

Effects of an Integrated Yoga Program in Modulating Psychological Stress and Radiation-Induced Genotoxic Stress in Breast Cancer Patients Undergoing Radiotherapy

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Effects of an integrated yoga program in modulating perceived stress levels, anxiety, as well as depression levels and radiation-induced DNA damage were studied in 68 breast cancer patients undergoing radiotherapy. Two psychological questionnaires—Hospital Anxiety and Depression Scale (HADS) and Perceived Stress Scale (PSS)—and DNA damage assay were used in the study. There was a significant decrease in the HADS scores in the yoga intervention group, whereas the control group displayed an increase in these scores. Mean PSS was decreased in the yoga group, whereas the control group did not show any change pre- and post-radiotherapy. Radiation-induced DNA damage was significantly elevated in both the yoga and control groups after radiotherapy, but the postradiotherapy DNA damage in the yoga group was slightly less when compared to the control group. An integrated approach of yoga intervention modulates the stress and DNA damage levels in breast cancer patients during radiotherapy.

Keywords: *yoga; meditation; radiotherapy; stress; DNA damage*

Breast cancer is a profoundly stressful disease posing both physical and psychological threats to the patient. Moreover, patients with breast cancer normally receive multimodal treatment over a long period. Psychological distress and trauma are commonly associated with the diagnosis of cancer.¹⁻³ Uncertainty about the prognosis of cancer and social isolation, along with physical symptoms or functional losses resulting from the disease or its treatment, are the most important factors. Due to these various difficulties,^{4,6} many patients believe that stress, including that which is caused by their cancer experience, may contribute to poor coping as well as recurrence or progression of their disease. In the past decade, there has been a growing interest among

cancer survivors in the use of various complementary therapies as adjuvants to conventional treatment in the anticipation of reducing the burden of stress and better coping with the treatment.⁷⁻⁹ There is a considerable use of these therapies in recent times in association with cancer treatment; therefore, there is a need to understand the links between social, psychological, and physiological determinants of health.¹⁰ Yoga is an ancient Eastern practice that has been used for therapeutic benefits worldwide and is being scientifically studied by many clinicians.¹¹ It has been suggested that “gentler” physical activities, such as yoga or tai chi, may help to promote regular participation in exercise, especially in chronic disease populations who face additional barriers to engaging in active lifestyles.^{10,12} There have been a number of studies including randomized trials that reported positive therapeutic outcomes following yoga programs, including our group.¹³ A wide range of benefits have been reported including improvements in asthma,¹⁴ immune function,¹⁵⁻¹⁷ hypertension,¹⁸⁻²⁰ cardiovascular effects,^{12,21,22} blood pressure,^{23,24} diabetes,²⁵ and serum cortisol levels.²³

The use of complementary and alternative medicine (CAM) as an adjuvant therapy in breast cancer patients

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has attracted the attention of many researchers worldwide.⁷ Burstein et al²⁶ reported that newly diagnosed early-stage breast cancer patients who were using CAM showed psychosocial stress and had low mental health scores 3 months after diagnosis. Meditation was originally used as a religious or spiritual practice; it has now been accepted worldwide as an effective tool to calm the mind and harmonize the physiological and psychological parameters.¹³ Meditation-based relaxation programs have been implemented in a number of randomized and pilot studies, particularly those done by Carlson et al,²⁷⁻²⁹ that reported reductions in total mood disturbance and specific symptoms of anxiety, depression, anger, and confusion. In all these studies, the main aim was to improve the quality of life of either breast cancer survivors or those who were undergoing treatment. There have been reports of improvement of quality of life (QOL) in breast cancer patients who underwent yoga-based programs or supportive counseling along with relaxation and imagery.^{30,31}

Inspired by the favorable outcome of these interventional studies, Carson et al³² recently reported significant improvement in pain as well as psychological parameters of metastatic breast cancer patients. Another recent study showed no physical improvement in breast cancer survivors over control patients after yoga intervention but a significant improvement in the global QOL scores and mood disturbance scores.³ In our recent study, Raghavendra et al³³ reported that breast cancer patients in a yoga program had significant improvement in chemotherapy-induced nausea and emesis in quality of life. The current study examines the effect of an intensive and integrated yoga program that is customized for breast cancer patients in modulating psychological and physiological stress.

