EFFECT OF YOGA THERAPY AS A PSYCHOTHERAPEUTIC INTERVENTION IN BREAST CANCER PATIENTS

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DOCTOR OF PHILOSOPHY (Ph.D.)

IN YOGA

By

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D E C L A R A T I O N

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I also declare that the subject matter of my thesis entitled "***EFFECT OF YOGA THERAPY AS A PSYCHOTHERAPEUTIC INTERVENTION IN BREAST CANCER PATIENTS"*** has not previously formed the basis of the award of any degree, diploma, associate ship, fellowship or similar titles.

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ABSTRACT

Background:

Breast cancer is a profoundly stressful disease posing both physical and psychological threats to the patient. Breast Cancer is rapidly catching up with Cervical Cancer as the most common type of cancer among urban Indian women. Treatment regimens for breast cancer pose serious side effects for these patients such as loss of breast, infertility, altered sexual functioning, hair loss, fear and anxiety, fatigue, nausea and vomiting, pain, infections and low blood counts, which grossly affect the patients overall quality of life (QoL). Earlier studies have demonstrated that chronic stressors are associated with continued down-regulation of immune function rather than adaptation and this is known to be mediated through HPA Axes dysregulation in cancer patients. Ancient scriptures proscribe mantras and manta japa to overcome fears, anxiety, cope with cancer and death. We have developed an integrated yoga program that uses Mahamrutyunjaya mantra as a part of mind sound resonance technique for alleviating fears in cancer patients. In an earlier study using this intervention we also found decrease in NK cell % following surgery and chemotherapy. Recent studies using a eight-week mindfulness based stress reduction program for early stage breast and prostate cancer patients have shown to decrease levels of salivary Cortisol in those with initially high values and also change the abnormal pattern of Cortisol secretion. Improvements were also seen in quality of life, moods, and decrease in stressful symptoms. We undertook this study to evaluate the role of Yoga in modulating mood, HPA Axes dysregulation and immune measures in both early stage II and III and metastatic cancer patients.

Aims and objectives:

1. To study the effect of "Integrated yoga program" in stage II & III breast cancer patients undergoing radiotherapy (BCS2/3) on their psychological morbidity and stress markers.

2. To study the effect of yoga on immune markers, stress levels and sleep. In stage IV breast cancer (BCS4) survivors.

Subjects:

Two separate RCTs were conducted to achieve the two aims There were 88(44Y and 44C) patients in BCS2/3 study and 91(46 Y and 45C) in BCS4 study.

Design:

Both BCS2/3 and BCS4 were prospective randomized two armed longitudinal controlled studies. Patients for both studies were selected from outpatients of Bangalore institute of oncology in Bengaluru and Bharath Hospital Institute of Oncology in Mysore, Karnataka India. Experimental group practiced a specific module of integrated approach of yoga therapy (IAYT) program designed to suit the two stages of the disease. These were taught 3-6 days per week in hospital premises for 1 hour/day for 6 weeks BCS2/3 and 2 days per week for 3 months with regular home practice for 1 hour / day with telephonic supervision and use of taped recorded instructions in BCS4 study. Control group had standard supportive therapy.

Assessments:

A. BCS2/3 study: (a) Stress marker - salivary Cortisol including diurnal salivary Cortisol rhythmicity, (b) Psychological assessments included Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale (PSS), European Organization for Research in the Treatment of Cancer – Quality of Life Questionnaire (EORTCQOL), Positive Affect and Negative Affect Schedule (PANAS) and Rotterdam Symptom Check List (RSCL).

B. BCS4 study:

a. Immune measurement - Natural Killer cell (NK cell) count.

b. Psychological Assessments included Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale (PSS), European Organization for Research in the Treatment of Cancer – Quality of Life Questionnaire (EORTCQOL), Insomnia rating scale (IRS) and Fatigue symptom inventory scale (FSIS).

Results:

In BCS2/3 study there was a significant decrease in mean salivary Cortisol level at 0600 hrs (p = 0.009) and pooled mean diurnal salivary Cortisol level (p = 0.03), anxiety (p < 0.001), depression (p = 0.002), perceived stress (p < 0.001), Negative affect (p = 0.004), psychological distress (p = 0.001) with significant improvement in Positive affect (p = 0.002), emotional function (p = 0.001), cognitive function (p = 0.01), activity level (p = 0.01) in yoga group as compared to control group.

In BCS4 Study:

The NK Cell % (p = 0.03) increased in yoga group as compared to control group and significant difference between groups in anxiety (p < 0.001), depression (p < 0.001), perceived stress (p < 0.001), pain (p = 0.04), insomnia (p = 0.002), sleep symptom distress (p < 0.001), fatigue (p = 0.05), fatigue severity (p < 0.001), fatigue frequency (p < 0.001), fatigue interference (p < 0.001), fatigue diurnal variation (p = 0.001) and significant improvement in role function (p = 0.03), emotional function (p < 0.05), Global quality of life (p = 0.01), sleep pattern (p < 0.001), sleep quality (p < 0.001) and total sleep rating (p < 0.001).

Conclusion:

Yoga improves mood, affect, quality of life and reduces stress , treatment related symptoms , anxiety and depression in patients with both BCS2/3 undergoing radiotherapy and BCS4. It improves sleep and reduces fatigue in BCS4. Yoga improves salivary Cortisol rhythm in cases with BCS2/3 and reduces NK Cell % in BCS4.

STANDARD TRANSLITERATION CODE

a	=	अ	ṅa	=	ङ	pa	=	प
ā	=	आ	ca	=	च	pha	=	फ
i	=	इ	cha	=	छ	ba	=	ब
ī	=	ई	ja	=	ज	bha	=	भ
u	=	उ	jha	=	झ	ma	=	म
ū	=	ऊ	ñ	=	ञ	ya	=	य
e	=	ए	ṭa	=	ट	ra	=	र
ai	=	ऐ	ṭha	=	ठ	la	=	ल
o	=	ओ	ḍa	=	ड	va	=	व
au	=	औ	ḍha	=	ढ	śa	=	श
m	=	अं	ṇa	=	ण	ṣa	=	ष
ḥ	=	अः	ta	=	त	ha	=	ह

ka	**=**	**क**	**tha**	**=**	**थ**	**kṣa**	**=**	**क्ष**
kha	**=**	**ख**	**da**	**=**	**द**	**tra**	**=**	**त्र**
ga	**=**	**ग**	**dha**	**=**	**ध**	**jña**	**=**	**ज्ञ**
gha	**=**	**घ**	**na**	**=**	**न**			

1. INTRODUCTION

1.1 Breast cancer global scenario

Cancer of the breast in women is a major health burden worldwide. It is also the primary cause of cancer death among women globally, responsible for about 375,000 deaths in the year 2000 (Ferlay J, Bray F et al. 2001). Patients with breast cancer normally receive multimodal treatment over a long period of time (Overgaard M, Hansen PS et al. 1997; Ragaz J, Jackson et al. 1997). Cancer diagnosis and treatment is a particularly potent stressor that is associated with physiological changes, fear of death, progression or recurrence of disease, treatment related distress, changes in QOL and social relationships, and an overall loss in sense of control (Redd WH, Silberfarb PM et al. 1991; Spiegel D 1997).

1.2 Breast cancer Indian scenario

Breast Cancer is rapidly catching up with Cervical Cancer as the most common type of Cancer among urban Indian women. In females, breast cancer was the leading site of cancer with a relative proportion ranging from 19.3% to 27.5% compared to cervical cancer.

1.3 Breast Cancer - A Psychosocial Disease

Breast cancer is a profoundly stressful disease posing both physical and psychological threats to the patient. Breast cancer patients confront a cascade of stressors, including the diagnosis itself, ongoing intrusive medical procedures and severe side effects of treatment, and a variety of personal, psychological, and physical losses (Stanton AL and Snider PR 1993; Carver CS, Pozo-Kaderman C et al. 1998). The diagnosis of cancer can bring about profound emotional reactions the common ones being shock and disbelief (Holland J 1973; Schmale AH 1974; Pfefferbaum B, Pasnau RO et al. 1977), anger directed against physician or family members (Greer S, Morris T et al. 1979), sadness, depression and personal grief may follow (Parkes CM 1975; Morris T, Greer HS et al. 1977; Maguire GP, Lee EG et al. 1978; Fawzy FI and Fawzy NW 1982). Most patients gradually accept reality and behavioral concomitants of these emotions such as anxiety; helplessness, hopelessness, guilt, insomnia, anorexia, irritability and inability to concentrate often manifest themselves (Peck A 1972). The prevalence of anxiety and depression in Indian cancer patients in Bangalore undergoing radiation treatment was 64% and 50% respectively (Chaturvedi SK, Prabha Chandra S et al. 1996). Cancer patients often have elevated levels of intrusive thoughts concerning their cancer and its treatment (Cella DF, Mahon SM et al. 1990; Epping-Jordan JE, Compas BE et al. 1994; Green BL, Rowland JH et al. 1998). Levels of intrusive thoughts are typically high at the time of diagnosis and may persist for months or even years

after the initial diagnosis and treatment (Epping-Jordan JE, Compas BE et al. 1999). Especially intense or prolonged intrusive thoughts seem to be associated with psychological distress (Lepore SJ, Silver RC et al. 1996; Epping-Jordan JE, Compas BE et al. 1999). Intrusive thoughts experienced by cancer patients have also been associated with posttraumatic stress disorder (PTSD), which may be elicited by a life-threatening illness (Cordova MJ, Andrykowski MA et al. 1995; Andrykowski M A, Cordova MJ et al. 1998; Smith MY, Redd WH et al. 1999). Such psychological distress and treatment is known to affect various dimensions of quality of life such as physical, emotional, social, functional and spiritual wellbeing and leads to hypothalamic-pituitary-adrenal (HPA) axis deregulation (Vedhara K, Tuinstra J et al. 2006; Thornton LM, Andersen BL et al. 2008) suppressing the immune response (Cohen S and Williamson GM 1991; Andersen BL, Kiecolt-Glaser JK et al. 1994; Spiegel D, Sephton SE et al. 1998) in both newly diagnosed and long-term survivors of breast cancer (Weitzer MA, Meyers CA et al. 1997; Shapiro S L, Lopez AM et al. 2001; Smith EM, Gomm SA et al. 2003; Vacek PM, Winstead-Fry P et al. 2003).

1.4 Effect of Stress on HPA-Axis dysfunction and Breast cancer

Cancer patients repeatedly endure physical and emotional events that activate stress-response mechanisms leading to elevated cortisol levels, a stress hormone and the end product of HPA axis in breast cancer patients both prior to and following treatment (McEven BS and Sapolsky RM 1995; Aragona M, Muscatello MR et al. 1996; Van der Pompe G, Duivenvoorrden HJ et al. 1997. Such repeated activation has been associated with HPA axis dysregulation and adverse health consequences (McEwen BS 1998). One sign of deregulation in this endocrine stress response system is altered circadian cortisol rhythms (Yehuda R, Teicher MH et al. 1996; Chrousos G and Gold PW 1998; Rosmond R, Dallman M et al. 1998). Elevated cortisol levels and

overall flattened diurnal profiles are reported in breast cancer patients compared to control women (Van der Pompe G, Antoni MH et al. 1996; Porter L S, Mishel M et al. 2003; Abercrombie H C, Giese-Davis J et al. 2004). Such abnormal patterns of cortisol have been reported in upto 70 to 75% of a sample of metastatic breast and ovarian cancer patients (Touitou Y, Bogdan A et al. 1996; Van der Pompe G, Antoni MH et al. 1996). Several studies have found out that such circadian abnormalities had prognostic value in predicting initial occurrences of breast cancer (Ticher A, Haus E et al. 1996) as well as associations with later stages of cancer development and with other prognostic indicators (Touitou Y, Bogdan A et al. 1996) such as early mortality from Metastatic breast cancer (Sephton SE, Sapolsky RM et al. 2000).

1.5 Yoga for Breast cancer

Yoga is a psychotherapeutic with its utility in numerous health care concerns where stress is believed to play a role. Such psychotherapeutic interventions are being used to help patients cope better, manage stress, reduce treatment related distress and improve their quality of life in cancer patients. Various components and types of yoga practices have shown beneficial effects in reducing distressful symptoms and improving sleep, mood, and quality of life in cancer patients (Bower JE, Alison Woolery MA et al. 2005). Results from randomized controlled studies have shown decreases in cortisol levels in non cancerous populations following yoga intervention (Michalsen A, Grossman P et al. 2005; Granath J, Ingvarsson S et al. 2006; Vedamurthachar A, Janakiramaiah N et al. 2006). Our earlier studies with yoga intervention have shown decreases in anxiety states (Raghavendra Rao M, Nagarathna Raghuram et al. 2009), reduction in chemotherapy-induced nausea and vomiting (Raghavendra RM, Nagarathna R et al. 2007) and improvement in immune response following surgery and chemotherapy (Rao RM, Telles S et al. 2008) in early breast cancer patients but have not assessed changes in cortisol

rhythms in these populations. Other studies that have shown improvements with yoga in patients undergoing adjuvant radiotherapy have used Mindfulness meditation as an intervention. It is desirable therefore to scientifically validate the effects of yoga intervention in reducing conventional treatment related distress and side effects, psychological morbidity and improving quality of life and diurnal cortisol rhythm and immunity in early and advanced breast cancer patients undergoing conventional cancer treatments.

Hence we chose to assess the effects of an integrated yoga program on mood states, salivary cortisol and NK cell counts in early (stage II and III) and stage IV breast cancer patients.

2. LITERATURE REVIEW

This has been presented in two parts. The first part is to cull out the literature from traditional texts on Mantras that have been used as an important component of the intervention in this study. The second part deals with the relevant scientific literature as a background for the work done.

2.1 Introduction

The intervention used for the experimental group is called integrated approach of yoga therapy. This has been developed by senior yoga experts with traditional knowledge and has been tried in patients with different life style related diseases including cancer. Specific modules have also evolved over thirty years of therapeutic research at VYASA. The module that is used for breast cancer patients has also been used in our earlier published studies. One of the components of this integrated module of yoga for breast cancer is called mind sound resonance technique

(MSRT) which is based on chanting of syllables *(Mantras)* that have been passed on through traditional scriptures. *Mantra* in its most literal sense means "to free from the mind." *Mantra* is therefore that which protects one from aberrations. *Mantra* is, at its core, a tool used by the mind which eventually frees one from the vagaries of the mind. In the strictest sense, a *Mantra* is a pure sound vibration which delivers the mind from its material inclinations and illusion. The resonance and vibrations produced by *Mantras* are known to act on the subtler layers of being and modulate the prana thereby controlling the mind. *Mantras* serve as a bridge between body and mind, breath and mind and mind and intellect and help transcend one to higher states of consciousness that is filled with more bliss or relaxation. MSRT is based on *Mahamrutyunjaya Mantra* that is known to remove fear of death and conveys the central idea of cycles of birth and death. Meditation on such a powerful *Mantra* and its meaning has been shown to help remove fears and allay anxiety in cancer patients. Patients with breast cancer report that this is a very useful practice and they tend to use it very frequently even while they are undergoing chemotherapy since it does not involve any body movement and is practiced in supine posture by very sick patients. The main aims and objectives of this literary exposition are as follows:

(i) Compile authentic information on *Mantras* from classical yogic and spiritual literature.

(ii) Study the basic principles and theory of *Mantra* based on traditional literature.

(iii) Define and present concept of a specific technique i.e., Mind Sound Resonance Technique.

(iv) Prerequisites and uses of *Mantras.*

(v) Integrated approach of Yoga in cancer: Towards a conceptual model.

(vi) Scientific basis of *Mantras*.

2.2 Background

The diagnosis and treatment of cancer causes severe psychological distress in cancer patients. This coupled with fear of recurrence, relapse, disfigurement, toxicity and cancer related intrusive thoughts can significantly reduce their well being, quality of life, immune response and survival. Understanding the conceptual basis of integrated approach of yoga therapy that describes the possibility of reversibility of any disease process by invoking the enormous healing potential within each cell helps these patients to achieve better psychological health that forms the basis of yoga therapy (Nagendra HR,2001).Understating the imperishable nature of our existence as portrayed in all Indian yoga and spiritual texts helps in altering one's self perception of cancer and death. This understanding needs to be supplemented by practices that have been incorporated in the module of IAYT program that operates at all levels of our existence.This helps build internal awareness and takes one across various levels of relaxation and conscious states facilitating removal of deep-rooted fears and subconscious suppressed stresses. Of interest in this study is the chanting of *Maha Mrutyunjayamantra* (the chant for winning over the fear of death) that forms a component of MSRT and is a perfect example of *Mantra Yoga*. This *Mantra* has been used since the *Vedic* ages to ward off fear, cure disease, remove misfortunes, instill confidence, instill calm and meditative mind and even conquer death as mentioned clearly in *Atharvaveda, Charaka Samhita, Sushruta and Patanjali Yoga Sūtras*. *Mantra* or chants are also subtle forms of *prāna* as mentioned in *Bhartrihari's Vākyapadiya* and act as a bridge between the mind and body, mind and intellect and finally between mind and the no mind state- a state of bliss and silence. The chanting of *Mantras* or prayers are known to alleviate the hidden thoughts, fears and intrusive thoughts as mentioned in *PYS- Sādhana pāda* (verse 32). The most popular meditative practice called transcendental meditation use

Mantras to transcend different levels of consciousness and instill calmness and peace. MSRT is a similar practice that uses both OM chanting and *Mahamrutyunjaya Mantra* to accomplish similar physiological and psychological benefits. In this literary exposition we will understand the meaning of *Mahamrutyunjaya Mantra*, its uses according to ancient texts and role of *Mantras* in general in the management of various diseases and afflictions. The neurophysiological connotations behind chanting *Mantras* and its relevance in cancer patients will also be explored.

2.3 Concept of Mantra ccording to ancient Indian texts

Understanding the concept of evolution in terms of the universal consciousness and supreme bliss will help altering ones perception towards cancer and death. This is facilitated by using an integrated yoga program that operates at all *kośas* (*Taittarīya Upanishad*) and helps build internal awareness and takes one across various levels of relaxation and conscious states facilitating removal of deep-rooted fears and misperceptions. Yoga is both, the goal as well as the means to achieve a state of perfect harmony. Yoga is a state of complete absorption, union (*Yoga sthiti*) with absolute Reality i.e., Universal Consciousness. Yoga is a systematic process of cessation of all mental modifications to reach that absolute reality. This is brought about by continuous practice (*abhyāsa*) and detachment of sense organs from their sense objects (*vairāgya*).The first step in this process is to shift the mind from *chanchalatā to ekāgratā*, leading to a state of *pratyāhāra* a process of sensory inhibition or withdrawal. The safest and the easiest method among all the yoga practices to reach *pratyāhāra* leading to a state of *Samādhi* is *Mantra yoga*. *Mantra* consists of words or vibrations that instill one-pointed concentration. Of interest in this study is the chanting of *Mahā Mrutyunjaya Mantra* that forms

the basis of Mind Sound Resonance technique (MSRT) (Nagendra HR, 2001) and is a perfect example of *Mantra* yoga

2.4. Compilation of authentic information on mantras from classical yogic and spiritual literature.

2.4.1.1 Definition and etymology of the word Mantra

According to Vedic texts

The Sanskrit word mantra- (m. म , also n. म) consists of the root man- "to think" (also in manas "mind") and the suffix -tra meaning, tool, hence a literal translation would be "instrument of thought". Another explanation is that the suffix -tra means "protection". *Mantra* in its most literal sense means "to free from the mind". *Mantra* is therefore that which protects one from aberration. According to *Vishnupurāńa*, it is said that in *Satyayuga* (The Golden Age), spiritual illumination is attained through meditation and in *Dwāparayuga* (Brazen Age) through worship. But in *Kaliyuga* (Iron Age), *Mahābhārata* declares that *Mantra japa* is the best amongst all spiritual practices. *Mantra* is, at its core, a tool used by the mind which eventually frees one from the vagaries of the mind. In the strictest sense, a *Mantra* is a pure sound vibration which delivers the mind from its material inclinations and illusion. Chanting of *Mantras* is one of the best spiritual *sādhana*. The process of production of *Mantras* or sound is described below (Devarupaananda 2007).

2.4.1.2 The process of articulation of sound

The philosophers of the Sanskrit language explain this principle called *sphota* as one by which the process of articulation occurs through the inner consciousness releasing bursts (*sphotas*), of energy in which the unity pervades. Even in the case of an articulated sound, the *sphota* itself is not subject to time divisions. Only the lower mind, the senses and the mechanical sources of sound are subject to time division.

Those who have learned to observe the arising of speech from the will of the spiritual self will comprehend what is being said here. Even closer to the truth are those who have experienced the *Mantra* arising as a vibration in various centers of consciousness.

To simplify:

1. The seed of knowledge bursts into the *Ātman*, the spiritual self.
2. *Ātman*, through its will, infuses it into *Buddhi*, the faculty of intelligence.
3. The process of mentation is begun; the *Buddhi* is agitated, vibrant.
4. The syllables are thought, becoming *Mantra* or secular words.
5. The mind awakens *tejas*, the illuminatory power that runs the entire personality systems.
6. This *tejas* impels the *prāńa* which moves the air.
7. The air pressed through the organs of articulations becomes the spoken word.
8. The volume or the force of the spoken word may vary but *sphota*, the process of consciousness, is an invariable constant. This is described in Fig 1.

चत्वारि वाक् परिमिता पदानि तानि विदुर्ब्राह्मणा ये मनीषिणः ।

गुहा त्रीणि निहिता नेङ्गयन्ति तुरीयं वाचो मनुष्याः वदन्ति ॥

कृष्णयजुर्वेद तैत्तरीय ब्राह्मण द्वितीयाष्ठक अष्ठम प्रपातक । ६३ मन्त्र ।

catvāri vāk parimitā padāni tāni vidurbrāhmaṇā ye manīṣiṇaḥ।

guhā trīṇi nihitā neṅgayanti turīyaṁ vāco manuṣyāḥ vadanti।।

kṛṣṇayajurveda taittarīya brāhmaṇa dvitīyāṣṭhaka aṣṭhama prapātaka

।63 mantra।

The complete process of production of words has four stages: *Parā, Pashyanti, Madhyama and Vaikhiri.* The first three are internal and yogic and can be experienced by yogis. The fourth stage of *Vaikhiri* is the audible speech which is used by all human beings.

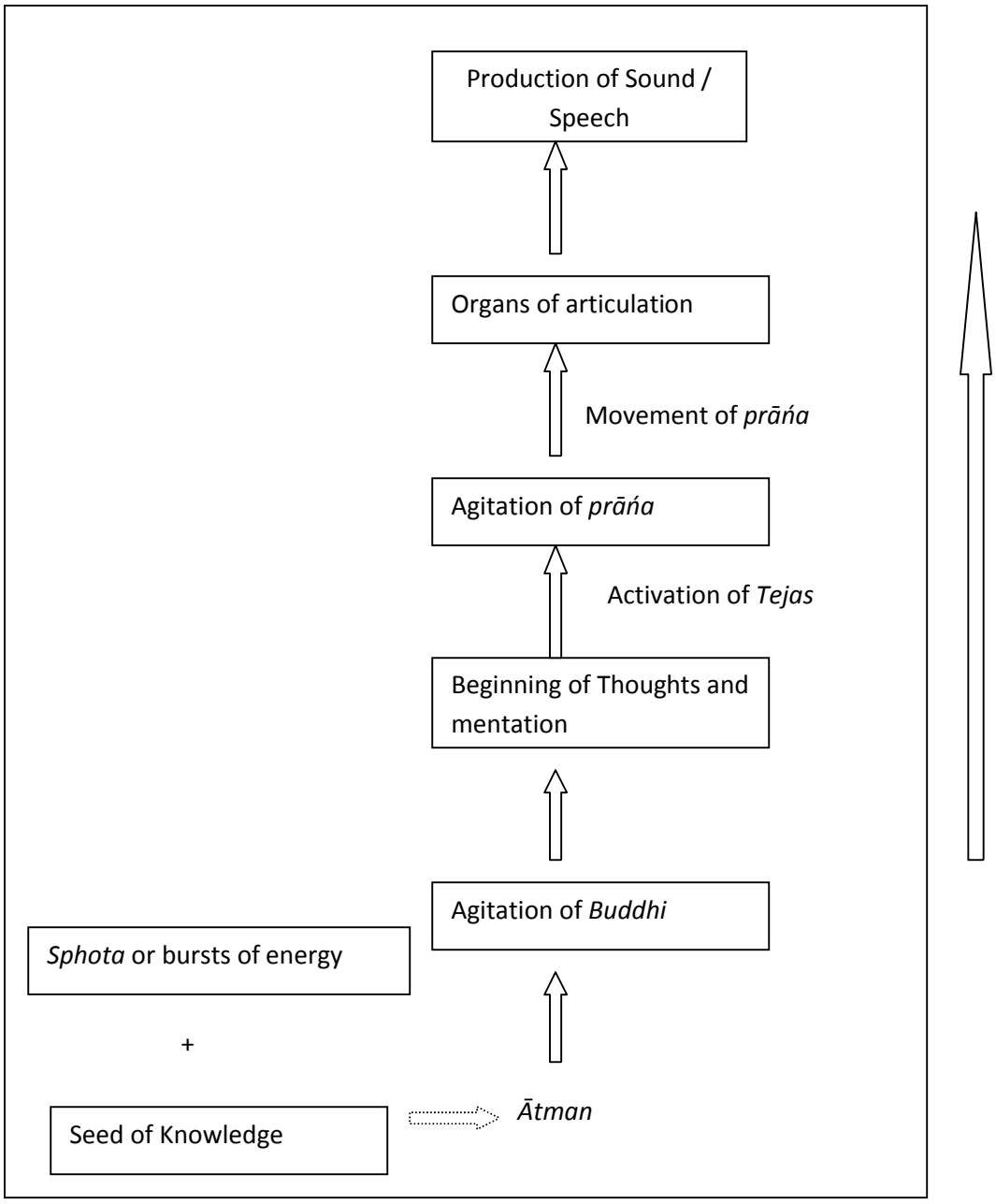


Figure 1: Process of development of Sound / Speech (Usharbudh Arya, 1985)

2.4.2 Study the basic principles and theory of Mantra based on traditional literature

2.4.2.1 Philosophical basis of Mantra yoga

A *Mantra* (*Devanāgarī* म) (or *Mantram*) is a religious or mystical syllable or poem, that has been used since the Vedic ages as spiritual conduits, words or vibrations that instill one-pointed concentration in the devotee. This has endeared its utility in realization of the universal consciousness which has manifested in the form of sound. This is more so emphasized in the *Bhagavad Gīta* that say:

ॐ तत् सत् श्री ।भ ।गी १७ ।२३

Om tat sat śrī|bha|gī 17|23

In the beginning was the word, thus is the importance of sound emphasized to us. It is interesting to learn that the formation of the universe out of chaos is brought about by sound. Certain sounds produce different sets of vibrations in the ether. Some of these are of such low frequency that they form particles of what we call matter. The clairvoyant primitive people actually saw the shapes produced in the ether by sounds. They represented these shapes as the letters of their alphabets. So most of the words and sounds of the early languages actually controlled and represented that which they expressed. Throughout history we learn of the deliberate and effective use of sound. Priests have always employed it creating certain definite reactions on the people by the use of chanting and intoning. In the ancient magical rites words, sounds and shapes were combined to gain certain ends.

Sound is therefore eternal and that it is the matrix of all creation. The science of sound holds the key to the mysteries of the universe. Even thought is a sound and sound is the cause not the effect of vibration. There can be sound without vibration. Yoga has developed

the theory of static sound; in developing this theory it says that there is no vacuum in this universe. Sound changes its property according to pitch, rhythm, volume, speed, frequency, harmony, intonation and utterance (Seal B 1985)**.** The sound energy has to be organized and channeled in particular way to produce particular results. *Mantra-yoga* is an attempt to organize and channelize sound energy to produce particular results (Usharbudh Arya 1985)**.**

Śabda (sound) occupies a very important place in *Sanātana Dharma* (Vedic Hinduism). Understanding and realization of *Śabda* is said to be the goal of life itself. The *Amrita Bindu Upanishad* proclaims that,

द्वे विद्ये वेदितव्ये तु शब्दब्रह्म परं च यत्।

शब्दब्रह्मणि निष्णातः परं ब्रह्माधिगच्छति ॥ अ।बि। १७

dve brahmaṇi veditavye śabda brahma paraṁ ca yat|

śabda brahmāṇi niṣṇātaḥ paraṁ brahmādhigacchati|| a|bi|17

Two vidyas (sciences) are fit to be known Shabda Brahman and Para Brahman. One who has completely mastered Shabda Brahman attains Para Brahman.

Also it is noted by Lakshmaṅa Deshikendra in *Śārada Tilaka Tantra* that the essence of all beings is itself the "*Śabda Bramhan"* (Desikendra 1978).

चैतन्यं सर्व भूतानां शब्द ब्रह्मेति मे मतिः ॥ शा।ति।तन्त्र।द्वितीय पटल।४६

caitanyaṁ sarva bhūtānāṁ śabda brahmeti me matiḥ|| śā|ti|tantra|dvitīya paṭala|46

"Chaitanya in all beings is Shabda Brahman".

Thus, the above statements from Hindu scriptures indicate that *śabda* is an integral part of our life. In Vedic literature, it is given that the *śabda Bramhan* is omni present through the sound of '*Om*'. The philosophical analysis of this '*Om'* is dealt in several upanishads (Prasad MG 1993).

Śabda is known form of seed sound and words takes another important form called *nāda*.The *nāda* refers to the flowing energy of sound which also refers to the expressions of chaitanya or consciousness. *Sāranga deva* in *Sangīta Ratnākara* (sarangadara 1978) says,

चैतन्यं सर्वभूतानां विवृतं जगदात्मना।

नाद ब्रह्म तदानन्दं अद्वितीयं उपास्महे॥ सं। र।प्रकीर्णकाध्यायः।४२

caitanyaṁ sarvabhūtānāṁ vivṛtaṁ jagadātmanā|

nāda brahma tadānandam advitīyam upāsmahe||

saṁ| ra|prakīrṇakādhyāyaḥ|42

"We worship *Nāda-Brahman*, that incomparable bliss, which is intrinsic in all the creatures as consciousness and is manifest in the phenomenon of this universe. Thus, the *nāda, śabda* and ananda are inseperable from consciousness.

It is also said that,

नकारं प्राणान्नामं दकारमनलं विदुः ॥

जातः प्राणाग्निसंयोगात् तेन नादः अभिधीयते ॥ सं ।र ।प्रकीर्णकाध्यायः ।५१

nakāraṁ prāṇānnāmaṁ dakāramanalaṁ viduḥ||

jātaḥ prāṇāgnisaṁyogāt tena nādaḥ abhidhīyate||saṁ| |ra|prakīrṇakādhyāyaḥ|51

The syllable *'nā'* represents the vital force and *'da'* represents the fire. Thus being produced by the interaction of vital force and fire is called "*nāda*". (Pandit Usharbudh Arya 1985).

This *nāda* which manifests as seven notes becomes the vehicle of emotional expressions through the nine rasas in the form of music and dance. The nine *rasas* (sentiments) are love (erotic), heroic, pathetic, marvelous, comic, odious, terrible, furious, and peaceful.

The words of a song denote this *śabda*(*pada*) while the singing tune denotes the expression of *nāda*. Thus, it is seen that *śabda* and *nāda* are connected by music. The modern scientific enquiry of sound which is also termed as acoustics has shown that the sound plays an essential role virtually in all aspects such as earth sciences, engineering, life sciences and arts. Sound in modern scientific view refers to the audible range, with infra and ultra sound covering the inaudible molecular vibrations of the medium. Similarly, in Hindu scriptures, *śabda* originating from the vibratory cause is termed as *āhata śabda*. It also refers to self – sustaining sound, without vibratory cause, termed as a*nāhata śabda* which is experienced only in higher (deeper) states of yoga.Thus it is seen that *śabda* (sound) encompasses the life itself (Swami Adiswarananada 2004).

2.4.2.2 Concept of evolution

The evolutionary order of elements is also stated in more explicit way in *Brahmānandavalli* of *Taittarīyopanishat* in *Krishna Yajurveda* in the following statements (Mahadeva shastry A 1990).

तस्मात् वा एतस्मात् आत्मनाकाशः संभूतः।

आकाशाद्वायुः वायोरग्निः अग्नेरापः अद्भ्यः पृथिवी।

पृथिव्या ओषधयः। औषधीभ्योन्नम्। अन्नात्पुरुषः।

तैत्तरीय उपनिषद् ब्रह्मानन्दवल्ली प्रथमवर्ग

tasmāt vā etasmāt ātmanākāśaḥ sambhūtaḥ।

ākāśādvāyuḥ vāyoragniḥ agnerāpaḥ adbhyaḥ pṛthivī।

pṛthivyā oṣadhayaḥ। auṣadhībhyonnam। annātpuruṣaḥ।

taittarīya upaniṣad brahmānandavallī prathamavarga

The meaning of the statements is as follows: From that verily, from this self (*Ātman*) is *ākāśa* (ether) born; from *ākāśa*, the air; from air the fire; from fire the water; from water the earth; from earth the plants; from plants the food; from food the man.

It is given in the statements above that, the production of elements begins from the all pervading *Ātman* (Bramhan). Then the first element *ākāśa* is born, here *ākāśa* refers to absolute space (which is mistaken for vacuum). This most subtle element *ākāśa* is qualified by sound as its property or *guńa*. Then from *ākāśa*, air comes into being with two properties or gunas namely touch which is its own and the sound property of *ākāśa* already evolved.Then from air, fire came into being having three properties composed of two preceding and property of form which is its own. Then from fire was born water with four properties, comprising its own

property of taste and the three preceding one. Then from water, earth came into being with five properties namely smell, taste, form, touch and sound.Then from earth the herbs, the food and the man came into being. Although, it is noted above that *vāyu* (air) came from *ākāśa* (ether) and so on, but truly the *vāy*u is born from *Ātman* assuming the form of *ākāśa*, as *ākāśa* is only an effect with *Ātman* as source and cause. The same is true in regard to birth of the other elements for which *Ātman* is the causal source (Mahadeva shastry A 1980)**.** Thus, the element property relationship can be written from subtle towards gross manifestation as below:

ELEMENT	**PROPERTIES**
Ether or Absolute space-Ākāśa	**Sound (Śabda)**
Air (Vāyu)……	**Sound and touch (Sparsha)**
	Sound,touch and form (Rūpa)
Fire(Agni)…….	
Water(Āpah)……	**Sound,touch,form and taste (Rasa)**
Earth (Prithwi)……	**Sound,touch,form,taste and smell(Gandha)**

It is seen from the above tabular representation that the most subtle and the first element namely ether or absolute space or *ākāśa* has only one guna or property, which is sound or *śabda*. The rest of the elements accumulate the previous properties with the most gross element namely earth or prithvi which has all the five properties which correspond to the five

senses. The *ākāśa* having *śabda* (sound) as its only property is also referred in several literature (Anand R 1979)**.** The *ākāśa śabda* is relationship is given by ' *Śabdaikaguńamākāśam*'.

