RESEARCH ARTICLE

Lack of Efficacy of Tai Chi in Improving Quality of Life in Breast Cancer Survivors: a Systematic Review and Meta-analysis

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Abstract

Background: It is controversial whether Tai Chi (TC) benefits breast cancer survivors (BCS) on quality of life (QoL). We therefore undertook a meta-analysis to assess this question. Materials and Methods: A computerized search through electronic databases was performed to identify relevant randomized controlled trials (RCTs). The primary outcome was QoL, while secondary outcomes included body mass index (BMI), bone mineral density (BMD), and muscle strength. Results: Five RCTs involving 407 patients were included in the meta-analysis. The pooled standardized mean differences were 0.10 (95% confidence interval (CI): -0.35-0.54) for physical well-being, 0.03 (95%CI: -0.18-0.25) for social/family well-being, 0.24 (95%CI: 0.02-0.45) for emotional well-being, 0.23 (95%CI: -0.03-0.49) for functional well-being, and 0.09 (95%CI: -0.19-0.36) for additional concerns. TC failed to improve BMI, BMD, and muscle strength. Conclusions: There is currently lack of sufficient evidence to support TC improving QoL and other important clinical endpoints.

Keywords: Breast cancer - Tai Chi - quality of life - meta-analysis

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Introduction

Breast cancer is the most frequent malignant tumor in women (Ferlay et al., 2010). In the last decades, the number of breast cancer cases has steadily increased, especially in low and middle income countries (Pedraza et al., 2012; Anaya-Ruiz et al., 2014). At present, breast cancer is generally treated with the possible medical treatment, i.e., a multidisciplinary approach is preferable (Saini et al., 2012). However, some studies found that older breast cancer survivors (BCS) showed multiple indications of decrements in their health-related quality of life (QoL), and bone mineral density (BMD) (Yusuf et al., 2013; Erdogan et al., 2014). The emotional impact of cancer diagnosis, symptoms, and related issues can be severe. In addition, treatments for BCS usually cause adverse side effects including decreases in functional capacity (e.g., muscle strength), which impair QoL (Morrow et al., 2002; Galvao et al., 2005). Physical activity or exercise can improve various domains of functional capacity in BCS (Galvao et al., 2005; Yaw et al., 2014). However, long-term adherence rates are typically low regarding general exercise such as walking and cycling (Pickett et al., 2002). Tai Chi (TC) has been developed since the 17th century in China and is a low-impact mode of physical activity with slow and gentle movements associating with health benefits. Some studies have found that TC shows some favourable effects on the promotion of cardiovascular fitness, and significantly increased psychological well-being including reduction of stress, anxiety, and depression, and enhanced mood in patients with chronic conditions (Esch et al., 2007; Hui et al., 2009; Liu et al., 2010; Park et al., 2010; Chang et al., 2011).

Up to now, there are published randomized controlled trials (RCTs) and non-RCTs evaluating a role of TC in BCS. Previous researches in BCS showed that TC improves functional capacity (Mustian et al., 2006), QoL (Mustian et al., 2008), and self-esteem(Mustian et al., 2004) and can regulate growth factors and binding proteins associated with weight gain and bone loss (Peppone et al., 2010; Janelsins et al., 2011). However, to our knowledge, these studies have a relatively small sample size with wide variation and convey mixed and inconclusive results. In addition, the latest systematic review included only 3RCTs and 4 non-RCTs suggested that TC failed to benefit BCS (Lee et al., 2010). Therefore, we have updated and performed a systematic review and meta-analysis of the latest RCTs to completely and critically assess the effects of TC on QoL and other important clinical outcomes in BCS, and offer valuable information for clinicians.

Materials and Methods

Data sources and searches

A computerized search was performed through PubMed, EMBASE, CINAHL, and Chinese Medical Databases (China National Knowledge Infrastructure)

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databases (up to Sep 2013) for original research articles using the following keywords: (*taiji OR taichi OR taiji chuan OR taichi qigong*) AND (*breast cancer OR breast tumor OR breast oncoma*). The search was limited to human subjects. No language restriction was imposed. Bibliographies of all potentially relevant retrieved studies, identified relevant articles (including unpublished and meta-analysis studies) and international guidelines were searched by hand.