It is known that radiation causes DNA damage to peripheral blood lymphocytes (PBLs) of patients undergoing radiotherapy treatment.^{34,35} We also reported a significant increase in radiation-induced DNA damage in breast cancer patients undergoing radiotherapy.³⁶ DNA damage in the form of telomere shortening has been linked to increased stress in a population of caregivers.³⁷ DNA repair capacity is also associated with psychological and physiological stress.³⁸⁻⁴⁰ Therefore in view of the fact that breast cancer patients are under stress and that they also undergo considerable radiation-induced DNA damage, we investigate in the present study the effect of an intensive yoga program on psychological parameters (Hospital Anxiety and Depression Scale [HADS] and Perceived Stress Scale [PSS]) as well as radiation-induced DNA damage in the PBLs derived from the breast cancer patients

pre- and post-radiotherapy, using both an intervention and a supportive counseling group.

Methods

Patients Recruitment

A randomized controlled study was initiated and a convenience sampling strategy was used to enroll patients in the study. The patients were recruited from 3 cancer hospitals in India, Bangalore Institute of Oncology (BIO), Manipal Hospital, Bangalore, India, and Bharat Cancer Hospital, Mysore, India. Clinical staff were informed of the study and invited to refer patients. Posters and leaflets announcing the study and inviting patient participation were posted in public areas of the clinic. A total of 68 patients were recruited from January 2004 until December 2005 who met the inclusion criteria of (1) recently operated breast cancer, (2) age between 30 and 70 years, (3) Zubrod's performance status 0-2 (ambulatory > 50% of time), (4) high school education, (5) treatment plan of radiotherapy or both adjuvant radiotherapy and chemotherapy, and (6) consent to participate in the study. Participants were excluded if they had any concurrent medical condition likely to interfere with the treatment; major psychiatric, neurological illness, or autoimmune disorders; cardiovascular illness; and any known metastases. The patients must not have had any exposure to other mutagens, smoking, or alcohol for at least 3 months prior to preradiation blood donation.

Of the 68 participants randomized to yoga and supportive therapy initially at the start of the study, 58 participants (yoga $n = 35$ and control $n = 23$) completed their prescribed radiotherapy treatment of 6 weeks and received a cumulative dose of 50.4 Gy. There were 10 dropouts either immediately after random assignment or in the course of the study in the control group who did not attend the yoga sessions (Figure 1). The reasons for dropouts were attributed to migration to other hospitals, use of other complementary therapies (eg, homeopathy or ayurveda), lack of interest or other concurrent interest, and chemotherapy-induced severe discomfort.

Randomization

Randomization was performed using a computer-generated random numbers table with group assignments that was sent to the clinics of the 3 recruiting hospitals, which was used sequentially to order group assignments during recruitment. The order of randomization was verified with the hospital date of admission