Thus, the statements refered above traces the evolution of the great elemental powers which have brought forth the external as well as the internal universes, that is the world that is outside man as well as the one that is within him (Subhash Kak 1999). The world outside is referred from cosmological point of view, however, so far as the inner world is concerned, as per yoga, their evolution takes place in the *chakras* which are strung in the sushumna, hence the saying that the chakras are abode of the elemental powers. The chakras namely *Mūlādhāra, Swādhiśtāna, Mańipura, Anāhata and Viśuddhi* correspond to abodes of five elemental powers earth, Water, Fire, Air and Space respectively. It is noted that in human body the location of the *chakras* correspond to, the coccygeal triangle at the termination of spinal cord (*Mūlādhāra*), the source of genitals (*Swādhiśtāna*), region of umbilicus (*Mańipura*), cardiac region (*Anāhata*), and the cavity of the throat (*Viśuddhi*)(Chamu SV 1982)**.**

The yoga maintains that if the mind could reach these chakras and pass from one to the other until it reaches the *Āgnā* chakra, then the reverse process of involution will take place leading to the realization of *Ātman*. This yoga based implications of elemental powers is only provided as an indication of the wealth of spiritual knowledge both practical abd theoritical, which needs to be acquired by a serious spiritual aspirant under a genuine yogi as *Sadguru* (Sriranga Sadguru 1991).

2.4.2.3 Concept of involution by Mantra Yoga

It is said that the union of the Word-Principle and *prāńa* that produces speech. Hence, is speech the function of *prāńa* or is *prāńa* the essence of speech? When one is in the process of articulating, moving from within outward, the speech is a function of *prāńa* a process of evolution of consciousness, but when one is using the *Mantra* to take speech to its origin, one is moving from coarser to finer, from body to essence a process of involution of consciousness or yoga. Then *prāńa* may very well be called the flavorful essence of speech, which is the "husk". The same applies to the relationship between mind and speech. The process of yoga involves transcending the *sthūla śarīra, sūkshma śarīra (panchatanmātrās, panchamahābhūtas, prāńa), kārańa śarīra (Manas, Buddhi, Chitta and Ahankāra), guńas* and finally *Mahat* to be one with pure consciousness (Subhash Kak 1999). It is said that pure Consciousness will dawn on whosoever has mastered the pathways for returning articulate diversified speech to its deeper origins in the Word-principle. This is the purpose of the practice of *japa*, mental recitation of *Mantra*. The same principle is much more elaborately explained by the philosophers postulating the fourfold unfoldment of speech. The four states of the progression from the Word Principle to articulate speech are called:

Parā – The supreme one

Pashyanti – The seeing one

Madhyama – The middle one

Vaikhiri – The articulated utterance.

To summarize the philosophy,

Parā: The transcendental Word-Principle in God (*Brahman, parameshvara, parama - shiva* etc.)

Briefly, *parā* is the knowledge as it exists within the ultimate consciousness of God. It represents the unity of all powers of will, knowledge and action. The phenomena, the objects, the names and the sounds of those names have not yet appeared in any diffusion of multiplicity, but dwell in the singularity of a great coalescence. In a yogi *parā* dwells in the thousand petal lotus (The *sahasrāra chakra* or the 7th *chakra*).

Pashyanti: This power becomes the *kundalini* in individuated beings. She descends to the *mūlādhāra* and *svādiśtāna chakras*. The individual being experiences a presence of energy which vibrates between the lowest and the highest centers. The divine consciousness has become individuated. In other words, the divine knowledge is being infused into the *jiva*, the spirit of individual life and consciousness. At this stage the *Mantras* are a pure vibration without yet a distinction into syllables. Of the three powers of God, will, knowledge and action which dwell undifferentiated in *parā, pashyanti* is called a seer, as God sees all knowledge inward. Without reaching here, an ordinary mortal does not become a seer.

Jnāna Śakti: The power of knowledge, crystallized in this seeing state, then brings into focus the will, *Icchā śakti*, to distinguish the phenomena that are lying within it. *Nāda*, the universal sound, is then heard in the heart center. It becomes, first, the sound of *Om*. As the diffusion of transcendental light and sound continues to occur the strings of *kundalini* produce an inner music. It is thus that all music began. This brings us to the next stage.

Madhyama: At this stage the Word-Principle becomes a state of intellect and mentation. The *kundalini* awakens the mind, and sends into it the vibrations from the various centers of consciousness. The differentiated syllables become the units of thought. Each syllable of the *Mantra* bears within it a ray of consciousness, a certain power, which becomes a particular psychic aspect. The knowledge revealed to the soul has been infused into the mind. At this point

the yogi experiences a stirring within himself. The *sphota*, the explosion, the bursting forth of the Word – principle, from divine to spiritual and from spiritual to mental plane, awakens the *prāńa.* The *Mantras* at this stage of experience cause a surge of the *prāńa* – wave which must then impel the airs of breath within the body to serve as vehicles between mind and *prāńa* on one hand and the sense of articulation on the other.

***Vaikhiri*:** Impelled by mind and *prāńa*, the airs divided into the areas of heart, throat, palate, etc., become the spoken word. Silence is now broken (Pandit Usharbudh Arya 1985).

To summarize, in *pashyanti*, as divine knowledge is being transfused into the individual spirit, the knowledge of the phenomena and the distinctive syllabic sounds exist like fruits in a seed.

In *madhyama*, the manifestation is diversified like many nuts in a single pod, the syllabic knowledge now remains in the mind and has become sequential. Intuitive wisdom now gives way to rationality. The *Mantras* are mental vibrations, and gradually become thoughts through their resonance, affecting *prāńa.*

In *vaikhiri*, the fruits, branches and twigs of language and words are all seen separately and one has to search for some semblance of unity behind them.

A seeker does not easily become a seer. He must traverse the path that the Word – Principle has taken to become an oral utterance. He must take the uttered *Mantra* and go upstream along the river *Saraswati*, the river of speech, the goddess of wisdom. As the *Mantra* is refined the seeker goes from *Vaikhari* to *Madhyama*, then to *Pashyanti*, where the silence is indivisible. At this point, the *Mantra* ceases to be a composition of words and syllables. *Madhyama* begins to merge into *Pashyanti*. In other words, the highest *Mantra 'Om'* comes as close as possible to the Word-Principle in God's Consciousness, representing all His powers, all the rays of consciousness. It is in this form that seed of all sounds exists in the depth of human intelligence.

It is only when the intelligence is pulled outwards, downwards, and into the realm of the senses of articulation that it emits nouns and verbs and, as the philosophers of *Tantra* claim, the mantras specific to the rays of consciousness.

Both the sound (*Nāda*) and the Word-Principle (*Śabda – Brahman*) exist originally in consciousness as one universal undivided point. Only in association with the realm of phenomena does it become "many" and divide into numerous sounds and words. According to *Vedānta* philosophy, the Word-Principle is *Nitya*, eternal.

Table no.1 Different States of Consciousness

States of Consciousness	Description	Word Principle	Representative state
PARĀ Supreme Om	Universal Consciousness with its seat in Sahasrāra Chakra	Knowledge as it exists within the ultimate consciousness of God – word principle	Bindu/Brahman
PASHYANTI Seeing One	Individuated Consciousness manifestation of Kundalini at Mūlādhāra and Swādhiśtāna Chakras. Mantras here are pure undifferentiated vibrations only activating various chakras Realization of this state makes one a Seer	Mantras are pure vibrations without distinction into syllables	Seer

MADHYAMA The Middle One	State of intellect and mentation Kundalini awakens mind Differentiated syllables become units of thought Knowledge revealed to soul is infused into mind The sphota of word principle awakens prāńa	Mantras are distinguished into syllables and agitate prāńa	Nāda and laya
VAIKHIRI	Impelled by mind and prāńa. The airs get redistributed in different areas of body to produce the sound / speech	Mantras are distinct sounds produced by articulation	Sound vibrations and Prāńa

According to *Pānini'*s grammar,

सिद्धे शब्दार्थ सम्बन्धे

Siddhe śabdārtha sambandhe

The words, their significance and the relationship between the two are eternal.

One such *Mantra* that has been known to reduce fear of death is the *Mahāmrutyunjaya Mantra* that forms the basis of Mind Sound Resonance technique (Satyaprakash Dube 2004).

2.4.3 Present concept of a specific technique i.e., Mind Sound Resonance Technique

Mantras are mental vibrations and become thoughts through their resonance. Saying any word produces an actual physical vibration. Over time, if we know what the effect of that vibration is, then the word may come to have meaning associated with the effect of saying that vibration or word. This is one level of energy basis for words. Another level is intent. If the actual physical vibration is coupled with a mental intention, the vibration then contains an additional mental component which influences the result of saying it. The sound or resonance is the carrier wave and the intent is overlaid upon the wave form, just as a colored gel influences the appearance and effect of a white light. In either instance, the word is based upon energy. But not all transcendental vibrations are actually called *Mantras* and not just any sound vibration will bring success. *Mantras* are syllables that produce specific resonance and vibrations with a specific spiritual intent and modulate the flow of *prāńa* thereby restraining the mind and senses from their sense objects and indrawing them into subtler aspects of their conscious states. By making use of these resonances one can move to subtler layers of consciousness stilling the manifestation of the consciousness until one attains self realization or bliss. This is facilitated by activation of *kundalini* and union of *madhyama* states with *pashyanti* as described earlier.

In *Mantra-yoga*, Brahman is known as *Bindu* which possesses a force or *Shakti* called *Bīja*; of the union of *Bindu* and *Bīja* or *śiva* and ś*akti* is born *Nāda* which is otherwise known as Logos *or Śabdabramha or Prańava*. A regular current of sound is incessantly rising from the *Mūlādhāra* upward and that sound emanates externally from the very centre of the Universe. The soul attached to an external life is subject to the working of the senses and is constantly running after sense objects, hence is utterly oblivious of this external ever working sound. When however by the strenuous *Sādhana* the outward movement of the senses is checked and the vital forces are brought to a standstill, the *Sādhaka* becomes competent to hear the internal sound.

The central ideal involved in the working of the *Mantras* is that certain sounds when uttered produce a disturbance in the *ākāśa* which is, in its turn, communicated according to severity of such a disturbance to the higher planes. It is reasonable to suppose that the greater the disturbance, the greater will be communication to the higher planes. The nature of the disturbance cannot be judged from the known laws of physics. All that we can say is that there exists some relationship between sounds and disturbance in the *ākāśa.* These sounds are known as *Bījākśaras*. There are various ways of interpreting a *Mantra* composed of various *Bījākśaras*. These *Bījākśaras* are not devoid of force since they are presided over by the *Devatās* which represent an aggregate of forces. One should clearly understand what particular force is intended to be invoked in a given *Mantra*.

In *Mantra-yoga* the repetition of God's name, *Om* or *Soham* is essential. The repetition with intense feeling brings in its wake absorption in the name itself. The effects of this absorption become visible in what is known as *Aśta sātwika*. When a person begins to repeat God's name and his repetition amounts to absorption, tears flow from his eyes, the body trembles and his breath becomes slow. When the mind is thus absorbed in God, his throat is choked with excess of joy, his hairs stand on end, his eyelids become half closed and his look becomes stationary. With the exultation resulting from these, he begins to sing songs of God's praise. Finally his mind is merged in *Samādhi*.

According to *Mantra-śāstra* all the *Bījās* originate from *Parā-vāni* which resides in the *Mūlādhāra*. The force latent in *Parā-vāni* which is sometimes known as *Kundalini* becomes manifest in the form of sounds which comprise the 50 letters of the Sanskrit analphabet. The first of all sounds that is heard is *Prańava* which represents the completeness of sound. It is held to be universal since it comes to mean *Prāńa* on this physical plane. Being thus the first of all sounds every sound or *Mantra* is considered to be its manifestation.

Mind Sound Resonance Technique was formulated based on a powerful *Mantra* called *Mahāmrutyunjaya Mantra* that helps one to realize their true state of being and at the same time removes fear of death. This has been devised mainly to remove fear and ignorance that are major obstacles in the spiritual pursuits. The vibrations and the meaning of this *Mantra* is known to pervade through all the *kośas* harmonizing their balance and functioning by Channelising the flow of *prāńa* at all levels, Sublimating emotions and inducing silence at *Manomaya kośas.* Stimulating Intellect and discriminatory power at the intellectual level and finally dwelling upon the existential states of silence and bliss at the *Ānandamaya kośa* level. This is facilitated through resonating vibrations that agitate the *prāńa* flow at various *chakras* and change the perceptible intellect that helps sublimate emotions and still the mind facilitating the inward journey to realize the state of happiness and bliss.

2.4.3.1 Mahā Mrityunjaya Mantra

ॐ त्र्यम्बकं यजामहे सुगन्धिं पुष्टिवर्धनम्।

om tryambakaṁ yajāmahe sugandhiṁ puṣṭivardhanam।

उर्वारुकमिव बन्धनात् मृत्योर्मुक्षीय मामृतात्॥

urvārukamiva bandhanāt mṛtyormukṣīya māmṛutāt।।

ॐ शान्तिः शान्तिः शान्तिः

om śāntiḥ śāntiḥ śāntiḥ ।

॥ तै । उप । चतुर्थ प्रश्न आन्ध्र पाठ । ७४ - मन्त्र ।

tai। upa। caturtha praśna āndhra pāṭha। 74 - mantra।

"*OM*. We worship and adore you, O three-eyed one, O Shiva. You are sweet gladness, the fragrance of life, which nourishes us, restores our health, and causes us to thrive. As, in due time, the stem of the cucumber weakens, and the gourd is freed from the vine, so free us from attachment and death, and do not withhold immortality."

Literal rendering:

three-eyed one / we praise / the fragrant / the beneficent

from attachment / even as the gourd from its stem / from death / liberate / not from immortality

Grammatical analysis:

tri-ambaka-m "the three-eyed-one" (accusative)

yajā-mahe "we praise" (1st pl. middle)

sugandhi-m "the fragrant" (acc.)

pusti-vardhana-m "the prosperity-increaser" (acc.)

urvāruka-m "disease, attachment, obstacles in life, and resulting depression" (acc.)

iva "-like"

bandhanāt "from attachment Stem (of the gourd); but more generally, unhealthy attachment" ("from the stem", ablative)

mrtyor "from death" (ablative)

mukśīya "may you liberate"

mā "not"

amrtāt from immortality (ablative)

There is a parallel formation *mrityor mārutam gamayeti/gamaya iti* "thus lead me from death to immortality" in the *Brhadāranyaka Upanishad* (*asato mā sad gamayā*) with *amritā* (immortality) in the accusative; having *amritāt* as ablative rather than accusative forces the interpretation of ma as "not" (and not "me")

The *Bīja Mantra* is given by *Kahola Rishi*; The *Mantra* is in *Gāyatrī chandas.* The *Mantra devata* (deity) is *Sri Mrityunjaya* (form of Shiva). This *Mantra* is to be used for meditation and at all times for protection from all evils.

This *Mantra* is addressed to Lord Shiva and is taught in the *Rig Veda* (7 *mandala* 59 Chapter) as well as the *Yajur Veda* (3-60) showing that it is a *Śruti* having been received by *Maharishi Vasishta*, the Kula Guru of *Bhagavan Sri Rāmachandra*.

Śukracharya said "The first *pāda* is and means - we worship or sing the praise of Lord *Tryambaka*. *Tryambaka* is the name of Lord Shiva as the father of the three worlds - *bhu, bhuva* and *svarga lokas*. He is the father and lord of the three *mandala's - Surya, Soma* and *Agni mandala*. He is *Maheśwara*, the lord of the three *Guna's - Satva, Rajas and Tamas*. He is the *Sadāshiva*, the teacher of the three *tatvas - Ātma tatva, Vidya tatva* and *Shiva tatva*. He is the father (cause and source) of the three energies (*agni*) - *Āvāhanīya, Grhapatya and Dakshināgni*.

He is the father of all physical creation through the three *mūrti bhūta - Prithvi* (solid), *Jala* (liquid) and *Tejas or agni* (energy). He is the lord of the three heavens created by the dominance of the three *Guńās - Rajas (Brahma), Satva (Vishnu)* and *Tamas (Shiva).* Know Him to be the *Nirākāra* (formless) *Sadāśiva* as He is above this physical mode and is their *Maheśwara*. This is the first foot of the *Mantra* (composed of eight syllables)."

"The second *pāda* of the *Mantra*," continued *Śukrāchārya*, "is *Sugandhim* refers to the fragrance of the flower that spreads in all directions, and in a similar way Shiva is present in the entire creation, both animate and inanimate. In all the *bhutas* (modes of existence), in the three *Guńas* (nature of creation as being *Satva, Rajas or Tamas*), in the ten *indriyas* (five *gnāna-indriyas* or senses and five *karma-indriyas* or organs of action), in all the *devas* (33 *devas* are the source of all illumination and enlightenment) and the *gańas* (hosts of demi-gods), Shiva exists and pervades as the illumine *Ātma* (soul) and is their essence. *Puśtivardhanam* is now being explained. That inward dwelling spirit (*Ātman*), the *Puruśa Śiva* is the real sustainer of *Prakriti* (and not vice-versa as all people perceive). Starting with the *mahātatva* (primordial state of matter/energy) to the individual parts of creation, the entire sustenance of the physically created beings (both animate and inanimate) is done by the imperishable *Purusha*. *You, I, Brahma, Vishnu*, the *Munis* and even *Indra* & *Devas* are maintained/sustained (by the *Ātma* and that is Him). Since the *Purusha* (*Ātma - Śiva*) is the granter of sustenance to *prakriti* (body/nature), he is '*Puśti - vardhana*'."

Having explained the first two *pāda* of the *Mantra*, *Śukrāchārya* continued to explain the remaining two *pāda*. He said " the next two *pāda* (consisting of sixteen syllables) is meaning - *Prabhu*! Just as the ripe cucumber is severed from the bondage of the creeper, in the same manner may we be delivered from death for the sake of immortality (*Moksha*).*Rudra deva* is like *amrita* (nectar of immortality). Those who worship Him with good *karma*, penance and

repentance, meditation, contemplation, prayer or praise, will surely renewed life and vigor. The strength of truth force (in this *Mantra*) is such that Lord Shiva shall definitely free the worshipper from the bondage of death because Shiva alone is the giver of bondage and *moksha*.

This is the *Mritasanjīvini Mantra* and has the power to give back life and rescue from death and great evils.

TRYAMBAKAM refers to the 'Three eyes' of Lord Shiva. '*Trya*' means 'Three' and '*Ambakam*' means eyes. These three eyes or sources of enlightenment are the *Trimūrti* or three primary deities, namely *Brahma, Vishnu* and *Shiva* and the three '*AMBA*' (also meaning Mother or *Śakti*' *are Saraswati, Lakshmi* and *Gouri*. Thus in this word, we are referring to God as Omniscient (*Brahma*), Omnipresent (*Vishnu*) and Omnipotent (*Shiva*). This is the wisdom of *Brihaspati* and is referred to as *Sri Duttatreya* having three heads of *Brahma, Vishnu* and *Shiva*.

YAJĀMAHE means, "We sing Thy praise".

SUGANDHIM refers to His fragrance (of knowledge, presence and strength i.e. three aspects) as being the best and always spreading around. Fragrance refers to the joy that we get on knowing, seeing or feeling His virtuous deeds.

PUŚTIVARDHANAM: *Pūshan* refers to Him as the sustainer of this world and in this manner. He is the Father (Pater) of all. *Pūshan* is also the inner impeller of all knowledge and is thus *Savitur* or the Sun and also symbolizes Brahma the Omniscient Creator. In this manner He is also the Father (Genitor) of all.

URVĀRUKAMIVA: '*urvā*' means "*vishāl*" or big and powerful or deadly. '*ārukam*' means 'Disease'. Thus *Urvāruka* means deadly and overpowering diseases. (The *Cucumber* interpretation given in various places is also correct for the word *Urvārukam*). The diseases are also of three kinds caused by the influence (in the negative) of the three *Gunā's* and are

ignorance (*Avidyā* etc), falsehood (*Asat* etc as even though Vishnu is everywhere, we fail to perceive Him and are guided by our sight and other senses) and weaknesses (*Shadripu* etc. a constraint of this physical body and Shiva is all powerful).

BANDHANĀT means bound down. Thus read with *urvārukamiva*, it means 'I am bound down by deadly and overpowering diseases'.

MRITYORMUKŚĪYA means to deliver us from death (both premature death in this Physical world and from the never ending cycle of deaths due to re-birth) for the sake of *Moksha* (*Nirvāńa* or final emancipation from re-birth).

MĀMRITĀT means 'please give me some *Amritam* (life rejuvenating nectar). Read with the previous word, it means that we are praying for some *'Amrit'* to get out of the death inflicting diseases as well as the cycle of re-birth.

2.4.3.2 How to chant the Mantra

According to *Agnipurāńa* :

उच्चैर्जपाद्विशिष्टः स्यादुपांशुर्दशभिर्गुणैः ।

जिह्वाजपे शतगुणः सहस्रो मानसः स्मृतः ॥ अ ।पु । २९३ । २८

uccairjapādviśiṣṭaḥ syādupāṁśurdaśabhirguṇaiḥ।

jihvājape śataguṇaḥ sahasro mānasaḥ smṛtaḥ।। apu। 293। 28

Loud chanting of *Mantras* (*Āhata*) is ten times better than to that of chanting in mind. Moderate way of chanting is hundred times better while chanting in mind (*Anāhata*) is thousand times better and the best amongst all other ways of chanting (Sunitha Saini 2004).

Mind Sound Resonance Technique involves chanting of *"A", "U", "M",* and "*Om*" as *Bīja Mantras* and *Mahāmrutyunjaya Mantra* in both *āhata* and *anāhata* phase. The resonating vibrations thus intercept between these two phases helps calm down both the subtler and gross planes of consciousness and helps the *Sādhaka* to still or correct the agitations in the mind and *Prāńa* flows. Speech thus acts as a bridge between *Prāńa* and mind and between mind and intellect thereby by stilling the mind and altering ones perception and helping him to ascend in the path of spirituality and bliss.

(iv) Define and present concept of a specific technique i.e., Mind Sound Resonance Technique.

2.4.3.3 Procedure of MSRT.

Briefly the steps involved in MSRT are elucidated below

1. Prayer

ॐ त्र्यम्बकं यजामहे सुगन्धिं पुष्टिवर्धनम् ।

उर्वारुकमिव बन्धनात् मृत्योर्मुक्षीय मामृतात् ॥

ॐ शान्तिः शान्तिः शान्तिः

om tryambakaṁ yajāmahe sugandhiṁ puṣṭivardhanam।

urvārukamiva bandhanāt mṛutyormukṣīya māmṛutāt||

om śāntiḥ śāntiḥ śāntiḥ

2.a) Loud chanting of A,U,M and AUM (3 rounds). Feel complete body resonance.

b) *Āhata – Anāhata* of A,U,M and AUM next time A-,U-,M –AUM (3 Rounds). Feel the resonance even with *anāhata* (mental) phase.

3. a) Loud chanting of Mrtyunjaya Mantra (MM)

om Trayambakaṁ yajāmahe sugandhiṁ puṣṭivardhanam

urvārukamiva bandhanāt mṛutyormukṣīya māmṛutāt

Om śāntiḥ śāntiḥ śāntiḥ (3 rounds)

Feel the pattern of resonant waves through out the body.

b) Āhata – Anāhata of Mrtyunjaya Mantra MM-,MM-,MM-(3 rounds)

Feel the pattern of resonance waves even with Anāhata phase.

4. Anāhata AUM (9 rounds)

Repeat AUM in the mind-feeling the resonant waves through out the body.

5. Ajapājapa AUM to SILENCE (9 rounds).

Feel the resonant waves of OM coming up and spreading throughout the body

and diffusing into silence (9 rounds).

6. Stay in SILENCE.

7. **RESOLVE**

8. **Closing Prayer**

सर्वे भवन्तु सुखिनः सर्वे सन्तु निरामयाः

सर्वे भद्राणि पश्यन्तु मा कश्चित् दुःखभाग्भवेत्॥

ॐ शान्तिः शान्तिः शान्तिः

sarve bhavantu sukhinaḥ sarve santu nirāmayāḥ

sarve bhadrāṇi paśyantu mā kaścit duḥkhabhāgbhavet||

om śāntiḥ śāntiḥ śāntiḥ

2.4.4 Pre-requisites and uses of Mantras

2.4.4.1 Rules to be followed by the person who is going to chant mantras:

A *sādhaka* who is interested in learning mantras should follow the following discipline as mentioned below:

मन्त्र शक्ति प्रशंसा

देवब्रह्मर्षिभिः प्रोक्ता मन्त्राः सत्यतपोमयाः।

भवन्ति नान्यथा क्षिप्रं विषं हन्युः सुदुस्तरम् ॥

विषं तेजोमयैर्मन्त्रैः सत्यब्रह्मतपोमयैः ।

यथा निवार्यते क्षिप्रं प्रयुक्तैर्न तथौषधैः ॥ सु ।क ।५ ।१०-१५

Mantraśakti praśaṁsā

devabrahmarṣibhiḥ proktā mantrāḥ satyatapomayāḥ।

bhavanti nānyathā kṣipraṁ viṣaṁ hanyuḥ sudustaram।।

viṣaṁ tejomayairmantraiḥ satyabrahmatapomayaiḥ।

yathā nivāryate kṣipraṁ prayuktairna tathauṣadhaiḥ।। su.ka।5।10-15

A man, while learning the *Mantras*, should forego sexual intercourse, animal diet, wine, honey etc., should take little diet, be self controlled and clean in body and spirit and (before learning ,*Mantras*), shall lie on the mattress of *kuśa* grass. For the successful application of his newly acquired knowledge, (*Mantras*), he shall devotedly worship the gods with offerings of perfumes, garlands of flowers, edibles, (animal) oblations etc., and with the appropriate *Mantras* sacred to them as well as with burnt offerings, since a *Mantra* chanted in an unclean spirit or body or accented or uttered incorrectly will not produce any effect. The medicinal compounds of anti-venomous drugs should also be employed in such cases (Kaviraja Ambikadutta Shastri 1998).

2.4.4.2 Uses of Mantras in treatment and medicine

Mantras have been used since time immemorial for management of various diseases. This section describes scriptural references for use of *Mantras* (Kaviraja Ambikadutta Shastri 1998; Sharma Bhagwan Dash RK 2000).

2.4.4.2.1 Mantras were used to protect king

पन्थानमुदकं छायां भक्तं यवसमिन्धनम्।

दूषयन्त्यरयस्तच्च जानीयाच्छोधयेत्तथा।

तस्य लिङ्गं चिकित्सा च कल्पस्थाने प्रवक्ष्यते॥ सु। सू ।३४।५-६

panthānamudakaṁ chāyāṁ bhaktaṁ yavasamindhanam।

dūṣayantyarayastacca jānīyācchodhayettathā।

tasya liṅgaṁ cikitsā ca kalpasthāne pravakṣyate।। su।sū।34।5-6

Physicians conversant with the curative virtues of drugs and minerals and priests well versed in *Vedic Mantras*, should jointly protect the king from death, whether due to idiopathic (*doshaja*) or extrinsic causes (Kaviraja Ambikadutta Shastri 1998).

2.4.4.2.2 Mantras in Psychological Disorder

बलिभिर्मङ्गलैर्होमैरोषध्यगदधारणैः।

सत्याचारतपोज्ञानप्रदाननियमव्रतैः॥

देवगोब्राह्मणानां च गुरूणां पूजनेन च ।

आगन्तुः प्रशमं याति सिद्धैर्मन्त्रौषधैस्तथा ॥ च । चि ।९।९३-९४

balibhirmaṅgalairhomairoṣadhyagadadhāraṇaiḥ ।

satyācāratapojñānapradānaniyamavrataiḥ।।

devagobrāhmaṇānāṁ ca gurūṇāṁ pūjanena ca।

āgantuḥ praśamaṁ yāti siddhairmantrauṣadhaistathā।। ca। ci।9।92-94

Daivavyapāshraya chikitsā: Exogenous type of *unmāda* gets cured by *bali* (sacrifices), *mangala* (recitation of auspicious mantras) *homa* (offering oblations to the fire), wearing talismans containing antitoxic herbs, observing truthfulness, maintenance of good conduct, practice of penance, charity, observance of scriptural rules and religious vows, offering prayer to the gods, cows, Brahmins and preceptors, and by application of perfected *Mantras* and medicines (Sharma Bhagwan Dash RK 2000).

2.4.4.2.3 Mantra in treatment of Cancer

Cancer was known to *Āyurvedic* physicians and named it as *arbuda* and *Mantra* was used to treat *arbuda*. Use of *Mantras* in treating exogenous swelling:

ते पुनर्यथास्वं हेतुव्यञ्जनैरादावुपलभ्यन्ते

निजव्यञ्जनैकदेशविपरीतैःबन्धमन्त्रागदप्रलेपप्रतापनिर्वापणादिभिश्चोपक्रमैरुपक्रम्यमा

णाः प्रशान्तिमापद्यन्ते ॥ च ।सू ।१८ ।५

te punaryathāsvaṁ hetuvyañjanairādāvupalabhyante nijavyañjanaikadeśaviparītaiḥ bandhamantrāgadapralepapratāpanirvāpaṇādibhiścopakramairupakramyamāṇāḥ praśāntimāpadyante ।। ca। sū ।18 ।5

The exogenous swelling starts with pain and then vitiates the *dośas*. Such swellings are cured when treated with therapies such as bandages including *Mantras*, administration of medicines, and application of ointment, fomentation and cold sponging (Sharma Bhagwan Dash RK 2000).

2.4.4.2.4 Mantra for Fear (of poison)

दुरन्धकारे विद्धस्य केनचिद्विषशङ्कया ।

विषोद्वेगाज्ज्वरश्छर्दिर्मूर्च्छा दाहोऽपि वा भवेत् ॥

ग्लानिर्मोहोऽतिसारश्चाप्येतच्छङ्काविषं मतम् ॥च । चि । २३ ।२२२

durandhakāre viddhasya kenacidviṣaśaṅkayā ।

viṣodvegājjvaraśchardirmūrcchā dāho'pi vā bhavet||

glānirmoho'tisāraścāpyetacchaṅkāviṣaṁ matam|| ca| ci| 23|222

Mantra is used as a treatment for *śanka viśa* (fear poison). When a person is bitten by something (non-poisonous creature) in pitch darkness, the fear of suspicion (*śanka*) of being bitten by a poisonous creature causes manifestation of symptoms of pseudo poison in the form of fever, vomiting, fainting, burning sensation, prostration, unconsciousness and diarrhea. This condition is called as *śanka viśa* (Sharma Bhagwan Dash RK 2000).

2.4.4.2.5 Mantra foremost treatment for poison

मन्त्रारिश्टो उत्कर्तननिष्पिडनाचूषण

अग्निपरिषेकः अवगाह रक्तमोक्षण वमन विरेचकोपऽधानानि

ह्रिदयावर्णाञ्जननस्यधूमलेहौषध प्रशमनानि

प्रतिसारणां प्रतिविषं संज्ञासंस्थापनं लेपः

मृतसंजीवनमेव च विंशतिरेति चतुबिराधिकः स्युपक्रमह् यथाये यत्र

च योज्यः श्रुणुतथातानु ॥ च । चि । २३ ।३६ ॥

mantrāriśṭo utkartananiṣpiḍanācūṣaṇa

agnipariṣekaḥ avagāha raktamokṣaṇa vamana virecakopa'dhānāni

hridayāvarṇāñjananasyadhūmalehauṣadha praśamanāni

pratisāraṇāṁ prativiṣaṁ sañjñāsaṁsthāpanaṁ lepaḥ

mṛrtasañjīvanameva ca viṁśatireti catubirādhikaḥ syupakramah yathāye yatra

ca yojyaḥ śruṇutathātānu|| ca| ci| 23|36||

The whole treatment modalities of poisoning are segregated into 24 procedures. They are **Manthra, Arishta bandhanam, Utkartanam, Nishpeedanam, Aachushanam, Agni karma, Parasheka, Avagaha, Raktha mokshana, Vamana, Vireka, Upadhana, Hrudayavarana, Anjana, Nasya, Dhooma, Leha, Oushadha, Pradhamana, Prathisarana, Prativisha, Sajna samsthapana, Lepa and Mrutha snjeevana.**

The first principle is prevention of further exposure to the poison. The Ayurvedic classical procedures like Manthra, Arishta bandhana, Utkarthana, Nishpeedana, Achushana, Agnikarma, Parisheka, Avagaha and Rakthamokshana can be contemplated here. The second principle is Removal of Unabsorbed Poison and is more relevant in ingested poisons. Vamana and Virechana shall be included here. The third principle is Use of an Antidote. The procedure of Hrudayavaranam can be discussed here. Removal of the Absorbed Poison is the fourth principle and all other procedures shall be integrated in. But some of the pure procedures like Prathivisham, Sanjasamsthapana and Mruthasanjeevana are very special to Ayurveda.

हिलिमिलिसंस्पृष्टे रक्ष सर्वभेषजोत्तमे स्वाहा इति महागन्धहस्ती नामाऽगदः ॥

च । चि ।२३ ।९४

hilimilisaṁspṛuṣṭe rakṣa sarvabheṣajottame svāhā iti mahāgandhahastī nāmā'gadaḥ||

ca| ci|23|94

Mahā- gandha- hasti is the recipe which is an antidote of poisons. This recipe instantaneously cures the ailments caused by the rats, spiders. All types of snakes, and poisons from all types of roots and rhizomes. While triturating the ingredients of this recipe, the *Mantra* ' hilimilisamsprishte raksha sarva bheshajottame svaha' is chanted. ***HILMILI*** is the *Bīja Mantra* (seed) of this incantation (and its association may protect this recipe which is the best among the remedies) (Sharma Bhagwan Dash RK 2000).

