Article published online: 2022-10-06

A Systematic Review Protocol on the Effect of Yoga Intervention on Inflammatory Biomarkers among Women with Breast Cancer

Kaini Cecilia Kaje[1] Fatima Dsilva[2] Latha T.[3] Sanal TS[4] Caren D'Souza[5] Shishir Kumar[6]

[1] Department of Nursing, Nitte Usha Institute of Nursing Sciences, Nitte (Deemed to be University), Mangalore, Karnataka India
[2] Department of Nursing, Nitte Usha Institute of Nursing Sciences, Nitte (Deemed to be University), Paneer, Deralakatte, Mangalore, Karnataka, India
[3] Department of Nursing, College of Nursing, All India Institute of Medical Sciences, Kalyani, West Bengal, India
[4] Department of Biostatistics; JDC Hospital & Research Centre, Trivandrum, India
[5] Department of Surgery, K.S. Hegde Medical Academy, Nitte (Deemed to be University) Mangalore, Karnataka, India
[6] Department of Psychiatry K.S. Hegde Medical Academy, Nitte (Deemed to be University) Mangalore, Karnataka, India

Address for correspondence Fatima Dsilva, PhD, Department of Nursing, Nitte Usha Institute of Nursing Sciences Nitte (Deemed to be University), Mangalore 575018, Karnataka, India (e-mail: fatima@nitte.edu.in).

J Health Allied Sci[NU]

Abstract

A systematic review protocol acts as a guide in the review process to prevent the introduction of bias, maintain transparency and allows reproducibility. Yoga intervention had been experimented on various health aspects such as physical functioning, health-related quality of life, psychosocial and emotional well-being among breast cancer populations, and the findings have been very encouraging. Studies are being performed on the effect of yoga intervention(s) at the molecular level by assessing the inflammatory cytokines and also stress hormones such as cortisol. This protocol is developed to escort in evaluating studies that have been performed on evidence-based yoga intervention at the level of cancer microenvironment, in women diagnosed with breast cancer, by assessing the inflammatory biomarkers and cortisol level, a primary stress marker, and a potent influence of inflammation. The findings will elucidate the picture of the cancer microenvironment as a result of yoga intervention.

Keywords

- breast cancer
- cancer microenvironment
- cortisol
- inflammatory biomarkers
- yoga

Background

Breast neoplasm commonly occurs in women, and it accounts for 25.1% of all cancers.[1] In the year 2020, the World Health Organization (WHO) reported more than 2.2 million cases and 6.85 lakhs deaths. Nearly 1 in 12 women develop breast cancer in their lifespan.[2] Rapid urbanization, migration of people from rural to urban, and its associated constituents, such as lifestyle and reproductive factors, escalated the incidence.[3,4] In developed countries, a hike in the prevalence is seen due to the advancement of technology, early diagnosis, and an increase in life span.[5] Improved prevention practices, early detection, and refined treatment services contributed to declined mortality.[6] However, a

DOI https://doi.org/10.1055/s-0042-1755583.
ISSN 2582-4287.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

surge in mortality was noted in the last 25 years in the developing nations and low-income regions,[7] which is attributed to seeking late medical care, poor awareness of BC, and inability to access health care.[8]

Breast cancer is a stressful event for a woman, irrespective of the stage and the prognosis.[9] Clinical studies reveal that stress and chronic depression are risk factors for the development and progression of cancer.[10] Maladaptive neuroendocrine responses, immunosuppression,[11] and aberrant activation of the hypothalamic pituitary adrenal (HPA) axis influence the release of inflammatory markers,[12] promoting the progression of cancer via activation of the sympathetic nervous system,[13] and enhancing the production of inflammatory cytokines.[14] Observations on stressed populations have reported elevated stress hormones and markers of inflammation such as tumor necrosis factor-α and interleukin-6 in the bloodstream.[15]

Several non-pharmacological interventions and or therapies are found to have a favorable impact on psychological and physiological health of patients with breast cancer. They are used as integrative therapies during and beyond cancer treatment to manage symptoms, prevent toxicities, and improve the quality of life. Behavioral interventions (-meditation/mindfulness/relaxation) and yoga are found to have a high certainty of substantial benefit in the context of depression and anxiety during cancer treatment.[16] It is also found to reduce stress markers, cortisol, and inflammatory cytokines.[17]