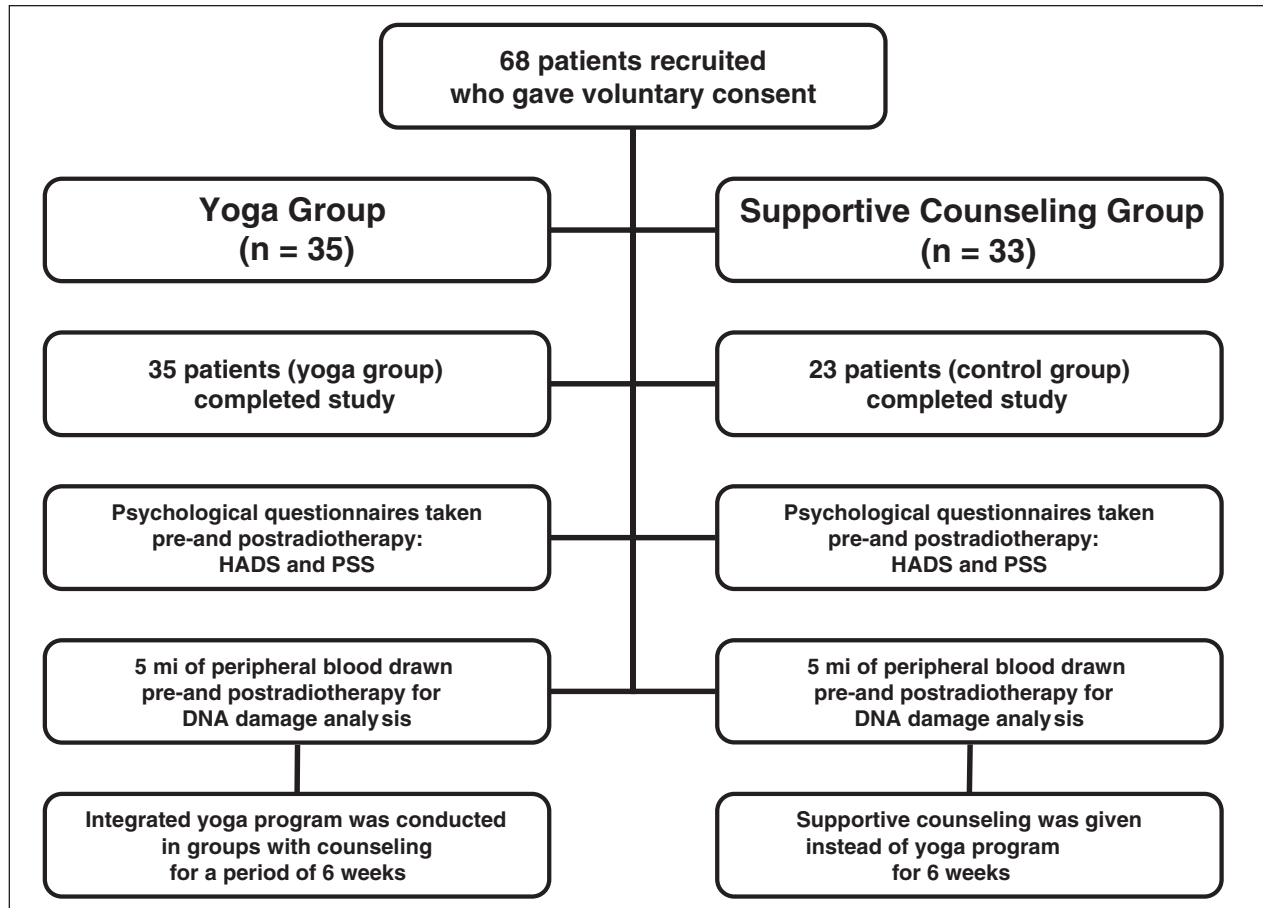


Figure 1. Flow chart of study recruitment, randomization, and trial procedure. HADS = Hospital Anxiety and Depression Scale; PSS = Perceived Stress Scale.

records for radiotherapy at intervals to make sure that field personnel had not altered the sequence of randomization to suit allocation of consenting participants into the 2 study arms. Of the 58 remaining patients in the study group, 35 were randomly assigned to the yoga intervention group and 23 patients were assigned to the supportive counseling group. Patients were all counseled, and consent was obtained prior to recruitment into the study. The project was approved by the institutional review boards of all 3 recruiting hospitals and SVYASA University India.

Blood Collection

Five milliliters of peripheral blood pre- and post-scheduled radiotherapy were collected by venipuncture vacutainer method. The blood samples were coded prior to the dispatch to the laboratory.