The following inclusive selection criteria were applied: (I) participants: patients with diagnosed breast cancer; (II) intervention: taichi or taiji chuan exercise with or without other treatments; (III) comparison: other treatments including standard support therapy, psychosocial support therapy, usual health care or other exercise forms; (IV) outcomes: the primary outcome was QoL, while the secondary outcomes included body mass index (BMI), BMD, and muscle strength; and (V) study design: RCT.

In addition, QoL evaluation scales included the Functional Assessment of Cancer Therapy-Breast (FACT-B), the Functional Assessment of Chronic Illness Therapy-Fatigue survey (FACIT-F), the Medical Outcomes Study 36-item short-form health survey (SF-36), and the World Health Organization quality of life brief questionnaire (WHOQOL-BREF). Higher QoL scores indicate better QoL.

Data extraction and quality assessment

To assess eligibility, data and trial quality information from the papers selected for inclusion in the meta-analysis were extracted independently by two investigators (JH Yan and L Pan). Extracted data were entered into a standardized Excel file and were checked by a third investigator (XM Zhang). Any disagreements were resolved by discussion and consensus.

The methodological quality of each trial was evaluated using the Jadad scale (Jadad et al., 1996). The quality scale ranges from 0 to 5 points. Higher scores indicate better reporting. The studies are said to be of low quality if the Jadad score is ≤ 2 and high quality if the score is ≥ 3 (Kjaergard et al., 2001). The risk of bias was assessed using the *Cochrane Handbook for Systematic Reviews of Interventions* (Revman version 5.1.0, The Cochrane Collaboration 2011). This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).

Data analysis

For continuous outcomes, weighted mean differences (WMDs) were used when studies measured the outcome on the same scale and standardised mean differences (SMDs) were used when studies measured the outcome on different scales. The measures were estimated from each study with the associated 95% confidence intervals (CIs) and pooled across studies using random effects model (DerSimonian et al., 1986). Heterogeneity across studies was tested by using the I^2 statistic, which was a quantitative measure of inconsistency across studies. Studies with an I^2 statistic of 25% to 50% were considered to have low heterogeneity, those with an I^2 statistic of 50% to 75% were considered to have moderate heterogeneity, and those with an I^2 statistic of >75% were considered to have a high degree of heterogeneity (Higgins et al., 2003). If I^2 >50%, potential sources of heterogeneity were identified by sensitivity analyses conducted by excluding one study according to study quality and investigating the influence of methodological quality of the combined estimates. Publication bias was not assessed because of the limited number (below 10) of studies included in each analysis. A p value < 0.05 was considered statistically significant. All data were combined using Revman 5.1.0 (http://ims.cochrane.org/revman).

Results

Bibliographic search results

A total of 108 potential studies was retrieved from the computer searches. Following screening of study titles and abstracts, 96 articles were considered to be unrelated to the aims of the study. Twelve potentially relevant studies identified for full-text analysis. Furthermore, two RCTs were excluded because of protocol for study design and one RCT was excluded due to unavailable data. Reasons for exclusion are presented in Figure 1. Finally, 9 RCTs were selected for this systematic review where there were 3 RCTs published in Chinese (He et al., 2011; Qiang et al., 2011; Wang et al., 2012), and others were published in English (Mustian et al., 2004; Mustian et al., 2006; Rausch 2007; Mustian et al., 2008). In addition, five RCTs resulted from the same population or trial were included in our study (Mustian et al., 2004; Mustian et al., 2006; Mustian et al., 2008; Janelsins et al., 2011; Sprod et al., 2012). Among them, only the trial performed by Mustian (2006) together with the other four RCTs (Rausch 2007; He et al., 2011; Qiang et al., 2011; Wang et al., 2012) was included in the meta-analysis.