Description of Yoga

Yoga, an ancient Indian origin for physical, mental, and spiritual therapy, is known to ease anxiety, alleviate depression, and improve the quality of sleep.[18] The word yoga is derived from the Sanskrit word "yug," the union of body and mind. It consists of eight disciplines called the yoga sutras, entitling the eight limbs: Yama (ethical disciplines), niyama (individual observances), asana (postures), pranayama (breath control), pratyahara (withdrawal of sense) Dharana (concentration), dhyana (meditation), and samadhi (self-realization, enlightenment).[19] Most forms of yoga practiced in Europe focus on postures, and many yoga traditions include only meditation or breathing techniques without specific physical components.[20]

Purpose of the Review

Yoga intervention (YI) as an integrative form of therapy for BC is a promising intervention.[21] It effectively addresses the cognitive, emotional, and physiological symptoms[22] and successfully manages the health-related quality of life, fatigue, anxiety/stress, depression/mood disorders, and fatigue.[23] It improves physical functioning, chemotherapy-induced nausea, vomiting, lymphedema, peripheral neuropathy, pain, and sleep disturbances,[24,25] which are caused by both psychologic distress and a physiological sequel following cancer progression and its treatment effect.[26] Yoga intervention is found to be a feasible intervention in patients with BC.[27] The use of behavioral interventions concomitantly with conventional therapies for protecting cancer patients from the deleterious effects of stress biology on cancer progression is proposed.[28]

Research and reviews on health-related quality of life, psychosocial health, and physical functioning performed among women with BC are heartening. However, the dearth of evidence on the impact of YI in the cancer microenvironment hampers the health care policy makers' decisions on whether or not to include YI in the mainstream management of BC.

Methodology

Inclusion criteria: Experimental studies (true-experimental, quasi-experimental, and pre-experimental) conducted on adult BC women with exclusive of YI, conducted in any of the following setup, hospital, outpatient department, oncology department, community-based, etc., that addresses the outcome in terms of inflammatory biomarkers and cortisol. No restrictions will be imposed on the duration or follow-up of the intervention.

Exclusion criteria: Studies conducted among adult non-BC population, case reports, and case series, interventions not exclusive of YI, and where the outcome measures are not inflammatory markers or cortisol.

Databases to Be Searched

The following databases were searched: Medline (PubMed), EMBASE, WOS, Scopus, CINAHL, Cochrane Central, and Google Scholar. Combined MeSH terms and keywords were used to locate studies published between 2000 and 2021. The language was restricted to English due to limited resources and the cost of translation involved.

Search Strategy

The PICO (population, intervention, comparative intervention, outcomes) component framework was used to identify the keywords for the review question[29,30] (►**Table 1**).

Boolean operators "OR," and "AND" were used to amalgamate the synonym of the search terms, and each component of PICO, respectively. Advanced search and truncation (*) were used, which let a root search term find alternate suffixes[29–31] (►**Table 2**).

Study Selection

The preferred reporting item for systematic review and meta-analysis (PRISMA) guidelines were adhered to[32] for the selection of studies. It is presented graphically in ►**Fig. 1**. Two steps were followed to execute the entire process. First, the titles and abstracts identified during the literature search were scrutinized for inclusion by the reviewers independently after the removal of duplicates. Selection criteria focused on whether the study addressed the interest outcomes to be evaluated (inflammatory markers and cortisol). Second full-text publication/manuscript was obtained from those qualified in the first step. The eligible studies were subjected to final data extraction.

Table 1 PICO framework

Population/participants	Breast cancer women on conventional treatment or palliative care, or BC survivors, and who are aged 19 years and older.
Intervention(s)	Any of the yoga intervention(s) – yama, niyama asana, pranayama, pratyahara, dharana, dhyana, and samadhi, surya namaskar, gentle yoga, hatha yoga, iyengar yoga, any type of kriyas in addition to regular conventional treatment and or none among BC survivors.
Comparison/comparator	It will not be restricted to any specific kind of intervention(s), it can comprise of any the following: no intervention, usual care, waitlist, or any other type of intervention in addition to regular conventional treatment and or none among BC survivors.
Outcome	Both anti-inflammatory and or pro-inflammatory markers, cortisol, which is measured before, and or after the yoga intervention in addition to the regular conventional treatment and or none among BC survivors.

