic groupings of interest. Lastly, because TCQ is a multi-component intervention, outcomes that can explore the biopsychosocial model of human health and healing may be appropriate. Measures of biological markers (e.g., inflammatory markers), complex physiological processes (e.g., aerobic capacity, bone metabolism, motor control), and behavioral measures (e.g., stress, mood, body awareness, perceived social support) should be evaluated and explored as mechanisms or mediators of the effects of TCQ.

Conclusion

TCQ shows promise in addressing cancer-related symptoms and QOL of cancer survivors. Larger and methodologically sound trials with longer follow-up periods are needed before definitive conclusions can be drawn, and cancer- and symptom-specific recommendations can be made.

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Compliance with ethical standards

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

Ethical approval For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

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