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Review Article

Does yoga decrease cancer-related fatigue in women with breast cancer? Systematic review of randomized controlled trials

Sergio Jiménez Morgan*

Faculty of Medicine, University of Costa Rica, Costa Rica

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***Correspondence:**
Dr. Sergio Jiménez Morgan,
E-mail: sergio.jimenezmorgan@ucr.ac.cr

ABSTRACT

In its most recent report, the International Agency for Research on Cancer revealed that 1.7 million new cases of breast cancer were diagnosed worldwide in 2012, which represented almost 12% of all cancer types diagnosed in human beings that year. The purpose of the study was to determine if the practice of yoga allows decreasing cancer-related fatigue in women diagnosed with breast cancer. Methodology of the study was taken from database search on Web of Science, Embase, Pubmed, and Cochrane Library, as well as manual reference registration. The eligibility criteria were: (a) randomized controlled trials; (b) measurement of fatigue as main or secondary outcome; (c) studies published until December 2016; (d) studies published in English, Spanish, French or Portuguese. The guidelines of the PRISMA statement were followed. Methodological quality of randomized controlled trials was evaluated with the PEDro scale. Out of the 255 registers found, 14 randomized controlled trials were included. In half of the studies no statistically significant differences were found between experimental and control groups. Only four studies included had a comparative group besides a control group. All studies included were of moderate or high methodological quality according to PEDro scale. Findings suggest that yoga may not be effective to decrease cancer-related fatigue in women diagnosed with breast cancer.

Keywords: Breast cancer, Cancer-related fatigue, Randomized controlled trials, Yoga

INTRODUCTION

In its most recent report, the International Agency for Research on Cancer revealed that 1.7 million new cases of breast cancer were diagnosed worldwide in 2012, which represented almost 12% of all cancer types diagnosed in human beings that year.[1] In the United States of America alone, the American Cancer Society estimated that as of January 1st 2014 a total of 3.1 million of women were breast cancer survivors, and that throughout 2015, 231, 840 new cases of invasive breast cancer as well as 60, 290 new cases of *in situ* breast cancer would be diagnosed; among all of those cases, it was expected that 40 290 women would die during that year.[2] The National Comprehensive Cancer Network defines cancer-related fatigue (CRF) as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning".[3]

It is considered one of the most common symptoms among patients diagnosed with any type of cancer, with frequencies as high as 90% or more among those treated with chemotherapy, radiotherapy or both.[4] Many factors may contribute to explain CRF: the emotional state of the person, elevated levels of proinflammatory cytokines, alterations in the mitochondrial metabolic pathways, insulin resistance, abnormal neuromuscular function, hypothalamic-pituitary adrenal axis dysregulation;

likewise, the tumoral metabolic activity, pharmacological anti-cancer treatments and particular factors of every patient (age, gender, comorbidities) may also explain cancer-related fatigue.[5,6] Due to technological advances and the increasingly detection of early breast cancer, as well as the development of new drugs, the survival rate at 5 years in the United States increased from 75.1% between 1975 and 1977 to 90.0% between 2001 and 2007.[7] These same authors estimate that by the year 2022 there will be 3786 610 American women survivors of breast cancer. When all of the above is considered, the development of better non-drug treatments (for example, physical exercise, psychological support, physiotherapy, education, among others) is essential to improve the quality of life of these women.

Yoga is a "mind-body" exercise that combines physical postures (asanas) with breathing exercises (pranayama) and meditation (dhyana).[8] In recent years, yoga has become an alternative used by many people as a complement to the practice of conventional exercise, as well as an adjuvant treatment in multiple pathologies including breast cancer.[9] This systematic review aims to determine if the practice of yoga could be an effective non-pharmacological treatment to decrease cancer-related fatigue in women diagnosed with breast cancer.

METHODS

Search procedure

The search was conducted between August and December 2016 using the keywords yoga, breast cancer, cancer-related fatigue and randomized controlled trials, as well as their related terms and synonyms in the electronic databases Web of Science, Embase, Pudmed and Cochrane Library. An example of the search strategy (Pubmed) corresponds to ("yoga"[MeSH Terms] OR "yoga"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND ("fatigue"[MeSH Terms] OR "fatigue"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomized controlled trial"[All Fields]). In addition, a manual reference search was performed on the records found.