2.4.5 Integrated approach of Yoga in Cancer: Towards a Conceptual Model

2.4.5.1 Use of mantras in integrated yoga program for Cancer

The diagnosis of cancer and its treatment causes severe psychological distress in cancer patients. Fear and anxiety associated with diagnosis of cancer, invasive treatment procedures, sexual dysfunction secondary to surgery and radiation and aversive reactions to chemotherapy are among the common treatment-related side effects observed in cancer patients. Clinical descriptions have noted cancer patient's fears of the treatment (e.g., being ''burned'' or ''equating radiotherapy with electric current'), causing sterility, sickness or vomiting and vast individual differences in their psychological reactions, which usually predisposes to anxiety. Earlier studies have shown that anxiety increases psychological distress and side effects following conventional treatment. Thus altered perception can be a root cause for exacerbation of symptoms in cancer patients. This has been attributed in part to subjects increased attentiveness to their somatic symptoms and development of aversive conditioned responses induced by anxiety. This leads to psychological morbidity that causes poorer treatment

outcome, poor treatment compliance, greater pain, longer hospital stays, more postoperative complications and immune suppression. Thus if ignorance and altered perception can exacerbate psychological and treatment related distress it can also sow seeds of discontentment, anxiety, negative affect and fear about the uncertain future leading to disease progression and abnormal neuro endocrine rhythms. This has been proved in numerous studies that have relied on cancer experience model to study psychoneuroendocrine and psychoneuroimmune aberrations. This is well described in the following verses:

परिणामतापसंस्कारदुःखैर्गुणवृत्तिविरोधाच्च दुःखमेव सर्वं विवेकिनः ॥प ।यो ।सू ॥

साधना पाद ।१५

pariṇāmatāpasaṁskāraduḥkhairguṇavṛttivirodhācca duḥkhameva sarvaṁ vivekinaḥ|pa|yo|sū|| sādhanā pāda|15

The affliction which is inherent in man is *tāpa* or anxiety. All pleasures are associated with anxiety, conscious or sub – conscious. Indulgence in pleasure or dependence for our happiness on attachment on the uncertain and passing things in the outer world owing to attachment, means fear that the money is lost and our security may be threatened. If we love people then there is a fear that those people may die or be taken away from us. It is that when the crisis comes that these fears emerge put our consciousness but they are always present in subconscious mind and secretly poison our life (Taimini IK 1986).

Table no.2: Psychological and Guńa manifestations in different stages of Cancer diagnosis and Treatment

	Diagnosis	Surgery	Radiotherapy	Chemotherapy	Survivor with recurrence/ Metastases
Cancer/ Treatment related side effects		Loss of breast Pain	Skin pigmentation Rashes	Nausea and vomiting, hair loss, infections, fatigue, pain and others	Pain and others depending on site of metastases
Psychological side effects	Denial	Lost of self esteem Image problems Pain Social isolation, loss of control	Fear	Fear, Image problems, helplessness, hopelessness Loss of control	Fear, helplessness, hopelessness Loss of control, Social isolation, low esteem
Psychological morbidity	Depression Anxiety	Depression Anxiety Perceived stress	Depression Anxiety Perceived stress	Depression Anxiety Perceived stress	Depression Anxiety Perceived stress
Guńas *	Rajas/ Tamas	Tamas/ Rajas	Tamas/ Rajas	Tamas/ Rajas	Tamas/ Rajas

* The first guńa is more predominant at this stage

2.4.5.2 Towards development of a model:

According to yoga philosophy psychological side effects such as anxiety, depression, nausea and vomiting, anticipatory symptoms fall under the category of *ādhija vyādhi*. Unlike other diseases neutropenia, anaemia, vomiting, gastritis due to chemotherapy, hair fall, and infections also fall predominantly under *anādhija vyādhi* though there is a little influence of the *Manomaya Kośa* imbalance (*ādhija*) in its causation (see fig). Thus wrong knowledge/perception coupled with fear of death or attachment could worsen the patient's psychological morbidity and disease progression. Since anticipatory and conditioned responses such as vomiting, pain and immune suppression are some of the commonest side effects observed in cancer patients. These can be only overcome if the altered perceptions to cancer diagnosis and treatment are removed. Numerous studies in the field of psychosocial oncology have demonstrated this very theory wherein coping with cancer by helplessness/ hopelessness vs fighting attitudes have very clearly brought to the fore the deleterious effects of coping negatively with cancer through decrease survival, increased stress arousal, immune suppression and faster disease progression. In yogic terms this means overcoming *Avidyā* and *Asmitā* with *Vairāgya* and *Abhyāsa*. *Vairāgya* should be established through right knowledge and perception and mental calmness brought about by sustained practice of *yoga*. *Mantra yoga* is one such powerful and easy practice that helps remove fear that binds us to this life and helps one to move to states of bliss with other yoga practices. Having fear in the background would never help anyone be relaxed or feel so with the yoga practices and it is here that a powerful *Mantra* such as *Mahāmrutyunjaya Mantra* plays an important role. Altering ones perception of death and dying and acceptance of the same will make all other symptoms and pains look trivial and help the subject move ahead transcending

conflicts at all the *kośas* and moving from a *tamas or rājasik* state to *sātvik* state of mind featured by bliss, happiness and positive affect.

This concept is well illustrated in the following verse:

शौचसंतोषतपः स्वाध्यायेश्वरप्रणिधानानि नियमाः ॥

प ।यो ।सू ॥ साधना पाद ।३२

śaucasantoṣatapaḥ svādhyāyeśvarapraṇidhānāni niyamāḥ||

pa|yo|sū|| sādhanā pāda|32

The purification of subtler vehicles which serve as expression of thoughts and emotions is difficult process. A pure mind thinks pure thoughts and feels pure emotions and it becomes difficult to entertain undesirable thoughts and emotions and the same way, it is difficult for an impure mind to entertain high and noble thoughts and emotions. The Hindu system of spiritual culture for the purification of subtler vehicles is the constant use of mantras and prayers. The purification through *mantras* is explained under *Niyama – shoucha* so that the agitation set in motion, day after day, gradually washes out, the entire undesirable element. **FEAR** as such can be considered as undesired element in cancer patients (Taimini IK 1986).

At an operations level *āsanās* remove obstacles in the flow of *prāńa* and slow down the mind at *Annamayakośa* level. *Prāńayama* helps channelise the *prāńa* through certain channels and chakras and instills mental calmness at *prāńamaya* and *manomayakośa* level. At *manomayakośa* level, Mind Sound Resonance Technique, Mind Imagery Relaxation Technique and Mastery of Emotions Technique helps calm down the mind. Physiological correlates of this

would be decrease in stress arousal and neuroendocrine hormones that is released in response to a stressful event. *Mahāmrutyunjaya Mantra* chanting leads to awakening of various chakras wherein vibrations of mantras help facilitate transcendence of consciousness to higher levels with higher levels of bliss. Finally understanding the philosophical basis of life and death by meditating on the meaning of *Mahāmrutyunjaya Mantra* helps remove fear of death and dying that is a major stressor for those with early or advanced breast cancers. This forms the operation at *Vignānamaya Kośa*. Along with this happiness analysis lays emphasis on present state of mind at *Ānandamaya Kośa* and assumes importance in facilitating a positive affect and reducing fear of dying leading to willful acceptance. At the *guńa* level the patients cease to transcend between states of *tamas* and *rajas* and move higher up to *satva* where mind is calm, quiescent and blissful (See Fig 1).

Table no. 3 Operational model for use of *Mantra* chanting in Cancer -

Cancer as *Ādhija Vyādhi- Cancer starts as imbalance at Manomayakosa. Corrections at all levels through incorporation of mantras*

levels of subtlities	***Annamaya kośa***	***Prāńamaya Kośa***	***Manomaya kośa***	***Vignānamaya Kośa***	***Ānandamaya Kośa***
Results of therapy			*Anxiety and Depression*	*Intellectual Clarity Acceptance of*	*Positive Affect Happiness*

	↓ Salivary Cortisol ↓ Stress arousal ↑ NK cell function	↓ RR ↓ Nausea ↑ Appetite	↓ Perceived Stress ↓ Negative Affect Sublimation of emotions	death/ pain etc	
operational details	***Annamaya kośa***	***Prāńamaya Kośa***	***Manomaya kośa***	***Vignānamaya Kośa***	***Ānandamaya Kośa***
Chanting mantras at all levels	*a. Bhojana mantra before eating* *b.Om during shavasana after Kriyas* *c.Synchronising Om chanting with movements during Sukshma vyayama & Asana*	*Aa,u,m,om during Pranayama and* *PET*	*a.* ***MSRT-mahamrityunjaya mantra,*** *b. MEMT- chant glories of lord and master* *c.MIRT* *Om chants during DRT*	*Maha vakyas for Shravana, Manana and Nidhidhyasana forHappiness Analysis*	*Anusandhana of 'Samatvam' as a mantra for blissful existence during activity or inactivity*

कर्मणः सुक्रुतस्याहुः सात्त्विकं निर्मलं फलम्।

रजसस्तु फलं दुःखमज्ञानम् तमसः फलम्॥

सत्त्वात्संजायते ज्ञानम्॥ श्री।भ।गी। १४। १६-१७

karmaṇaḥ sukrutasyāhuḥ sāttvikaṁ nirmalaṁ phalam|

rajasastu phalaṁ duḥkhamajñāanam tamasaḥ phalam||

sattvātsañjāyate jñānam|| śrī|bha|gī 14| 16 -17

When Rajas dominates it results in pain and tamas in ignorance. It is from satva that knowledge arises (Swami Tapasyananda 2005).

The goal of yoga is to understand the nature of the self and universal consciousness that encompasses it. Understating the fact that all of us go through cycles of birth and death bound by the laws of *karma* and *samskārās* and this body is just a perishable vehicle taking us in this journey. One needs to make use of this vehicle to escape the cycles of birth and death form the basic tenets of yoga and Indian philosophy. Understanding this doctrine would help cancer patients come out of the fears associated with cancer and death and would help change their attitude from fear to that of acceptance and bliss making living with cancer a not so distressing experience. To bring about this change one needs control the mind through a systematic process of yoga that helps restrain senses, sublimates emotions, calms mind, clarifies intellect, admonishes ego and transcends one to higher states of consciousness.

The methodology of yoga is to control and purify the subconscious (region of *vāsanās and samskārās*) with the help of conscious effort. Restlessness of body is to be overcome by slow and mindful practice of postures (ā*sanās*). Irregular breath, an indicator of mental restlessness, is to be made regular by smooth and rhythmic breathing (*prānāyāma*).The out going thoughts and improper tendencies of the mind must be substituted by cultivating of moral and ethical virtues. The fear and attachment to this life should be overcome by chanting the *Mahāmrutyunjaya Mantra*. Emotions have to be sublimated using the Mastering the emotions technique. Chanting *Mantras* also help in this process as they are also a form of *Bhakti Yoga*.

This is illustrated in the following verse

सततं कीर्तयन्तो मां यतन्तश्च द्रुढव्रताः ।

नमस्यन्तश्च मां नित्ययुक्ता उपासते ॥ श्री ।भ ।गी । ९ ।१४

satataṁ kīrtayanto māṁ yatantaśca druḍhavratāḥ|

namasyantaśca māṁ nityayuktā upāsate|| śrī|bha|gī 9|14

Glorifying Me always, strivin, firm in vows, prostrating before me, they worship me with devotion, ever steadfast. (Swami Tapasyananda 2005)**.**

Positive affect and blissful states have to be experienced using happiness analysis and relaxation techniques. By constant practice one move to deeper understanding of the concepts and moves to higher levels of bliss that would help ally fears and distress in cancer patients.

2.4.6 Scientific basis of Mantra chanting

A study conducted by Bernardi J et al., on Effect of rosary prayer and yoga mantras on autonomic cardiovascular rhythms included electrocardiogram, respiration and blood pressure using transcranial Dop-pler ultrasonography with a 2 MHz probe. The recordings were done during sponta-neous breathing (3 minute sequences) and controlled breathing (6 minute sequences) during free talking and during recitation of the Ave Maria in Latin, with one subject reciting the priest's part and another the response (no instruction was given as to time to be taken); and during six minutes of controlled breathing. Recordings were also obtained during repetition of a typical yoga *mantra* "om-mani-padme-om." Results of this study showed that both the Ave Maria and the yoga *mantra* had similar effects, slowing respiration to around 6/min and thus having a marked effect on synchronization and also increased variability in all cardiovascular rhythms.

The respiratory rate was 14.1 (4.8) per minute during spontaneous breathing which slowed down during free talking, and it slowed down further during the recitation of the Ave Maria and of the mantra, in both cases to close to the 6/min (10 s period). Free talking reduced the respiratory rate more irregularly. The breathing was markedly more regular during slow breathing, the Ave Maria, and the *mantra*, whereas it was less regular during free talking than during spontaneous breathing. Remark-ably, the regularity of breathing seen during recitation of the Ave Maria or of the mantra was similar to regu-larity during controlled breathing at 6/min, indicating that these methods could stabilize the respiratory rate as effectively as precisely timed control. The spectral peaks of respiration and of all cardio-vascular signals were synchronized during the Ave Maria and the *mantra* sequences, as they occurred at the same frequency. In addition, the spectral peak of respiration was narrower during the Ave Maria

sequence than during spontaneous breathing and free talking, again as a consequence of more regular breathing. This increased modulation in cardiovascular rhythms influenced the cardiovascular control mechanisms: the arterial baroreflex sensitivity increased on change from spontaneous breathing to controlled slow breathing at 6/min and from free talk-ing to the Ave Maria, or from free talking to the mantra.(Bernardi L, Sleight P et al. 2001)

Another study by Bormann J.E. et al., examined the Efficacy of Frequent *Mantram* Repetition on Stress, Quality of Life, and Spiritual Well-Being in out patient veterans. The 5 week intervention consisted of weekly 90 minute frequent mantra repetition program to a sample of veterans and to assess its efficacy on perceived stress, state and trait anxiety, state and trait anger, symptoms of posttraumatic stress disorder (PTSD), quality of life, and spiritual well-being. Results showed that mantram repetition significantly reduced symptoms of stress, anxiety and improved quality of life and spiritual well-being.(Bormann JE, Smith TL et al. 2005)

Another study by Bormann J.E. et al., examined the efficacy of a psycho-spiritual intervention of *mantram* repetition—a word or phrase with spiritual associations repeated silently throughout the day–on psychological distress (intrusive thoughts, stress, anxiety, anger, depression), quality of life enjoyment and satisfaction, and existential spiritual well-being in HIV-infected adults. Results over a period showed a significant improvement in reducing trait-anger and increasing spiritual faith and spiritual A total of 93 participants were randomly assigned to mantram (n = 46) or attention control group (n = 47).connectedness. Actual mantram practice measured by wrist counters was inversely associated with non-HIV related intrusive thoughts and positively associated with quality of life, total existential spiritual well-being, meaning/peace, and spiritual faith (Bormann JE, Gifford AL et al. 2006).

Another study by Wolf DB and Abell N examined the Effects of Meditation Techniques on Psychosocial Functioning.93 normal volunteers were randomly assigned to Maha *mantra* chanting group (n=31), placebo mantra chanting group (n=31) and control group (n=31). Outcome measures were assessed using Vedic Personality Inventory (VPI) measures the three gunas—sattva, rajas, and tamas, the Generalized Contentment Scale (GCS) measures the magnitude of nonpsychotic depression and the Index of Clinical Stress measures subjective aspect of stress in a generalized, unidimensional form. The treatment (*mantra* chanting) group was taught to chant the maha *mantra* ("hare krishna hare krishna krishna krishna hare hare/hare rama hare rama rama rama hare hare"), and the alternate *mantra* (placebo mantra chanting) group was taught to chant the alternate *mantra* ("sarva dasa sarva dasa dasa dasa sarva sarva/sarva jana sarva jana jana jana sarva sarva") which resembles a Sanskrit mantra but without meaning. Both the group participants were made to chant three rounds of 108 *mantras* per day for four weeks. Results indicated a significant decrease in stress, depression and tamas, significant improvement in satva in *mantra* chanting group compared to other groups (Wolf DB and Abell N 2003).

3. REVIEW OF SCIENTIFIC LITERATURE

3.1 Introduction and General overview of breast cancer

3.1.1 Breast Cancer Global Scenario, Demographics and region

Cancer of the breast in women is a major health burden worldwide. It is the most common cause of cancer among women in both high-resource and low-resource settings, and is responsible for over one million of the estimated 10 million neoplasm diagnosed worldwide

each year in both sexes(Ferlay J, Bray F et al. 2001). It is also the primary cause of cancer death among women globally, responsible for about 375,000 deaths in the year 2000(Ferlay J, Bray F et al. 2001). According to IARC Cancer database, Breast Cancer is increasing in endemic proportions in developed countries. United States of America has the highest prevalence and mortality ratio from Breast Cancer followed By China, India, Russia Germany, France, United Kingdom and Italy (WHO, IARC, 2001). It is the most common cancer in women, accounting for 16% of cancer-related deaths and ranking second only to lung cancer as a leading cause of cancer-related mortality (Landis S, Murry T et al. 1998).

Incidence rates and mortality rates increase dramatically with age (Garfinkel L 1995). Breast cancer incidence has a distinctive age-specific curve (Fig. 3). The rapid rate of increase before the menopause (ages 40–50) slows down after that, probably owing to diminishing levels of circulating estrogens (Henderson BE, Ross R et al. 1988).Women of higher socioeconomic status, married women, women living in urban versus rural areas have the highest rates. The prevalence is least in African countries. Table 3.1 clearly shows a trend for increase in prevalence of breast cancer in developed countries. Among the less developed nations India stands first in line, factors may be mainly attributed to life style change, western influence and urbanization.

As a consequence of changing exposures to reproductive and nutrition-related determinants over time, women are at increasingly high risk of breast cancer, with incidence rates increasing in most countries and regions of the world in the past few decades. The most rapid rises are seen in developing countries, where breast cancer risk has historically been low relative to industrialized countries. Increasing trends in developing areas are often considered the result of the ‘westernization’ of lifestyles, an ill-defined surrogate for changes in factors such as childbearing, dietary habits and exposure to exogenous estrogen, towards a distribution closer in profile to that of women in industrialized countries. The advancements in the treatment of

breast cancer has considerably increased the life span, and patients who eventually die are living longer between diagnosis and death enduring cancer symptoms and treatment side effects for a longer time(Sephton SE, Sapolsky RM et al. 2000). Patients with breast cancer normally receive multimodal treatment over a long period of time (Overgaard M, Hansen PS et al. 1997; Ragaz J, Jackson et al. 1997); therefore it is also necessary to take care of the related morbidity that accumulates over time. Most women with breast cancer usually undergo surgery and 4-6 months of chemotherapy followed by 6 weeks of radiotherapy. They then receive palliative radiation and chemotherapy if the cancer relapses or reoccurs. A cancer diagnosis and treatment is a particularly potent stressor that is associated with physiological changes, the fear of death, progression or recurrence of disease, treatment related distress, changes in QOL and social relationships, and an overall loss in sense of control (Redd WH, Silberfarb PM et al. 1991; Spiegel D 1997). Therefore supportive care strategies which help patients cope with their diagnosis and treatment and improve their functional quality of life are the need of the hour.

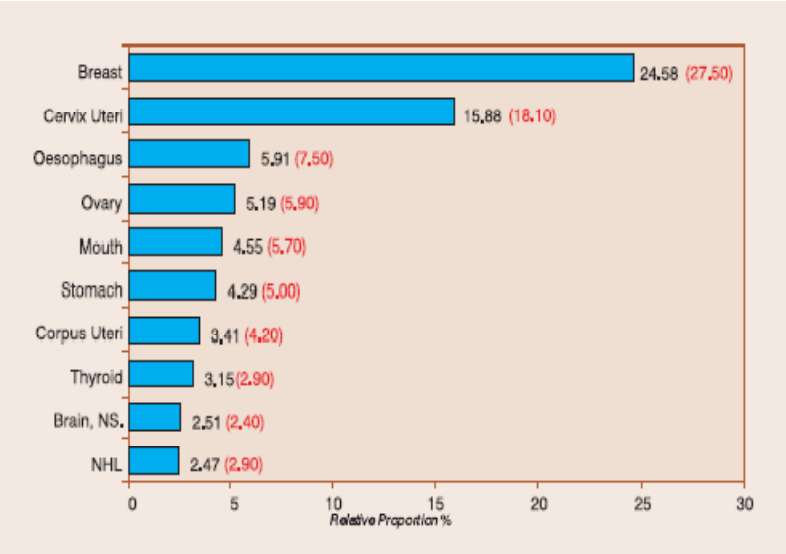
Table 3.1 EPIDEMIOLOGY - OF BREAST CANCER (GLOBOCAN 2000, Cancer incidence, prevalence and mortality worldwide, estimated values, IARC Press, 2001.)

	CASES (Prevalence)	ASR (W) (Age standardized rate)	CRUDE Prevalence	DEATHS	ASR (W) (Age standardized rate)	CRUDE death rate
World	1050346	34.94	35.66	372969	12.41	12.51
More developed countries	579285	94.93	63.22	189203	31.01	18.61
Less developed countries	471063	19.66	23.07	183768	7.67	9.12
Eastern Africa	13615	10.98	20.19	6119	4.93	9.18
Middle Africa	3902	8.07	13.46	1775	3.67	6.18
Northern Africa	18724	21.83	28.3	8388	9.78	12.83
Southern Africa	5537	23.21	31.78	2504	10.50	14.45
Western Africa	17389	15.60	24.82	7830	7.02	11.29
Caribbean	6210	32.40	33.78	2310	12.05	12.51

Central America	18663	27.42	36.20	5888	8.65	11.63
South America	69924	40.03	45.14	22735	13.02	14.77
Northern America	202044	128.71	90.41	51184	32.61	21.38
United States of America	183494	129.97	91.39	45553	32.27	21.22
Eastern Asia	142656	19.67	18.12	38826	5.35	4.90
China	106014	17.09	16.39	28787	4.64	4.51
South-Eastern Asia	55907	21.52	25.57	24961	9.61	11.50
South Central Asia	129620	17.89	22.20	62212	8.59	10.80
India	79124	16.13	19.10	40607	8.28	9.91
Western Asia	20155	21.96	27.87	8459	9.22	11.82
Eastern Europe	110975	68.63	49.43	43058	26.63	17.24
Northern Europe	54551	113.32	73.23	20992	43.61	24.58
Southern Europe	65284	88.50	56.23	25205	34.17	19.14
Western Europe	115308	123.28	78.22	40443	43.24	23.47
Australia/New Zealand	12748	111.19	82.71	3427	29.88	20.76
Melanesia	2102	107.35	82.58	704	35.91	25.94
Micronesia	62	23.73	37.51	28	10.73	17.19
Polynesia	127	41.55	55.15	58	18.66	24.92

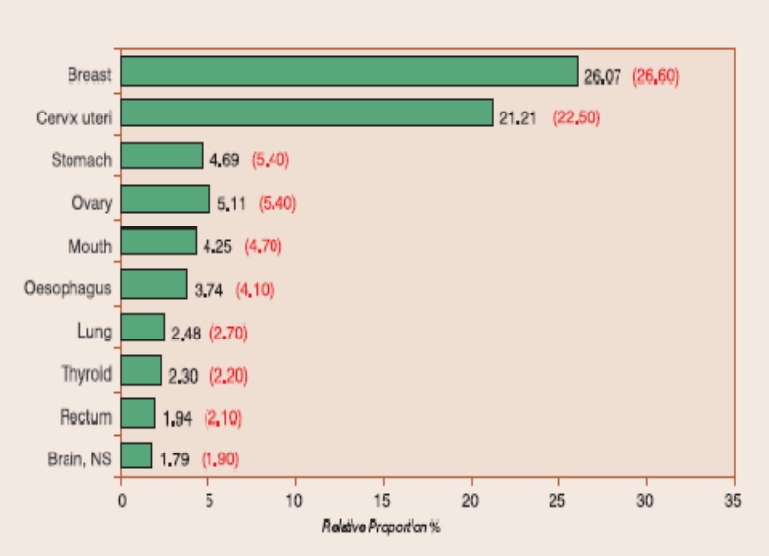
Note: Crude rate: A crude rate is the ratio of the number of people in which the event of interest happens in a specified time period to the size of the population who may experience this event during the same time period. There are no adjustments made when a crude rate is given. Age adjusted/standardized rate: A statistical method allowing comparisons of populations that takes into account age-distribution differences between populations. Most incidence and death data in SEER are age-adjusted, although some tables, in contrast, present the crude rate (#6). Age-adjusting takes the 2000 US population distribution and applies it to other time periods under consideration. This assures that such rates do not reflect any changes in the population age distribution.

Fig 2. Incidence rates of female cancers in Bombay, Delhi, Madras and Bangalore (2001-2003), National Cancer registry Program.

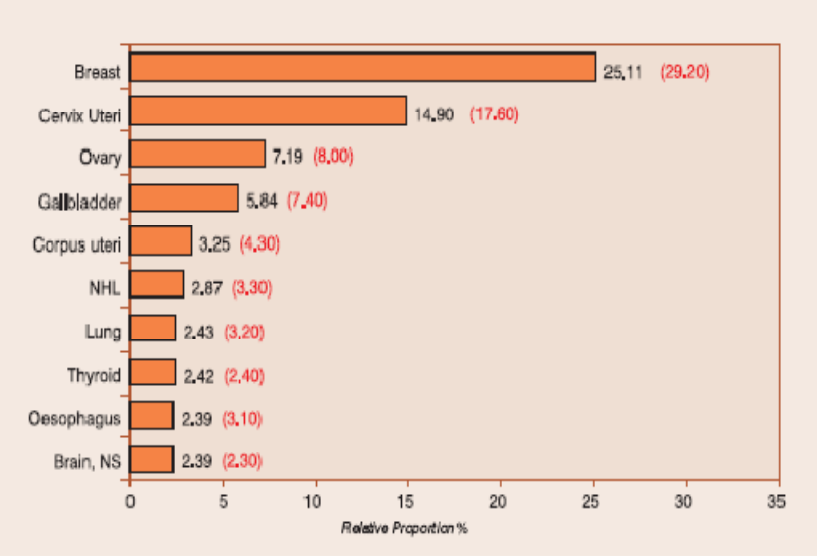


Ten Leading Sites of Cancer per 100,000 - Bangalore (2001-2003)

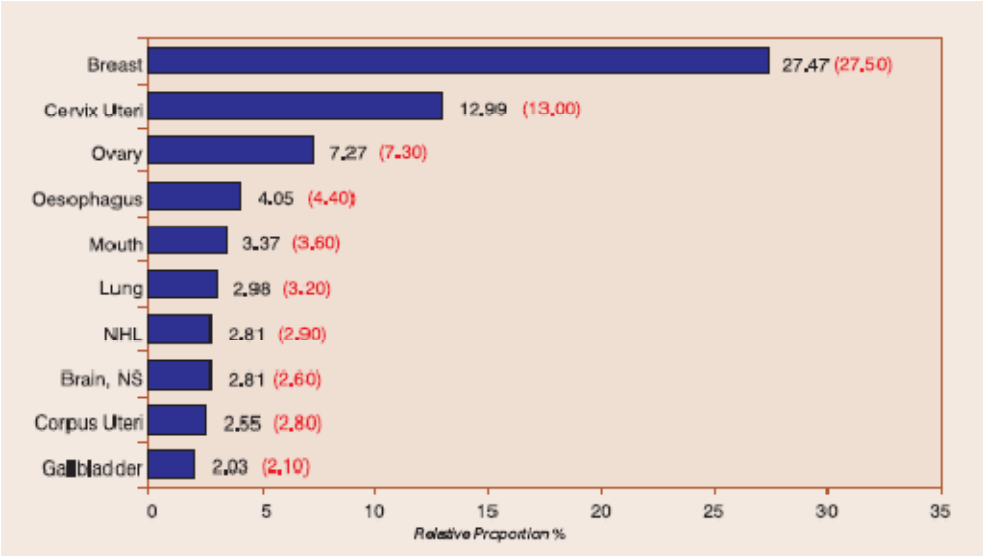
Ten Leading Sites of Cancer per 100,000 - Chennai (2001-2003)



Ten Leading Sites of Cancer per 100,000 - Delhi (2001-2003)



Ten Leading Sites of Cancer per 100,000 - Mumbai (2001-2003)



3.1.2 Breast Cancer Scenario in India

Breast Cancer is rapidly catching up with Cervical Cancer as the most common type of Cancer among urban Indian women. In females, breast cancer was the leading site of cancer in all registries except Barshi with the relative proportion ranging from 19.3% to 27.5%. According to NCRP data, every year 80,000 new cases of Breast Cancer are detected in Indian cities. The disease claims 35,000 lives every year, up by 8 per cent since 1990 today. In 1970, for instance, the incidence of Breast Cancer in India was barely 20 per 1, 00,000 urban women. Today, that number has shot up to 29.3 nearly a 50 per cent jump. Among the Parsis in Mumbai, a relatively westernized community in which few women have children and fewer breast-feed them, the incidence rate is higher at 43.8 per 1,00,000 women. Comparatively, in rural areas the incidence is only 8.5. This is still far less than the West, where one out of nine women gets the disease. But urban India is not far behind; the incidence of Breast Cancer is likely to double in the next 10 years (Shah P, Bapsy P et al. 2005).

3.1.2.1 National Cancer Registry Program

Generation of authentic data, analysis and interpretation, conduct of epidemiological studies and development of human resources are the major objectives of NCRP, which is functioning since 1981-82. The data from population based Cancer registries from 2001-2004 show that the Age Adjusted Incidence Rate (AAR) varied between 43.8 to 114.9/100,000 among men and 39.8 to 116.5/100,000 among females. Among males cancer of the stomach continued to be the most predominant site of cancer closely followed by lung, oesophagus, prostate, brain and others. Among females, cancer of the breast is the first leading site of cancer followed by cervix, oesophagus, ovary, mouth, stomach and others. The incidence rate of stomach Cancer is high in Bangalore. The most common site of Cancer in men in all the registries of major cities (except

Bangalore where stomach Cancer is the commonest) is lung. The common sites of Cancer in women include Breast, Cervix. Cancer of the breast in women has shown an increase in all urban registry areas.

3.1.2.2 Scenario in Bangalore

According to the latest report (2004) of Population Based Cancer Registry set up at KMIO (Kidwai Memorial Institute of Oncology). During the year 2001- 2003, a total number of 6112 male and 7247 female cases were registered. There is Gradual increase in the total number of cases compared to the previous years. The common Cancers among males were stomach [AAR (age adjusted ratio): 9.0%], Lungs (AAR: 8.5%), Oesophagus (AAR: 7.5%), Prostate (6.3 %) and Brain (3.7%). Among the females the common sites of Cancers were Breast (AAR: 27.5%), cervix (AAR: 18.1%), oesophagus (AAR: 7.5%), ovary (5.9%), Mouth (5.7%) and Stomach cancers (5.0%) [ ]

3.1.3 Breast Cancer - A Psychosocial Disease

Breast cancer is a profoundly stressful disease posing both physical and psychological threats to the patient. Breast cancer patients confront a cascade of stressors, including the diagnosis itself, ongoing intrusive medical procedures and severe side effects of treatment, and a variety of personal, psychological, and physical losses(Stanton AL and Snider PR 1993; Carver CS, Pozo-Kaderman C et al. 1998). Such psychological distress and morbidity following diagnosis and treatment in early breast cancer patients affects about 80% of the patients during initial stages of their treatment (Hughes J 1982; Derogatis L R, Marrow G R et al. 1983; Farber JM, Weinerman BH et al. 1983; Stefanek ME, Derogatis LP et al. 1987). Cancer patients often experience adjustment difficulties,

including distress; fear of death, recurrence, or progression of disease; changes in quality of life and social relationships; and an overall loss of control (Redd WH, Silberfarb PM et al. 1991; Spiegel D 1997). The diagnosis of cancer can bring about profound emotional reactions the common ones being shock and disbelief (Holland J 1973; Schmale AH 1974; Pfefferbaum B, Pasnau RO et al. 1977), anger directed against physician or family members (Greer S, Morris T et al. 1979), sadness, depression and personal grief may follow (Parkes CM 1975; Morris T, Greer HS et al. 1977; Maguire GP, Lee EG et al. 1978; Fawzy FI and Fawzy NW 1982). Most patients gradually accept reality and behavioral concomitants of these emotions such as anxiety; helplessness, hopelessness, guilt, insomnia, anorexia, irritability and inability to concentrate often manifest themselves (Peck A 1972). The question "Why me?" is asked and feelings of persecution are common (Bahnson C 1975). Cancer patients often have elevated levels of intrusive thoughts concerning their cancer and its treatment (Cella DF, Mahon SM et al. 1990; Epping-Jordan JE, Compas BE et al. 1994; Green BL, Rowland JH et al. 1998). Levels of intrusive thoughts are typically high at the time of diagnosis and may persist for months or even years after the initial diagnosis and treatment (Epping-Jordan JE, Compas BE et al. 1999). Especially intense or prolonged intrusive thoughts seem to be associated with psychological distress (Lepore SJ, Silver RC et al. 1996; Epping-Jordan JE, Compas BE et al. 1999). Intrusive thoughts experienced by cancer patients have also been associated with posttraumatic stress disorder (PTSD), which may be elicited by a life-threatening illness (Cordova MJ, Andrykowski MA et al. 1995; Andrykowski M A, Cordova MJ et al. 1998; Smith MY, Redd WH et al. 1999).

3.1.4 Stress and Breast cancer

The prognostic significance of several psychological factors has been studied in patients with various cancers, and most commonly in breast cancer. A more favorable medical outcome has been found for cancer patients who react to their diagnosis with denial or fighting spirit compared to those who reacted with stoic acceptance or hopelessness/ helplessness (Greer S, Morris T et al. 1979; Watson M and Ramirez A 1991; Walker LG, Heys SD et al. 1997a). This coping response of hopelessness /helplessness is correlated with depression and anxiety (Chaturvedi SK, Prabha Chandra S et al. 1996).