Study characteristics

The main characteristics of 9 RCTs included in the systematic review are presented in Table 1. These studies were published between 2004 and 2012. The size of the trial ranged from 19 to 134. Patients were mainly elderly. The patient classification and the type of TC were inconsistent, and two RCTs did not specify the patient classification. In addition, follow-up ranged from 10 to 24 weeks and exercise time lasted 40 to 90 minutes. The

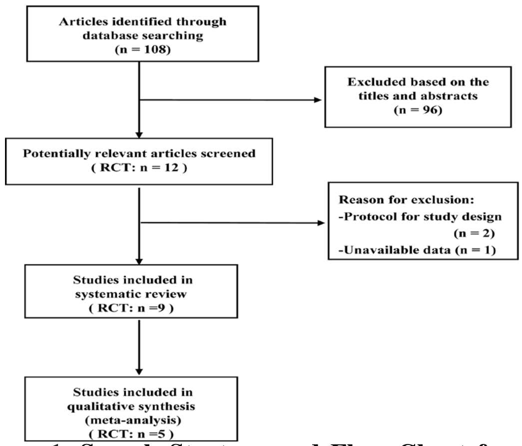

Figure 1. Search Strategy and Flow Chart for this Meta-Analysis. RCT: randomized controlled trial

Table 1. Characteristics of Randomized Controlled Trials Included in the Meta-Analysis

		Patient condition		Intervention (Tai Chi) group				Control group	
First author/Year	Patients No.; BMI, Mean, kg/m² (I/C)	Age, Mean, yrs (I/C)	Study group (n)	Type or style	Outcomes	Duration(wk)/ ExerciseTime	Frequency	Intervention	Study design/ Jadad score
Janelsins/2011, Sprod/2012	19; 24.89/24.97	Stages 0-IIIb, 54.33/52.70	Tai Chi (9); Control (10)	15-move short form of Yang-style	BMI, QoL (SF-36)	12 / 60 min	Three times weekly	Psychosocial support therapy	RCT/3
He/2011	110; 26.1/26.9	NA, 53.1/52.4	Tai Chi (55); Control (55)	24-form of Tai Chi style	BMI, BMD, muscle strength, QoL (FACT-B)	16 / 40-50 min	Three times weekly	Conventional rehabilitation	RCT/3
Mustian/2004, 2006, 2008	21; 25.1/25.3	Stages 0–IIIb, total: 52	Tai Chi (11); Control (10)	15-move short form of Yang-style	BMI, muscle strength, QoL (FACIT–F)	12 / 60 min	Three times weekly	Psychosocial support therapy	RCT/3
Qiang/2011	120; 26.13/26.84	NA, 53.19/52.96	Tai Chi (60); Control (60)	24-form of Tai Chi style	BMI, BMD, muscle strength, QoL (FACT-B)	16 / 40-50 min	Three times weekly	Traditional music rehab gymnastics	RCT/3
Rausch/2007	22; NA	Stages I and II, range: 33-69	Tai Chi (13); Control (9)	8-move short form of Tai Chi	QoL (FACT-B)	10 / 60-90 min	One time weekly	Spiritual growth and standard health care	RCT/1
Wang/2012	134; total: 47.19	Stages I-III, NA	Tai Chi (63); Control (71)	24-form of Tai Chi style	QoL (WHOQOL-BREF)	12/ 40 min	Twice a day	Conventional rehabilitation	RCT/2

*BMI: body-mass index; I/C: Intervention/Control; QoL: quality of life; RCT: randomized controlled trial; NA: not applicable; SF-36: the Medical Outcomes Study 36-item short-form health survey; BMD: bone mineral density; FACT-B: the Functional Assessment of Cancer Therapy-Breast; FACIT–F: the Functional Assessment of Chronic Illness Therapy-Fatigue survey; WHOQOL-BREF: the World Health Organization quality of life brief questionnaire

number of TC training frequency ranged from one to three times weekly in eight RCTs while the frequency was twice a day in one RCT (Wang et al., 2012). Moreover, the Jadad score of the studies included ranged from 1 to 3 and Risk of bias analysis showed in Figure 2.