Documents that were not initially located in full text were requested directly to the main authors and in cases where no response was obtained, both tracking and acquisition of the full text files were managed through a Librarian of SIBDI (Library System, Documentation and Information) of the University of Costa Rica. No restrictions were set on the insertion date ranges of each database. The guidelines established in the PRISMA statement were followed for the preparation and reporting of this systematic review.[10] The management of bibliographic references and file storage was done with Mendeley software version 1.15.3. The data of interest extracted from the articles included in the review were coded and organized with Microsoft Excel® 2010. Bibliographical references of those files that failed in meeting the eligibility criteria, and were not included in the systematic review, were stored in an additional file (Annexure 1), which also contains the exclusion criteria for each case.

Eligibility criteria

To be included in the systematic review, the studies had to meet the following requirements: (a) randomized controlled trials. Studies were eligible only if they were published as full papers; (b) measurement of fatigue as main or secondary outcome; (c) studies published until December 2016; (d) studies published in English, Spanish, French or Portuguese.

Extraction of data of interest

For each article included in the analysis, the following data were extracted: authors, year of publication, country of publication, sample size, average age of participants, anti-cancer treatment (chemotherapy, radiotherapy, post-treatments, or combination), intervention characteristics (experimental and control group sizes, type of yoga, intervention length in weeks, frequency of practice, type of control or comparison group), and main outcomes.

Methodological quality evaluation

The PEDro scale is a validated, widely used scale employed in several fields of study to evaluate randomized controlled trials methodological quality.11 It consists of 11 items with a score ranging from 0 to 10 points. Criteria correspond to: (1) specification of eligibility criteria (which is not taken into account when calculating scores); (2) random allocation of subjects to groups; (3) concealed allocation of subjects to groups; (4) similar groups at baseline; (5) blinding of all subjects; (6) blinding of therapists or main researchers; (7) blinding of assessors who measured at least one key outcome; (8) measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; (9) all subjects received treatment or control conditions as allocated; (10) results of between-group statistical comparisons were reported for at least one key outcome; (11) point measures and measures of variability for at least one key outcome are provided.[11]

According to Velthuis et al, items 5 and 6 were not taken into account due to the type of intervention and participants, resulting in a range of scores from 0 to 8.[12] A score of 4 points was used as a cut-off, so that a study with a score below 4 points was considered to be of low methodological quality.[13]

RESULTS

Figure 1 shows the flowchart of the search and selection process of studies. Out of the total of 255 initial records, 14 randomized controlled trials were included for review.[14-26,28] The list of excluded documents (n = 143), together with the exclusion reasons for each, can be found in Annex 1.