During the initial visit, demographic information including age, marital status, education, occupation, obstetric and gynecologic history, medical history,

and intake of medications were obtained, and clinical data were abstracted, including the history of breast cancer, investigative notes, and radiotherapy and chemotherapy treatment regimen.

Questionnaires

The patients were asked to complete questionnaires at various assessment points and were assisted by the field personnel if they sought any clarification. The research assistants were trained in imparting questionnaires.

Hospital Anxiety and Depression Scale

This is a 14-item questionnaire developed by Snaithe and Zigmond and used for screening for depression and anxiety in hospital patients. It has a high reliability of .62 to .8 and correlates strongly with *DSM-IV* criteria for depression and anxiety. The Depression subscale and the Anxiety subscale both have maximum scores of 21 points.

*Perceived Stress Scale*⁴¹

The 10-item version of the PSS, which was designed for use with community samples, is now the most widely used self-report measure of psychological stress. Participants respond how often during the past month they experienced thoughts and feelings such as “felt that you were unable to control the important things in your life,” “felt that things were going your way,” or “been unable to control irritations in your life.” The maximum score on the PSS is 40 points.

DNA Damage Study

Alkaline Single-Cell Gel

Electrophoresis (Comet) Assay

Peripheral blood lymphocytes were isolated by density gradient method from the blood collected from the patients before and after radiotherapy. The cells were washed in ice-cold 1× PBS, and resuspended in Hanks balanced salt solution with 10% dimethyl sulfoxide with ethylenediamine tetra-acetic acid. The cells were then suspended in (0.75%) molten low melting point agarose (at 37°C) and immediately pipetted onto the comet slides (Trevigen, Gaithersburg, MD). Electrophoresis was done as per the vendor’s suggestions. After electrophoresis, slides were briefly rinsed in neutralization buffer (500 mmol/L Tris-HCl, pH 7.5), air-dried, and stained with propidium iodide dye. Three hundred to 400 randomly chosen comets were analyzed per sample. The extent of DNA damage observed was expressed as number of comets analyzed per 100 cells, which corresponded to the fraction of the DNA damage in the peripheral blood lymphocytes of the patients, and the data were compared using suitable statistics (SPSS software version 10) between pre- and postradiotherapy in the yoga and control groups of patients. The comet slides were coded and analyzed blinded. The slides were decoded after the analysis.

Integrated Yoga Program⁴²

The randomly assigned intervention group was trained under a group of expert yoga trainers for 6 weeks. In the beginning, only meditative practice as well as slow stretching and loosening exercises were taught to the patients. They were motivated and counseled at the beginning, and the various postures (*asanas*) were meticulously taught. The special techniques designed for the cancer patients included guided imagery of cancer cells, positive thought provocation, and chanting of various sounds according to the respective religious beliefs of the patients. During the middle period of the trial, group awareness

practices were given. They were also provided with the audio and video tools to practice at home and were followed up via telephone during weekends to ensure continuity of practice. Special care was taken for patients who suffered from surgery-associated side effects such as numbness or pain. The patients were familiarized with various breathing practices called *Pranayama* (voluntary regulated nostril breathing). Each session was of 90 minutes duration, with full-time breath awareness and complete relaxation. At the end of each session, deep relaxation was given in the form of soothing sound vibrations and guided imagery called yoga *nidra*. These practices are thought to build inner awareness and attention of mental phenomena. This is known to alter the perceptions and mental responses to both external and internal stimuli, slow down reactivity and responses to such stimuli, and instill a greater control over stressful situations, which promotes physical well-being and mental calmness. Control-group patients were given supportive counseling and advised to take light exercise.