Meta-analysis of primary outcome measures

Six trials reported QoL (Rausch 2007; Mustian et al., 2008; He et al., 2011; Qiang et al., 2011; Sprod et al., 2012; Wang et al., 2012). The aggregated results suggested that the TC group was not associated with significantly reduced on QoL subscales (physical well-being: n=339; SMD=0.10, 95%CI=-0.35-0.54, p=0.67, p for heterogeneity=0. 01, I^2=76%; social/family well-being: n=339; SMD=0.03, 95%CI=-0.18-0.25, p=0.77, p for heterogeneity=0.53, I^2=0%; functional well-being: n=227; SMD=0.23, 95%CI=-0.03-0.49, p=0.09, p for heterogeneity=0.71, I^2=0%; additional concerns: n=205; SMD=0.09, 95%CI=-0.19-0.36, p=0.53, p for heterogeneity=0.88, I^2=0%) (Figure 3), but TC significantly improved emotional well-being (n=339; SMD=0.24, 95%CI=0.02-0.45, p=0.03, p for heterogeneity=0.37, I^2=0%). The test of physical well-being for the heterogeneity was significant. Therefore, we performed sensitivity analyses to explore potential source of heterogeneity according to study quality. Exclusion of the low quality trial conducted by Wang et al. (Wang et al., 2012) resolved the heterogeneity, but did not change the results (n=205; SMD=-0.12; 95%CI=-0.39-0.15; p=0.39; p for heterogeneity=0.48; I^2=0%). In addition, further exclusion of other studies one by one, but, did not materially alter the results and the heterogeneity [(n=242; SMD=0.25, 95%CI=-0.28-0.78, p=0.36, p for heterogeneity=0.04, I^2=77%) (He

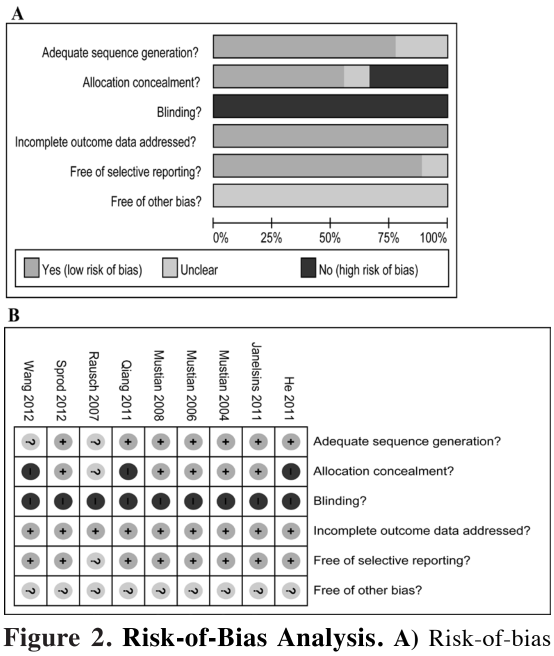

Figure 2. Risk-of-Bias Analysis. A) Risk-of-bias summary: the authors' judgments about each risk-of-bias item for the each included studies. **B)** Risk-of-bias graph: the authors' judgments about each risk-of-bias item presented as percentages across all included studies

et al., 2003), (n=231; SMD=0.15, 95%CI=-0.57-0.88, p=0.68, p for heterogeneity=0.006, I^2=87%) (Qiang et al., 2011), respectively].

Meta-analysis of secondary outcome measures

TC failed to improve secondary outcome measures including BMI, BMD, and muscle strength (Figure 4). In detail, three trials reported BMI (Mustian et al., 2006; He et al., 2011; Qiang et al., 2011). The aggregated results suggested that TC did not significantly reduce BMI (n=226; WMD=0.67 kg/m^2; 95%CI=-0.13-1.47; p=0.10; p for heterogeneity=0.70; I^2=0%) (Figure 4-A). Subsequently, two RCTs reported BMD (He et al., 2011; Qiang et al., 2011). TC was not associated with significantly improved BMD on L2-4 (n=205; WMD=0.10 g/cm^2; 95%CI=-0.10-0.29; p=0.32; p for heterogeneity=0.0002; I^2=93%) (Figure 4-B) and femur (n=205; WMD=0.02 g/cm^2; 95%CI=-0.01-0.05; p=0.22; p for heterogeneity=0.24; I^2=28%) (Figure 4C). Due to only two RCTs pooled in the analysis for L2-4, we couldn't perform sensitivity analyses to explore potential source of heterogeneity. Finally, the same two RCTs also reported muscle strength on wrist and elbow (He et al., 2011; Qiang et al., 2011). The aggregated results suggested that the TC group was not associated with significantly improved on wrist muscle strength (n=205; WMD=0.60 kg; 95%CI=-0.14-1.33; p=0.11; p for heterogeneity=0.63; I^2=0%) (Figure 4-D) and elbow muscle strength (n=205; WMD=0.57 kg; 95%CI=-0.40-1.55; p=0.25; p for heterogeneity=0.29; I^2=11%) (Figure 4-E).