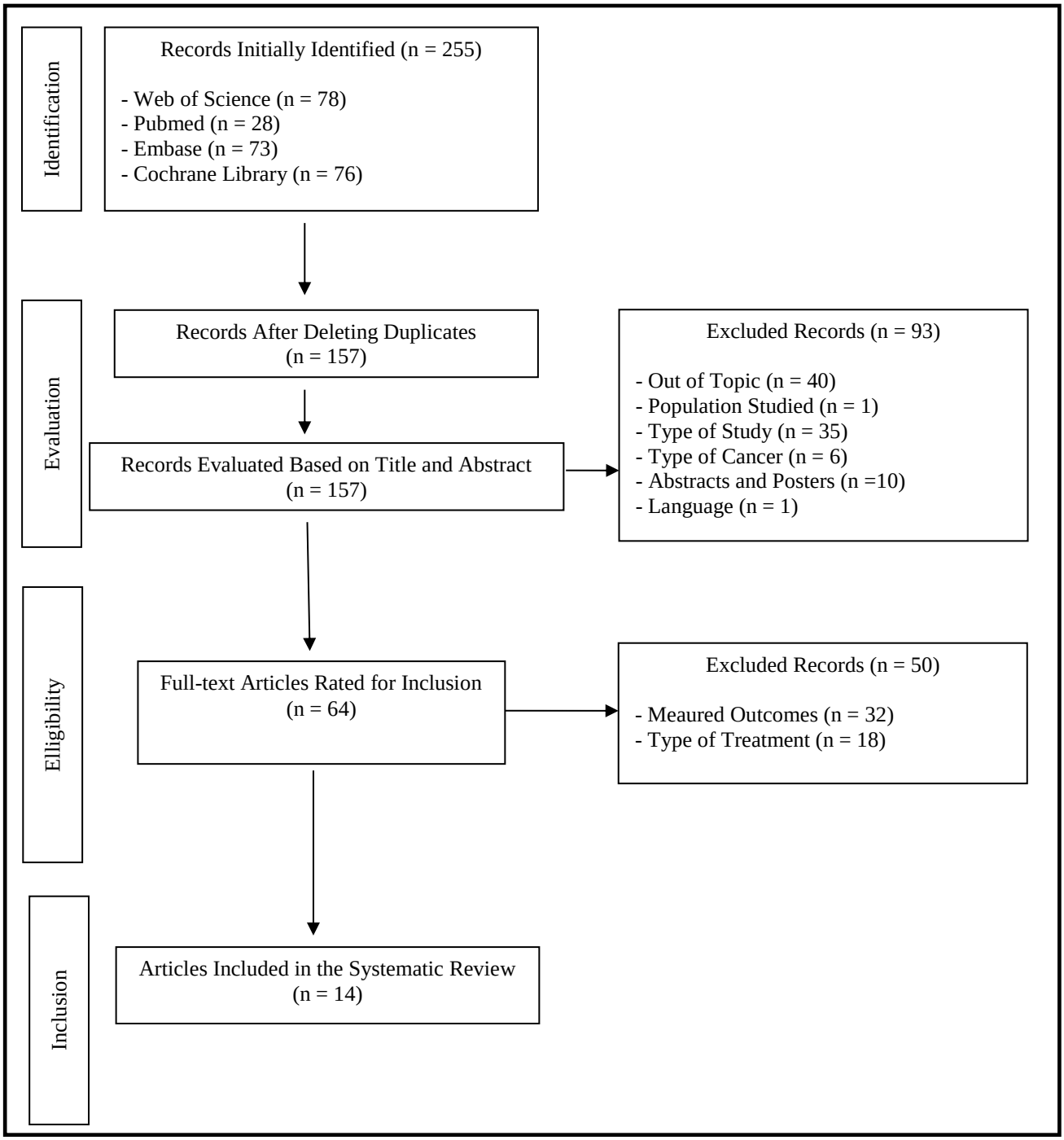

Figure 1: Flow chart for the selection of studies.

Table 1 describes the main characteristics of each study. A total of 64.28 % (n = 9) of studies were conducted in the United States of America, 14.28 % (n = 2) in India and the remaining three studies were conducted in Germany, Turkey and China. In 35.71 % (n = 5) of studies the participants were post-treatment patients, in

28.57 % (n = 4) they were receiving radiotherapy and in 21.43 % (n = 3) of cases they were under chemotherapy. In the remaining studies (n = 2) treatments were mixed or women were in the post-surgery phase.[16,17] The more employed yoga style was Iyengar (n = 3) and Hatha yoga (n = 3). Three of the studies (21.43 %) did not specify the type of yoga while in two cases (14.28 %) the experimental group focused only on breathing exercises or pranayama.[17-21] In the remaining three studies the yoga styles employed were Vyasa yoga, Anusara yoga23 and restorative yoga.[22-24]

Table 1: Main characteristics of included studies.