Breast cancer is a profoundly stressful disease. The diagnosis of breast cancer, treatment, and treatment sequelae can pose considerable amount of psychological and emotional distress and affects about 80% of the patients during initial stages of their treatment (Hughes J 1982). Anxiety and depression are the commonest psychiatric problems encountered in cancer patients. Patients with breast cancer undergoing radiation treatment also report anxiety and depression before, during and after the treatment (Chaturvedi SK, Prabha Chandra S et al. 1996; Wengstrom Y, Haggmark C et al. 2000). Anxiety and depression on the one hand and the positive and negative affect on the other are correlated. Positive affect reflects general levels of well-being, energy and high activity whereas Negative affect reflects subjective distress, undifferentiated bad moods and low self concept. Negative affectivity is related with both anxiety and depression while the absence or low positive affect is strongly related to depression (Boon MT and Peters FP 1999). Ritterband showed that cancer patients had a lower level of positive feelings than healthy controls, is a predominant factor for depression and did not find any differences for negative feelings(Ritterband LM and Spielberger CD 2001) where as in a study by Vogt showed that low positive affect and high negative affect are associated with higher anxiety and depression in survivors of breast, colorectal and prostate cancer(Vogt E, van

der Heide A et al. 2005), they also showed the factors related to positive and negative affect, positive affect is negatively related to higher levels of fatigue and positively related to physical, role, cognitive functioning and to enhanced social activities (Watson D 1988; Vogt E, van der Heide A et al. 2005) whereas negative affect is positively related to pain, fatigue and symptom reporting while negatively related to physical, role and cognitive functioning(Watson D and Pennebaker JW 1989; Vogt E, van der Heide A et al. 2005).

However, the psychological impact of the diagnosis and women's emotional responses vary considerably depending on the patient's psychological make-up and coping abilities, and the availability of emotional support. Treatment regimens for breast cancer can pose serious side effects for these patients such as loss of breast, infertility, altered sexual functioning, hair loss, fatigue, nausea and vomiting, pain, infections and low blood counts, which grossly affect the patients overall quality of life (QOL) (Levenson JL, Bemis C et al. 1994). Many of these side effects can act as potent short term and long term stressors constantly influencing patients to make lifestyle changes to cope and adjust with these problems and seek supportive care (Umesh SB 1998).

Quality of life is an important concern and outcome of cancer treatment. Several studies have documented that both diagnosis and treatment of breast cancer have an impact on quality of life (Ganz P, Coscarelli A et al. 1996; Shapiro S L, Lopez AM et al. 2001). Further, there is evidence to suggest that decrements in quality of life are related to treatment related distress and psychological well being (Levenson JL, Bemis C et al. 1994; Shapiro S L, Lopez AM et al. 2001). Various dimensions of quality of life such as physical, emotional, social, functional and spiritual wellbeing are affected in both newly diagnosed and long-term survivors of breast cancer (Weitzer MA, Meyers CA et al. 1997;

Shapiro S L, Lopez AM et al. 2001; Smith EM, Gomm SA et al. 2003; Vacek PM, Winstead-Fry P et al. 2003).

However, growing evidence suggests that psychosocial and psycho-educational interventions are beneficial adjunctive treatments for cancer patients(Carey M and Burish TG 1988; Anderson BL 1992; Tjisburg R, van Knippenberg FC et al. 1992; Fawzy FI, Fawzy NW et al. 1993; Meyer T and Mark MM 1995; Tooley GA, Armstrong SM et al. 2000).Patients who have used active behavioral coping methods have reported positive affective states, decrease in anxiety and depression, higher levels of self esteem and fewer physical symptoms while those with avoidance coping showed greater depression, anxiety and lower quality of life (Classen C, Hermanson KS et al. 1994).

Anxiety and depression are the commonest psychiatric problems encountered in cancer patients. It has been repeatedly acknowledged that many psychiatric disorders in cancer patients are not detected diagnosed or treated (Derogatis L R, Marrow G R et al. 1983). The prevalence of depression in cancer patients ranges from 4.5% to 58% (Lansky S B, List M A et al. 1985). Patients with breast cancer undergoing radiation treatment also report anxiety and depression before, during and after the treatment (Chaturvedi SK, Prabha Chandra S et al. 1996; Wengstrom Y, Haggmark C et al. 2000). The prevalence of anxiety and depression in Indian cancer patients in Bangalore undergoing radiation treatment was 64% and 50% respectively (Chaturvedi SK, Prabha Chandra S et al. 1996). There is a very high correlation between anxiety and depression in cancer patients (Cassileth BR, Lush EJ et al. 1984). The factors for the occurrence of depression is related to the cancer itself, those various factors includes reaction to disfigurement caused as a result of surgery (Umesh SB 1998), CNS Metastasis (Levine DN, Silberfarb PM et

al. 1978), Advanced stages of cancer (Bukberg J, Penman D et al. 1984), Several medications such as Steroids, chemotherapeutic agents, estrogen etc (Umesh SB 1998), Associated Pain (Glover J, Dibble SL et al. 1995). Although recent clinical studies have not found a relationship between depression and cancer outcome (Cassileth BR, Lusk EJ et al. 1985).Studies show that depression influences treatment related distress in cancer patients (Cassileth BR, Lush EJ et al. 1984) and warrant clinical attention because of their clear adverse effects on the quality of life of cancer patients. Another study has shown depression to be related to decreased survival age in metastatic breast cancer patients (Sephton SE, Sapolsky RM et al. 2000).

3.1.5 Conventional cancer treatment related side effects and its Relationships to psychological distress

Patients with breast cancer normally receive multimodal treatment over a long period of time(Overgaard M, Hansen PS et al. 1997; Ragaz J, Jackson MS et al. 1997).The advancements in the treatment of breast cancer has considerably increased the life span, and patients who eventually die are living longer between diagnosis and death enduring cancer symptoms and treatment side effects for a longer time(Sephton SE, Sapolsky RM et al. 2000), therefore it is also necessary to take care of the related morbidity that accumulates over time. Most women with breast cancer usually undergo surgery and 4-6 months of chemotherapy followed by 6 weeks of radiotherapy. They then receive palliative radiation and chemotherapy if the cancer relapses or reoccurs. Treatment regimens for breast cancer can pose serious side effects for these patients such as loss of breast, infertility, altered sexual functioning, hair loss, fatigue, nausea and vomiting, pain, infections and low blood counts, which grossly affect the patients overall quality of life

(QOL)(Levenson JL, Bemis C et al. 1994). Fear and anxiety associated with invasive treatment procedures, sexual dysfunction secondary to surgery and radiation and problems associated with extended hospital care and aggressive medical treatment are among the most common treatment related side effects observed in cancer patients. Treatment related problems typically involve anxiety in anticipation of painful procedures, conditioned reactions to treatment and acute/chronic pain resulting from tissue damage. Many of these side effects can act as potent short term and long term stressors constantly influencing patients to make lifestyle changes to cope and adjust with these problems and seek supportive care (Umesh SB 1998).

Treatment related side effects such as loss of breast can bring about anxiety, lack of self esteem, image concerns, altered feelings of sexuality and isolation. Radiation and chemotherapy can cause increased fatigue. Chemotherapy can lead to more distressing side effects mentioned above including, myelosuppression, life threatening infections, loss of hair and multi-system toxicity etc. These somatic changes invariably cause immense psychological distress and induce psychological symptoms in cancer patients. Reductions/ efficient management of these somatic symptoms and toxicity can also be expected to reduce the psychological distress (Burish TG and Tope DM 1992).

3.1.5.1 Conventional cancer treatment with radiotherapy and associated psychological distress

Radiotherapy (RT) is one of the earliest treatments for cancer and plays an important role in the care of cancer patients. Ever since the discovery of x-rays by Roentgen in 1895, the therapeutic delivery of large doses of radiation has been used in an attempt to eradicate tumors. Radiotherapy is one of the most effective means by which local/ regional control of cancer is obtained. Cancer patients may receive radiotherapy as their primary treatment but it can also be given as adjuvant treatment alone after surgery or along with chemotherapy. About 45% of patients with malignancy require radiotherapy. Approximately 50% of these patients are treated with the intention to cure, whereas the other 50% is treated palliatively. The intention of curative radiotherapy is to target the cancer cells to arrange local control. The treatment field of radiotherapy typically includes the tumor site and if indicated the lymph nodes that drain the area. Unfortunately, there are also normal cells which are very close to the cancer cells. Because it is not possible to exclude normal cells from the treatment field, radiation also affects normal tissue, which can cause a number of side effects. Common side effects can include fatigue, skin irritation at the site of the radiation beams, nausea, diarrhea, and gastrointestinal symptoms. These side effects may persist till several weeks after treatment and then will disappear for most patients (King KB, Nail LM et al. 1985; Nail LM, King KB et al. 1986; Graydon J E 1994; Caffo O, Fellin G et al. 1996; Walker BL, Nail LM et al. 1996; Fransson P and Widmark A 1999). Studies have shown that a cancer patient also faces psychological problems when they are treated with RT(Peck AB 1977; Forester BM, Kornfeld DS et al. 1978). Since the late 1970s, the number of studies focusing on psychological responses to RT has grown rapidly. These studies measured a wide range of aspects of psychological functioning, including depression, anxiety, negative and positive mood, and psychological well-being or distress.

Anxiety and depression are the commonest problems encountered while undergoing Radiation treatment. Patients with breast cancer undergoing radiation treatment also report anxiety and

depression before, during and after the treatment (Chaturvedi SK, Prabha Chandra S et al. 1996; Wengstrom Y, Haggmark C et al. 2000). The prevalence of anxiety before RT is estimated to be about 10-20% whereas the prevalence of depressive symptoms before RT is estimated to be about 1.5-8% (Maraste R, Brandt L et al. 1992; Maher EJ, Mackenzie C et al. 1996). The prevalence of anxiety and depression in Indian cancer patients in Bangalore before undergoing radiation treatment was 46% and 42% respectively (Chaturvedi SK, Prabha Chandra S et al. 1996).

During RT, In a qualitative study by Munro et al. (1989) patients were asked to report which problems associated with RT caused the most distress (N=110). Feelings of anxiety were among the ten most troublesome problems defined within 24 hours of following the first dose of RT (Munro AJ, Biruls R et al. 1989).Three studies reported decrease of such anxiety by the end of the radiotherapy on last day compared to first day (Rahn AN, Mose S et al. 1998; Mose S, Budischewski KM et al. 2001). Another study by Rahn et al. (1998) reported that 40% of the patients felt anxious about undergoing RT and 54% were afraid of the treatment's possible side effects on the first day of RT. They also reported Feelings of such anxiety decreased during the next sessions. That is, at the last day of treatment, 19% of the patients reported that they had felt anxious most of the time or during the whole treatment. Where as a study by Leopold et al (1998) reported symptoms of depression to be a more potent distressor than feelings of anxiety during the first week of RT. About 12% of the patient had a major depression disorder and 29% had a minor depression disorder (Leopold KA, Ahles TA et al. 1998). Three more studies also reported depressive symptoms during RT ranging from 31% to 33%(Irwin PH, Kramer S et al. 1986; Jenkins C, Carmody TJ et al. 1998). In addition, one qualitative study showed that depressive symptoms were mentioned as one of the problems experienced by patients after starting RT (Munro AJ and Potter S 1996). Psychological Distress was also reported during RT.

Nail et al. (1986) revealed that the level of negative mood, as measured by the Profile Of Mood Status (POMS) peaked during the last week of RT, when subjects were experiencing a relatively high level of severe side effects(Nail LM, King KB et al. 1986). In contrast to Nail et al. (1986), a study of Oberst et al. (1991) found no peak of negative mood during treatment and, as a group, the patients reported little affective mood disturbance during treatment. One problem with the Oberst et al. study is that they did not specify the moment of measurement, thus complicating the examination of differences among studies (Oberst MT, Hughes SH et al. 1991). Finally, Rahn et al. (1998) found that, at the last day of treatment, 38% of the women in the study reported emotional distress induced by receiving RT (Rahn AN, Mose S et al. 1998). The prevalence of anxiety and depression in Indian cancer patients in Bangalore during radiation treatment was 64% and 50% respectively (Chaturvedi SK, Prabha Chandra S et al. 1996).

After the completion of RT most of the studies reported decrease in Anxiety (Irwin PH, Kramer S et al. 1986; Wallace L M, Priestman S G et al. 1993), Wallace et al.,1993 reported 6% of patients reported feelings of Anxiety at the end of RT compared to 17.5% before RT. Whereas other studies found rather high percentages of feelings of anxiety after RT, ranging from 13% to 52%(Caffo O, Fellin G et al. 1996; Chaturvedi SK, Prabha Chandra S et al. 1996; Maher EJ, Mackenzie C et al. 1996). Studies after RT, revealed great variability in depression symptoms, ranging from 8%-48% of the patients reporting depressive symptoms. Munro et al. (1989) showed that patients interviewed at the end of treatment reported depressive symptoms as one of the ten most troublesome problems.

3.1.6 Stress its Perception and Endocrine System

The word ‘Stress’ was defined by Hans Sale, a physician and endocrinologist who instigated stress research, as “the non-specific response of the body to any demand” (Sale H 1936). Sale

also emphasised the distinction between 'Stressor' (the cause) and 'Stress' (the effect) (Selye H 1975a).

Stress is defined by Lazarus and Folkman (1984) as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being". This definition includes both primary and secondary appraisals, which, according to Lazarus and Folkman (1984), describe the initial evaluation of an event or situation's relevance to one's well-being (primary appraisal) and an evaluation of the resources available to deal with this potential threat (secondary appraisal). According to this view of stress, it is not just the occurrence of an event that poses a threat to well-being, but also the person's appraisal or perception of that threat (Lazarus RS and Folkman S 1984).

When a situation is perceived as stressful, the Hypothalamic-Pituitary-Adrenal (HPA) axis becomes activated, causing a cascade of hormones to be produced that may (in turn) negatively impact immunity and health outcome.

Stressor:

Life events (such as trauma, disease, exercise and life-changing experiences) challenge an individual's capacity to adapt to inner and outer demands. These challenges may be physiologically arousing and/or emotionally taxing, and these events may lead to cognitive and behavioral responses.

Physiological stressors (including trauma, infection and starvation) affect human organ systems directly through catabolic changes (energy consuming changes). Psychological stressors (stimuli which arouse human emotions) can also affect human organ systems through the effects of psychological stress, both directly via the psycho-neuro-endocrino-immune network (i.e. appraisal of stressor acts as an input in the network) and by modulation of human behaviour

including eating habits, exercise, smoking and self-medication. These changes takes place in order to maintain the homeostasis or to bring the stability to protect the body is termed as Allostasis (Sterling P and Eyer J 1988) and this persistent long term cumulative physiologic response to stress is called Allostatic load (McEwen BS and Stellar E 1993). The stress response is time-dependent and divided into three overlapping temporal stages: the stage of alarm reaction, the stage of resistance and the stage of exhaustion (Perdrizet GA 1997).

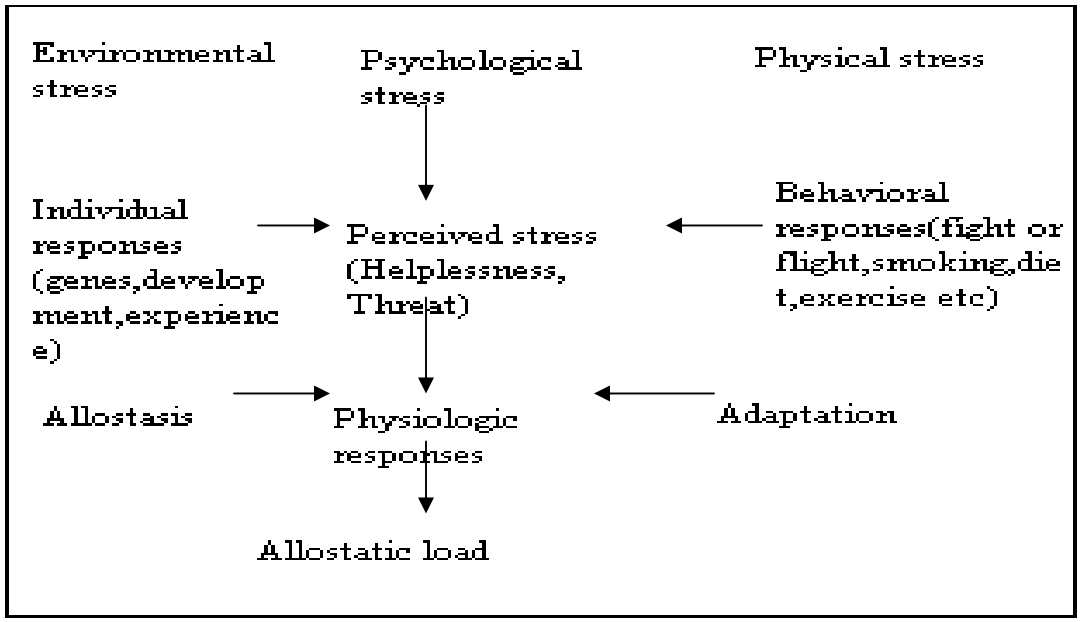
Four situations are associated with allostatic load. The first and most obvious is frequent stress. For example, surges in blood pressure can trigger myocardial infarction in susceptible persons (Muller JE, Tofler GH et al. 1989). In the second type of allostatic load, adaptation to repeated stressors of the same type is lacking, resulting in prolonged exposure to stress hormones, as was the case for some of the people subjected to the repeated-public-speaking challenge (Kirschbaum C, Prussner JC et al. 1995).

In the third type of allostatic load there is an inability to shut off allostatic responses after a stress is terminated. As we have noted, the blood pressure in some people fails to recover after the acute stress of an arithmetic test (Gerin W and Pickering TG 1995) and hypertension accelerates atherosclerosis (Kaplan JR, Pettersson K et al. 1991). Women with a history of depressive illness have decreased bone mineral density, because the allostatic load of chronic, moderately elevated serum Cortisol concentrations inhibits bone formation (Michelson D, Stratakis C et al. 1996). Intense athletic training also induces allostatic load in the form of elevated sympathetic and HPA-axis activity, which results in weight loss, amenorrhea, and the often-related condition of anorexia nervosa (Boyar RM, Hellman LD et al. 1977; Loucks AB, Mortola JF et al. 1989).

In the fourth type of allostatic load, inadequate responses by some allostatic systems trigger compensatory increases in others. When one system does not respond adequately to a stressful stimulus, the activity of other systems increases, because the under active system is not

providing the usual counter regulation. For example, if cortisol secretion does not increase in response to stress, secretion of inflammatory cytokines (which are counter regulated by cortisol) increases (Munck A, Guyre PM et al. 1984) leading to the negative consequences of inflammatory response.

Fig 3. The Stress Response and Development of Allostatic load.



The perception of stress is influenced by one's experiences, genetics, and behavior. When the brain perceives an experience as stressful, physiologic and behavioral responses are initiated, leading to allostasis and adaptation. Over time, allostatic load can accumulate, and the overexposure to mediators of neural, endocrine, and immune stress can have adverse effects on various organ systems, leading to disease.

Stress related life-events have often been examined either in healthy populations using academic examinations where NK-cells, in particular, were measured as a stress-related marker(Glaser R, Kiecolt-Glaser JK et al. 1985; Kiecolt-Glaser JK, Glaser R et al. 1986; Gruzelier JH, Levy J et al. 2001; Gruzelier JH, Smith F et al. 2001; Kiecolt-Glaser JK, Marucha PT et al. 2001),

or in patient populations (i.e. clinically stressed individuals) who are persistently exposed to the presence of life-long diseases. These life-long diseases often used in the literature include malignancy (breast cancer in particular)(Spiegel D, Bloom JR et al. 1989; Antoni MH, Lehman JM et al. 2001; Bakke AC, Purtzer MZ et al. 2002).

In recent decades, two major axes have been proposed as an important pathways in the stress response: (1) the sympathetic nervous system-adreno-medulla (SAM) and (2) the hypothalamus-pituitary-adrenal (HPA) axes(de Kloet ER, Vreugdenhil E et al. 1998; de Kloet ER 2000; Downing JE and Miyan JA 2000; Yang EV and Glaser R 2002; Heuser I and Lammers CH 2003).

The 'fight or flight' response (Cannon WB 1914; Cannon WB 1934) and emotions like anxiety and/or fear are known to be associated with increased activity in the sympathetic-adreno-medullary system (SAM) and hypothalamus-pituitary-adrenal system (HPA). Activation of sympathetic-adreno-medullary system affects the physiological process by release of epinephrine (as a response to the sympathetic neural activity) from the adrenal glands travels through the blood stream and acts as a hormone in various organs. Whereas Activation of hypothalamus-pituitary-adrenal system affects the physiological process by release of Cortisol is a major stress related hormone (Hucklebridge F, Sen S et al. 1998). The major hypothalamic components of the HPA axis involve CRH and vasopressin, which are secreted into the pituitary portal circulation from nerve terminals in the external zone of the median eminence (Munck A, Guyre PM et al. 1984; Turnbull AV and Rivier CL 1999) and drive the release of ACTH from the anterior pituitary. ACTH is derived from a larger precursor protein, propiomelanocortin (POMC). ACTH stimulates the synthesis and secretion of cortisol from the adrenal cortex. Therefore, production of glucocorticoids is under control of the central nervous system-hypothalamic-pituitary-adrenal axis. Cortisol, in turn, can inhibit the release of CRH and ACTH through negative

feedback. The net result is a finely tuned system that can respond to illness and other stresses with rapid alterations in the release of cortisol (Beishuizen A and Thijs LG 2003). The effect of cortisol upon individual target cells, however, is suggested to vary from suppressive to stimulatory, i.e. suppressive, preparative, permissive and stimulatory actions (Sapolsky RM, Romero LM et al. 2000). Exposure to frequent or severe stress over a period of time may lead to increased sensitization of the hypothalamic-pituitary-adrenal (HPA) axis resulting in pronounced stress response (Rosmond R, Dallman M et al. 1998; Heim C, Ehlert U et al. 2000). Such abnormalities in the trajectory of the daytime slope of cortisol have been observed in about 10% of normal populations(Stone AA, Schwartz JE et al. 2001), and at higher levels among subjects undergoing psychological stress (e.g., depression, unemployment, post-traumatic stress disorder)(Irwin M, Daniels M et al. 1988; Ockenfels MC, Porter L et al. 1995; Yehuda R, Teicher MH et al. 1996) and some types of physical stress (e.g., shift work and excessive workloads) (Caplan R, Cobb S et al. 1979; Shinkai S, Watanabe S et al. 1993). Both axes are responsive to stress and may become dysregulated under conditions of chronic stress (Chrousos G 1992). Chronic or repeated stress may cause prolonged reactivity resulting in states of heightened arousal (Sterling P and Eyer J 1981), or activity outside the normal range of function of stress response systems. As a consequence, stress response systems may become dysregulated. One sign of dysregulation in this endocrine system is altered circadian rhythms (Yehuda R, Teicher MH et al. 1996; Chrousos G and Gold PW 1998; Rosmond R, Dallman M et al. 1998). Circadian rhythms are a potentially important indicator of the regulatory competence of stress response mechanism because they reflect the capacity of a system to turn on and off appropriately. Chronic psychosocial stressors may cause the circadian rhythms of neuroendocrine stress response systems to become disrupted. For example, disruption of HPA axis rhythms has been linked with psychological distress including depression (Deuschle M, Schweiger U et al. 1997),

post-traumatic stress disorder(Yehuda R 2002), chronic stress(Chrousos G and Gold PW 1998), and unemployment(Ockenfels MC, Porter L et al. 1995).

3.1.6.1 Cortisol, Stress, HPA Axis

Cortisol is the primary stress hormone secreted from the adrenals. Cortisol is a pluripotent hormone acting on multiple tissues to regulate numerous aspects of metabolism, growth and physiological functioning, which makes it essential for survival in critical illness (Munck A, Guyre PM et al. 1984). Cortisol has a vital supportive role in the maintenance of vascular tone, endothelial integrity, vascular permeability and the distribution of total body water within the vascular compartment, and potentiates the vasoconstrictor actions of catecholamines. During immune challenge, glucocorticoids play important roles as immunosuppressants, limiting the extent of inflammation (Munck A, Guyre PM et al. 1984; McEwen BS, Biron CA et al. 1997; Sapolsky RM, Romero LM et al. 2000).

Corticosteroid-binding globulin (CBG) is a specific plasma transport protein that binds cortisol with high affinity.18 Under basal conditions, 90–95% of plasma cortisol is bound to CBG, and it is generally believed that the fraction of CBG-bound cortisol has a limited access to target cells and, therefore, is biologically inactive (Siiteri PK 1982). CBG is a 'negative acute phase protein' and levels of CBG are reduced during stress (Fleshner M, Deak T et al. 1995), inflammation or infection/sepsis (Garrel DR 1996; Bernier J, Jobin N et al. 1998).

Accurate estimates of unbound cortisol can now be made easily from saliva samples (Kirschbaum C and Hellhammer D H 1994), which has led to strong interest in the use of cortisol as a convenient biomarker for stress (Theorell, 2003; Yehuda et al., 2003).Cortisol, a component of the stress response, mobilizes glucose for "fight or flight" behaviour and suppresses or

counter-regulates less immediate physiological processes such as immune function (McEwen BS 1998). Among most healthy individuals, Cortisol levels are highest before and just after awakening and decrease throughout the day (Stone AA, Schwartz JE et al. 2001), however, several researchers have demonstrated that significant between subjects variation in diurnal Cortisol rhythm exists (Smyth J M, Ockenfels M S et al. 1997; Stone AA, Schwartz JE et al. 2001) with 10%-20% of healthy individuals exhibiting aberrant rhythms. Research with healthy populations has indicated that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may result from the cumulative effects of repeated stress (McEwen BS 1998). Altered diurnal Cortisol profiles have been associated with chronic stress (Chrousos G and Gold PW 1998), depression (Deuschle M, Schweiger U et al. 1997), unemployment (Ockenfels MC, Porter L et al. 1995), and posttraumatic stress disorder (Yehuda R, Teicher MH et al. 1996). Clear evidence of HPA-axis hyperactivity has been found in patients with melancholic depression, alcoholism, and eating disorders (Heim C, Ehlert U et al. 2000) (for an overview see Ehlert, Gaab & Heinrichs, 2001). Other areas in which HPA-axis malfunctioning was established are posttraumatic stress disorder, stress-related bodily disorders like idiopathic pain syndromes, and chronic fatigue syndrome. These conditions are associated with diminished HPA activity (Heim C, Ehlert U et al. 2000). Such HPA axis dysregulation is also associated with increased risk for a number of other diseases such as type 2 diabetes, stroke and cardiovascular disease (Rosmond R and Bjorntorp P 2000).

3.1.6.2 Stress, HPA-Axis dysfunction and Breast cancer

Data suggests that these stress responses as a result of cancer poses numerous physical and emotional stresses. While disease and treatment exert a heavy physiological toll, accompanying anxiety about diagnosis and prognosis, taxing medical treatments, and disruption of social,

vocational, and family functioning constitute a series of psychological stressors. Such stress and mood disorders may contribute to dysregulation in several important circadian systems, including hormonal, sleep and autonomic rhythms in women with breast cancer (Touitou Y, Bogdan A et al. 1996; Bovbjerg D H 2003; Sephton S and Spiegel D 2003). Cancer patients repeatedly endure physical and emotional events that activate stress-response mechanisms leading to elevated cortisol level a stress hormone and the end product of HPA axis in breast cancer patients both prior to and following treatment (McEven BS and Sapolsky RM 1995; Aragona M, Muscatello MR et al. 1996; Van der Pompe G, Duivenvoorrden HJ et al. 1997), including the hypothalamic–pituitary–adrenal (HPA) axis. Such repeated activation has been associated with HPA axis dysregulation and adverse health consequences (McEwen BS 1998).One sign of dysregulation in this endocrine stress response system is altered circadian cortisol rhythms (Yehuda R, Teicher MH et al. 1996; Chrousos G and Gold PW 1998; Rosmond R, Dallman M et al. 1998). Cortisol levels are usually high before awakening and decrease over the course of the day (Posener JA, Schildkraut JJ et al. 1996) and such repeated physical and emotional stress leading to abnormal patterns of Cortisol secretion such as flattened, high levels or erratic fluctuations (Touitou Y, Bogdan A et al. 1996; Van der Pompe G, Antoni MH et al. 1996), such elevated cortisol levels and overall flattened diurnal profiles is reported in breast cancer patients compared to control women (Van der Pompe G, Antoni MH et al. 1996; Porter L S, Mishel M et al. 2003; Abercrombie H C, Giese-Davis J et al. 2004), such abnormal patterns of cortisol have been reported in upto 70 to 75% of a sample of Metastatic breast and ovarian cancer patients (Touitou Y, Bogdan A et al. 1996; Van der Pompe G, Antoni MH et al. 1996). Such aberration of Cortisol rhythms are linked with both physical stress of cancer (Mormont MC and Levi F 1997) and psychological stress (Deuschle M, Schweiger U et al. 1997). Such cortisol rhythms are more disrupted in patients with more advanced disease (Touitou Y, Levi F et al.

1995; Touitou Y, Bogdan A et al. 1996) and such flattened diurnal salivary Cortisol rhythms predict early mortality from Metastatic breast cancer (Sephton SE, Sapolsky RM et al. 2000).

Several studies have found out that such circadian abnormalities had prognostic value in predicting initial occurrences of breast cancer (Ticher A, Haus E et al. 1996) as well as associations with later stages of cancer development and with other prognostic indicators (Touitou Y, Bogdan A et al. 1996). The authors speculate that these abnormal circadian cortisol rhythms represent compromised HPA axis functioning, which may be responsible for poorer outcomes (Spiegel D and Sephton SE 2001; Antoni MH 2003; Lutgendorf SK and Costanzo ES 2003) and earlier mortality in cancer patients.

One way in which diurnal cortisol dysregulation is thought to affect disease progression is through its suppressive effects on the immune system, Most of the effector cells of the immune system exhibit receptors for many neuroendocrine products of HPA and SAM axes such as cortisol and catecholamines (Madden KS, Felten SY et al. 1989; Madden KS and Livnat S 1991; Madden KS 2003), which can influence changes in immune cell trafficking (Benschop RJ, Schedlowski M et al. 1997), proliferation, cytokine secretion, antibody production and cytolytic activity (Dhabar FS and McEven BS 2001). For example, Miller, Cohen, and Ritchey (2002) (Miller GE, Cohen S et al. 2002) posit that chronic stress impairs the ability of the immune system to respond to glucocorticoids. When infection or injury occurs, the immune system mounts an inflammatory response to assist with the healing process. Glucocorticoids, such as cortisol, regulate the inflammatory response to infection and injury by terminating the inflammatory cascade once it is no longer needed. However, when glucocorticoid production remains elevated for prolonged periods of time (e.g., under conditions of chronic stress), white blood cells respond by downregulating the number and/or function of receptors that bind glucocorticoids, leading to a decreased ability of white blood cells to respond to the anti-inflammatory actions of

cortisol. Consistent with this “glucocorticoid resistance hypothesis”, Miller et al. (2003) note that chronic stress may impair glucocorticoids’ ability to inhibit the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF-α). These pro-inflammatory cytokines are released by white blood cells and serve to direct white blood cells to the location of injury or infection, initiate the production of other molecules in the inflammatory response, and improve certain white blood cells’ ability to kill. However, sustained, high circulating levels of these cytokines can be toxic and damaging (Munck A and Guyre P 1991), particularly among individuals with cancer (Kelley KW, Bluthe RM et al. 2003).

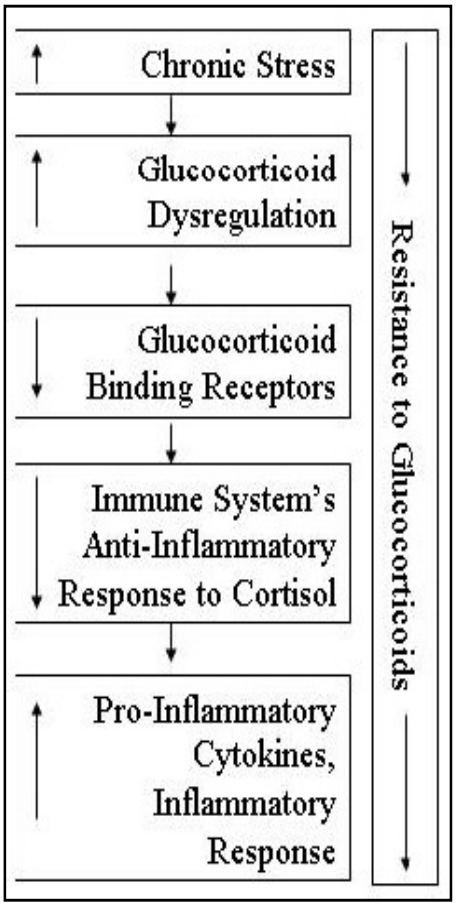


Figure 4: Glucocorticoid resistance model

Endocrine mediators, such as cortisol, enhance vascular endothelial growth factor (VEGF) pro-angiogenic cytokine production (Lutgendorf SK, Cole S et al. 2003). Thus, cortisol dysregulation may also affect disease progression in cancer through enhanced angiogenesis.

Glucocorticoids, such as cortisol, appear to impact the Th1/Th2 balance during nocturnal sleep. Petrovsky and Harrison (1997, 1998) (Petrovsky N and Harrison LC 1997; Petrovsky N and Harrison LC 1998) found that nocturnal sleep promoted a shift toward Th1 dominance which is possibly mediated by the cortisol nadir typically found during early sleep. Furthermore, Dimitrov, Lang, Fehm, and Born (2004) (Dimitrov S, Lange T et al. 2004) found that corticosteroids altered the Th1/Th2 balance, producing a Th2 dominant response by inhibiting

the Th1 cytokines. Thus, in light of the findings described above in which Th2 dominance is found among more advanced disease, dysregulated nocturnal cortisol not only threatens to disrupt the Th1/Th2 balance but may promote disease progression through inducing Th2 dominance.