Results

A total of 58 patients completed the study (Table 1). Among the entire study population, 30 (52%) did not undergo chemotherapy immediately after surgery. Patients underwent a total of 28 cycles of radiotherapy; 5 (9%), 16 (28%), and 7 (11%) underwent 1, 2, and more than 2 cycles of chemotherapy, respectively. In the study cohort, 26 patients (45%) had stage II breast cancer, and 32 (55%) had stage III breast cancer, whereas 27 (46%) had histological grade II breast tumors, and 31 (54%) had grade III breast tumors. Thirty-four women (59%) were menstruating, and 24 (41%) had attained menopause, whereas 5 (9%) had undergone a hysterectomy. Fourteen (24%) had a history of stressful events in the past, whereas the majority (44, 76%) did not report any stressful or traumatic experience in the past.

Anxiety and Depression Scores

There was a significant decrease in the anxiety levels in the yoga intervention group from a mean of 8.5 (SD = 1.6) at baseline to a mean of 4.1 (SD = 1.0) (48.2%) after the 6 weeks of the yoga program (Figure 2, Table 2). In the control group, the mean anxiety score increased from 8.2 (SD = 1.1) to 10.5 (SD = 1.8) (28%) (Figure 3). Based on repeated measures ANCOVA, controlling for baseline values of each dependent variable, the change in anxiety was significantly different between the groups ($P < .001$).

The postradiotherapy depression score for the intervention group decreased from a mean of 8.0 (SD = 1.9)

Table 1. Demographic Particulars of the Patients Included in the Clinical Trial.

	Demographic Particulars					
	All Patients		Yoga group		Control Group	
	Age Mean = 44 yrs (SD = 1.3)		Age Mean = 47 yrs (SD = 1.1)		Age Mean = 43 yrs (SD = 1.5)	
	N = 58	%	N = 35	%	N = 23	%
Radiation Dose						
50.4 Gy (28 cycles)						
Cycles of chemotherapy						
None	30	52	14	40	16	70
1	5	9	3	9	2	9
2	16	28	12	34	4	17
> 2	7	11	6	17	1	4
Stage of breast cancer						
II	26	45	16	46	10	43
III	32	55	19	54	13	57
Grade of breast tumor						
II	27	46	17	48	10	43
III	31	54	18	52	12	57
Menopausal status						
Pre	34	59	18	51	16	69
Post	24	41	17	49	7	31
Stressful events in life						
Yes	14	24	10	28	4	17
No	44	76	25	72	19	83
Posthysterectomy	5	9	3	8	2	9

Data were abstracted on the history of breast cancer, investigative notes, and radiotherapy and chemotherapy treatment regimen.

Table 2. Comparative Scores of HADS, PSS, and DNA Damage of the Yoga and Control Groups (Mean ± SD)

Group	HADS-A		HADS-D		PSS		DNA Damage	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Yoga, n = 35								
(Mean)	8.5	4.1*	8.0	3.4*	20.4	14.9*	2.6	24.3*
SD	1.6	1.0	1.9	0.5	2.8	2.4	0.4	1.70
Control, n = 23								
Mean	8.2	10.5*	7.8	9.7*	19.0	20.4*	2.8	28.8*
SD	1.1	1.8	0.9	1.2	2.1	2.5	0.4	0.9

HADS = Hospital Anxiety and Depression Scale; PSS = Perceived Stress Scale.

* $P < .001$ (P values for ANCOVA scores).

at baseline to a mean of 3.4 (SD = 0.5) (57.5%) after the yoga program (Figure 2, Table 2). In the control group, the score increased from 7.8 (SD = 0.9) at baseline to 9.7 (SD = 1.2) (24%) (Figure 3, Table 2). Based on repeated measures ANCOVA, controlling for baseline values of each dependent variable, the change in depression was significantly different between the groups ($P < .001$).

Stress Scores

In the yoga group (Figure 4, Table 2), the mean perceived stress score (PSS) decreased from 20.4

(SD = 2.8) at baseline to 14.9 (SD = 2.4) postradiotherapy (26.9%), whereas the control group (Figure 5, Table 2) showed no change pre- and postradiotherapy (mean = 19.0 [SD = 2.1] at baseline and mean = 20.4 [SD = 2.5] postradiation).