Study and Country	MA (SD) in years N (total)	Stage of anti-cancer treatment	Intervention characteristics	Main outcomes
Banasik et al[14] United States	EG: 63.33±6.9 CG: 62.4±7.3 18 women	At least 2 months PT	D: 8 weeks EG (n = 9): Iyengar yoga, 90 min twice a week CG (n = 9): waitlist	EG: significant decrease of fatigue (p = 0.046)
Bower et al[15] United States	EG: 54.4±5.7 CG: 53.3±4.9 31 women	At least 6 months PT	D: 12 weeks EG (n = 16): Iyengar yoga, 90 min twice a week CG (n = 15): healthcare education, 120 min once a week	EG: significant decrease of atigue (p = 0.032)
Chakravarty et al[20] India	EG: 43.57±8.5 CG: 43.57±8.5 160 women	Daily RT during 6 weeks after concluding surgery and QMT	D: 6 weeks EG (n = 80): pranayama, 2 sessions/day, 5 days/week CG (n = 80): conventional healthcare	EG: significant decrease of fatigue (p < 0.001)
Chandwani et al[22] United States	EG: 52.38±1.35 CompG: 51.14±1.32 CG: 52.11±1.34 163 women	RT during 6 weeks	D: 6 weeks EG (n = 53): Vyasa yoga, 60 min 3 sessions/week CompG (n =56): stretching exercises, 60 min 3 sessions/week CG (n = 54): waitlist	EG: significant decrease of fatigue with respect to CG (p = 0.04) GComp: significant decrease of fatigue with respect to CG (p = 0.02) No significant differences between EG and CG
Danhauer et al[24] United States	EG: 54.3±9.6 CG: 57.2±10.2 44 women	2 - 24 months PT	D: 10 weeks EG (n = 22): restorative yoga, 75 min once a week CG (n = 22): waitlist	No significant differences between EG and CG (p = 0.23)
Dhruva et al[21] United States	EG: 52.4±14.6 CG: 56.0±11.9 16 women	QMT	D: along the course of 2 QMT cycles EG (n = 8): pranayama, 60 min once a week CG (n = 8): conventional healthcare during 1st QMT cycle; pranayama during 2nd cycle	No significant differences between EG and CG (p = 0.29)
Kiecolt-Glaser et al[26] United States	EG: 51.8±9.8 CG: 51.3±8.7 200 women	3 years PT, and at least 2 months post-QX or post-QMT	D: 12 weeks EG (n = 100): Hatha yoga, 90 min twice a week CG (n = 100): waitlist	No significant differences between EG and CG at post-test, but there were differences 3 months post-intervention (p = 0.002) in favor of the EG
Littman et al[28] United States	EG: 60.6±7.1 CG: 58.2±8.8 63 women	At least 3 months PT	D: 6 months EG (n = 32): Viniyoga (Hatha yoga), 2 to 3 75 min, supervised sessions/week, and 2 to 3 30 min, non-supervised sessions/week (for a total of 5 sessions/week) CG (n = 31): waitlist	No significant differences between EG and CG (ES = +1.9, CI –1.0 to +4.9)
Lötzke et al[25] Germany	EG: 51.0±11.0 CompG: 51.4±11.1 92 women	QMT	D: 12 weeks EG (n = 45): Iyengar yoga, 60 min once a week + home practice 20 min/day	No significant decrease of fatigue in EG (p = 0.863) nor in CompG (p = 0.180)