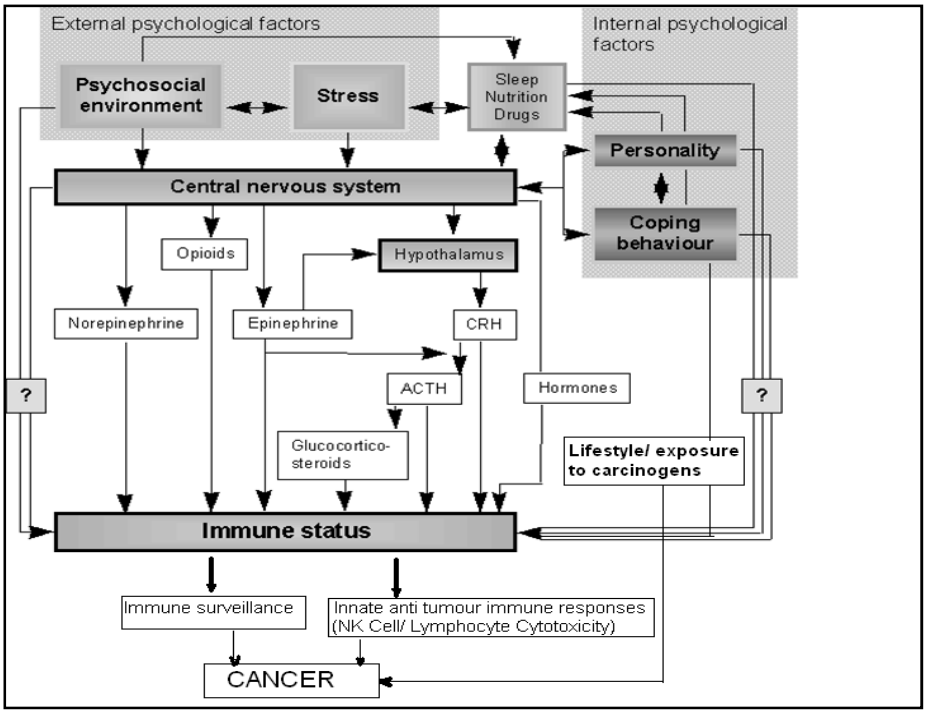
The immunosuppressive effects of cortisol have also been linked to natural killer cells, an important component of innate immunity. Natural killer cells exert cytotoxic effects against viruses and neoplastic cells and may inhibit tumor growth and metastasis (Herberman R 1985; Trinchieri G 1989; Whiteside TL and Herberman RB 1995). Cortisol has been shown to inhibit natural killer cell activity in peripheral blood leukocytes (Gatti G, Cavallo R et al. 1987). Among individuals with cancer, cortisol-induced suppression of natural killer cell activity may lead to tumor growth and/or metastasis.

A number of studies have found a link between stress and immunity among cancer patients. In an extensive review of the PNI findings related to cancer, Kiecolt-Glaser, Robles, Heffner, Loving, and Glaser. (2002b) (Kiecolt-Glaser JK, Robles TF et al. 2002) report that psychological distress has been linked to impaired ability to repair damaged cellular DNA involved in cancer as well as the inhibition of apoptosis (Kiecolt-Glaser JK, McGuire L et al. 2002). Specifically, psychosocial stress has been linked to decreased methyltransferase synthesis, which plays an important role in DNA report in certain forms of tumors (Glaser R, Thorn BE et al. 1985). In a study of malignant melanoma, Fawzy et al. (1993) (Fawzy F.I, Fawzy N.W et al. 1993)found that psychosocial factors were related to faulty apoptosis, which is a process involving programmed cell death that is important in the defense against cancer cells.

In light of the findings pointing to the relationship between psychosocial stress and altered immune/endocrine functioning and disease outcome, evidence exists that stress-reduction

interventions may be able to counteract these relationships by reducing stress and improving immune/endocrine functioning. McGregor et al. (2004) (McGregor BA, Antoni MH et al. 2004)examined the effects of a 10-week cognitive-behavioral stress management (CBSM) intervention on psychosocial and immune functioning among women with early stage breast cancer. She found that women receiving the CBSM intervention displayed more benefit-finding and improved lymphocyte proliferation compared to women in the control condition. Cruess et al. (2000b) (Cruess DG, Antoni MH et al. 2000) also examined the effects of a 10-week CBSM intervention with women with early stage breast cancer. He reported that women who participated in the intervention showed increased benefit finding and reductions in serum cortisol compared to women in the control condition. Furthermore, psychosocial interventions among women with breast cancer have been shown to normalize cortisol responsivity to acute stress (Van der Pompe G, Antoni MH et al. 1996).

Fig 5: Biopsychosocial model (modified) for cancer causation and progression.



3.1.7 Social Support, Emotional Expression and HPA Axis

Social support has been described as providing both a generalized beneficial effect and a buffering effect on health (for review, see (Cohen S and Wills TA 1985). As a buffer between stress and illness, social support likely operates to eliminate or reduce the physiological reaction to stress by modulating stress appraisal or enabling reappraisal (Cohen S and Wills TA 1985; Levine S, Coe C et al. 1989). The importance of supportive social relations in respect to health has been demonstrated by a number of large-scale studies (for reviews, see Refs. (Cohen S 1988; House JS, Landis KR et al. 1988; Uchino BN, Cacioppo JT et al. 1996). In a major review, House et al. (House JS, Landis KR et al. 1988) demonstrated the strength of relationship between social integration and age-adjusted mortality is comparable to the effect of such standard health behavior risk factors as smoking and serum cholesterol levels. Intervention studies have demonstrated that enhancing social support results in increased length of life as well as quality of life in cancer patients (Spiegel D, Bloom JR et al. 1989; Richardson JL, Zarnegar Z et al. 1990;

Spiegel D 1992; Fawzy F.I, Fawzy N.W et al. 1993; Van der Pompe G, Antoni M et al. 1996; Van der Pompe G, Duivenvoorrden HJ et al. 1997), although not all studies show this effect (Linn MW, Linn BS et al. 1982; Iinyckyj A, Farber J et al. 1994). There is linking evidence between the social support and specific physiological mechanisms to the maintenance of health and illness (Jemmott JB III and Locke SE 1984; Cohen S 1988).The effect of psychosocial factors on cancer progression is hypothesized to be mediated by behavioral and/or biological pathways. Behavioral mechanisms include the patient's tendency to maintain a healthy lifestyle (e.g., diet, exercise, sleep, and smoking habits), their choice for or against physician-recommended treatments for cancer, and their adherence with those treatments. A biological pathway gets activated by numerous physical and emotional stresses imposed by a cancer diagnosis (e.g., medical treatments, anxiety about diagnosis/prognosis, and disruption of social functioning) leading to endocrine stress-response mechanisms including the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS) (Sephton S and Spiegel D 2003). However, the current literature does not clearly support the effects of social supporting factors on neuroendocrine function or activity of the HPA axis (for review, see Ref. (Uchino BN, Cacioppo JT et al. 1996). Cortisol, the end product of HPA activation, is a reliable physiological stress measure (Kirschbaum C, Strasburger C et al. 1989; Kirschbaum C and Hellhammer D H 1994), but little attention is paid to understand the relationship between different components of social support and cortisol and thus remains largely unresolved (Uchino BN, Cacioppo JT et al. 1996). Studies have examined cortisol under naturalistic settings. Frequency of emotional support and instrumental support, are negatively related to urinary cortisol in samples collected over a 12-hour period as well as other neuroendocrine measures in older men but not in older women (Seeman TE, Berkman LF et al. 1994). In a study of pregnant women, both perceived social support and pregnancy support also related negatively to serum cortisol levels (Wadhwa PD,

Dunkel-Schetter C et al. 1996). Conversely, a naturalistic study of preterm mothers on postpartum day 5 found no association between social support and cortisol sampled from breast milk (Groer MW, Humenick S et al. 1994).Other studies have showed no association between social support and urinary cortisol in a group of 12-year-old boys (Arnetz BB, Edgren B et al. 1985) where as higher diurnal mean cortisol levels were higher among patients who reported less appraisal, belonging and tangible support in women with metastatic breast cancer.(Turner-Cobb JM, Sephton SE et al. 2000).Other studies have also shown that abnormal patterns of cortisol is seen with people reporting greater distress, less functional relationships such as extent to which the participant reported positive feelings about relationships and utilize them for support and comfort and such abnormal patterns are found to be predictive of mortality in women with breast cancer (Sephton SE, Sapolsky RM et al. 2000; Adam EK and Gunnar MR 2001; Vedhara K, Miles J et al. 2003). Supportive relationships seem to modulate stress-induced immunosuppression (e.g., medical students undergoing examination stress) (Kiecolt-Glaser JK, Ricker D et al. 1984). Remarkably, psychosocial factors such as social support and interpersonal relationship seem to mitigate the effect of stress on NK cells, even among cancer patients. In a sample of stage I and II breast cancer patients, Levy and her colleagues (Levy SM, Herberman RB et al. 1990) reported an association between NK-cell activity (NKCA) and perceived support from their physician, as well as with the active coping strategy of active social support seeking. Levy and colleagues conclude that the quality of family support and overall mood may potentially predict disease progression in patients whose cancer does recur.

A recent study of immune function in women after surgical treatment for regional breast cancer found that higher stress levels were a significant predictor of poorer NK cytotoxicity, poor NK-cell response (Andersen BL, Farrar WB et al. 1998).

3.1.8 The role of Psychotherapeutic interventions in modulating psychological stress and HPA Axis

Psychotherapeutic interventions for cancer patients have been emphasized for the last decade. Helping patients to live their lives as fulfilling as possible during their battles with cancer is a high priority. Studies have also shown that psychological factors can result in behavioral and regulatory-system changes that may affect the future health of the patient and the disease course (Andersen BL, Kiecolt-Glaser JK et al. 1994; Van der Pompe G, Antoni MH et al. 1994; Bovbjerg DH and Valdimarsdottir H 1998). Treating affective states and reducing the psychosocial factors in cancer patients, may help in improving the treatment compliance, reduce treatment related distress and help patient's coping strategies. Growing evidence suggests that psychosocial and psycho-educational interventions are beneficial adjunctive treatments for cancer patients (Carey M and Burish TG 1988; Anderson BL 1992; Tjisburg R, van Knippenberg FC et al. 1992; Fawzy F.I, Fawzy N.W et al. 1993; Meyer TJ and Mark MM 1995). Patients who have used active behavioral coping methods have reported positive affective states, decrease in anxiety and depression, higher levels of self esteem and fewer physical symptoms while those with avoidance coping showed a greater depression, anxiety and lower quality of life (Classen C, Hermanson KS et al. 1994).

Various Psychotherapeutic interventions have been used in cancer patients, such psychotherapeutic intervention includes social support, cognitive-behavioral techniques, coping skills training, information delivery and supportive-expressive group work. All these psychotherapeutic interventions included a focus on education, coping strategies and emotional support (Cain EN, Kohorn EI et al. 1986; Telch CF and Telch MJ 1986;

Cunningham AJ and Tocco EK 1989; Fawzy FI, Cousins N et al. 1990; Samarel N, Fawcett J et al. 1997; Helgeson VS, CohenS et al. 1999).They also included stress management (Telch CF and Telch MJ 1986; Cunningham AJ and Tocco EK 1989; Fawzy FI, Cousins N et al. 1990; Samarel N, Fawcett J et al. 1997) or behavioral training such as hypnosis or progressive relaxation (Cain EN, Kohorn EI et al. 1986; Telch CF and Telch MJ 1986; Cunningham AJ and Tocco EK 1989; Fawzy FI, Cousins N et al. 1990; Samarel N, Fawcett J et al. 1997), Such therapies are imparted individually as well as in groups.

The literature on psychosocial treatment provides uniform evidence for an improvement in mood, coping, adjustment, vigour, and decrease in distressful symptoms among breast cancer patients. (Morrow GR and Morell C 1982; Jacobs C, Ross RD et al. 1983; Forester B, Kornfeld DS et al. 1985; Fawzy FI, Cousins N et al. 1990a; Anderson BL 1992; Burish TG and Tope DM 1992; Iinyckyj A, Farber J et al. 1994; McArdle JMC, George WD et al. 1996; Bottomley A 1997; Owen JE, Klapow JC et al. 2001; Redd WH, Montgomery GH et al. 2001; Mundy EA, DuHamel KN et al. 2003). They help in better coping with the disease by encouraging open expression of emotions and assertiveness in assuming control over the course of the treatment, life decisions, relationships and even influencing survival time (Spiegel D and Yalom I 1978; Spiegel D, Bloom JR et al. 1981; Spiegel D, Bloom JR et al. 1989; Fawzy FI, Cousins N et al. 1990). Most of these interventions facilitate reinforcing social support and stress reduction required to cope effectively with the stressful situations. Several studies have shown beneficial effects of stress reduction over support only interventions (Telch CF and Telch MJ 1986; Greer S, Moorey S et al. 1992). Most of these psychosocial interventions use relaxation and

autogenic training to facilitate stress reduction (Deberry S, Davis S et al. 1989; Burish TG, Snyder SL et al. 1991; Decker TW, Cline-Elsen J et al. 1992; Vasterling J, Jenkins RA et al. 1993; Walker LG, Walker MB et al. 1999; Yang EV and Glaser R 2002; Hidderly M and Holt M 2004). These interventions increase perceived control, decrease the potential stigma associated with having a "psychiatric problem," and provide a supportive environment where patients can discuss their thoughts, fears, and concerns (Meyerowitz B, Heinrick RL et al. 1989; Baum A, Herberman H et al. 1995). Psychosocial interventions have been shown to specifically decrease depression and anxiety and to increase self-esteem and active-approach coping strategies (Fawzy FI, Cousins N et al. 1990).

Studies have demonstrated an intervention effect of psychosocial support on cortisol levels, but research investigating the association between social support and neuroendocrine functioning has been less conclusive (for review,see ref. Uchino BN, Cacioppo JT et al. 1996). Effects of both acute and chronic life stress on neuroendocrine function are well documented (Mason JW 1968; Kirschbaum C, Prussner JC et al. 1995; Kiecolt-Glaser JK, Glaser R et al. 1997; Turner-Cobb JM, Steptoe A et al. 1998). Studies have demonstrated a significant decrease in plasma cortisol following 13-week group psychotherapy and 10-week cognitive-behavioral stress management program among patients of early stage breast cancer (Van der Pompe G, Duivenvoorrden HJ et al. 1997), another study also demonstrated decreased plasma cortisol and increased circulating lymphocytes following 10-week psychological intervention among post surgical breast cancer patients (Schedlowski M, Jung C et al. 1994).One more study also demonstrated a significant reduction in salivary cortisol level following a two day music therapy at a cancer help center on mixed cancer population (Burns SJ, Harbuz MS et al. 2001). Another recent study by YU Hong-

luan, et al., evaluated the effects of brief structured psychotherapy in a randomized controlled study on 60 women with breast cancer in perioperative period, intervention group received 45-minute structured intervention before the operation, the control group had 45 minutes' free talk without intervention showed a significant reduction in anxiety, depression, negative coping scores, and significantly higher self-esteem and positive coping scores and also showed a decrease in plasma cortisol level in intervention group compared to control group (YU Hong-luan, LI Ying et al. 2007). Whereas two more studies on cancer patients showed no change in cortisol level among them one study showed a non significant reduction in serum cortisol following 4 weeks of abdominal breathing training using biofeedback among twenty-five breast cancer patients who had completed adjuvant chemotherapy (Kim KS, Lee SW et al. 2005). Another recent study by Nunes DF et al., evaluated the effects of relaxation and visualization therapy (RVT) randomized controlled study on psychological distress, cortisol levels, and immunological parameters on 34 breast cancer patients undergoing radiotherapy. Intervention group received group RVT for 24 consecutive days and control group received only radiotherapy showed a significant reduction in stress, anxiety, and depression scores. However, cortisol levels as well as proliferation remained unchanged following RVT (Nunes DF, Rodriguez AL et al. 2007). Whereas studies have also shown beneficial effects of various psychotherapeutic intervention on cortisol levels in healthy population also. Studies documented significant reduction in cortisol level following a humorous video show which is related to increase in positive affect (Berk L, Bittmen B et al. 1997; Buchanan T, al'Absi M et al. 1999). Another study also demonstrated a significant reduction in cortisol level following 3 months of resource-activating stress management training on 54 healthy male participants in intervention group compared to control group (Storch M, Gaab J et al. 2007).

3.2 Complementary and alternative therapies

As many as two thirds of adult cancer patients use some form of complementary therapy (CT) during or following standard medical treatment. Determining prevalence rates of cancer patients' use of CT and making comparisons across studies of CT is difficult because of inconsistent definitions among researchers, patients, and providers of what constitutes a complementary and/or alternative therapy (Ernst E and Cassileth BR 1998; Adler SR 1999; Verhoef MJ, Hilsden RJ et al. 1999; Cassileth BR and Deng G 2004) Generally, the definition of CT focuses on the fact that the methods are used in conjunction with, rather than as a substitute for, conventional cancer treatment. Specifically, for example, CT is defined by the American Cancer Society as "those [methods] that patients use along with conventional medicine" (2000).The use of CAM (Complementary and Alternative Medicine) therapies in cancer ranges from 10% to more than 60% (Ernst E and Cassileth BR 1998; Adler SR 1999; Verhoef MJ, Hilsden RJ et al. 1999; Cassileth BR and Deng G 2004). The data monitor 2002 survey indicated that 80% of cancer patients used CAM modalities. There was also found to be an average prevalence rate of 56.6% in a population of patients with hematologic malignancies in an Indian study (Gupta M, Shafiq N et al. 2002). Such CAM therapies have been particularly popular among women with breast cancer (Wyatt GK, Friedman LL et al. 1999; Morris KT, Johnson N et al. 2000; Tagliaferri M, Cohen I et al. 2001); the frequency of use among these patients ranges from 28%15 to 72%. (Adler SR 1999). Research suggests that breast cancer patients who employ CAM tend to be younger and have higher levels of education and income. (Adler SR 1999; Burstein HJ, Gelber S et al. 1999; Verhoef MJ, Hilsden RJ et al. 1999; Wyatt GK, Friedman LL et al. 1999; Moschèn R, Kemmler G et al. 2001). In terms of medical parameters, CAM use appears to be more common among women with late-stage breast cancer than among those with early-stage cancer. (Verhoef MJ, Hilsden RJ et al. 1999; Lee MM, Lin SS et al. 2000) With regard to lifestyle behaviors, regular exercise, not smoking, social integration (e.g., involvement in community or

religious groups), and support group attendance have all been found to be associated with the use of CAM. (Boon H, Stewart M et al. 2000; Lee MM, Lin SS et al. 2000). Finally, a patients' emotional state may influence the use of CAM; a few reports suggest that women who employ CAM report more symptoms of depression as well as anxiety about cancer recurrence than do nonusers. (Burstein HJ, Gelber S et al. 1999; DiGianni LM, Garber JE et al. 2002). Women with breast cancer use various forms of CAM, including exercise, dietary/nutritional therapies, massage, acupuncture, herbs, and prayer/spiritual healing. (Vande CreeK L, Rogers E et al. 1999; Morris KT, Johnson N et al. 2000; Tagliaferri M, Cohen I et al. 2001; DiGianni LM, Garber JE et al. 2002). Despite the widespread use of CAM, most women do not abandon conventional treatments but rather use CAM as a supplement to standard medical care.(Tagliaferri M, Cohen I et al. 2001). Mind body therapies are found to be the most widely used complementary therapy among the cancer patients (Ernst E and Cassileth BR 1998). Most of these mind body therapies focus on principles of stress reduction. Techniques of stress management that have proven helpful include progressive muscle relaxation (Sloman R 1995; Arakawa S 1997), guided imagery (Burish TG, Snyder SL et al. 1991; Baider L, Uziely B et al. 1994; Walker LG, Walker MB et al. 1999) and meditation (Cacioppo JT, Malarkey WB et al. 1995; Massion A, Teas J et al. 1995; Coker KH 1999; Speca M, Carlson LE et al. 2000). Stress management programs delivered prior to treatment have enabled patients to tolerate therapy with less reported side effects (Burish TG and Tope DM 1992; Manyande A, Berg S et al. 1995; Syrjala K, Donaldson DW et al. 1995; Arakawa S 1997). Meditation may help decrease intrusive thoughts or the tendency to ruminate on or to avoid thoughts about stressors, a behavior that exacerbates the impact of stress if it continues for prolonged periods (Horowitz M, Wilner N et al. 1979; Devine D, Parker A et al. 2003). Even though stress-reduction methods are many and varied, they all are based on the

same principles of attention diversion, relaxation and cognitive restructuring. Yoga is one such modality which has been found to use many of the above techniques with promising results.

3.3 Yoga

Yoga is an ancient, Indian science and is one among the six great Indian philosophies which has evolved over thousands of years. In the spiritual dimension yoga is a path towards attainment of super conscious states beyond sensory perception and knowledge. It deals with the physical, mental, moral and spiritual wellbeing of an individual (Iyengar BKS 2000). References to yoga are made throughout the Vedas, ancient Indian scriptures that are among the oldest texts in existence (Vidyankar P 1998).The earliest systematic description of this practice and various philosophies was codified into 196 aphorisms in the classic treatise the "Yoga Sutras" of Patanjali, dating back to 900 B.C. (Taimini I 1961), which helped to define the modern practice of yoga [Swami Prabhavananda]. This pragmatic description enumerates eight stages of yoga, which if practiced systematically allows one to attain a state of sublimation of all mental modifications in the mind and super consciousness (*Samadhi*). These systematic yoga techniques include yamas (moral doctrines), niyamas (disciplines), asanas (postures), pranayama (regulated nostril breathing/breath control), pratyahara (introspection/ in drawing mind away from perceptible external sensory stimuli), dharana (concentration), dhyana (meditation) and finally to attain a state of Samadhi (absorption). Attainment of such a contemplative absorptive state has been elucidated to confer a blissful state of mind and body. Similar references to these practices can be found in Buddhist scriptures who equate these yogic practices to mindful exercises. This is also popularly known as Mindfulness Based Stress Reduction (MBSR) program.

World over, the term yoga usually refers to the third and fourth limbs, asana and pranayama, although traditionally the limbs are viewed as interrelated. It is important to note that each of these approaches represents a distinct intervention, in the same way that psychodynamic, cognitive behavioral, and interpersonal therapies each involve different approaches to psychotherapy (Bower JE, Alison Woolery MA et al. 2005). However, ancient Indian yoga scriptures have alluded that each of these 8 limbs (steps) affects different aspects of health. Accordingly a holistic concept of health has been proposed in the Upanishads which states that every human being has five existential states. The gross physical body or *annamaya kosa* with organs and systems, the subtle functional body or *pranamaya kosa* responsible for all physiological functions, the mind with thoughts and emotions as the *manomaya kosa* , the intellect or the reasoning as *vignanamaya kosa* and finally the inherent blissful states of awareness called the *anandamaya kosa*. The psychosomatic phenomena of disease is explained as a change in perception and ignorance in *vignanamaya kosa* leading to mental turmoil or stress in *manomayakosa* which, percolates as physiological changes in the *pranamaya kosa* to finally culminate in organic changes in the physical body or *annamayakosa*. By using different yoga practices to act at all these 5 levels we can correct the imbalances at each of these *kosas* and restore the homeostasis. For e.g. we use asanas and kriyas at *annamaya kosa* level, pranayama at *Pranamaya kosa* , relaxation and meditation at *manomaya kosa* level, counseling at vignanamayakosa and finally by increasing ones internal awareness of these levels with these practices and relaxing we attain deeper states of bliss which is responsible for restoring the homeostasis. By integrating all these practices for attaining health and well being we have developed an integrated yoga module for cancer to act at all these levels.

3.3.1 Yoga research-clinical applications

Yoga is traditionally believed to have beneficial effects on physical and emotional health. Over the last several decades, investigators have begun to subject these beliefs to empirical scrutiny. Most of the published studies on yoga were conducted in India, although a growing number of trails have been conducted in the United States and other Western countries. Various studies used diverse styles of yoga and consequently emphasized different components (e.g. postures, breathing, mediation and relaxation) and involved varying degrees of intervention intensity. Of note, yoga has demonstrated effects on a variety of other outcomes, including cardiopulmonary, musculoskeletal, perceptual and cognitive function. Several research studies over the years have shown yoga as a very useful mind-modifying technique with potential applications in the promotion of positive health, prevention and treatment of disease, as well as in rehabilitation.

Normal volunteers were shown to have a better sense of well-being following ten months of yoga physical postures (Ray US, Mukhopadhyaya S et al. 2001). Bera and Rajapurkar (1993) have shown that one year yoga training in school students can improve ideal body weight, bone density and cardiovascular endurance along with a significant reduction in fat fold and body circumference measurements. Such promotive health benefits are due to its ability to establish stable autonomic balance (Singh S, Malhotra V et al. 2004), development of hypo metabolic state (Wallace RK, Benson H et al. 1971) improvement of physical efficiency (Ray US, Mukhopadhyaya S et al. 2001), improvement of thermoregulatory efficiency (Selvamurthy W, Ray US et al. 1988), increase in cardiopulmonary functions (Raub JA 2002), improved mood states(Wood C 1993; Woolery A, Myers H et al. 2004; Lavey R, Sherman T et al. 2005) and a tranquil state of mind to combat stress (Joseph CD 1983).

As a preventive role studies have demonstrated possible role of yoga in reducing cardiovascular risk, as yoga establishes a healthy metabolic profile (Bijlani RL, Vempati RP et al. 2005) and

reduce hypertension (Datey KK, Deshmukh SN et al. 1969; Sainani GS 2003). Preventive role in NIDDM is due to improved insulin kinetics, reduction in insulin resistance and increase in glucose utilization (Sahay BK and Sahay RK 2002).

Yoga has also been used for therapeutic benefit in numerous health care concerns where mental stress was believed to play a role. Yoga practices have shown to reduce airway sensitivity and improve pulmonary functions and decrease medication score in asthmatics (Nagarathna R and Nagendra HR 1985). Yoga has been used in rehabilitating patients with arthritis in elderly population (Garfinkel M, Schumacher HR Jr et al. 1994). It has been found to retard progression of coronary artery disease (Manchanda SC, Narang R et al. 2000) and control blood glucose levels in NIDDM (Jain SC, Uppal A et al. 1993). It has also been found useful in pulmonary tuberculosis, preventing epileptic seizures, improving pregnancy outcomes (Narendran S, Nagarathna R et al. 2005).

In addition, we consider yoga studies conducted with noncancerous patients that examined psychological and somatic symptoms that are common among cancer populations, including sleep, fatigue, depressed mood, and pain (Patrick DL, Ferketich SL et al. 2003). A limited number of published trails have examined yoga interventions for individuals with depression. A research team in India found that patients with untreated melancholic depression who were randomly assigned to receive sudarshan Kriya yoga, which involves specific breathing exercises, showed significant improvements in depressed mood that were comparable to those seen in patients assigned to receive medication or electroconvulsive therapy (Janakiramaiah N, Gangadhar BN et al. 2000). Significant reductions in depressed mood were also found among college students with depression who were randomly assigned to practice a specific yoga relaxation pose for 30 days (Kumar SS, Kaur P et al. 1993). Yoga interventions may also be beneficial for sub clinical

depression. A recent trial found that college students with mild depressive symptoms randomly assigned to a 5 week Iyengar yoga intervention showed significant improvements in depressed mood and anxiety compared with a wait-list control group (Woolery A, Myers H et al. 2004). This intervention emphasized poses that are thought to alleviate depression, including backbends, standing poses, and inversions (Iyengar BKS 2000). Similar effects on mood have been observed in uncontrolled studies. For example, a six-session yoga and meditation intervention was effective in reducing depression and anxiety among dementia caregivers (Waelde LC, Thompson L et al. 2004).

Studies conducted with healthy individuals further support the mood-enhancing effects of yoga. Two randomized trials, both conducted in India, found that yoga interventions including postures, breathing and relaxation/meditation led to significant reductions in anxiety and depression among college and medical students (Malathi A and Damodaran A 1999; Ray US, Mukhopadhyaya S et al. 2001). A third study found no changes in anxiety or depression but significant improvements in well being (including general health and sleep quality) among healthy soldiers randomly assigned to practice postures, breathing, and meditation for 3 months (Harinath K, Malhotra AS et al. 2004). In two nonrandomized trials, a single session of yoga was associated with significant reductions in perceived stress and negative affect (West J, Otte C et al. 2004) and improvements in mood (Netz Y and Lidor R 2003) that were comparable to changes seen with aerobic exercise. In another report, 30 minutes of yoga stretching and breathing led to increases in mental and physical energy, alertness, and enthusiasm relative to relaxation and visualization (Wood C 1993).

3.3.2 Mindfulness – Based Stress Reduction

MBSR is a technique similar to that of yoga developed by Kabat-Zinn at the university of Massachusetts Medical Center in 1979. An operational working definition of mindfulness is 'moment-to-moment non-judgmental awareness'. Mindfulness has also been defined as a Zen-like approach to meditation, in which the individual focuses completely on the activity or event occurring at that moment. MBSR is a specific highly structured psycho educational and skill based therapy package that combines mindfulness meditation (also known as vipassana or insight meditation (Ott MJ 2004) with hatha yoga exercises. Research to date has included assessment of MBSR interventions for chronic pain (Kabat-Zinn J, Lipworth L et al. 1985), anxiety (Miller JJ, Fletcher KE et al. 1995).

3.3.3 Scientific studies on Yoga

One of the first published studies (Joseph CD 1983) of yoga for cancer patients was conducted in India. This early trial, which lacked a control group, examined the effects of yoga among 50 ambulatory cancer patients undergoing daily radiation therapy. The yoga intervention consisted of two 90-minute sessions per week and was conducted in groups of 10 to 12 patients. Patients were taught "a series of simple Yogic relaxation exercises; no strenuous exercises were given". No information was provided on the number of sessions attended. There was no formal pre and post intervention assessment; instead patients indicated whether or not they perceived benefits in particular domains. Benefits reported included improvement in particular domains. Benefits reported included improved appetite (22%), and improved sleep (22%), improved bowel habits (26%), and feeling of peace and tranquility (20%). Of note, more recent trials have focused on similar outcomes, particularly sleep and relaxation.

In 2004, Cohen and colleagues published a randomized, controlled trial of Tibetan yoga for cancer patients (Cohen L, Warneke C et al. 2004). Tibetan yoga is less common than Indian

techniques in the United States and has received less empirical scrutiny. The intervention consisted of 7 weekly sessions that included three components: controlled breathing and visualization: mindfulness; and simple postures from the Tibetan yoga practices of Tsa lung and Trul khor done with specific breathing patterns. The general goals of the intervention were to reduce stress and improve patient's quality of life. Yoga group participants were encouraged to practice the techniques at least once per day. Thirty-nine participants with stage I-IV lymphoma were randomly assigned to either the yoga group or a wait list control group. Twenty one percent of participants were receiving chemotherapy at the time of the study, and the remainder had completed chemotherapy within the past 12 months. Patients completed questionnaires assessing mood, energy, and sleep at baseline and at 1 week, 1 month, and 3 months post intervention. One intervention group participant dropped out before study onset and 8 patients did not complete the follow up questionnaires. Thus, analyses focused on 30 subjects, with 16 in the yoga group and 14 in the control group. Results suggest that this intervention was feasible for this patient population and had beneficial effects on certain aspects of quality of life. Over half (58%) of patients assigned to the yoga intervention attended at least 5 of the 7 sessions, 32% attended 2 to 3 sessions, and 10% attended only 1 session. Participants practiced an average of two times per week at home. Yoga group participants reported significant improvements in overall sleep quality compared to controls, including falling asleep more quickly, sleeping longer, and using fewer sleep medications. There were no intervention effects on fatigue, depressed mood, anxiety, or cancer-related distress.

Cohen and colleagues recently completed a second trial of Tibetan yoga for breast cancer patients, which were presented at the annual meeting of American Psychosomatic Society (Cohen L, Thornton B et al. 2005). The yoga intervention consisted of 7 weekly sessions as described above, with home practice encouraged. Fifty-eight women with stage I-III cancer

were randomly assigned to either the yoga group or a wait list control group. Almost half (48%) of participants were undergoing active treatment. Patients completed measures of mood, sleep, cancer-related distress, cancer-related symptoms (including pain, fatigue, nausea, appetite and cognitive disturbance) and quality of life at baseline and at 1 week, 1 month, and 3 months post intervention.

Results again support the feasibility and potential efficacy of this yoga program, although the benefits seen in this study differed from those evidenced in the initial trial. Data on adherence was not available, but 63% of yoga participants reported that they found the yoga program useful and over 70% reported that they practiced at least once a week. Compared to controls, the yoga group reported fewer cancer-related symptoms at the 1 week follow up. In contrast to results seen in the first trial, no effects on sleep were observed, and there were no intervention effects on mood or quality of life. It is possible that the different outcomes observed in these two trials were due to differences in the study samples, including type of cancer (lymphoma vs. breast), stage of disease (stage I-IV vs. stage I-II), and percentage of patients undergoing active treatment.

A third randomized, controlled trial of yoga for cancer patients was recently published in a non-peer reviewed yoga journal (Culos-Reed S, Carlson LE et al. 2004). This 7 week intervention was based on Hatha yoga and was influenced by Iyengar techniques and kinesiology. During weekly 75 minute classes, participants were taught modified versions of yoga postures that involved gentle stretching and strengthening exercises and finished with 15 minutes of relaxation in corpse pose (i.e., Shavasana). The general goals of this intervention were to improve physical fitness, reduce stress and improve mood and quality of life. Thirty-eight participants were randomly assigned to either the intervention group or a wait list control. The sample included a

mixed group of cancer survivors (primary breast cancer survivors) who were a minimum of 3 months post treatment (mean = 56 months post diagnosis). Participants completed measures of mood, stress, quality of life, and physical activity before and immediately after the intervention. Weight and physical function (grip strength, flexibility and 6 minute walk) were also assessed. Results provide preliminary evidence for the efficacy of this program, although the analysis plan did not allow for a direct comparison of changes in intervention vs. control group participants. Instead, the investigators compared post intervention scores in the two groups (without a consideration of pre intervention scores) and evaluated the significance of changes within the yoga group from pre intervention to post intervention. No information was provided on adherence. There were no significant differences between the yoga and control groups at pre intervention. At post intervention, yoga group participants reported lower levels of total mood disturbance and stress and higher levels of global quality of life and pain than control participants reported. Increases in pain were attributed to increased body awareness. Yoga participants walked a longer distance in the 6 minute walk test and had a lower resting heart rate at post intervention than the control participants, although they also had a higher body weight. No significant differences were observed on measures of fatigue, sleep disturbance, cognitive function, or physical activity. Examination of change scores within the yoga group showed improvements on only two measures: cardiopulmonary stress symptoms (one of 10 dimensions of stress evaluated) and distance walked from pre intervention to post intervention. Overall, results suggest that this intervention may have beneficial effects on cardiopulmonary symptoms and certain aspects of physical function, which is consistent with research conducted with noncancerous population[5]. Effects on mood, stress and other aspects of quality of life are tenuous and require more careful statistical evaluation.