Table 2 Search terms

Population		Intervention		Outcome measures
"Breast cancer" OR "Breast neoplasm*" OR "Breast tumor*" OR "Inflammatory breast cancer" OR "Breast Carcinoma*" OR "Breast malignancy*" OR "Cancer of Breast*"	AND	Yoga OR "gentle yoga" OR "Hatha Yoga" OR "Raja Yoga" OR "Iyengar Yoga" OR Pranayama* OR "Brahmari pranayama" OR "Anuloma-Viloma" OR "nostril breathing*" OR "Alternate nostril breathing" OR "surya namaskar" OR "surya-namaskar" OR "Suryanamaskar" OR "asana*" OR Shavasana OR Trikonasana OR Tadasana OR "Kapalabhat*" OR "Yoga therap*" OR yama OR niyama OR asana OR pratyahara OR dharana OR dhyana OR samadhi.	AND	Biomarker* OR "Inflammatory Biomarker*" OR "Biological marker*" OR Interleukin* OR "inflammatory marker*" OR "anti-inflammatory marker*" OR "pro-inflammatory marker*" OR cytokine* OR chemokine* OR "Tumor necrosis factor Alpha" OR "Tumor necrosis factor-Alpha" OR "TNF-α" OR "CRP" OR "C-Reactive-Protein" OR "cell natural killer" OR "natural killer cell*" OR "NK Cell" OR "Cortisol" OR "Diurnal cortisol" OR Immunologic OR "Inflammatory factor*" OR "Interferon-gamma" OR "IFN-gamma"

Data Extraction

Data extracted were as follows:

- Population: country of origin, sample size, and age of study subjects.

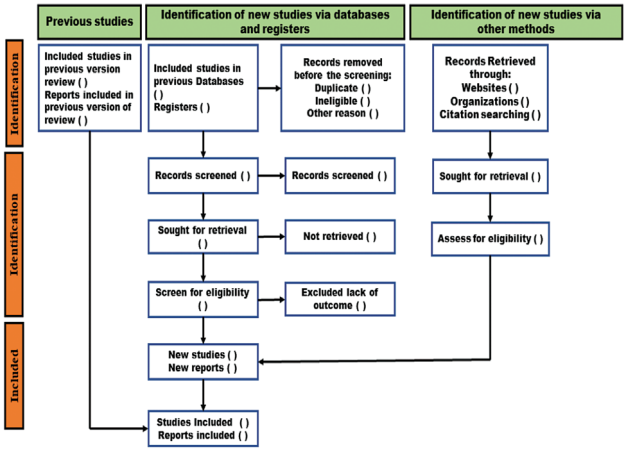

Fig. 1 PRISMA flow chart.

- Methods: study design and methods of subject allocation.
- Interventions: types of YI, frequency, and duration, mode, and provider.
- Comparator/control group details: type, frequency, duration, mode, and provider.
- Outcomes: anti-inflammatory and pro-inflammatory markers, cortisol, and unit of measurements.
- Studies with more than one publication, the updated version will be considered for analysis.

Risk of Bias (Quality) Assessment

The risk of bias for each study was assessed using the Cochrane risk-of-bias tool for randomized trials (RoB 2) developed by Julian PT Higgins, Jelena Savović, Matthew J Page, Roy G Elbers, Jonathan AC Sterne for randomized control trials. Judgment used was "Low risk of bias," "High risk of bias," and "unclear" indicating unknown risk of bias.[33]

For nonrandomized studies, we used the Cochrane recommended tool for assessing the risk of bias in a nonrandomized study developed by Jonathan AC Sterne, Miguel A Hernán, Alexandra McAleenan, Barnaby C Reeves, Julian PT

Higgins. Judgments for each bias domain, and overall risk of bias were "Low, " "Moderate, " "Serious, " or "Critical."[34]

Measurement of Treatment Effect

Outcomes were classified as continuous outcomes and expressed in standardized mean difference with a 95% confidence interval according to the Cochrane handbook for a systematic review of interventions. If the outcome is reported in terms of categorical data, then the risk ratio and its 95% CI were computed.