			CompG (n = 47): conventional physical exercise, 60 min once a week + home practice 20 min/day	No significant differences between both groups
Moadel et al[16] United States	EG: 55.11±0.07 CG: 54.23±9.81 128 women	48% of participants in active treatment (mixed)	D: 12 weeks EG (n = 84): Hatha yoga, 90 min once a week CG (n = 44): waitlist	No significant differences between EG and CG (ES = –0.02, CI – 3.90 to +3.11)
Stan et al[17] United States	EG: 61.4±7.0 CompG:63.0±9.3 34 women	4 – 12 months post-QX and at least 2 months post-QMT or RT	D: 12 weeks EG (n = 18): yoga (style not specified), 90 min at least 3 sessions/week at home using a DVD, CompG (n = 16): resistance bands exercises, 20 min at least 3 days/week at home using a DVD, 8 to 10 repetitions per exercise	No significant differences between EG and CompG at pre-test, post-test or 3 months later (CI – 4.2 to +17.0)
Taso et al[23] China	49.27±10.23 60 women	QMT	D: 8 weeks EG (n = 30): Anusara yoga, 60 min twice a week CG (n = 30): conventional healthcare	EG: significant decrease of fatigue (F = 62.95, p < 0.001) and its impact on daily life (F =53.53, p < 0.001)
Vadiraja et al[18] India	MA not stated 88 women	RT	D: 6 weeks EG (n = 44): yoga (style not specified), 60 min at least 3 days/week at the hospital and the remaining days at home CG (n = 44): healthcare education, 15 min once every 10 days	Significant difference between EG and CG in favor of EG (ES = 0.33, CI – 31.40 to – 10.04)
Yagli et al[19] Turkey	EG: 68.58±6.17 CompG: 68.88±2.93 20 women	Minimum 6 months after concluding QMT	D: 8 weeks EG (n = 10): yoga (style not specified), 60 min once a week CG (n = 10): conventional physical exercise (type and intensity not specified), 60 min once a week	Significant decrease of fatigue in both groups (EG, p = 0.002; CG, p = 0.008) Significant difference between EG and CG at post-test in favor of EG (p = 0.013), with no differences at pre-test

MA (mean age); SD (standard deviation); N (sample size); PT (post-treatments); QMT (chemotherapy); RT (radiotherapy); COM (combination of treatments); QX (surgery); D (duration of intervention and frequency of sessions); EG (experimental group); CG (control group); CompG (comparison group); ES (effect size); CI (confidence interval); DVD (digital versatile disc).

Table 2: Methodological quality of included studies using the PEDro Scale (modified to 8 points).

Study	Randomized Allocation	Concealed Allocation	Similar Groups	Blinding of Researchers	Measures Obtained in >85% of participants	Participants received treatment as allocated	Statistical Comparisons Between Groups	Point and Variability Measures	Total (0 to 8)
Banasik et al[14]	+	-	+	-	+	+	+	+	6
Bower et al[15]	+	+	+	-	+	+	+	+	7
Chakravarty et al[20]	+	+	+	-	+	+	+	+	7
Chandwani et al[22]	+	-	+	-	+	+	+	+	6
Danhauer et al[24]	+	-	+	-	+	+	+	+	6
Dhruva et al[21]	+	+	+	-	+	+	+	+	7
Kiecolt-Glaser et al[26]	+	+	+	+	+	+	+	+	8
Littman et al[28]	+	-	+	-	+	+	+	+	6
Lötzke et al[25]	+	-	+	-	+	+	+	+	6
Moadel et al[16]	+	-	+	-	+	+	+	+	6
Stan et al[17]	+	-	+	-	+	+	+	+	6
Taso et al[23]	+	-	+	-	+	+	+	+	6
Vadiraja et al[18]	+	+	+	-	+	+	+	+	7
Yagli et al[19]	-	-	-	-	+	+	+	+	4

In most of the randomized controlled trials included in this review (71.43%, n=10) yoga was compared to a control group in which participants did not perform any exercise (i.e., waitlists or conventional health care). In 28.57% (n=4) the researchers included a comparison group where participants performed whether stretching exercises, conventional physical exercisesor resistance bands exercises.[17,19,21,25] In 50% of the studies there were no statistically significant differences between experimental and control groups.

Table 2 shows methodological quality assessment using the PEDro scale. The lowest score was 4 points, while 57.14 % (n=8) of studies scored 6 points, 28.57% (n=4) 7 points and only one study reached the maximum score.[19,26]

DISCUSSION

Although there were found several randomized controlled clinical trials with moderate and high methodological quality in this field, the results reported by different authors are heterogeneous and do not allow saying with certainty that yoga is effective to reduce fatigue in these patients.