A small pilot study was recently conducted by these investigators to evaluate the effect of this yoga program on a hormonal measure of stress–salivary cortisol. Study results were reported at the annual meeting of the American Psychosomatic Society (Carlson LE, Culos-Reed N et al. 2005). Twenty participants with mixed cancer diagnoses who had completed cancer treatment were randomly assigned to the yoga intervention (n=10) or a wait list control (n=10). The majority of participants were women. Participants provided saliva samples to assess diurnal cortisol rhythm and also completed measures of mood, stress and quality of life before and after the 7 week intervention. Analyses were conducted to compare scores on these measures at post intervention. Results indicated that yoga group participants reported significantly better quality of life and less mood disturbance at post intervention than controls, although failure to consider pre intervention scores renders these findings preliminary. No group differences were observed in mean cortisol levels or diurnal cortisol slope, although given the small sample size, short intervention period, and the fact that the yoga intervention was not necessarily designed to impact the endocrine system.

A pilot study was conducted by these investigators to evaluate the effect of this randomized yoga program on physical and psychological benefits afforded by a 7-week yoga program for cancer survivors. Thirty eight participants were randomly assigned to the yoga intervention (n=20) or control group (n=18). All participants completed pre- and post-testing assessments immediately before and after the yoga program. The yoga program participants (M age=51.18 (10.33); 92% female) included primarily breast cancer survivors, on average 55.95 (54.39) months post-diagnosis. Results indicated that significant differences between the intervention and the control group at post-intervention were seen only in psychosocial (i.e. global quality of life, emotional function, and diarrhea) variables. There were also trends for group differences, in the hypothesized directions, for the psychosocial variables of emotional irritability,

gastrointestinal symptoms, cognitive disorganization, mood disturbance, tension, depression, and confusion. Finally, there were also significant improvements in both the program participants and the controls from pre- to post-intervention on a number of physical fitness variables. These initial findings suggest that yoga has significant potential and should be further explored as a beneficial physical activity option for cancer survivors. Future research might attempt to include a broader range of participants.

Another pilot study conducted by (Carson JW, Carson KM et al. 2007) Carson JW et al to evaluate the effect of yoga-based palliative intervention, the Yoga of Awareness Program, in a sample of women with metastatic breast cancer. Thirteen women completed the intervention (mean age=59; mean time since diagnosis=7 years; two African American, 11 Caucasian). Outcome measures were assessed using daily measures of pain, fatigue, distress, invigoration, acceptance, and relaxation during two pre intervention weeks and the final two weeks of the intervention. The eight-week protocol included gentle yoga postures, breathing exercises, meditation, didactic presentations, and group interchange. During the study, four participants had cancer recurrences, and the physical condition of several others deteriorated noticeably. Despite low statistical power, pre-to-post multilevel outcomes analyses showed significant increases in invigoration and acceptance. Lagged analyses of length of home yoga practice (controlling for individual mean practice time and outcome levels on the lagged days) showed that on the day after a day during which women practiced more, they experienced significantly lower levels of pain and fatigue, and higher levels of invigoration, acceptance, and relaxation. These findings support the need for further investigation of the effects of the Yoga of Awareness Program in women with MBC.

Another pilot study conducted by Danhauer SC, et al to evaluate the effect Restorative yoga (RY) intervention as a supportive therapy for women diagnosed with ovarian or breast cancer. Fifty-one women with ovarian (n = 37) or breast cancer (n = 14) with a mean age of 58.9 years enrolled in this program; the majority (61%) were actively undergoing cancer treatment at the time of enrollment. Outcome measures were assessed using self-reported fatigue, psychological distress and well-being, and quality of life at baseline, immediately post intervention, and 2 months post intervention. The intervention includes 10 weekly 75-minute RY classes that combined physical postures, breathing, and deep relaxation. Results indicated significant improvements for depression, negative effect, state anxiety, mental health, and overall quality of life. Fatigue decreased between baseline and post intervention follow-up. Health-related quality of life improved between baseline and the 2-month follow-up. Qualitative feedback from participants was predominantly positive; relaxation and shared group experience were two common themes (Danhauer SC, Tooze JA et al. 2008).

Another study by, Moadel and colleagues examined the effects of yoga among underserved breast cancer patients. (Moadel AB, Shah C et al. 2007). The 12 week intervention consisted of weekly 90 minute yoga classes based on Hatha yoga that included gentle stretching, breathing exercises, and meditation/sitting relaxation. Classes were done in a chair or on the floor, depending on ability and limitations, with blankets and blocks for support. An audiotape and compact disk were provided for daily at-home practice. Women with stage I-III breast cancer were randomly assigned to the yoga group (n=84) or a wait-list control group (n=44). All had been diagnosed with cancer within the past 5 years (mean =1.09 years), and 48% of participants were receiving medical treatment throughout the study, 31% experienced a change in treatment status. Participants were 42% African American, 31% Hispanic, and 23% white. Participants completed measures of quality of life at baseline and 3 months post intervention.

Within the total intervention group (n=108), there was considerable variability in adherence to the 12-week intervention, with a range of zero to 19 classes attended. Nearly three quarters of study dropouts did not participate in the intervention at all. Although 26 study completers (31%) did not attend classes, eight of these patients reported practicing yoga at home at least a few times per week. The mean number of classes attended by active class participants was 7.00 ± 3.80 classes. No changes were seen in either group in physical, functional, or spiritual well-being or in symptoms of fatigue. Secondary analyses of 71 patients not receiving chemotherapy during the intervention period indicated favorable outcomes for the intervention group compared with the control group in overall QOL, emotional well-being, social well-being, spiritual well-being, and distressed mood. Lower adherence was associated with increased fatigue, radiotherapy, younger age and no antiestrogen therapy.

Recent study conducted by Raghavendra Rao et al., from this institution included Ninety-Eight recently diagnosed stage II and III breast cancer patients in a randomized controlled trial comparing the effects of a yoga program with supportive therapy during their conventional cancer treatments. The main objectives of the study were to evaluate the effects of yoga intervention on mood states, treatment related symptoms and toxicity, Quality of life and Immune outcomes in breast cancer patients undergoing conventional cancer treatments. Psychometric assessments Speilberger's State Trait Anxiety Inventory, Beck's Depression Inventory, Symptom Checklist, Functional Living Index of Cancer, Common Toxicity Criteria and Morrow Assessment of Nausea and Emesis done before and after surgery, before, during and following radiotherapy and chemotherapy. Immune assessments were serum immunoglobulins, cytokines such as IL2Ralpha, TNF alpha, IFN gamma and T lymphocyte subsets such as CD4+%, CD8+%, CD3+% and CD56+% were assessed before and after surgery, radiotherapy and chemotherapy. A total of 69 patients contributed data at the second assessment (post surgery-4

weeks after surgery), 67 patients during and following radiotherapy and 62 patients during and following chemotherapy. The intervention group received “integrated yoga program” and the control group received “supportive counseling sessions” both imparted as individual sessions. The yoga intervention included sessions with didactic lectures and interactive sessions on philosophical concepts of yoga and importance of these in managing day-to-day stressful experiences (10 minutes) beginning every session. Followed by a preparatory practice (20 minutes) with few easy yoga postures, breathing exercises and pranayama and yogic relaxation. The subjects were then guided through any one of the meditation practices for next 30 minutes which included focusing awareness on sounds and chants from Vedic texts (Telles S, Nagarathna R et al. 1998), or breath awareness and impulses of touch emanating from palms and fingers while practicing yogic mudras, or a dynamic form of meditation which involved practice with eyes closed of four yoga postures interspersed with relaxation while supine, thus achieving a combination of both “stimulating” and “calming,” practice (Telles S, Reddy SK et al. 2000). In meditation, participants developed clarity in their thinking, learn to observe their own mind, decrease negative mind states and develop positive mind states and maintain equipoise in their emotions. These sessions were followed by informal individual counseling sessions that focused on problems related to impediments in home practice, clarification of participant’s doubts, motivation, and supportive interaction with spouses. The participants were also informed about practical day-to-day application of awareness and relaxation to attain a state of equanimity during stressful situations and were given homework in learning to adapt to such situations by applying these principles. The subjects underwent 4 such in person sessions during their pre and post operative period and were asked to undergo 3 in person sessions every week for 6 weeks during their adjuvant radiotherapy treatment in the hospitals with self practice as homework on the remaining days. During chemotherapy subjects underwent in person sessions during their

hospital visits for chemotherapy administration (once in twenty one days) and were also imparted in person sessions by their trainer once a week and were asked to practice daily for an hour for six days/week as homework. Results from this study showed a significant decrease in anxiety states during radiotherapy and chemotherapy in the yoga group as compared to controls. There was a significant decrease in anxiety trait following surgery, radiotherapy and chemotherapy in the yoga group as compared to controls. Compared to control group, yoga group reported significant decrease in depression following surgery and during and following radiotherapy and chemotherapy which is published recently (Raghavendra Rao M, Nagarathna Raghuram et al. 2009). There was also a significant decrease in severity and distress of symptoms following surgery and decrease in number of symptoms, severity and distress, during and following radiotherapy and chemotherapy. There was also a significant improvement in overall quality of life at all follow-up assessments in yoga group, compared to controls. There was a significant decrease in post chemotherapy nausea frequency and intensity, and anticipatory vomiting and nausea intensity in yoga group, compared to controls (Raghavendra RM, Nagarathna R et al. 2007). There was a decrease in overall toxicity score in yoga group as compared to controls. Post operatively, yoga intervention significantly reduced duration of hospitalization, drain retention, interval for suture removal and post operative complications (Raghavendra Rao M, Nagendra HR et al. 2008). Yoga group had significantly higher CD56% counts and lesser plasma TNF alpha levels and serum IgA levels following surgery as compared to controls. Yoga group also showed significantly higher CD56% counts after 24 weeks of intervention than controls (Rao RM, Telles S et al. 2008).

3.3.4 Scientific studies on Yoga and Mindfulness – Based Stress Reduction in Cancer

A Canadian research group has conducted several studies with cancer patients that included modified yoga exercises as part of a mindfulness meditation based stress reduction (MBSR) program (Speca M, Carlson LE et al. 2000; Carlson LE, Speca M et al. 2003; Carlson LE, Speca M et al. 2004). The MBSR intervention was based on the work of Kabat-Zinn and colleagues (Kabat-Zinn J 1990) and included the following components: (1) theoretical material related to mindfulness, relaxation, meditation, yoga and the body-mind connection, (2) experiential practice of meditation and yoga during the group meetings and home–based practice, and (3) group process focused on solving problems concerning impediments to effective practice, day-to-day applications of mindfulness, and supportive interactions between group members. Yoga exercises were a central part of the intervention. Gentle, often modified yoga stretches were practiced for approximately 30 minutes in each 90 minute session, with a focus on body awareness rather than form. A booklet and audiotape were also provided.

One of the first studies on mindfulness meditation in cancer was conducted in men with prostate cancer (Coker KH 1999). Coker conducted a study using mindfulness meditation for men with prostate cancer and found that mindfulness meditation was beneficial in reducing stress, leading to strengthening of the immune system function, addressing quality of life questions, enhancing general health and wellness, providing personal and existential growth, and augmenting the body's natural oncostasis through production of melatonin.

A second study was conducted with 109 cancer patients who were heterogeneous in terms of type and stage of cancer (Speca M, Carlson LE et al. 2000). Participants were randomly assigned to either the intervention group (n=61) or a waitlist control group (n=48). They completed mood and stress measures at baseline and immediately following the 7 week intervention. Compliance with this treatment program was good; among the participants in the intervention

group, approximately 64% attended 6 or more sessions (out of 7), 23% attended 4 or 5 sessions, and 13% attended 3 or fewer (of note, these patients were considered to be "dropouts" and not included in the analyses). Further, the average daily meditation time for intervention participants was 32 minutes. Results showed a beneficial effect on total stress and mood disturbance, with a 65% reduction in total mood disturbance in MBSR participants compared to a 12% reduction in controls. More conservative intent–to-treat analysis yielded a similar pattern of results. In regression analysis, the number of minutes of at home practice predicted greater declines in total mood disturbance.

A second uncontrolled trial conducted by this research group focused on patients with early-stage breast and prostate cancer (Carlson LE, Speca M et al. 2003; Carlson LE, Speca M et al. 2004). The intervention was similar to that described above but was provided over 8 weeks and included a 3 hour silent retreat between weeks 6 and 7. All 59 study participants were at least 3 months post treatment (median=6 months, range=3 months to 2 years). Participants completed measures of mood, quality of life, stress and health behaviors, and they also provided blood and saliva samples for immune and hormonal analysis before and after the intervention. Results from this trial provide further support for the feasibility and efficacy of this intervention for cancer patients, although the absence of a control group renders the findings preliminary. In addition, the specific outcomes that improved in this trial differed somewhat from those in the first study. Analyses were based on 42 patients (33 with breast cancer, 9 with prostate cancer) who attended 7 or more sessions and completed both the pre intervention and post intervention measures. The average daily practice time was 24 minutes of meditation and 13 minutes of yoga. The intervention group showed significant improvements in overall quality of life, total stress and health behaviors such as caffeine use, exercise, and appetite. However, in contrast to the first trial, no changes were observed in mood. There was also no significant

change in cancer-related symptoms, including fatigue, nausea, and pain. Results for sleep quality were mixed. The differences in study results may have been due to differences in the study samples, particularly differences in stage of disease (stage I-IV vs. stage I-II) and percentage of participants undergoing cancer treatment. Changes in intracellular cytokine production were observed, but there were no changes in average daily salivary cortisol, diurnal cortisol slope, plasma dehydroepiandrosterone sulfate (DHEAS), or salivary melatonin.

A similar mindfulness-based stress reduction program was evaluated in a sample of women with breast cancer, focusing specifically on sleep disturbance (Shapiro SL, Bootzin RR et al. 2003). The intervention was adapted from the work of Kabat-Zinn and consisted of six weekly 2-hour sessions and one 6-hour silent retreat. Participants were instructed in sitting meditation, body scan, and Hatha yoga, which was described as "stretches and postures designed to enhance greater awareness and to balance and strengthen the musculoskeletal system". Didactic material on effects on stress was also presented and cognitive–behavioral methods of coping discussed. All participants were originally diagnosed with stage II breast cancer, were post treatment (mean=13.4 months, range=2 to 25 months), and were randomly assigned to either the intervention program or to a "free choice" control group that was encouraged to engage in stress management activities. Participants completed sleep diaries before the intervention and at 1 week, 3 months, and 9 months after the intervention. One woman dropped out of each group before study onset. Follow up data were available from 86% of study participants (n=54).

Despite reasonable adherence, this intervention had a minimal effect on sleep disturbance. Eighty-four percent of women who began the intervention program completed at least four of the seven sessions. Results showed no change in sleep quality or efficiency in the intervention group relative to the control condition. However, there was some evidence that participants in

the intervention group who engaged in more informal practice of mindfulness techniques (such as bringing mindfulness awareness to daily activities) were more likely to feel refreshed after sleep at post intervention. A recent study showed improvement in quality of life following 7 week yoga program (Culos-Reed SN, Carlson LE et al. 2006).

Another recent mindfulness-based stress reduction program uncontrolled trial conducted by Carlson LE, et al was evaluated in a sample of early stage breast and prostate cancer patients focusing on quality of life (QoL), symptoms of stress, mood and endocrine, immune and autonomic parameters. The intervention consisted of eight-week MBSR program that incorporated relaxation, meditation, gentle yoga and daily home practice. Demographic and health behaviors, QoL, mood, stress symptoms, salivary cortisol levels, immune cell counts, intracellular cytokine production, blood pressure (BP) and heart rate (HR) were assessed pre- and post-intervention, and at 6- and 12-month follow-up. Fifty-nine, 51, 47 and 41 patients were assessed pre- and post-intervention and at 6- and 12-month follow-up, respectively, although not all participants provided data on all outcomes at each time point. Linear mixed modeling showed significant improvements in overall symptoms of stress which were maintained over the follow-up period. Cortisol levels decreased systematically over the course of the follow-up. Immune patterns over the year supported a continued reduction in Th1 (pro-inflammatory) cytokines. Systolic blood pressure (SBP) decreased from pre- to post-intervention and HR was positively associated with self-reported symptoms of stress. This program was associated with enhanced quality of life and decreased stress symptoms, altered cortisol and immune patterns consistent with less stress and mood disturbance, and decreased blood pressure. These pilot data represent a preliminary investigation of the longer-term relationships between MBSR program participation and a range of potentially important biomarkers.

Another non-randomized controlled design study by Witek-Janusek L et al was conducted to evaluate the effect and feasibility of a mindfulness based stress reduction (MBSR) program on immune function, quality of life (QOL), and coping in women recently diagnosed with breast cancer. Early stage breast cancer patients, who did not receive chemotherapy, self-selected into an 8-week MBSR program or into an assessment only, control group. Outcomes were evaluated over time. The first assessment was at least 10 days after surgery and prior to adjuvant therapy, as well as before the MBSR start-up. Further assessments were mid-MBSR, at completion of MBSR, and at 4-week post-MBSR completion. Women with breast cancer enrolled in the control group (Non-MBSR) were assessed at similar times. At the first assessment (i.e., before MBSR start), reductions in peripheral blood mononuclear cell NK cell activity (NKCA) and IFN-gamma production with increases in IL-4, IL-6, and IL-10 production and plasma cortisol levels were observed for both the MBSR and Non-MBSR groups of breast cancer patients. Over time women in the MBSR group re-established their NKCA and cytokine production levels. In contrast, breast cancer patients in the Non-MBSR group exhibited continued reductions in NKCA and IFN-gamma production with increased IL-4, IL-6, and IL-10 production. Moreover, women enrolled in the MBSR program had reduced cortisol levels, improved QOL, and increased coping effectiveness compared to the Non-MBSR group. In summary, MBSR is a program that is feasible for women recently diagnosed with early stage breast cancer and the results provide preliminary evidence for beneficial effects of MBSR; on immune function, QOL, and coping.

The existing studies have included patients with a variety of diagnoses (e.g. lymphoma, breast, prostate), stages of disease, and treatment status (e.g. on vs. off treatment). Despite this heterogeneity, the interventions appear to have been well tolerated by participants, and adherence has generally been good. Of note, most of the trials utilized “gentle” poses and stretching that could be performed even by patients with functional limitations. It is likely that

this careful approach minimized adverse consequences of treatment and improved compliance. Studies conducted with noncancerous populations further demonstrate the feasibility and adaptability of yoga interventions for individuals with chronic medical conditions.

Results also provide preliminary support for the efficacy of yoga interventions for cancer patients. Positive effects have been seen on a variety of outcomes, including sleep quality, mood, stress, cancer-related distress, cancer related symptoms, and overall quality of life, as well as functional and physiological measures. These effects were evident across a number of different therapeutic approaches, some of which incorporated both postures and seated mindfulness/meditation practice (e.g. Tibetan yoga, mindfulness, based stress reduction) and others that emphasized yoga postures and relaxation. It should be noted that several of these trials had methodological limitations that render the findings preliminary, including small sample size, lack of a control group, and inadequate statistical analyses. Results from the cancer trials are bolstered by studies conducted with noncancerous populations, which have demonstrated positive effects on similar outcomes (e.g. improvements in mood and fatigue). These studies were typically more methodologically rigorous than those conducted with cancer populations and often included active control groups (e.g. relaxation, exercise, and medication), lending further support to results. It is important to note that the studies reviewed here represent only some of the possible benefits of yoga. A growing body of research has shown positive effects of yoga on outcomes ranging from cardiopulmonary function (Raub JA 2002), to perceptual and motor skills (Telles S, Ramprabhu V et al. 2000), which may also be relevant for cancer patients and survivors.

3.3.5 Summary of Literature

Table 3.3.5.1: Summary of effects of stress on cortisol responses

Authors	Study Sample	Stressors	Hormone measures	Outcome
(Kirschbaum C, Prussner JC et al. 1995)	20 healthy male subjects	Exposed 5 times to same psychological stress (public speaking & Mental arithmetic in front of an audience) with one stress session per day	Cortisol	Increased cortisol on each of the five days, the mean response decreased from day 1 to 2:no further attenuation on the remaining days
(Singh A, Petrides JS et al. 1999)	27 healthy men categorized as 14 high responders and 13 low responders based on ACTH response to high intensity exercise after pretreatment with dexamethasone	Psychological stress such as interview and mental arithmetic test	Plasma ACTH, Cortisol, Heart rate, Blood pressure	Increased heart rate, BP, ACTH, Cortisol in both high responder and low responder.
(Vedhara K, Cox N.K.M et al. 1999)	50 spouses of dementia patients	Care giving of a family member with severe illness	Cortisol, IgG Ab titres, flu vaccine ,	Increased cortisol and poor antibody response to influenza vaccine, caregivers may be more vulnerable to infectious disease
(Weber B, Lewicka S et al. 2000)	25 severely depressed patients & 30 control patients	Relationship between cortisol, cortisone & Depression	Cortisol and Cortisone	Increased cortisol and cortisone in patients with depression compared to controls

(Schommer NC, Hellhammer DH et al. 2003)	65 healthy subjects (38 men and 27 women)	Trier social stress test (TSST) three times with a 4 week interval between stress sessions	ACTH, Plasma cortisol, Salivary cortisol, epinephrine, nor epinephrine, heart rate	Increased salivary free cortisol, plasma cortisol, ACTH & heart rate after each of the three stress sessions.

Authors	**Study Sample**	**Stressors**	**Hormone measures**	**Outcome**
(Porter LS, Mishel M et al. 2003)	33 breast cancer & 21 women with no history of breast cancer	Mammography	Salivary cortisol and psychological questionnaire	Increased salivary cortisol in breast cancer survivors 1 month before mammogram and increased cortisol around the mammogram in controls
(Adam EK, Hawkley LC et al. 2006)	156 older adults	Day to day dynamics of experience	Diurnal salivary cortisol level on waking, 30 minutes after waking and at bed time	Prior day feelings of lonliness, sadness, threat and lack of control were associated with a high cortisol awakening response the next day.
(Haussmann MF, Vleck CM et al. 2007)	12 undergraduate students	Presentation stress, fasting stress, competition stress	Salivary cortisol	Elevated salivary cortisol in response to each of these stresses compared with basal conditions

Table 3.3.5.2 Summary of effects of psychotherapeutic interventions on Cortisol and NK cells:

Authors	Study Sample	Intervention	Immune/hormone measures	Survival outcomes
(Schedlowski M, Jung C et al. 1994)2}	Post surgical breast cancer	10 week behavioral intervention	Decreased plasma cortisol and increased circulating lymphocytes	not reported
(Van der Pompe G, Duivenvoorrden HJ et al. 1997)7}	breast cancer patients	13 week existential-experiential group psychotherapy vs. Wait listed controls	decrease in plasma cortisol, prolactin, NK cell%, CD4%, CD8% and reduced lymphoproliferative responses in intervention group after 13 weeks	not reported
(Fawzy FI, Cousins N et al. 1990; Fawzy F.I, Fawzy N.W et al. 1993)7}	malignant melanoma (Int, n=35); (Cont, n=26)	6 weeks group intervention on stress management, education, support, problem solving and coping skills training	increase in LGLs, NK Cells and decrease in CD4	Both short term and long term changes
(Turner-Cobb JM, Sephton SE et al. 2000)7}	103 metastatic breast cancer patients	cross sectional study comparing quality of social support to diurnal cortisol rhythms and levels	better quality of social support is related to lower cortisol levels but not slope	not reported
(Burns SJ, Harbuz MS et	29 mixed cancer	Music therapy	Increased well being, relaxation,	not reported

al. 2001)7}	population		salivary IgA, and Decreased salivary cortisol	
(YU Hong-luan, LI Ying et al. 2007)6}	60 women with breast cancer in perioperative period	Intervention group received 45 min structured psychotherapy and control group had 45 minutes free talk before operation	Intervention showed decreased anxiety, depression, negative coping scores and decreased plasma cortisol compared to control.	not reported

Table 3.3.5.3: Summary of Yoga interventions in cancer patients

Authors, year	Subjects and setting	Design	Outcomes
(Joseph CD 1983)7}	50 Cancer patients undergoing radiotherapy	Uncontrolled pre post design	Improved self reported symptoms of appetite, well being, sleep
(Coker KH 1999)1}	Prostate cancer patients	Uncontrolled preliminary study MBSR intervention	Reduction in stress enhancing general health and wellness, increased production of melatonin
(Speca M, Carlson LE et al. 2000)8}	Heterogeneous cancer population, (n=61 in yoga and n=48 in control)	Randomized wait list control design; 7 week MBSR intervention	Better compliance to intervention and improved mood states
(Shapiro SL, Bootzin RR et al. 2003)4}	breast cancer patients	RCT – MBSR vs. free choice as controls	Improvement in daily sleep quality in both groups
(Cohen L, Warneke C et al. 2004)7}	39 stage I-IV lymphoma subjects at different stages of treatment	Randomized wait list control design 7 weekly sessions of Tibetan Yoga	Improved sleep quality
(Carlson LE, Speca M et al. 2004)2}	Breast and Prostate cancer patients (n=59)	Uncontrolled study 8 weeks MBSR	Improvement in Qol, stress, & health behaviors, no changes in mood, cancer related symptoms , salivary cortisol, DHEA and

			melatonin levels, Change in intracellular cytokines
(Culos-Reed S, Carlson LE et al. 2004)9}	38 mixed cancer survivors	Randomized wait list control design; 7 weekly sessions of Hatha Yoga	Reduced mood disturbance, stress and improved Qol, Cardiopulmonary functions and physical function
(Cohen L, Thornton B et al. 2005)8}	58 stage I-III breast cancer patients	Randomized wait list control design; 7 weekly sessions of Tibetan Yoga	Fever cancer related symptoms no improvements in mood, Qol and sleep
(Carlson LE, Culos-Reed N et al. 2005)0}	20 mixed cancer survivors	Randomized wait list control design; 7 weekly sessions of Hatha Yoga	reduced mood disturbance and improved Qol, No change in cortisol slope or diurnal rhythms
(Culos-Reed SN, Carlson LE et al. 2006)7}	Breast cancer survivors(n=20 in yoga and n=18 in control)	Randomized wait list control design; 7 week yoga program	Improvement in psychosocial (i.e. global quality of life, emotional function, and diarrhea variables at post assessments
(Moadel AB, Shah C et al. 2007)8}	128 stage I-III breast cancer patients (n=84 in yoga and n=44 in control)	Randomized wait list control design; 12 weekly sessions of Hatha Yoga (90 minutes weekly)	Poor adherence, Primary analysis did not show any Improvements. Secondary analysis on 71 subjects not receiving chemotherapy showed improvement in QOL, emotional well being, social well being, spiritual wellbeing and distressed

			mood in yoga group.
(Carson JW, Carson KM et al. 2007)7}	13 metastatic breast cancer patients	Uncontrolled pre post study, 8 week yoga program	Increased invigoration, acceptance, decrease pain, fatigue and increased relaxation on the day of practice of yoga.
(Raghavendra RM, Nagarathna R et al. 2007)7}	62 stage II & III breast cancer undergoing active chemotherapy (n=28 in yoga and n=34 in supportive control)	RCT – Yoga vs. Supportive therapy as controls, 60 min daily yoga practice of both supervised and home practice, control group received supportive therapy and coping during hospital visits	Decrease in post chemotherapy induced nausea frequency, intensity, anticipatory nausea intensity and vomiting in yoga as compared to controls. Positive correlation between nausea and vomiting to anxiety, depression and distressful symptoms.
Carlson LE, Speca M et al, 2007	49 breast cancer and 10 prostate cancer patients.	Uncontrolled study with 8 week MBSR program and followed them up till one year	Significant improvement in overall symptoms of stress and significant decrease in cortisol, Th1 cytokines, Systolic blood pressure, and positive correlation between Heart rate and self reported symptoms of stress.
(Rao RM, Telles S et al. 2008)0}	37 stage II & III breast cancer undergoing active treatment (n=16 in yoga and n=21 in supportive	RCT – Yoga vs. Supportive therapy as controls, 60 min daily yoga practice of both supervised and home practice, control group received supportive therapy and coping during	Significant decrease in NK cell% in control group from baseline to post surgery & from baseline to post chemotherapy and no significant decrease of NK cell% in yoga group, NK cell% was higher in yoga

	control)	hospital visits	group post chemotherapy compared to control.
(Danhauer SC, Tooze JA et al. 2008)0}	51 breast and ovarian cancer (Ovary=37 and Breast=14) undergoing active treatment	Uncontrolled pre post study with 10 weekly 75 minutes restorative yoga	Significant decrease in depression, negative affect, state anxiety, fatigue and improvement in mental health and overall quality of life.
Raghavendra M Rao, Nagendra HR et al, 2008	98 stage II & III breast cancer undergoing surgery treatment (n=45 in yoga and n=53 in supportive control) 69 provided data	RCT – Yoga vs. Supportive therapy as controls, 60 min daily yoga practice of both supervised and home practice, control group received supportive therapy and coping during hospital visits	Significant decrease in state, trait anxiety, depression, symptom severity, distress and improvement in QOL in yoga group compared to control, Significantly lesser decrease in CD56% cells and lower levels of SIgA in yoga group compared to control group.
(Raghavendra Rao M, Nagendra HR et al. 2008)8}	98 stage II & III breast cancer undergoing surgery treatment (n=45 in yoga and n=53 in supportive control) 69 provided data	RCT – Yoga vs. Supportive therapy as controls, 60 min daily yoga practice of both supervised and home practice, control group received supportive therapy and coping during hospital visits	Significant decrease in the duration of hospital stay, days of drain retention, suture removal in yoga group compared to control group. There was also significant reduction in plasma TNF alpha following surgery in yoga group compared to control group.
(Witek-Janusek L, Albuquerque K et al. 2008)5}	Early stage breast cancer who did not received chemotherapy	Non randomized controlled study with 8 weeks of MBSR and only assessment control group	At baseline (before MBSR start) reduction in NK cell activity and IFN gamma with increased IL-4, IL-6 & IL-10 and plasma cortisol. Over time restoration in

			NKCA & Cytokine in MBSR program group and decrease in control group. Decrease cortisol, improved QOL, Increased coping in MBSR group compared to controls.
Raghavendra M Rao, Nagarathna R et al, In press	98 stage II & III breast cancer undergoing treatment (n=45 in yoga and n=53 in supportive control) 38 who had similar treatments like surgery+ radiotherapy +chemotherapy provided data	RCT – Yoga vs. Supportive therapy as controls, 60 min daily yoga practice of both supervised and home practice, control group received supportive therapy and coping during hospital visits	Significant decrease of state and trait anxiety in yoga group as compared to control group and positive correlation between anxiety and symptom severity and distress.

3.3.6 The present study

Though results offer evidence for beneficial effects in cancer patients, it should be noted that several of the above reported previous trials had methodological limitations that render the findings preliminary, including small sample size, heterogeneity in sample and disease stage, lack of a control group and randomization, and inadequate statistical analyses and intervention. Moreover, these studies report benefit finding generally in cancer patients and do not address specific issues such as treatment related distress, toxicity and quality of life. In this prospective study we evaluate the effects of an integrated yoga program on mood states, quality of life; treatment related symptoms, toxicity and immune responses in early operable breast cancer patients undergoing conventional cancer treatment. We hypothesize that yoga intervention would help improve post operative outcomes, improve moods, quality of life, reduce treatment

related symptoms and toxicity and improve innate and antitumor immune responses in breast cancer patients undergoing conventional treatment.

3.3.7 Relevance of the Study

There is an increase in incidence of breast cancer in India over the last two decades. Even though advancements in conventional cancer treatment have seen case fatality rates diminishing, patients who live have to endure cancer treatments and related distress for a longer time than ever before. Psychotherapeutic interventions are being used to help patients cope better, manage stress, reduce treatment related distress and improve their quality of life. Yoga is one such intervention which has its utility in numerous health care concerns where stress is believed to play a role. It is desirable therefore to scientifically validate the effects of yoga intervention in reducing conventional treatment related distress and side effects, psychological morbidity and improving quality of life and immunity in early and advanced breast cancer patients undergoing conventional cancer treatments.

4. OBJECTIVES OF THE STUDY

Two studies were conducted to evaluate the effects of Integrated Yoga Program.

4.1 STUDY 1: Breast cancer stage 2 and 3 (BCS2/3)

4.1.1 Objectives

To evaluate the effects of an integrated yoga program on mood states, perceived stress, affect, treatment related symptoms, quality of life and diurnal salivary cortisol rhythms in early stage breast cancer patients undergoing adjuvant radiotherapy.

The effects measured in two groups (yoga and control) of early stage breast cancers undergoing Radiation therapy were:

1. Psychological morbidity - Anxiety, Depression and Perceived stress using self report scales.
2. Psychological distress and Mood changes including Positive and Negative affect using self report scales.
3. Treatment related symptoms.
4. Total Quality of life
5. Endocrine response such as salivary cortisol and diurnal cortisol rhythm.

4.1.2 Hypotheses

Yoga group will report a greater reduction in psychological morbidity, perceived stress, treatment related distress and normalization of salivary cortisol rhythms with better improvements in positive affect and QoL than the supportive therapy control group.

4.1.3 Null hypotheses

The yoga group will show changes similar to control group in psychological morbidity, perceived stress, and treatment related distress, QoL and diurnal salivary cortisol rhythms.

4.2 STUDY 2: Metastatic Breast cancer (BCS4)

4.2.1 Objectives

To evaluate the effects of an integrated yoga program on mood states, perceived stress, sleep, fatigue, quality of life, diurnal salivary cortisol rhythms and natural killer cell counts in metastatic breast cancer survivors.

The effects measured in two groups (yoga and control) of Metastatic breast cancer survivors were:

1. Psychological morbidity including Anxiety, Depression and Perceived stress using self report scales.
2. Sleep and Fatigue assessments using self report scales.
3. Total Quality of life
4. Endocrine and Immune responses such as Cortisol, Diurnal cortisol rhythm and NK Cell assay.

4.2.2 Hypotheses

Yoga group will report a greater reduction in psychological morbidity, perceived stress, treatment related distress, fatigue, normalization of diurnal salivary cortisol rhythms with better improvements in positive affect, sleep, QoL and NK cell counts than the supportive therapy control group.

4.2.3 Null hypotheses

The yoga group will show changes similar to control group in psychological morbidity, perceived stress, treatment related distress, fatigue, diurnal salivary cortisol rhythms, affect, sleep, QoL and NK cell counts.

4.3 Research Questions

1. Is Integrated Approach of Yoga therapy program effective in reducing the psychological morbidity in patients with early breast cancer during radiotherapy?
2. Can yoga program reduce the treatment related symptoms in cancer patients?
3. Can yoga improve the quality of life in patients with cancer?
4. Are there scriptural references for the use of mantra chanting in the treatment of diseases and its possible use in cancer patients?
5. Are there scriptural references for Mind Sound Resonance Technique that is used as a specific technique in the yoga module in cancer?
6. Can Yoga program help in modulating abnormal diurnal salivary cortisol levels in cancer patients?
7. Can yoga increase Natural Killer Cell count in advanced cancer patients?