Assessment of Heterogeneity

The statistical heterogeneity between studies was assessed using the chi-square test. A significant level of p-value ≤ 0.10 was considered significant heterogeneity.

Assessment of Reporting Bias

Funnel plots of the effect estimate against the standard errors were generated using the Review Manager software. Publication bias was assessed by visual analysis of funnel plots, with symmetrical funnel plots indicating low risk and asymmetrical funnel plots indicating high risk of publication bias.

Strategy for Data Synthesis

For continuous outcome (serum inflammatory biomarkers), data were pooled using a random-effect model. Studies homogenous in nature in terms of study designs, population characteristics, and the outcome were pooled. For meta-analysis using a random effect model, if not, the result was synthesized narratively. We performed the subgroup analysis based on the availability of data on the stages of cancer and BC survivors.

Conclusion

To curtail bias and maintain transparency and reproducibility, this protocol was developed to guide the systematic review process for the evaluation of YI's effect on inflammatory biomarkers among women with BC. The findings will elucidate the effect of YI at the level of the cancer microenvironment.

Ethics and Dissemination

Institutional ethics clearance was not required as the data were collected from already conducted research studies. However, studies subjected to be included in this review should have ethics clearance.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

The authors would like to express their gratitude to the NITTE Deemed to be University for their assistance and support.

References

1 Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. Asian Pac J Cancer Prev 2016;17(S3):43–46
2 World Health Organization. Africa S. Breast cancer. World Health Organization. Breast Cancer 2021:1–7. Accessed August 2, 2022 at: https://www.who.int/news-room/fact-sheets/detail/breast-cancer
3 Shetty P. India faces growing breast cancer epidemic. Lancet 2012; 379(9820):992–993. Doi: 10.1016/S0140-6736(12)60415-2
4 Rojas K, Stuckey A. Breast cancer epidemiology and risk factors. Clin Obstet Gynecol 2016;59(04):651–672. Doi: 10.1097/GRF.0000000000000239
5 Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world.. Asian Pac J Cancer Prev 2016;17:43–46. Doi: 10.7314/apjcp.2016.17.s3.43. PMID: 27165206
6 DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69(06):438–451
7 Azamjah N, Soltan-Zadeh Y, Zayeri F. Global trend of breast cancer mortality rate: a 25-year study. Asian Pac J Cancer Prev 2019;20 (07):2015–2020
8 Mehdi S, Hosein H, Tayebe R, Mahin A. Prevalence of anxiety among breast cancer patients: a systematic review and meta-analysis. Breast Cancer 2020;27(02):166–178
9 Tsaras K, Papathanasiou IV, Mitsi D, et al. Assessment of depression and anxiety in breast cancer patients: prevalence and associated factors. Asian Pac J Cancer Prev 2018;19(06):1661–1669. Doi: 10.22034/APJCP.2018.19.6.1661
10 Armaiz-Pena GN, Cole SW, Lutgendorf SK, Sood AK. Neuroendocrine influences on cancer progression. Brain Behav Immun 2013; 30(30, Suppl)S19–S25. Doi: 10.1016/j.bbi.2012.06.005
11 Rao RM, Vadiraja HS, Nagaratna R, et al. Effect of yoga on sleep quality and neuroendocrine immune response in metastatic breast cancer patients. Indian J Palliat Care 2017;23(03): 253–260. Doi: 10.4103/IJPC.IJPC_102_17
12 McGregor BA, Antoni MH. Psychological intervention and health outcomes among women treated for breast cancer: a review of stress pathways and biological mediators. Brain Behav Immun 2009Feb;;23(02):159–66. Doi: 10.1016/j.bbi.2008.08.002. Epub 2008 Aug 22. PMID: 18778768; PMCID: PMC2660328
13 Gosain R, Gage-Bouchard E, Ambrosone C, Repasky E, Gandhi S. Stress reduction strategies in breast cancer: review of pharmacologic and non-pharmacologic based strategies. Semin Immunopathol 2020;42(06):719–734. Doi: 10.1007/s00281-020-00815-y
14 Kiecolt-Glaser JK, Loving TJ, Stowell JR, et al. Hostile marital interactions, proinflammatory cytokine production, and wound healing. 2015;62
15 Hoge EA, Bui E, Palitz SA, Schwarz NR, Owens ME, Johnston JM, Pollack MH, Simon NM. The effect of mindfulness meditation training on biological acute stress responses in generalized anxiety disorder. Psychiatry Res 2018 Apr;262:328–332. Doi: 10.1016/j.psychres.2017.01.006. Epub 2017 Jan 26. PMID: 28131433; PMCID: PMC5526744
16 Greenlee H, Balneaves LG, Carlson LE, et al; Society for Integrative Oncology. Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer. J Natl Cancer Inst Monogr 2014;2014(50):346–358. Doi: 10.1093/jncimonographs/lgu041
17 Lengacher CA, Reich RR, Paterson CL, et al. A large randomized trial: effects of mindfulness-based stress reduction (MBSR) for breast cancer (BC) survivors on salivary cortisol and IL-6. Biol Res Nurs 2019;21(01):39–49. Doi: 10.1177/1099800418789777
18 Harder H, Parlour L, Jenkins V. Randomised controlled trials of yoga interventions for women with breast cancer: a systematic literature review. Support Care Cancer 2012;20(12):3055–3064