Table 1 shows that in 50% (n=7) of the studies the intervention with yoga was effective to obtain a significant decrease of fatigue in the participants of each sample. In this regard, it is important to highlight, in coincidence with what was proposed by Cramer, Lauche, Langhorst, and Dobos, that these significant results in favor of the experimental group were mainly in those studies that had a control group without any treatment (i.e., waiting list, conventional healthcare, and healthcare education), which coincides with the findings of this systematic review.[27]

On the contrary, in those studies that included a comparison group where participants performed conventional physical exercise (either aerobic or resistance exercise) and stretching, yoga was not superior.[17,22,25] Only in the study of Yagli et al. yoga had a greater effect to decrease fatigue in comparison with the conventional physical exercise, which must be interpreted with caution because of the very small sample (20 participants) and, besides, because the authors did not specify the type of exercise in the control group, nor the volume and intensity.[19] In addition, it should be noted that this study was the one that presented the lowest score on the PEDro scale between all of the included.

Another aspect that must be considered corresponds to the length of the interventions. 92.85 5% (n=13) of the randomized controlled clinical trials included in this systematic review did not exceed 12 weeks, except one that lasted for six months.[28] This could have influenced the results of those studies that did not show significant results in favor of yoga since, in general, they had a short duration.[29]

Yoga is an ancient practice that has its origin in India. Its practice typically combines physical postures (asanas), breathing exercises (pranayama) and meditation techniques (dhyana). The various combinations of those components have led to many styles or currents of yoga, amongst which the following can be mentioned: Bikram yoga, Broota Relaxation Technique, Chair yoga, Dru yoga, Integral yoga, Kirtan Kriya, Kripalu yoga, Laughter yoga, Rajyoga meditation, Sahaj yoga, Satyananda yoga, Siddha Samati yoga, Sudarshan Kriya yoga, Surya Namaskar yoga, Tibetan yoga, Viniyoga, Vinyasa yoga, Hatha yoga, Iyengar yoga. Despite all of this variety and that some styles emphasize on asanas or pranayama, until now there is no evidence to support that one style of yoga in particular is better than another.[27] This suggests that the choice of one style over the other when designing a randomized controlled trial would be subject only to the availability of certified instructors or to the particular preference of the participants.

In relation to the methodological quality of the studies included in this systematic review, it is important to note that due to the type of interventions it is virtually impossible to blind participants and researchers, which could represent an important source of bias.[29] It is also important to highlight that only 35.71% (n=5) of the studies reported the process of masking of subjects.

Internal validity of randomized controlled trials in this field of study could be augmented by standardizing the designs of the experimental groups in relation to the total time of the intervention, the duration of the sessions and the weekly frequency of practice, as well as the inclusion or exclusion of not supervised (at home) sessions. Table 1 shows that almost no study repeated the same scheme of treatment for the experimental groups.

The main external validity threat identified in this systematic review is the mixing of participants from different stages of breast cancer treatments. In 35.71% (n=5) of the studies the patients were in post-treatments phase, in 28.57 % (n=4) they were on treatment with radiation therapy, and in 21.43 % (n=3) with chemotherapy. In the remaining studies (n=2) the treatments were mixed16 or patients were post-surgery.[17] In this regard, it is of high importance to highlight that, to the present date, there is insufficient evidence regarding in which of the breast cancer phases (pre, during or post treatments) patients would benefit the most with the practice of yoga.

Buffart et al. found a moderate effect of yoga (ES=– 0.51, 95% CI=−0.79 to −0.22) to reduce fatigue in cancer patients and survivors, but their meta-analysis included patients with different types of cancer.[29] Their results contrast with the findings of Lin et al, who did not find a reduction of fatigue with yoga interventions (theses authors also included different types of cancer in their meta-analysis).[30] To the best of the author's knowledge, to the present date there is only one meta-analysis that

included participants with breast cancer exclusively (see O'Neill et al, abstract available only), which did not find significant effects of yoga to reduce cancer-related fatigue in women with breast cancer either.[31]

CONCLUSION

Yoga may not be effective to decrease cancer-related fatigue in women diagnosed with breast cancer. Further randomized controlled trials are encouraged in order to determine whether yoga may be useful for the reduction of fatigue depending on the stage of treatment (i.e., post-treatment, radiotherapy, chemotherapy, post-surgery, and their combinations), with larger sample sizes, a longer duration of the interventions and a more homogeneous design of the yoga programs that are used for the methodological design of randomized controlled trial on this topic.

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