DNA Damage

The extent of radiation-induced DNA damage was estimated by alkaline single-cell gel electrophoresis (Figure 6). The DNA damage due to radiation was significantly elevated in both the yoga and control groups after radiotherapy. The postradiotherapy DNA damage

Yoga Intervention Modulates Genotoxic Stress Following Radiotherapy

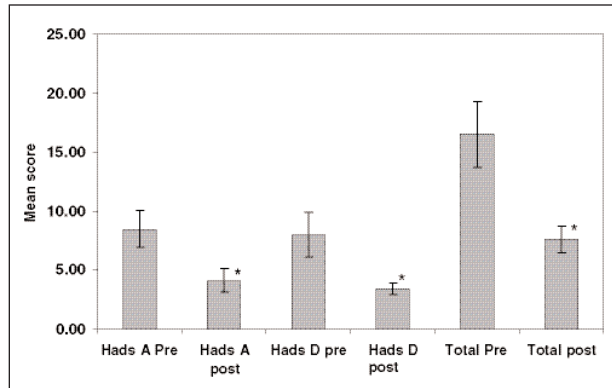


Figure 2. Mean Hospital Anxiety and Depression Scale (HADS) scores of the yoga intervention group. The HADS subscale scores showed significant decreases after the 6-week intervention. The total HADS score also showed decrease from the baseline ($P < .001$, repeated measures ANCOVA).

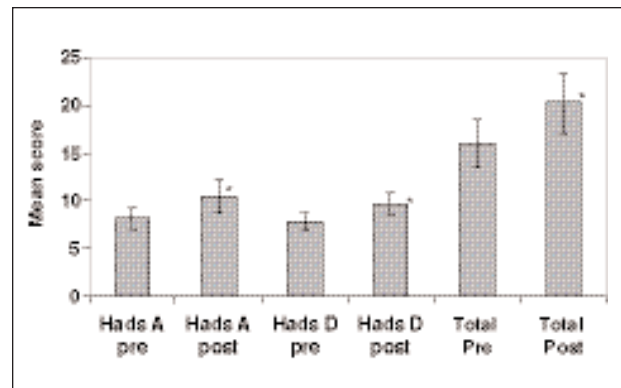


Figure 4. Mean Hospital Anxiety and Depression Scale (HADS) scores of the control group. HADS subscale scores showed significant increases after the 6-week waiting period. The total HADS score also showed an increase from the baseline ($P < .001$ repeated measures ANCOVA).

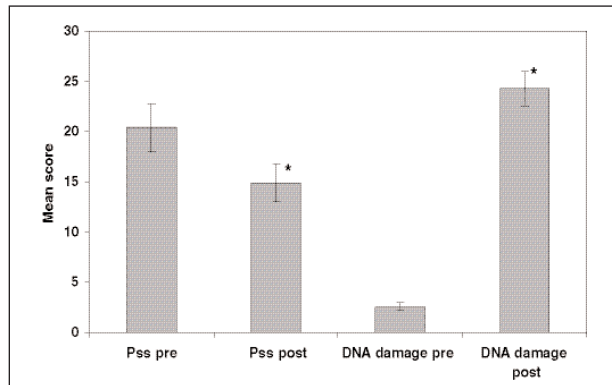


Figure 3. Perceived Stress Scores (PSS) and mean DNA damage frequency of the yoga intervention group. PSS scores showed significant decrease after the 6-week intervention. DNA damage showed significant increase after the radiation treatment ($P < .001$, repeated measures ANCOVA).