19 Sharma M, Lingam VC, Nahar VK. A systematic review of yoga interventions as integrative treatment in breast cancer. J Cancer Res Clin Oncol 2016;142(12):2523–2540. Doi: 10.1007/s00432-016-2269-2
20 Cramer H, Lauche R, Klose P, Lange S, Langhorst J, Dobos GJ. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. (Review) Cochrane Database Syst Rev 2017;1(01):CD010802
21 Sharma M, Lingam V, Nahar V. Yoga as an integrative therapy for breast cancer. J Altern Complement Med 2016;22(06):A92
22 Emerson D, Sharma R, Chaudhry S. Yoga Therapy in Practice. International Journal of Yoga Therapy 2009;19(19):123–128
23 McCall M. Yoga intervention may improve health-related quality of life (HRQL), fatigue, depression, anxiety and sleep in patients with breast cancer. Evid Based Nurs 2018;21(01):9
24 Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. Health Psychol 2007 Nov;26(06):660–667. Doi: 10.1037/0278-6133.26.6.660
25 Greenlee H, DuPont-Reyes MJ, Balneaves LG, Carlson LE, Cohen MR, Deng G, Johnson JA, Mumber M, Seely D, Zick SM, Boyce LM, Tripathy D. Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment. CA Cancer J Clin 2017 May 6;67(03):194–232. Doi: 10.3322/caac.21397. Epub 2017 Apr 24. PMID: 28436999; PMCID: PMC5892208
26 Vadiraja HS, Rao RM, Nagarathna R, et al. Effects of yoga in managing fatigue in breast cancer patients: a randomized controlled trial. Indian J Palliat Care 2017;23(03):247–252. Doi: 10.4103/IJPC.IJPC_95_17
27 Buffart LM, van Uffelen JGZ, Riphagen II, et al. Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. BMC Cancer 2012;12(01):559. Doi: 10.1186/1471-2407-12-559
28 Thaker PH, Sood AK. Neuroendocrine influences on cancer biology. Semin Cancer Biol 2008;18(03):164–170
29 Butler A, Hall H, Copnell B. A guide to writing a qualitative systematic review protocol to enhance evidence-based practice in nursing and health care. Worldviews Evid Based Nurs 2016;13(03):241–249
30 Riesenberg LA, Justice EM. Conducting a successful systematic review of the literature, part 1. Nursing 2014;44(04):13–17
31 Bettany-Saltikov J. Learning how to undertake a systematic review: part 1. Nurs Stand 2010;24(50):47–55, quiz 56
32 Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(07):e1000097. Doi: 10.1371/journal.pmed.1000097
33 Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial | Cochrane Training. In: Cochrane Training. Published online 2021:1–50. https://training.cochrane.org/handbook/current/chapter-08
34 Sterne JA, Hernan MA, McAleenan A, et al. Assessing risk of bias in a non-randomized study | Cochrane Training. In: Cochrane Handb Syst Rev Interv. 2021; version 6. https://training.cochrane.org/handbook/current/chapter-25