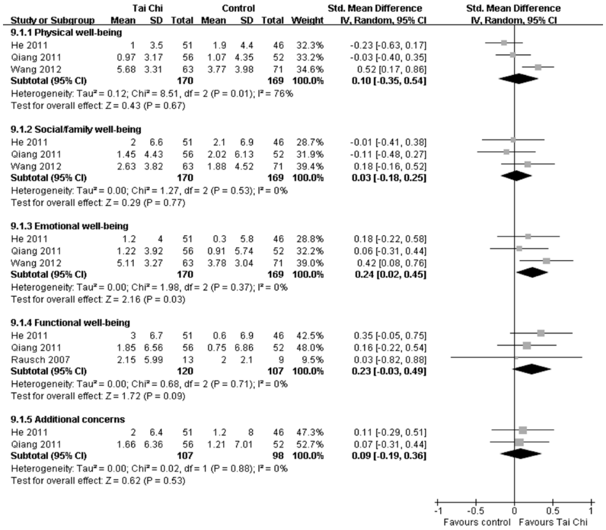

Figure 3. Forests Plot of the Meta-Analysis of RCTs Comparing Tai Chi Group with Control Group for Change in Quality of Life. Each block represents a study and the area of each block is proportional to the precision of the mean treatment effect in that study. The horizontal line represents each study's 95% confidence intervals (CI) for the treatment effect. The centre of the diamond is the average treatment effect across studies, and the width of the diamond denotes its 95%CI

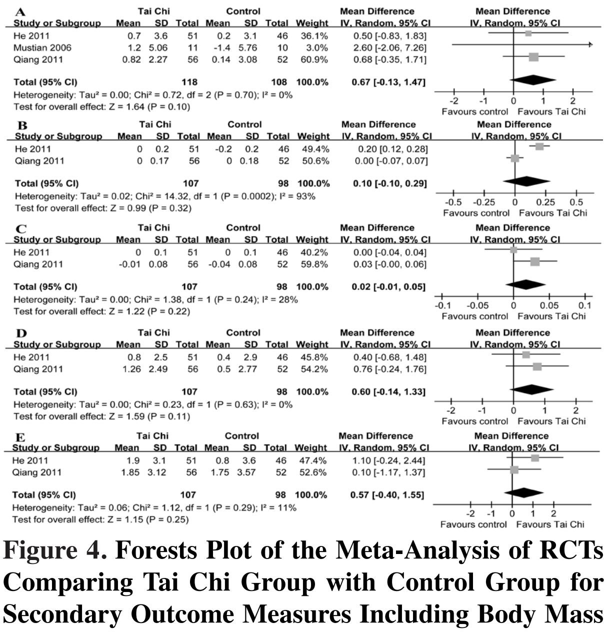

Figure 4. Forests Plot of the Meta-Analysis of RCTs Comparing Tai Chi Group with Control Group for Secondary Outcome Measures Including Body Mass Ivndex. A) bone mineral density; **B**) L2-4; **C**) femur), and muscle strength; **D**) wrist; **E**) elbow)

Discussion

The findings of our meta-analysis suggest that TC failed to improve other QoL subscales except emotional well-being and to alter other important clinical outcomes including BMI, BMD, and muscle strength in BCS.