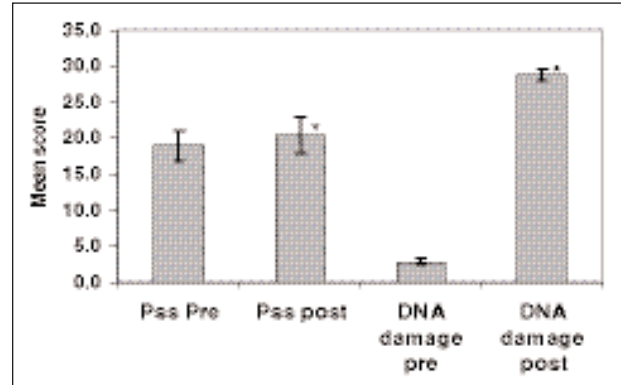


Figure 5. Mean Perceived Stress Score (PSS) and mean DNA damage frequency of the control group. The baseline score of PSS showed significant increase after the 6-week waiting period. The DNA damage showed significant increase after the radiation treatment ($P < .001$ repeated measures ANCOVA).

was lower by 14.5% (mean = 24.3 [SD = 1.7]) in the yoga group when compared to the control group (mean = 28.8 [SD = 0.90]). Based on repeated measures ANCOVA, controlling for baseline values of each dependent variable, the differential in DNA damage in the 2 groups was significantly different ($P < .001$). The baseline DNA damage was mean = 2.6 (SD = 0.4) and mean = 2.8 (SD = 0.4) for the yoga and control groups, respectively, which was significantly correlated (Pearson's correlation coefficient = .97) with postradiotherapy values (SPSS version 10).

Discussion

The results of our study suggest that the patients who were recruited into the yoga group and the wait-listed control group both had significant degrees of background stress and anxiety at the beginning of the

study (Figure 7). These data correlate with the previous reports by other groups such as Carlson et al.²⁷⁻²⁹ and Carson et al.³² The recruitment and randomization processes resulted in 2 groups whose general equivalence was confirmed by analysis of demographic factors and preintervention test scores. More patients in the yoga group, however, underwent 2 or more cycles of chemotherapy than in the control group, which would tend to dispose them toward greater levels of DNA damage. The background anxiety and depression levels can be attributed to the severe traumatic experience of cancer as a disease as well as the anticipation of end of life as a crisis situation.^{4,6} The decrease in the anxiety and depression levels can be attributed to the relaxation response gained from the integrated yoga approach, which had lowered the stress-induced arousal in traumatized patients.

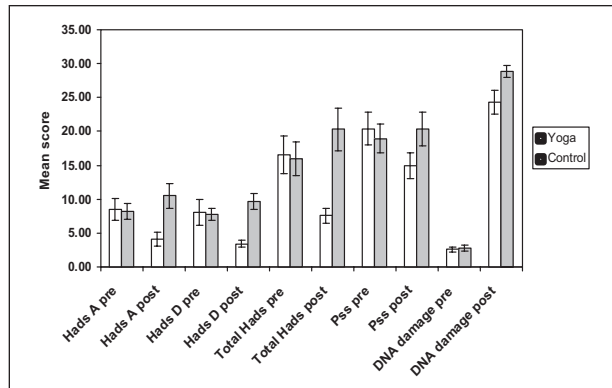


Figure 6. Comparative Hospital Anxiety and Depression Scale (HADS), Perceived Stress Score (PSS), and DNA damage frequency scores of the yoga intervention and the control group. Baseline HADS, PSS, and DNA damage did not differ significantly in the yoga and control groups. In comparison to the control group, the yoga group showed significant decreases in the anxiety, depression, and the perceived stress scores when compared to the preintervention baseline. Although both groups showed increased DNA damage, the yoga group showed significantly less damage when compared to the control group.