5. METHODS

5.0 GENERAL

In this study we compared the effect of "Integrated yoga based stress reduction program" with a standard "Education and Supportive therapy" as control intervention in early stage breast cancer patients undergoing radiation treatment for cancer and in Metastatic Breast Cancer survivors.

5.1 SUBJECTS

5.1.1 General

Two separate RCTs were conducted. There were 88 (44Y and 44C) patients in early stage 2/3 breast cancer (BCS2/3) study and 91(45Y and 46C) in Metastatic stage 4 breast cancer (BCS4) study. They were recruited to participate in randomized controlled trials comparing the effects of an "Integrated yoga based stress reduction program" with standard "education and supportive therapy sessions" on mood states, quality of life, endocrine and immune responses during the course of their conventional cancer treatment.

5.1.2 Source of Subjects

Eighty-eight women with stage II and III breast cancer with a group mean age of 49.10 yrs $\pm$ 9.45 yrs who were registered in hospital based cancer registry of Bangalore Institute of Oncology and Bangalore and Bharath Hospital and Institute of Oncology, Mysore, and advised Radiation therapy were recruited for BCS2/3 study.

Ninety one Metastatic breast cancer survivors (group mean age 50.54 yrs $\pm$ 8.53 yrs) registered in hospital based cancer registry of Bangalore Institute of Oncology, were recruited for BCS4 study.

The recruitments were carried out from January 2004 to June 2007.

5.1.3 Selection criteria

5.1.3a Inclusion Criteria

BCS2/3 study:

Patients were included if they met the following criteria:

i) Women with diagnosed breast cancer stage 2 or 3 who were advised and planned to undergo radiation therapy at the two selected hospitals.

ii) Age between 30 to 70 years.

iii) Zubrod's, performance status 0- 2 (ambulatory > 50% of time).

iv) High school education.

v) Willingness to participate in the study.

BCS4 study:

Patients were included if they met the following criteria:

i) Women diagnosed with stage 4 breast cancer within six months to two years after diagnosis - either recurrent disease or presenting for the first time with stage 4 disease.

ii) Age between 30 to 70 years.

iii) Zubrod's performance status 0- 2 (ambulatory > 50% of time).

iv) High school education.

v) Willingness to participate in the study.

5.1.3b Exclusion Criteria

BCS 2/3 Study

Patients were excluded if they had

(i) Any concurrent medical condition that was likely to interfere with the treatment.

(ii) Major psychiatric, neurological illnesses or autoimmune disorders.

(iii) Any known metastasis.

(iv) Those who are on hydrocortisone medications or have HIV

(v) Pregnant and lactating mothers or planning to conceive during the study period

(vi) Those who are recruited for clinical trials involving investigational new drugs.

(vii) Prior practice of yoga in the last six months.

BCS 4 Study

Exclusion criteria were:

i) Duration of metastasis more than one year.

ii) Brain metastasis.

iii) Those undergoing chemotherapy/ radiotherapy during the study period except for treatment of bone metastases with bisphosphonates/ zoledronic acid.

iv) Those on hydrocortisone medications.

v) A concurrent medical condition likely to interfere with the treatment.

iv) Any major psychiatric, neurological illness or autoimmune disorders.

(viii) Those who are on hydrocortisone medications or have HIV

(ix) Pregnant and lactating mothers or planning to conceive during the study period

(x) Those who are recruited for clinical trials involving investigational new drugs.

v) Prior practice of yoga in the last six months.

vi) Prior chemotherapy other than treatment of bone metastases mentioned above in the last 2 weeks.

5.1.4 Recruitment

Patients were recruited for early stage breast cancer study through radiation Oncologists from Bangalore Institute of Oncology, Bangalore and Bharath Hospital and Institute of Oncology,

Mysore, after they were advised radiation treatment and satisfied selection criteria. Similarly, patients were recruited from Bangalore Institute of Oncology, Bangalore through Medical Oncologists if they satisfied selection criteria for Metastatic breast cancer study and gave their consent to participate in the study.

5.1.5 Consent and Ethical Considerations

The institutional review boards of Swami Vivekananda Yoga Anusandhana Samsthana and Bangalore Institute of Oncology in Bangalore approved the study. Signed Informed consent was obtained from all the participants at the study start. (See Informed consent specimen in appendix 8).

The details of the study were explained to the participants and their informed consent was obtained.

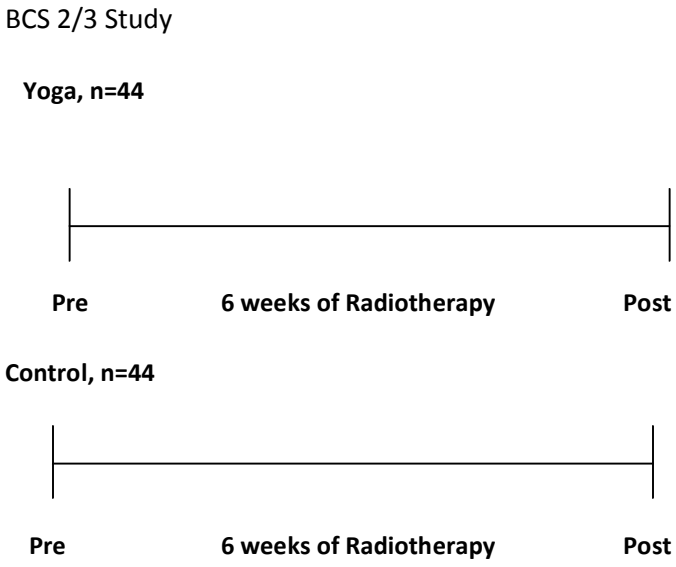
5.1.6 Sample size

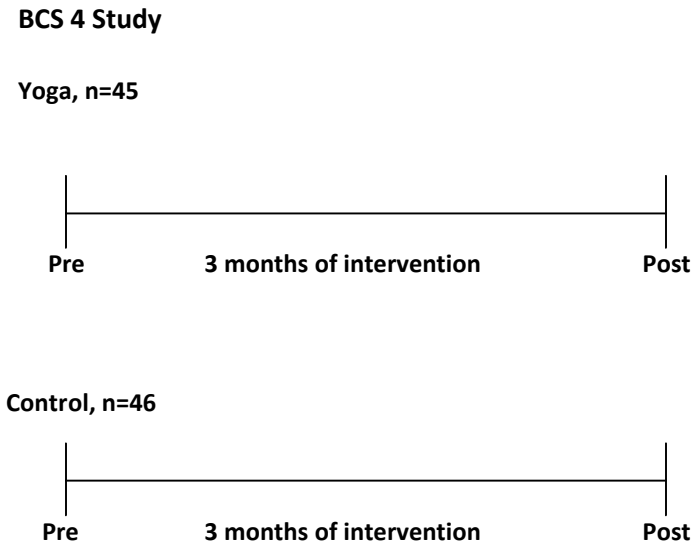
Earlier study with Mindfulness Based Stress Reduction Program (MBSR) had shown a modest effect size (ES = 0.38) on EORTC QLC30 global quality of life measure (Carlson LE, Speca M et al. 2003).We used G power to calculate the sample size with $\alpha = 0.05$ and $\beta = 0.2$ and above effect size of 0.38 for repeated measures ANOVA between factor effects. The sample size thus required was (n=44) in each group. Earlier study at SVYASA used FLIC as a measure of quality of life. Hence, we chose to calculate the sample size based on the findings from the above study using MBSR as the outcome measure was similar to ours used in this study. Secondly, earlier studies were only on stage I-III breast cancer patients and not on metastatic breast cancer patients.

5.2 STUDY DESIGN

Both BCS2/3 and BCS4 were prospective randomized two armed longitudinal controlled studies. Patients for both studies were selected from outpatients and inpatients of Bangalore institute of oncology in Bengaluru and Bharath Hospital and Institute of Oncology in Mysore, Karnataka India. Subjects satisfying the selection criteria were randomly allocated to receive either integrated yoga based stress reduction program or standard education and supportive therapy before starting their conventional treatment and were followed up with the interventions covering the duration of their adjuvant radiotherapy for BCS2/3 study. For BCS4 breast cancer study, participants were followed up to three months with the interventions. The assessments were done before and at the end of the study period, i.e. after receiving 25cGy of radiation or 45 days of radiation therapy in BCS2/3 study and after three months of yoga intervention in case of BCS4 study. Stage IV breast cancers were not undergoing any form of conventional treatment such as radiotherapy/ chemotherapy. Those who did receive them during the course of intervention were considered as dropouts.

Figure 6: Study Design





5.2.1 Randomization

Consenting participants were randomly allocated to either yoga or supportive therapy groups using random numbers generated by a random number table at a different site by a person who had no part in the trial. Randomization was performed using opaque envelopes with group assignments, which were opened sequentially in the order of assignment during recruitment with names and registration numbers written on their covers. The order of randomization was verified with the hospital date of admission records prior to surgery at study intervals to make sure that field personnel had not altered the sequence of randomization to suit allocation of consenting participants into 2 study arms. In both the studies, if participants were found to be eligible on prescreening and after consent, completed all baseline measures before being randomized to either yoga arm or supportive therapy. Participants in BCS2/3 study were randomized before starting their adjuvant radiotherapy. Following randomization, participants underwent respective interventions.

5.2.2 Period of Study

This randomized controlled trial was conducted between January 2004 to June 2007 by two institutions, Swami Vivekananda Yoga Anusandhana Samsthana and Bangalore Institute of Oncology in Bangalore.

5.2.3 Masking and Blinding

Being a popular intervention, it was not possible to mask the yoga intervention from the subjects. However the investigators (treating oncologists) were blind to the intervention and subjects were asked not to disclose the type of intervention (yoga or supportive therapy) to them. Secondly, the saliva and blood samples were blinded from the technicians who analyzed the coded samples at a site different from the study center. The samples and data were unblinded only at the conclusion of the study.

5.2.4 Study procedure

Subjects were recruited from Bangalore Institute of Oncology, Bangalore and Bharath Hospital and Institute of Oncology, Mysore, by radiation oncologists soon after they were advised radiation treatment and if they satisfied the selection criteria for early stage breast cancer study. Similarly, patients were recruited from Bangalore Institute of Oncology, Bangalore by Medical oncologists if they satisfied selection criteria for Metastatic breast cancer study. Patients were taken to study for both groups after they gave consent to participate in the study. Subjects were then scheduled for an interview with the Research Assistant (RA) and during this interview, the demographic information, medical history form were completed by the RA and the patients completed assessment questionnaires supervised by the RA who clarified instructions and answered questions, which took approximately 30 minutes for each study. A prospective randomly allocated controlled design was adopted wherein subjects were allocated

to receive either yoga or supportive therapy prior to their primary treatment through random numbers generated by a random generation table. Assessments included a battery of psychological questionnaires as well as saliva and blood draws for endocrine and immune measures. Psychological assessments were done before and after radiation treatment i.e, before and after 25cGy of radiation over a period of 45 days in early stage breast cancer study and before and after 3 months of intervention in Metastatic breast cancer study. Blood draws were carried out for Natural killer (NK) cells assay count before and after intervention period in Metastatic breast cancer study. Salivary samples were collected before and after the treatment in both the studies for the assessment of salivary Cortisol and diurnal Cortisol rhythmicity.

In this study, 80 early stage breast cancer patients and 91 Metastatic breast cancer patients were recruited to participate in a randomized controlled trial comparing the effects of an "integrated yoga based stress reduction program" with standard "education and supportive therapy sessions" on mood states, quality of life, conventional treatment related symptoms, sleep, Cortisol levels, rhythmicity and immune responses such as Natural killer (NK) cell count during the course of their conventional cancer treatment. Baseline assessments were done on 88 patients in case of early stage breast cancer and 91 patients in case of Metastatic breast cancer patients prior to their treatment. A total of 76 patients contributed data to the current analyses in early stage breast cancer and 66 patients contributed data to the current analyses in Advanced or Metastatic breast cancer patients. The Reasons for dropouts were attributed to migration to other hospitals, use of other complementary therapies (e.g. Homeopathy or Ayurveda), lack of interest, time constraints and other concurrent illness (See trial profile; appendix 3). Among the 75 study completers in BCS2/3 study only 56 gave saliva samples and in BCS4 study 46 out of 66 completers gave the saliva samples as per protocol. 10 subjects (Yoga, n=3, Control, n=7) in BCS2/3 and 15 subjects (Yoga n=5, Control, n=10) in BCS 4 study were not

comfortable in giving saliva samples. Subjects who missed collecting saliva sample on consecutive days at the same time were excluded from analysis (BCS2/3 study, n = 9 and BCS4 study, n=5).

5.3 INTERVENTIONS

The intervention group received "integrated yoga program" and the control group received "supportive counseling sessions" both imparted as individual sessions. The objectives of this yoga intervention as described to participants were i) to develop an opportunity to understand ones personal responses to daily stress and explore ways and means to cope with them ii) to learn concepts and techniques which bring about stress reduction and change in appraisal and iii) to enable the participants to take an active part in their self care and healing.

We developed an integrated yoga module comprising various practices which have been described in ancient texts to act at different levels of our existence. As described previously in section 3.3.4 we used the following practices of yoga to act at these five levels of existence.

5.3.1 Practices at Annamaya kosa or the physical body level: These practices included loosening exercises and asanas or postures done with awareness (See appendix 6 for more details).

5.3.2 Practices at Pranamaya kosa level or the physiological or functional body: These practices included breathing exercises, pranayama and pranic energisation technique to act at the pranic level to correct pranic imbalances. These practices are known to affect higher brain centers and stabilize the autonomic nervous system, reduce oxygen consumption and bring thermoregulatory efficiency and could therefore be used to correct the imbalances created by stress (See appendix 6 for more details).

5.3.3 Practices at Manomaya kosa level or the mind level: These included yoga relaxation techniques and advanced meditation techniques such as Cyclic Meditation, Mind Sound Resonance Technique and Mind Imagery Relaxation Technique. These practices have been validated in normal populations and are known to reduce oxygen consumption, reduce stress and affect the autonomic nervous system (See appendix 6 for more details).

5.3.4 Practices at Vignana maya kosa level or intellect level: These included yogic counseling or notional correction where in participants were given didactic lectures on message of Vedas and Upanishads and various paths of yoga to attain the same. This is important as most cancer patients perceive cancer as a threat and have fears about recurrence and dying. We used mind imagery relaxation technique to instill hope and reduce fear in these subjects. (See appendix 6 for more details).

5.3.5 Practices at Aananda maya kosa level or the blissful state: Involved happiness analysis and experience of deeper states of relaxation and bliss through these practices (See appendix 6 for details).

5.3.6 Overview of yoga intervention: The yoga practices consisted of a set of *asanas* (postures done with awareness) breathing exercises, *Pranayama* (voluntarily regulated nostril breathing), *meditation* and yogic relaxation techniques with imagery. These practices were based on principles of attention diversion, awareness and relaxation to cope with stressful experiences.

The sessions began with didactic lectures and interactive sessions on philosophical concepts of yoga and importance of these in managing day-to-day stressful experiences (10 minutes) beginning every session. This was followed by a preparatory practice (20 minutes) with few easy yoga postures, breathing exercises and pranayama and yogic

relaxation. The subjects were then guided through any one of these meditation practices for next 30 minutes which included focusing awareness on sounds and chants from Vedic texts (Telles S, Nagarathna R et al. 1998), or breath awareness and impulses of touch emanating from palms and fingers while practicing yogic mudras, or a dynamic form of meditation which involved practice with eyes closed of four yoga postures interspersed with relaxation while supine, thus achieving a combination of both "stimulating" and "calming," practice (Telles S, Reddy SK et al. 2000). In meditation, participants try to develop clarity in their thinking, learn to observe their own mind, decrease negative mind states and develop positive mind states and maintain equipoise in their emotions. These sessions were followed by informal individual counseling sessions that focused on problems related to impediments in home practice, clarification of participant's doubts, motivation, and supportive interaction with spouses. The participants were also informed about practical day-to-day application of awareness and relaxation to attain a state of equanimity during stressful situations and were given homework in learning to adapt to such situations by applying these principles.

The subjects were given booklets and instructions on these practices and were encouraged to pursue relevant themes and gain greater depth through proficiency in practice. Subjects were provided audiotapes of these practices for home practice using the instructor's voice so that a familiar voice could be heard on the cassette.

Study 1: Subjects undergoing radiotherapy were asked to attend yoga sessions at least a minimum of 3 days/ week over a six week period or a maximum of 5 days/ week.

Study 2: Subjects were asked to attend yoga intervention at least 2 times / week for a period of 12 weeks. The control groups in both the studies were imparted supportive counseling during their hospital visits. Patients in study 1 underwent atleast 18 in person sessions while those in study 2 underwent 24 in person sessions with home practice on remaining days. Patients were asked to maintain a diary noting their daily activity, daily yoga schedule, duration of practice, intake of medications, and distressing symptoms if any etc.

Their homework was monitored on a day to day basis by their instructor who conducted weekly house visits and participants were also encouraged to maintain a daily log listing the yoga practices done, use of audiovisual aids, duration of practice, experience of distressful symptoms and diet history. There were two instructors in all one being a physician in naturopathy and yoga and other a trained and certified therapist in yoga from the yoga institute. They together supervised and imparted the yoga intervention while supportive therapy intervention was imparted by trained social workers and counselors at the cancer hospital (See Appendix for details of yoga intervention).

5.3.7 Control Intervention - Supportive counseling sessions:

Supportive counseling sessions as control intervention included two important components "Education and reinforcing Social support". The reasons why we chose to have education and supportive therapy sessions as control intervention are three fold.

This was used as a control intervention to control for the nonspecific effects of the program that may be associated with adjustment such as attention, support and a sense of control. In fact, these didactic educational interventions are known to improve quality of life of women with breast cancer (Helgeson VS, CohenS et al. 1999; Helgeson VS, Cohen S et al. 2000) and serve as

an effective coping preparation in controlling chemotherapy related side effects (Burish TG, Snyder SL et al. 1991).

Even though the use of education and supportive therapy is a form of enhanced usual care, if yoga program does not provide any benefit over this intervention, then we will know that didactic educational programs should be integrated within the standard of care.

Similar supportive sessions have been used successfully as a control comparison group to evaluate psychotherapeutic interventions (Telch CF and Telch MJ 1986; Greer S, Moorey S et al. 1992). These sessions aimed at enriching the patient's knowledge of their disease and treatment options, thereby reducing any apprehensions and anxiety regarding their treatment and also involved interaction with the patient's spouses. Subjects and their caretakers were invited to participate in a introductory session lasting 60 minutes before starting any conventional treatment where in they were given information about each conventional treatment and management of its related side effects, dietary advice, providing information about a variety of common questions and showing a patient coping successfully. This counseling was extended over the course of their adjuvant radiotherapy and chemotherapy cycles during their hospital visits (once in 10 days, 15 minute sessions) and participants were encouraged to meet their counselor whenever they had any concerns or issues to discuss. Subjects in the supportive therapy group also completed daily logs or dairies on treatment related symptoms, medication and diet. While the goals of yoga intervention were stress reduction and appraisal change, the goals of supportive therapy were education, reinforcing social support and coping preparation.

5.4 OUTCOME MEASURES

At the initial visit before randomization demographic information, medical history, clinical data, intake of medications, investigative notes and conventional treatment regimen were ascertained from all consenting participants. The outcome measures ascertained could be grouped into following categories:

Assessments in Early stage breast cancer study:

5.4.1 Mood states

Mood states were assessed using standard self-report questionnaires such as the Hospital Anxiety and Depression Scale (HADS) for anxiety and Depression, Perceived stress scale (PSS).

5.4.1.1 Hospital Anxiety and Depression Scale (HADS)

The outcome measures were Anxiety and Depression assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond AS and Snaith RP 1983). It is a widely used self-report instrument designed to assess the dimensions of anxiety and depression in non-psychiatric populations (Herrmann C 1997; Bjelland I, Dahl AA et al. 2002). It is a 14 -item questionnaire that consists of two sub-scales of seven items designed to measure levels both of anxiety and depression. Each item is rated on a scale from 0 (“not at all”) to 3 (“very much”). The reliability of the HADS (all 14 items), HADS-A and HADS-D sub-scales are 0.85, 0.79 and 0.87 respectively, (Rodgers J, Martin CR et al. 2005).

5.4.1.2 Perceived stress scale (PSS):

Perceived stress levels were assessed using Perceived Stress Scale (PSS) (Cohen S, Kamarck T et al. 1983) questionnaire. This self-rated scale includes 14 items scored on a 5-point scale. This

scale is used to assess the degree to which participants appraise their daily life as unpredictable, uncontrollable, and overwhelming (e.g., “In the last month, how often have you felt that you were unable to control the important things in your life?”). This has a reliability of 0.85 (Cohen S, Kamarck T et al. 1983).

5.4.1.3 Positive affect and Negative affect schedule:

Positive affect and Negative affect was assessed using the PANAS scale (Watson D 1988). PANAS contains two subscales, each consisting of 10 items: positive affect (PA) and negative affect (NA). PA reflects the extent to which a person feels enthusiastic, active, and alert. A high PA score reflects a state of high energy, full concentration, and pleasurable engagement. In contrast, NA is a general dimension of subjective distress subsuming a variety of aversive mood states, and a high NA score indicates more distress. Patients were instructed to indicate how they had been feeling during the last two weeks. The reliability of this descriptive scale has been reported to range from 0.86 to 0.90 for PA and from 0.84 to 0.87 for NA (Watson D 1988).

5.4.2 Health related quality of life:

Health related quality of life was assessed using the European Organization for the Research and Treatment of Cancer-Quality of Life (EORTC-Qol-C30 questionnaire version 1) (Neil K. Aaronson, Sam Ahmedzai et al. 1993). This 30-item questionnaire provides a measure on the following dimensions: global health status, physical, role, emotional, cognitive and social functioning (with high scores representing good quality of life) as well as fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties (high scores indicating high levels of symptomatology). The reliability of this descriptive scale during the study has been reported to range from 0.52 to 0.89 for functional and global quality of life

scales. Assessments were carried out before starting and at the end of the radiotherapy treatment.

5.4.3 Fatigue Symptom Inventory:

The FSI, developed in the United States in 1998, is a 14-item self-report measure designed to assess the intensity (4 items), daily pattern (1 item), and duration of fatigue (2 items), as well as its impact on quality of life (7 items)(Hann DM, Jacobsen PB et al. 1998; Hann DM, Denniston MM et al. 2009) Twelve items consists of 11-point Likert-type scale (0 = not at all fatigued; 10 = extremely fatigued) and 1 item is composed of the number of days in the past week the patients felt fatigued. However, one item related to daily pattern of fatigue provides qualitative information and is not included in the total fatigue score. The higher the total fatigue score, the more severe the level of fatigue. The scale development process involved a review of the literature on fatigue in cancer patients and on chronic fatigue in general. Thus, the scale was intended to be used to compare fatigue in various groups of patient and nonpatient populations (Hann DM, Jacobsen PB et al. 1998). Based on 2 previous studies, Cronbach alpha coefficients of the subscale of impact on quality of life FSI ranged from 0.93 to 0.95 (Hann DM, Jacobsen PB et al. 1998; Hann DM, Denniston MM et al. 2009). The FSI has also demonstrated test-retest reliability, construct validity, divergent validity, convergent validity, and discriminant validity (Hann DM, Jacobsen PB et al. 1998).

5.4.4 Rotterdam symptom checklist (RSCL):

The Rotterdam Symptom Checklist is a 39-item scale which has been widely used as a brief measure of quality of life in cancer patients. It covers important domains of psychological distress, physical status (disease and treatment items), functional status and global quality of

life. Evidence of its reliability and validity has been found in a number of research settings. It comprises three subscales and includes one global question: 'How would you describe your quality of life during the past week?' Responses range from 'extremely poor' to 'excellent' on a 7-point scale. The psychological symptom subscale contains 8 symptoms. Respondents are asked to indicate the frequency with which they have experienced each symptom in the past week on a 4-point scale, ranging from 'not at all' (0) to 'very much' (3). Possible scores on this scale therefore range from 0 to 24.The physical symptom subscale contains 22 symptoms; scores on this scale range from 0 to 66. The third subscale assess whether respondents are able to perform eight activities, given their condition in the past week. Responses range from 'unable' (0) to 'without help' (3) and the possible range of scores on this subscale is from 0 to 24 (De Haes JCJM, Knippenberg FCE et al. 1990; de Haes JC and Olschewski M 1998).

5.4.5 Salivary cortisol measures:

Saliva Collection and storage: Participants were trained to collect their saliva by chewing on a cotton swab and dribble the saliva to a plastic holder resting inside a sterile centrifuge tube. Samples were collected at 0600hrs, 0900hrs and 2100 hours for three consecutive days. The samples were stored in refrigerator and delivered to study personnel after 3 days. Samples were then centrifuged to remove mucous, freeze and stored at -70^0C in eppendorf tubes for analysis.

Quantifications of salivary cortisol:

Salivary cortisol levels were assessed using enzyme immunoassay (EIA) method using kits manufactured by Salimetrics Inc, USA. The test samples were run in duplicates and readings taken on a micro plate reader (Bio Rad, USA). The tests were standardized under controlled laboratory conditions using standards, positive and negative controls provided along with the kit

by the manufacturer. The plates were read at 450nm and a standard curve was plotted on a graph for each run by plotting the log of cortisol concentrations on 'y' axis and log of O.D reading on 'x' axes and best fit line determined by regression analyses. The values were then extrapolated with the graph by using the mean O.D readings of the duplicate wells and plotting their corresponding concentration on the graph. The detection range with these kits was 0.012 to 3.0Hgm/dl. The intra assay coefficient ranged from 3.35% to 3.65% and inter assay coefficient from 3.75% to 6.41% with these samples. Mean cortisol levels for specific time points over a 3-day period were extrapolated.

5.4.6 Natural Killer cells (CD56%) Measures:

Blood sample collection: All subjects in metastatic breast cancer study were asked to provide blood samples at the study start and at the end of intervention. About 5ml of heparinised blood sample was collected in vacuettes under sterile conditions. All the blood samples were collected between 8 am to 12 am to reduce diurnal variability.

Quantification of Natural Killer cells (CD56%):

The NK cell assay was done using reagents and antibodies from DAKO Corporation, USA in a Beckson Dickenson Flow Cytometer. Flow cytometer measures and analyses optical properties of single cells passing through a focused laser beam, analysis of hundreds of cells per second provides a statistically significant picture, when the cells pass through the laser beam they disrupt and scatter the laser light which is detected as forward scatter (FSC) and side scatter (SSC). While forward scatter is related to cell size the side scatter is an indicator of cells internal complexity. Cells are stained with monoclonal antibodies coupled with fluorescent dye FITC and the conjugated samples were acquired using flow cytometer, when acquiring, blood cells are

segregated into different populations- lymphocytes, monocytes and erythrocytes using cell quest pro software version 3.1. The cytometer processes the electronic signals resulting from each cell and creates numeric value for each parameter. Each cell count acquired is taken as one event. Before acquiring this is set based on the availability of the cells in the sample (it's set for 10,000 events). Once acquisition is done the cells segregated are analyzed by encircling the cell population in FSC/ SSC PLOT. Stained cells are separated from the unstained cells by Gating. The cytometer processes the electronic signals resulting from each cell and creates numeric value for each parameter thereby total number of NK cells and %NK cells are calculated.

5.4.7 Measurement accuracies and error analysis:

We used a 96 well ELISA plate reader (Bio Rad, USA) for assessment of cortisol and Flow Cytometer (Beckson Dickenson, USA) for assessment of serum Natural Killer cells (CD56%). The error variances and details regarding trouble shooting and calibration are given in appendix.

5.5 DATA ANALYSIS

Data were analyzed using Statistical Package for Social Sciences version 10.0 for PC windows 2000.

Analysis of baseline data: The data of baseline and follow-up of both the groups were assessed with tests for normality and homogeneity using Shapiro- Wilks test and one way ANOVA.

Analysis of within and follow up measures:

BCS2/3 study: The data was normally distributed. We used analysis of covariance to study the effects of intervention on outcome measures at follow-up assessments using their respective

baseline measure as a covariate. Paired sample't' test was done to see within group changes. All analyses were carried out with intention to treat principle to account for missing values and dropouts.

Mean cortisol levels for specific time points over a 3-day period were extrapolated. The diurnal cortisol response was evaluated by calculating the area under curve for time 0600, 0900 and 2100 hrs using zero as a reference point. We used area under the curve (AUC) a frequently used method in endocrinological research to comprise information that is contained in repeated measurements over time. This helps to limit the amount of statistical comparisons between groups in order to minimize correction of the α-error probability. With the *AUC* variables, the number of repeated measurements is irrelevant and thus, the number of statistical comparisons only depends on the number of groups to be compared. With the two *AUC* formulas AUCg for baseline diurnal cortisol measurements and AUCi increase in the area under the curve with respect to AUCg for post measure using trapezoidal method, (Pruessner J C, Kirschbaum C, Meinlschmid G, et al,2003) different aspects of the time course of the repeated measurements could be assessed. The slope of diurnal cortisol rhythm was analyzed using Random Coefficient Modeling (i.e., ''linear mixed models''), which has been advocated by some researchers (e.g., Smyth et al., 1998), Rogosa and Saner (1995). Slopes were compared at baseline and at post measurements in both the groups.

BCS4 study: The raw cortisol values were skewed and were log transformed ($\log_{10}$) before analysis. We used analysis of covariance to study the effects of intervention on outcome measures such as diurnal salivary cortisol and NK Cell counts at follow-up assessments using their respective baseline measure as a covariate. Paired sample't' test was done to see within group changes. Cortisol slope was compared at baseline and post intervention between groups

similar to procedures adopted above for BCS2/3 study. Alternatively, non-parametric Mann Whitney U test and Wilcoxon Signed rank test were also done for variables with skewed distribution. Bivariate relationships were determined between change scores of outcome variables following yoga intervention in the yoga group. However though some bivariate relationships were identified they did not satisfy criteria for mediation moderation testing (Baron and Kenny, 1986).

6. RESULTS

Recapitulation: Outcome measures such as measures of mood states (anxiety, depression, perceived stress, positive affect and negative affect); treatment related side effects and Quality of life were assessed at baseline (pre radiation) and following radiotherapy. Diurnal cortisol measures were assessed at baseline and following radiotherapy in both the groups in case of early stage breast cancer patients undergoing adjuvant radiotherapy. Outcome measures such as measures of mood states (anxiety, depression, perceived stress), treatment related side effects and Quality of life, Fatigue and Sleep measures were assessed at baseline (before intervention) and following intervention. Diurnal cortisol measures and Natural killer cell count were assessed at baseline and following intervention in both the groups in case of metastatic breast cancer patients. Analysis of covariance using the respective baseline measure as a covariate and repeated measures Analysis of variance was done to assess the effect with post hoc Bonferroni correction. When the data were ordinal or were not normally distributed or had significant variance then non parametric Mann Whitney U tests were done to compare between groups and Wilcoxon's Signed rank test was done to compare within group differences. The results of the study are described under the following headings:

Study 1-Early stage breast cancer undergoing radiotherapy	Study 2-Metastatic breast cancer Survivors
Baseline measures	Baseline measures
Measures of mood states	Measures of mood states
Treatment related distress	Treatment related distress
Quality of life	Quality of life
Diurnal cortisol measures	Fatigue and sleep
	Diurnal cortisol measures and NK cell counts

6.1 BCS2/3 Study- Results of patients with breast cancer stages 2/3

6.1.1 Baseline Measures

At the study start prior to radiotherapy treatment in case of BCS 2/3 study and before intervention in case of BCS 4 study demographic information, medical history, clinical data were ascertained from all consenting participants. Outcome measures such as measures of mood - Anxiety and depression, perceived stress, positive and negative affect, quality of life, treatment related side effects, fatigue and sleep parameters were assessed using standard self report questionnaires. Participants were also required to give saliva samples for cortisol measures and blood samples for immune measures.

6.1.1.1 Socio demographic and Medical Characteristics of the Study sample

The mean age of participants was 46 ± 9.13 yrs in yoga and 48.45 ± 10.21 yrs in control group. All patients had mastectomy as primary treatment, 16 subjects received

radiotherapy following mastectomy and 59 subjects received radiotherapy following mastectomy and three cycles of chemotherapy. Participants in both groups were comparable with respect to socio-demographic and medical characteristics. The proportion of subjects with stage II and III tumor, and pre and post menopausal status did not differ significantly. A goodness of fit test run on all these demographic variables did not show any significant changes between yoga and supportive therapy groups ($p > 0.05$) (Table 6.1.1.1).

Table 6.1.1.1: Demographic and medical characteristics

	All Subjects		Yoga group		Control group		
	N=88	(%)	N = 44	(%)	N =44	(%)	P value
Stage of Breast Cancer							
I	5	5.7%	2	4.5 %	3	6.8%	0.54
II	18	20.4%	11	25.0%	7	15.9%	
III	65	73.9%	31	70.5%	34	77.3%	
Grade of Breast Cancer							
I	1	1.1%	1	2.3%	0	0	0.76
II	33	37.5%	21	51.1%	10	22.7%	
III	54	61.4%	22	47.7%	34	77.3%	
Menopausal status							
Pre	48	54.5%	26	59.1%	23	52.3%	0.43
Post	40	45.5%	18	40.9%	21	47.7%	
Histopathology type							
IDC	72	81.8%	37	84.1%	35	39.7%	0.87
ILC	7	7.9%	2	4.5%	5	11.4%	
IPC	3	3.4%	2	4.5%	1	2.2%	

DCI	2	2.2%	2	4.5%	0	0%	
CC	2	2.2%	1	2.3%	1	2.2%	
PC	2	2.2%	0	0	2	4.5%	
Regimen of RT given							
After Chemotherapy	68	77.3%	32	72.7%	37	84%	0.32
After surgery	20	22.7%	12	27.3%	7	15.9%	
Marital Status							
Single	2	2.2%	1	2.3%	1	2.2%	0.43
Married	86	97.8%	43	97.7%	43	97.8%	

IDC- Infiltrating Ductal Carcinoma, IPC- Infiltrating Papillary Carcinoma, ILC- Infiltrating Lobular Carcinoma, CC- Comedo Carcinoma, PCPapillary Carcinoma.

6.1.1.2: Comparison of baseline measures between groups.