The main finding of our meta-analysis seems to be similar to the latest systematic review (Lee et al., 2010), which suggested that TC failed to benefit BCS because of the insufficient evidence. In detail, the authors aggregated 2 RCTs with a total of 38 patients to perform a meta-analysis on QoL, however, the data synthesis from Mustian (2006) were not correct (Lee et al., 2010). Furthermore, most of the included trials suffered from a lack of adequate allocation concealment, the lower risks of bias and the sufficient sample size. Hence, the evidence presented in this systematic review is clearly limited. This point was noted by the authors of the previous study (Lee et al., 2010).

For the present meta-analysis, we pre-stated rigorous inclusion criteria to produce robust results, and combined the latest six RCTs to increase the sample size and improve test performance. With the added statistical power of having 202 cases as opposed to 205 controls, the current meta-analysis showed that TC significantly improved emotional well-being, but failed to improve other QoL subscales. Substantial heterogeneity was observed in analyzing physical well-being; our sensitivity analyses suggested that the heterogeneity resulted from one trial (Wang et al., 2012). We believed this trial maybe the potential reason resulting in the heterogeneity because the trial of TC training frequency with twice a day was significantly more than the other trials. Furthermore, considering that it makes a huge difference if we compare a new intervention to usual care or to a comparative intervention, the potential heterogeneity between study results may be derived from the heterogeneity of the control condition. Needs to be emphasized that SMDs were used because studies measured the outcome on different scales, we believed that the potential heterogeneity existed in our study due to different scales evaluating QoL. We also believed that these inconsistent evaluation scales limited the meta-analysis and interpretation of the results; hence, future research should pay attention to consistent evaluation scale on QoL. In addition, our results suggested that TC failed to improve BMI, BMD, and muscle strength in BCS. Considering the limiting RCTs included in the meta-analysis, future studies are needed to investigate these effects.

It is very important to consider that the results of meta-analysis are needed to compare with the minimum clinically important difference (MCID), and further show that whether the effects of TC in BCS have important clinical significance. The MCID defined as the smallest difference considered significant by the average patient is the latest standard for deciding the effectiveness of interventions in clinical trials (Jaeschke et al., 1989). The MCID of 7-8 points identified for FACT-B is currently accepted (Eton et al., 2004). However, we failed to compare our results with the MCID. In detail, QoL was evaluated by 4 different scales including FACT-B, SF-36, WHOQOL-BREF and FACIT-F in our study, which limited our results compared with the MCID for FACT-B. In addition, regarding to other meta-analytical endpoints such as BMI, BMD, and muscle strength, whether these data are indicative of a clinically meaningful difference is difficult to assess with lack of a MCID for these outcomes in BCS.

Our study had numerous limitations. First, our study was based on 9 RCTs with wide variation in a relatively sample size; but, in fact, not more than 2-3 studies are available for the outcomes. Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Second, the targeted population varied greatly (e.g., patients of different age and stages, pre- and postmenopausal, and ethnicity, etc.). Third, adopted TC protocols (e.g., TC type, duration, and training frequency) and study designs differed. These factors may have a potential impact on our results. Furthermore, considering that blinding prevents ascertainment bias and protects the sequence after allocation (Schulz et al., 2002), the poor quality of RCTs without the appropriate blinding could cause potential bias. Finally, some missing and unpublished data may lead to bias.

The present study provides additional clues that may be helpful for future research on the interesting topic. First, it remains unknown regarding an appropriate TC type, duration, and training frequency for BCS. Therefore, further studies are needed to focus on these parameters. Next, future researchers should pay more attention to consistent evaluation scale on QoL or other clinical endpoints. Finally, some RCTs included in our study do not report the side effects or adverse events and compliance of TC. Although these are not the focus of our study, future study should pay attention to these.

In conclusion, despite its numerous limitations, our study still is clinically valuable. The current limited evidence suggests that there is a lack of sufficient evidence to support TC benefiting the management of BCS in improving QoL and other important clinical outcomes. However, given the poor RCTs and the potential heterogeneity, further well-designed RCTs are needed to substantiate the current findings and investigate the effects of TC on QoL as well as other important clinical endpoints in BCS.

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Jun-Hong Yan, Lei Pan and Xiao-Min Zhang contributed equally to this work and should be regarded as first co-authors. No funding supports from this study. We declare that we have no conflict of interest.

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