



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

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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

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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 symptoms²² 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 suffixes²⁹⁻³¹ (► **Table 2**).

Study Selection

The preferred reporting item for systematic review and meta-analysis (PRISMA) guidelines were adhered to³² 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

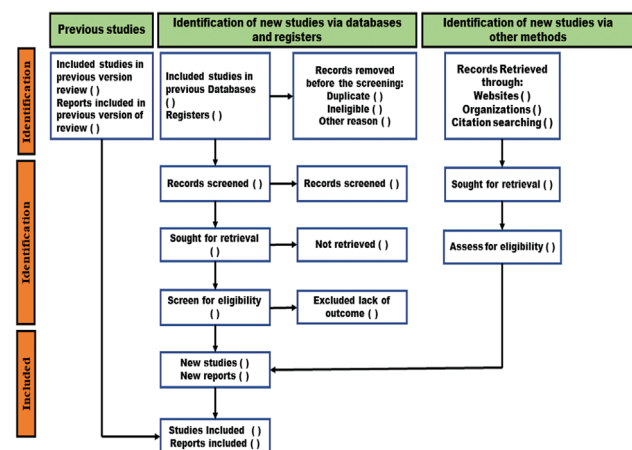
Population		Intervention		Outcome measures
“Breast cancer” OR “Breast neoplasm” OR “Breast tumor” OR “Inflammatory breast cancer” OR “Breast Carcinoma” OR “Breast malignancy” OR “Cancer of Breast”	AND	Yoga OR “gentle yoga” OR “Hatha Yoga” OR “Raja Yoga” OR “Iyengar Yoga” OR Pranayama” OR “Brahmari pranayama” 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.

- 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.

**Fig. 1** PRISMA flow chart.

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.

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Conflict of Interest

None declared.

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