The perceived stress was also reduced significantly in the intervention group when compared to the control cohort. This is also similar to the findings of Casso et al,³⁰ Rosenbaum et al,³¹ and Carson et al.³² Although there were a few patients in the control population who reported improvement in their sleep quality and anxiety levels, the depression scale increased over the period of the study in the control group. Radiation-induced DNA damage has been widely studied and reported by many, including our previous study.³⁶ In another work, Mozdarani et al³⁴ showed that there was an elevated spontaneous frequency of micronuclei in a breast cancer group compared to a control group. They also showed that breast cancer patients were 30% more sensitive to ionizing radiation than the age- and sex-matched control population. Scott et al³⁵ reported that breast cancer patients displayed radiation susceptibility when compared to control. We have reported significant genomic instability in breast cancer patients who underwent radiotherapy.³⁶

In the present study, an effort has been made to investigate radiation-induced DNA damage as a genotoxic stress and its correlation with the psychological stress levels of the patients. Alkaline gel electrophoresis technique (comet assay) was used as described by Poonepalli et al.⁴³ Comet assay is a very sensitive tool to study DNA damage.⁴⁵ In another study, Epel et al³⁷ reported a significant correlation with telomere length in the PBLs and psychological stress in controlled study. Subsequently, Epel et al⁴⁴ reported a significant correlation with telomere

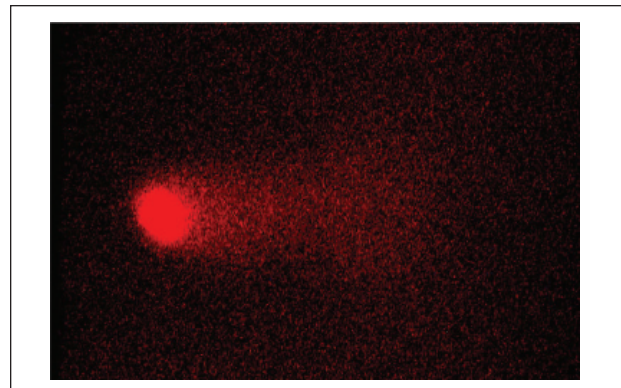


Figure 7. Representative image of a comet from a postradiotherapy treated leukocyte nuclei of a patient stained with propidium iodide dye and showing considerable tailing, indicating DNA damage.

dysfunction and stress in cardiovascular disease. In our previous work,³⁶ we also reported a significant correlation between radiation-induced DNA damage and telomere dysfunction in breast cancer patients. Telomere maintenance is strongly associated with DNA damage and repair.^{45,46} Psychological stress is also associated with faulty DNA repair capacity in lymphocytes.^{39,40} Later, Cohen et al³⁸ showed reduced DNA repair capacity in anxious students.

We speculate that the reduced DNA damage in the intervention group as compared to the control group may be linked to lower psychological stress. The background DNA damage levels in both the control group and the intervention group may be associated with the varied dose of chemotherapy and increased levels of anxiety. There is a converging link between the psychological (QOL, anxiety, depression, mood disturbances, perceived stress)^{3,27-33} and physiological stress at the molecular level such as cortisol levels, catecholamines, DNA damage, telomere length, and DNA repair capacity.^{34-40,44-46} Buettner et al⁷ reported in a large-scale survey of more than 2000 patients undergoing various complementary treatments that yoga was the most effective among all the CAMs in decreasing anxiety and depression and improving the QOL of breast cancer patients. In the current study, we investigated the possible link of stress at the molecular level. Much work remains to be done to substantiate the findings of the above-mentioned groups, including our study.

Limitations of our study include the small population size, also faced by other groups.^{28,30-32} In the hospital clinical outpatient setting, it is difficult to conduct large patient trials with physiological parameters such as DNA damage involved. No specific data were obtained on compliance with the yoga program while patients were at home. In addition, the number of

dropouts from the control group was large, and the control group lacked activities that would account for the effects of time and attention from medical personnel and yoga instructors received by the yoga group. The supportive counseling group does, however, account for any gradual reduction in stress scores due to natural adjustment to the diagnosis and the treatment situation. Larger and more specific trials in the future may prove effective in deciphering the mechanistic link between emotional trauma and psychological and physiological stress.

In summary, our study showed preliminary data to support the influence of stress on the coping route at the molecular level. Along with earlier studies,^{16,47} the present study highlights the potential of an outpatient yoga-based program and supportive counseling to reduce adverse effects of the conventional treatment modality and to benefit cancer patients overall.

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