All outcome measures were compared at baseline between groups using one way Analysis of Variance. There was no significant difference in baseline measure between groups suggesting that the groups were homogenous at baseline (See Table 6.1.1.2)

Table 6.1.1.2 Comparison of baseline values between groups using one way ANOVA

Baseline Scores	**Yoga (n=42)**	**Control (n=34)**	**One Way ANOVA**	**Baseline Scores**	**Yoga (n=42)**	**Control (n=34)**	**One Way ANOVA**

	Mean (SD)		'p' value		Mean (SD)		'p' value
HADS-A	8.05 (3.9)	9.35 (3.9)	0.06	Fatigue	44.8 (22.9)	50.5 (22.4)	0.37
HADS-D	7.6 (4.02)	8.0 (3.5)	0.32	Pain	33.7 (26.7)	42.5 (28.5)	0.19
PSS	20.8 (6.1)	21.4 (6.2)	0.41	Dyspnoea	8.13 (17.9)	12.12(18.3)	0.57
PANAS-P	24.1 (7.4)	22.0 (7.3)	0.06	Insomnia	47.2 (34.1)	34.3 (25.7)	0.07
PANAS-N	22.4 (10.8)	25.1 (9.2)	0.10	Nausea and vomiting	13.4 (21.5)	11.1 (14.2)	0.56
Physical Function	72.7 (22.7)	62.4 (29.9)	0.08	Appetite loss	21.9 (24.3)	20.2 (26.3)	0.69
Role Function	74.4 (33.8)	68.2 (37.1)	0.65	Diarrhea	3.3 (12.5)	3.03 (12.8)	1.00
Emotional Function	55.9 (19.6)	50.58(18.1)	0.16	Constipation	6.5 (20.0)	7.1 (21.7)	1.00
Cognitive Function	85.43 (17.5)	79.4 (21.5)	0.53	Psychological distress	6.9 (3.4)	7.83 (3.6)	0.11
Social Function	51.8 (25.1)	52.2 (24.1)	0.89	Physical distress	13.5 (6.2)	14.23 (7.7)	0.64
Global Quality of Life	58.8 (18.2)	57.32(17.9)	0.86	Activity level	20.2 (5.8)	18.23 (6.2)	0.18
Cortisol 0600 hrs	0.33 (0.17)	0.38 (0.31)	0.47	Cortisol 2100	0.19 (0.14)	0.16 (0.15)	0.45

Cortisol 0900 hrs	0.26 (0.16)	0.24 (0.23)	0.78	Mean Cortisol	0.25 (0.13)	0.25 (0.21)	0.34

6.1.1.3: Comparison of baseline values with normative data

Baseline values of outcome measures in our study were compared with measures in normal populations as quoted in earlier studies and literature. (See table 6.1.1.3)

Table 6.1.1.3: The baseline values in comparison with normative data

Sl. No	Parameter	Radiation (n=88)	Metastatic (n=66)	Normative data (Females)
		Mean (SD)	**Mean (SD)**	**Mean (SD)**
1	Hospital Anxiety	8.76 (3.92)	7.70 (3.33)	6.14 (3.76)
2	Hospital Depression	7.83 (3.69)	8.00 (4.36)	3.68 (3.07)
3	Perceived stress	20.77 (5.91)	18.68 (7.67)	18.87 (7.6)
4	Positive Affect	23.25 (7.75)		31.3 (7.7)
5	Negative Affect	23.40 (9.92)		16 (5.9)

HADS: The baseline values on HADS-A scale were above the normal cut off score (Crawford JR, 2001) with the means falling under the category of mild anxiety in both early breast and metastatic breast cancer population. While self reported anxiety was lesser in advanced breast

cancer group as compared to early breast cancer group, self reported depression score was more in the advanced breast cancer group as compared to early breast cancer group. According to the authors who designed the HADS test it is recommended that, for the Anxiety and Depression scales alike, raw scores between 8 and 10 identify mild cases, 11–15 moderate cases, and 16 or above, severe cases (Snaith & Zigmond, 1994).

PSS: The normative data for perceived stress scores in US population between 30-65 years is similar to that of our study sample (Cohen S, 1983). Since PSS is not a diagnostic instrument, there is no cut-off score. There are only comparisons between people in a given sample (Cohen Williamson, 1988).

PANAS: The positive and negative affect in a community sample has norms much below that seen in our study population. This would mean that stressors that breast cancer patients experience would have contributed to increase in negative affect and decrease in positive affect (Watson D,1988b and Crawford JR, 2004).

6.1.2 Results following intervention in two groups BCS2/3 study

Measures of Mood States

6.1.2.1 Anxiety scores (HADS-A)

Analysis of covariance on post measures using baseline anxiety as a covariate showed significant difference between groups with better decrease in self-report anxiety in yoga compared to control group [$F(1,73) = 15.4$, $p < 0.001$,ES-0.31, PC-26.22%]. Paired-samples *t*-test done to assess within group change showed a significant decrease in self-reported anxiety scores with in yoga group ($t = 7.24$, $p < 0.001$) and control group ($t = 2.15$, $p = 0.04$) following intervention (Table 6.1.2.1).

6.1.2.2 Depression scores (HADS-D)

Analysis of covariance on post measures using baseline depression scores as a covariate showed a significant difference between groups with better decrease in self-report depression in yoga group compared to controls [F(1,73) = 10.7, p = 0.002, ES- 0.31, PC-26.94%]. Paired-samples t-test done to assess within group change showed a significant decrease in self- report depression within yoga (t = 6.26, p < 0.001) and control groups (t = 3.23, p = 0.01) (Table 6.1.2.1).

6.1.2.3 Perceived Stress Scale score (PSS)

Analysis of covariance on post measures using baseline perceived stress score as a covariate showed a significant difference between groups with better decrease in perceived stress in yoga compared to control group [F(1,72)=18.05, p <0.001, ES-0.36, PC-20.97%]. Paired-sample t-test done to assess within group change showed a significant decrease in perceived stress in yoga group only (t = 5.5, p < 0.001) and not in the control group (t = 1.42, p = 0.17) (Table 6.1.2.1).

Table 6.1.2.1: **Changes in anxiety, depression and perceived stress yoga and control groups following intervention - ANCOVA with baseline measure as a Covariate**.

	Yoga (n=42)			**Control (n=34)**				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size (Cohen's f)**	**(Y-C) % Change**
Anxiety	8.05 (3.87)	4.88 (3.34)*** †††	39.38	9.35 (3.98)	8.12 (3.80) *	13.16	0.31	26.22

Depression	7.57 (4.02)	4.14 (3.45) ** ††	45.31	8.00 (3.47)	6.53 (3.78) **	18.38	0.31	26.94
Perceived Stress Score	20.78 (6.10)	15.17 (4.83) *** †††	27.00	21.41 (6.22)	20.12 (5.87)	6.03	0.36	20.97

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using paired t test

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ for between group change using ANCOVA.

6.1.2.4 PANAS-Positive Affect

Analysis of covariance on post measures using baseline positive affect score as a covariate showed significant difference between groups with better increase in self-report positive affect in yoga compared to control group [F(1,86) = 12.0, p = 0.001, ES-0.11, -15.86%]. Paired-samples t-test done to assess within group change showed a significant increase in self-reported positive affect scores with in yoga group (t = -3.50, p = 0.001) and not in the control group (t = -0.08, p = 0.93) following intervention (Table 6.1.2.2).

6.1.2.5 PANAS-Negative Affect

Analysis of covariance on post measures using baseline negative affect as a covariate showed significant difference between groups with better decrease in self-report negative affect in yoga compared to control group [F(1,86) = 22.6, $p < 0.001$, ES-0.16, 33.69%]. Paired-samples *t*-test done to assess within group change showed a significant decrease in self-reported negative affect scores with in yoga group ($t = 6.00$, $p < 0.001$) and not in the control group ($t = 1.35$, $p = 0.18$) following intervention (Table 6.1.2.2).

Table 6.1.2.2: Comparison of scores for Positive Affect and Negative Affect using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga (n=42)			Control (n=33)				
Variable	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size (Cohen's f)**	**(Y-C) % Change**
PANAS-Positive	24.10 (7.37)	28.02 (7.23)** ††	-16.27	22.03 (7.27)	22.12 (8.68)	-0.41	0.11	-15.86

PANAS-Negative	22.43 (10.78)	12.95 (10.33)**††	42.26	25.06 (9.16)	22.91 (10.75)	8.58	0.16	33.69

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using paired t test

†† $p < 0.01$, ††† $p < 0.001$ for between group change using ANCOVA.

6.1.3 Quality of life BCS2/3 study

EORTC QLC30

6.1.3.1 Functional scales

Physical function:

Analysis of covariance on post measures using baseline physical function as a covariate did not show significant difference between groups [F (1, 85) = 0.32, $p = 0.57$, ES-0.005, 8.07%]. Paired-samples *t*-test done to assess within group change did not show a significant change in self-reported physical function scores in both the groups, yoga group ($t = -0.15$, $p = 0.88$) and control group ($t = -1.85$, $p = 0.07$) following intervention (Table 6.1.3.1).

Role function:

Analysis of covariance on post measures using baseline role function as a covariate also did not show significant difference between groups [F(1,85) = 1.29, $p = 0.26$, ES-0.02, 8.77%]. Paired-samples *t*-test done to assess within group change did not show a significant change in self-

reported role function scores in both the groups, yoga group (t = -1.07, p = 0.29) and control group (t = 0.25, p = 0.80) following intervention (Table 6.1.3.1).

Emotional Function:

Analysis of covariance on post measures using baseline emotional function as a covariate showed significant difference between groups with better increase in self-report emotional function in yoga compared to control group [F(1,85) = 17.2, p < 0.001, ES-0.14, -22.16%]. Paired-samples t-test done to assess within group change showed a significant increase in self-reported emotional function within yoga group (t = -6.25, p< 0.001) and not in the control group (t = -1.51, p = 0.14) following intervention (Table 6.1.3.1).

Cognitive function:

Analysis of covariance on post measures using baseline emotional function as a covariate showed significant difference between groups with better increase in self-report cognitive function in yoga compared to control group [F(1,85) = 4.42, p = 0.04, ES-0.09,-8.61%]. Paired-samples t-test done to assess within group change did not show a significant change in self-reported cognitive function in both the groups, yoga group (t = -1.83, p = 0.07) and control group (t = 0.56, p = 0.58) following intervention (Table 6.1.3.1).

Social function:

Analysis of covariance on post measures using baseline social function as a covariate showed significant difference between groups with better increase in self-report social function in yoga compared to control group [F(1,85) = 5.77, p = 0.02, ES-0.02,-18.13%]. Paired-samples t-test

done to assess within group change showed a significant increase in self-reported social function scores with in yoga group (t = -1.97, p= 0.05) and not in the control group (t = 1.18, p = 0.25) following intervention (Table 6.1.3.1).

6.1.3.2 EORTC QLC30 –Quality of Life

Global Quality of Life:

Analysis of covariance on post measures using baseline global quality of life as a covariate also did not show significant difference between groups [F(1,85) = 1.30, p = 0.26, ES-0.004,-7.02%]. Paired-samples t-test done to assess within group change did not show a significant change in self-reported global quality of life scores in both the groups, yoga group (t = -1.67, p = 0.10) and control group (t = -0.11, p = 0.91) following intervention (Table 6.1.3.1).

Table 6.1.3.1: Comparison of scores for functional scales and Global quality of life of EORTC QoLC30 scores using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga (n=42)			Control (n=33)				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size, Cohen's f**	**(Y-C) % Change**
Physical Function	72.68 (22.70)	73.17 (25.54)	-0.67	62.42 (29.98)	67.88 (30.39)	-8.75	0.005	8.07
Role Function	74.39 (33.77)	79.27 (35.31)	-6.56	68.18 (37.12)	66.67 (40.83)	2.21	0.02	-8.77
Emotional Function	55.94 (19.59)	74.23 (21.27)** ††	-32.70	50.58 (18.13)	55.91 (21.93)	-10.54	0.14	-22.16
Cognitive Function	85.43 (17.51)	90.70 (14.88)†	-6.17	79.41 (21.52)	77.47 (25.53)	2.44	0.09	-8.61
Social Function	51.82 (25.12)	57.83 (22.85)*†	-11.60	52.20 (24.07)	48.79 (23.70)	6.53	0.02	-18.13
Global Quality of Life	58.75 (18.18)	63.21 (21.00)	-7.59	57.32 (17.89)	57.65 (21.10)	-0.58	0.004	-7.02

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using paired t test

†† $p < 0.01$, ††† $p < 0.001$ for between group change using ANCOVA.

6.1.3.3 EORTC QLC30 –Symptom scale:

Analysis of covariance on post measures using baseline symptom scores as a covariate showed significant difference between groups for fatigue [F(1,85) = 14.49, $p < 0.001$, ES-0.33,33.15%], pain [F(1,69) = 4.83, $p = 0.03$, ES-0.14,29.09%], insomnia [F(1,71) = 12.44, $p = 0.001$, ES-0.47,58.37%] and appetite loss [F(1,71) = 13.32, $p < 0.001$, ES-0.38,94.91%] . Paired-samples *t*-test done to assess within group change for symptom scale showed significant decrease in symptom scores in yoga group alone for fatigue ($t = 3.45$, $p = 0.001$), nausea & vomiting ($t = 2.08$, $p = 0.04$), pain ($t = 2.37$, $p = 0.02$), insomnia ($t = 5.67$, $p < 0.001$) but not in the control group. There was no significant change in appetite loss in yoga group ($t = 1.59$, $p = 0.12$) but there was a significant increase in appetite loss in control group ($t = -2.90$, $p = 0.007$). There was no significant change across groups for symptoms such as dyspnoea, diarrhea and constipation ((Table 6.1.3.2).

Table 6.1.3.2: Comparison of scores for symptom scale of EORTC QoLC30 scores using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga(n=42)			Control (n=33)					
Outcome Variables	**PRE Mean (SD)**	**POST Mean (SD)**	**% Change**	**PRE Mean (SD)**	**POST Mean (SD)**	**% Change**	**Adjusted mean (Y-C) 95%CI**	**(Y-C) % Change**	**Effect size**
Fatigue	44.76 (22.89)	31.37 (21.79) **††	29.92	50.46 (22.41)	52.09 (24.24)	-3.23	-20.72 (-31.40 to -10.04)	33.15	0.33
Pain	33.74 (26.74)	23.17 (27.10) *†	31.33	42.47 (28.49)	41.52 (32.57)	2.24	-18.36 (-32.39 to -4.32)	29.09	0.14
Dyspnoea	8.13 (17.92)	5.69 (12.69)	30.01	12.12 (18.29)	10.13 (17.63)	16.42	-4.44 (-11.47 to	13.59	-1.51

							2.59)		
Insomnia	47.15 (34.14)	21.14 (26.62) **††	55.16	34.34 (25.66)	35.44 (32.11)	-3.20	-14.31 (-27.91 to -0.69)	58.37	0.47
Nausea and vomiting	13.41 (21.48)	6.91 (13.93) *	48.47	11.11 (14.23)	6.69 (13.09)	39.78	0.22 (-6.10 to 6.55)	8.69	0.05
Appetite Loss	21.95 (24.28)	15.45 (19.86) **††	29.61	20.20 (26.27)	33.39 (28.79)	-65.30	-17.95 (-29.25 to -6.65)	94.91	0.38
Diarrhea	3.25 (12.48)	0.81 (5.21)	75.08	3.03 (12.81)	4.07 (13.83)	-34.32	-3.26 (-7.92 to 1.41)	109.40	0.01
Constipation	6.50 (20.03)	6.50 (20.03)	0.00	7.07 (21.66)	8.11 (22.08)	-14.71	-1.61 (-11.38 to 8.17)	14.71	0.14

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using paired t test

†† $p < 0.01$, ††† $p < 0.001$ for between group change using ANCOVA.

6.1.4 Rotterdam symptom check list

Psychological distress:

Analysis of covariance on post measures using baseline psychological distress as a covariate showed significant difference between groups with greater decrease in self-report psychological distress in yoga compared to control group [F(1,83) = 14.1, p < 0.001, ES-0.39, PC- 33.98%]. Paired-samples *t*-test done to assess within group change showed a significant decrease in self-reported psychological distress scores with in yoga group alone (t = 5.83, p< 0.001) following intervention (Table 6.1.4).

Physical distress:

Analysis of covariance on post measures using baseline physical distress as a covariate showed significant difference between groups with better decrease in self-report physical distress in yoga compared to control group [F(1,85) = 5.45, p = 0.02, ES-0.33, PC- 30.82%]. Paired-samples *t*-test done to assess within group change showed a significant decrease in self-reported physical distress scores with in yoga group alone (t = 2.81, p= 0.007) following intervention (Table 6.1.4).

Activity Level:

Analysis of covariance on post measures using baseline activity level as a covariate also did not show significant difference between groups [F(1,85) = 3.34, p = 0.07, ES-0.14, PC- -6.89%].Paired-samples *t*-test done to assess within group change did not show significant changes in self-reported activity level scores in both the groups, yoga (t = -0.39, p = 0.69) and controls (t = 1.38, p = 0.17) following intervention (Table 6.1.4).

Table 6.1.4: Comparison of scores for distress and activity on Rotterdam symptom check list scores using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga (n=42)			Control (n=33)					
Outcome Variables	**PRE Mean (SD)**	**POST Mean (SD)**	**% Change**	**PRE Mean (SD)**	**POST Mean (SD)**	**% Change**	**Adjusted mean (Y-C) (95% CI)**	**Effect size**	**(Y-C) % Change**
Psychological distress	6.90 (3.36)	4.15 (3.28) ** ††	39.86	7.83 (3.55)	7.37 (3.65)	5.87	- 3.22 (- 4.81 to -1.63)	0.39	33.98
Physical distress	13.52 (6.16)	9.98 (7.04) ** ††	26.18	14.23 (7.70)	14.89 (8.36)	- 4.64	- 4.91 (- 8.45 to -1.37)	0.33	30.82
Activity Level	20.20 (5.78)	20.35 (5.35)	-0.74	18.23 (6.19)	17.11 (6.47)	6.14	3.24 (0.52 to	0.14	- 6.89

5.95)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using paired t test

†† $p < 0.01$, ††† $p < 0.001$ for between group change using ANCOVA.

6.1.5 Diurnal salivary cortisol levels:

Analysis of covariance (ANCOVA) was used to assess between group differences using baseline cortisol value (for the corresponding time) as a covariate. There was a significant decrease in mean salivary cortisol level at 0600 hrs in yoga group compared to control group [F (1, 56) = 7.45, p = 0.009, ES-0.24, 28.07%]. There was also a significant decrease in pooled mean diurnal salivary cortisol level in yoga group as compared to controls [F (1, 53) =5.14, p = 0.03, ES-0.27, 24%]. Cortisol slopes in both groups were computed using a linear mixed effects model using R software. There was no significant difference in the slopes between groups at baseline (p = 0.2074, t = -1.25) but there was a significant decrease in cortisol slope in yoga group as compared to controls post intervention (p = 0.015, t = -2.45). Paired-samples t-test to assess within group change following intervention showed a significant decrease in mean salivary cortisol levels at 0600 hrs (t = 4.21, p < 0.001) and pooled diurnal mean cortisol in yoga group only (t =2.79, p = 0.01), but not in the control Group (t = 0.34, p < 0.74), (t = - 0.04, p = 0.96) (Table 6.1.5).

Table 6.1.5: Comparison of Mean values of diurnal cortisol levels using paired‘t’ test and analysis of co-variance (ANCOVA).

	Yoga (n=27)		Control (n=29)	

Outcome Variables	Pre Mean (SD)	Post Mean (SD)	% Change	Pre Mean (SD)	Post Mean (SD)	% Change	Effect Size (Cohen's f)	(Y-C)% Change
0600 Hrs	0.33 (0.17)	0.22 (0.15) *†	33.33	0.38 (0.31)	0.36 (0.24)	5.26	0.24	28.07
0900 Hrs	0.26 (0.16)	0.19 (0.14)	26.92	0.24 (0.23)	0.24 (0.23)	0.00	0.21	26.92
2100 hrs	0.19 (0.14)	0.16 (0.16)	15.79	0.16 (0.15)	0.16 (0.14)	0.00	0.14	15.79
Mean pooled diurnal cortisol	0.25 (0.13)	0.19 (0.13) *†	24.00	0.25 (0.21)	0.25 (0.18)	0.00	0.27	24.00

- $p < 0.05$ for within group change using paired 't' test.
- † $p < 0.05$ for between group change using ANCOVA.

6.1.6 Bivariate relationships

Bivariate relationships were determined between change score of anxiety, depression, perceived stress and changes in quality of life sub scales and cortisol following yoga intervention

in yoga group using Pearson correlation coefficients. There was a significant negative correlation of physical function with anxiety (p= 0.03), perceived stress (p= 0.04), negative affect (p = 0.01), psychological distress (p = 0.001), physical distress (p = 0.002) and positive correlation with activity level (p = 0.03). There was a significant positive correlation between changes in emotional function with positive affect (p = 0.02) and negative correlation with negative affect (p = 0.001), psychological distress (p = 0.001) and physical distress (p = 0.01) following intervention. There was a significant negative correlation of changes in role function with perceived stress (p = 0.01) and changes in global quality of life with psychological distress (p = 0.02). There was a significant positive correlation between changes in global quality of life with positive affect (p = 0.002) (Table 6.1.6).

Table 6.1.6 Bivariate relationships between changes in anxiety, depression, perceived stress, affect, distress and quality of life sub scores following intervention in yoga group using Pearson correlation analysis.

Variable	Physical	Role Fn	Emotional	Cognitive	Social Fn	Global

	Fn		Fn	Fn		QOL
Anxiety	-0.33*	-0.13	-0.30	-0.02	-0.27	-0.17
Depression	-0.21	-0.20	-0.15	-0.20	-0.29	-0.23
Perceived stress	-0.33*	-0.43**	-0.26	-0.07	-0.01	-0.01
Positive affect	0.15	0.19	0.36*	0.22	0.13	0.48**
Negative affect	-0.38*	-0.16	-0.52**	-0.06	-0.19	-0.21
Psychological distress	-0.52**	-0.22	-0.63**	-0.27	-0.09	-0.36*
Physical distress	-0.48**	-0.34	-0.41**	-0.38*	-0.21	-0.29
Activity level	0.35*	0.29	0.15	0.40**	0.07	0.23

***p* values < 0.05, ** *p* values < 0.01 for Pearson correlation. Fn-Function

6.1.7 Bivariate relationships between changes in psychological distress, quality of life and salivary cortisol

There was a significant positive correlation between changes in morning salivary cortisol (6 am) levels with changes in negative affect (p= 0.01) and psychological distress (*p* = 0.05) and significant negative correlation between changes in global quality of life with evening 9pm salivary cortisol levels (*p* = 0.01) following intervention in the yoga group (See table 6.1.7).

Table 6.1.7 Bivariate relationships between changes in measures of stress, Affect, Distress,

Variable	0600 cortisol level	0900 cortisol level	2100 cortisol level	Mean diurnal cortisol level
Anxiety	0.28	0.07	0.01	0.15
Depression	0.26	0.02	-0.15	0.03
Perceived stress	0.07	0.10	-0.21	-0.02
Positive affect	-0.09	-0.13	0.39	0.02
Negative affect	0.49*	0.11	-0.03	0.26
Psychological distress	0.38*	0.09	-0.14	0.06
Physical distress	0.24	0.03	-0.10	0.04
Activity level	-0.31	-0.11	-0.19	-0.24
Physical Fn	-0.16	0.06	0.07	0.06
Role Fn	-0.06	0.13	-0.26	-0.02
Emotional Fn	-0.19	-0.20	0.16	-0.07
Cognitive Fn	-0.13	-0.04	0.27	0.07
Social Fn	0.01	0.02	0.22	0.14
Global QOL	-0.09	0.07	-0.56**	0.29

Daily activity, Functional scale, Global quality of life, with changes in diurnal salivary cortisol levels following intervention in yoga group.

*p values < 0.05, ** p values < 0.01 for Pearson correlation. Fn- Function

6.1.8 Adherence to Intervention

Adherence to intervention was good in our study with 56.7% attending 20-25 supervised sessions and 13.7% attending >25/30 supervised sessions over a six week period in the early breast cancer study (See tables 6.1.8a and 6.1.8b).

Table 6.1.8a: Comparison of change scores for affect and Quality of life in yoga group attending yoga classes (<20 and >20 classes).

		Change Scores							
Attendance category		**Positive affect**	**Negative affect**	**Quality of life**	**Physical function**	**Role function**	**Emotional function**	**Cognitive function**	**Social function**
<20 classes n=12	Mean	-4.1	10.1	-5.27	-5.3	-5.4	-23.3	-8.3	1.9
	(SD)	(4.3)	(9.7)	(19.1)	(17.5)	(33.5)	(16.6)	(12.8)	(23.7)

>20 classes n=35	Mean (SD)	-3.2 (7.8)	8.5 (10.1)	-5.2 (16.2)	2.3 (22.1)	-10 (33.9)	-17.8 (17.6)	-6.6 (20.3)	-5.3 (21.3)

Table 6.1.8b Comparison of change scores for anxiety, perceived stress, depression and diurnal cortisol in yoga group attending yoga classes (<20 and >20 classes).

		Change Scores						
Attendance Category		**6am cortisol**	**9am cortisol**	**9pm cortisol**	**Mean cortisol**	**Anxiety**	**Depression**	**Perceived Stress**
<20 classes n=6	Mean (SD)	0.18 (0.12)	0.25 (0.25)	0.03 (0.05)	0.15 (0.09)	3.2 (2.1)	3.2 (3.3)	6.3 (7)
>20 classes n=21	Mean (SD)	0.09 (0.13)	0.02 (0.15)	0.03 (0.19)	0.04 (0.12)	3.2 (3.1)	3.5 (3.7)	5.4 (6.4)

6.2 Results of BCS 4 study

6.2.1 Baseline Measures:

6.2.1.1 Socio-demographic and Medical Characteristics of the Study sample

The mean age of participants was 48.9 ± 9.1 yrs in yoga and 50.2 ± 9.2 yrs in control groups. 26 subjects underwent surgery, chemotherapy, radiotherapy and chemotherapy, 11 subjects received chemotherapy and radiotherapy and 8 subjects underwent surgery and radiotherapy as primary treatment. Participants in both groups were comparable with respect to socio-demographic and medical characteristics. A goodness of fit test run on all these demographic variables did not show any significant changes between yoga and supportive therapy groups ($p > 0.05$).

Table 6.2.1.1 Demographic and medical characteristics of the initially randomized sample in BCS4 Study.

Variable	Yoga (n=45)	Control (n=46)	Total (n=91)	'p' value
	Mean (SD)	Mean (SD)	Mean (SD)	
Age in years	48.9 (9.1)	50.2 (9.2)	49.6 (9.1)	0.76
Duration of cancer (in months)	44.3 (27.5)	38.6 (31.6)	41.6 (29.4)	0.24
Duration of disease free survival (in months)	28.4 (32.1)	20.5 (30.9)	24.6 (31.4)	0.33
Duration of metastatic	18.1 (9.9)	17.9 (9.3)	17.9 (9.6)	0.71

disease (in months)				
Treatment regimen		**n (%)**		
S+CT+RT+CT	26 (57.8%)	22 (47.8%)	48 (52.7%)	
CT+RT	11 (24.4%)	17 (36.9%)	28 (30.8%)	0.86
S+CT+RT	8 (17.8%)	7 (15.2%)	15 (16.5%)	

6.2.1.2 Comparison of baseline measures between groups.

All outcome measures were compared at baseline between groups using one way Analysis of Variance. There was no significant difference in baseline measure between groups suggesting that the groups were homogenous at baseline (See Table 6.2.1.2).

Table 6.2.1.2 Comparison of baseline values between groups using one way ANOVA

Mean (SD)				**Mean (SD)**			
Baseline Scores	**Yoga (n=35)**	**Control (n=31)**	**One Way ANOVA 'p' value**	**Baseline Scores**	**Yoga (n=35)**	**Control (n=31)**	**One Way ANOVA 'p' value**
HADS-A	6.6 (3.5)	8.9 (2.6)	0.01	Fatigue Severity	17.2 (9.1)	17.94 (6.9)	0.71
HADS-D	6.7 (3.9)	9.5 (4.3)	0.01	Fatigue Frequency	8.7 (4.8)	9.5 (3.9)	0.46

PSS	16.5 (8.9)	21.2 (5.0)	0.01	Interferance	23.3 (16.9)	25.6 (16.1)	0.57
Physical Function	70.1 (22.4)	51.6 (22.4)	0.01	Diurnal variation	3 (1.4)	2.77 (1.12)	0.47
Role Function	68.6 (34.5)	51.6 (32.8)	0.05	IRS Symptom distress	20.9 (20.5)	32.2 (31.9)	0.10
Emotional Function	70.9 (17.7)	62.9 (20.7)	0.09	IRS Sleep Parameter	6.9 (6.8)	7.52 (6.7)	0.72
Cognitive Function	81.9 (22.2)	72.1 (27.6)	0.11	IRS QOL	14.1 (6.4)	16 (6.13)	0.22
Social Function	55.3 (29.1)	48.4 (27.8)	0.33	IRS Total Scores	43 (34)	55.8 (41.3)	0.18
Global Quality of Life	54.1 (23.2)	46 (15.5)	0.10	2100 hrs cortisol	0.09 (0.1)	0.12 (0.2)	0.94
0600 hrs cortisol	0.22 (0.2)	0.22 (0.3)	0.92	NK Cell Count	209.2 (123.1)	192.7 (130.3)	0.92
00 hrs cortisol	0.11 (0.1)	0.14 (0.2)	0.33	NK %	9.68 (4.3)	10.33 (5.6)	0.43

6.2.2 Results after the intervention in two groups in BCS4 study

Measures of Mood States

6.2.2.1 Anxiety scores (HADS-A):

Non Parametric Mann-Whitney test done to assess between group change showed significant difference between groups with better decrease in self-report anxiety in yoga compared to control group (z=-2.63, *p*< 0.01, ES-1.9, PC-55.98%).Non Parametric Wilcoxon test done to assess within group change showed significant decrease in self-reported anxiety in yoga group only (z = -4.12, *p* < 0.001) not in the control group (z =

-0.99, *p* = 0.32) (Table 6.2.2.1).

6.2.2.2 Depression scores (HADS-D):

Non Parametric Mann-Whitney test done to assess between group changes showed significant difference between groups with better decrease in self-report depression in yoga compared to control group (z=-3.00, *p*< 0.01, ES-1.6, PC-53.59%).Non Parametric Wilcoxon test done to assess within group change showed significant decrease in self-reported depression in yoga group only (z = -4.42, *p* < 0.001) not in the control group (z = -0.19, *p* = 0.85) (Table 6.2.2.1).

6.2.2.3 Perceived Stress scores (PSS):

Non Parametric Mann-Whitney test done to assess between group changes showed significant difference between groups with better decrease in self-report perceived stress in yoga compared to control group (z=-2.49, *p*= 0.01, ES-1.4, PC-32.57%).Non Parametric Wilcoxon test done to assess within group change showed significant decrease in self-reported perceived stress in yoga group only (z = -3.46, *p* = 0.001) not in the control group (z = -0.62, *p* = 0.54) (Table 6.2.2.1).

Table 6.2.2.1: Comparison of scores for Anxiety, Depression and Perceived stress scores using Mann-Whitney test between yoga and control groups with respective baseline measure as a covariate.

	Yoga (n=35)			Control (n=31)				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size, (Cohen's d)**	**(Y-C) % Change**
Anxiety	6.60 (3.54)	3.40 (2.93) ***†††	48.48	8.94 (2.62)	9.61 (3.58)	-7.49	1.9	55.98
Depression	6.66 (3.99)	2.86 (2.93) *** †††	57.06	9.52 (4.31)	9.19 (4.65)	3.47	1.6	53.59
Perceived Stress Score	16.49 (8.93)	10.09 (7.25) *** †††	38.81	21.16 (5.01)	19.84 (6.19)	6.24	1.4	32.57

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using Wilcoxon test

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ for between group change using Mann-Whitney test..

6.2.3 EORTC QLC30

6.2.3.1 Functional scales

Physical function:

Non Parametric Mann-Whitney test done to assess between group change did not show significant change in physical function in yoga group compared to control group (z=-1.85, p = 0.06, ES-1.0, PC-16.7%). Non Parametric Wilcoxon test done to assess within group change did not show significant change in physical function in yoga group (z = -1.68, p = 0.09) and in the control group (z = -0.47, p = 0.63) (Table 6.2.3.1).

Role function:

Non Parametric Mann-Whitney test done to assess between group change showed significant improvement in role function in yoga group compared to control group (z=-2.22, p = 0.03, ES-1.3, PC-30.2%).Non Parametric Wilcoxon test done to assess within group change showed significant improvement in role function in yoga group (z = -3.23, p < 0.01) not in the control group (z = -0.27, p = 0.79) (Table 6.2.3.1).

Emotional function:

Analysis of covariance on post measures using baseline emotional function as a covariate showed significant difference between groups with better increase in self-report emotional function in yoga compared to control group [F(1,63) = 13.6, p < 0.001, ES-0.14, -22.16%]. Paired-samples t-test done to assess within group change showed a significant increase in self-reported emotional function scores with in yoga group (t = -2.68, p= 0.01) and not in the control group (t = 0.61, p = 0.54) following intervention. (Table 6.2.3.1).

Cognitive function:

Analysis of covariance on post measures using baseline emotional function as a covariate showed significant difference between groups with better increase in self-report cognitive function in yoga compared to control group [F(1,63) = 21.56, $p < 0.001$, ES-0.09,-8.61%]. Paired-samples *t*-test done to assess within group change did not showed a significant increase in self-reported cognitive function scores with in yoga group ($t = -3.82$, $p < 0.01$) and not in the control group ($t = 0.52$, $p = 0.61$) following intervention. (Table 6.2.3.1).

Social function:

Analysis of covariance on post measures using baseline social function as a covariate showed significant difference between groups with better increase in self-report social function in yoga compared to control group [F(1,63) = 12.26, $p < 0.01$, ES-0.02,-18.13%]. Paired-samples *t*-test done to assess within group change showed a significant increase in self-reported social function scores with in yoga group ($t = -3.55$, $p< 0.01$) and not in the control group ($t = -0.62$, $p = 0.54$) following intervention (Table 6.2.3.1).

6.2.3.2 EORTC QLC30 –Quality of Life

Global Quality of Life:

Analysis of covariance on post measures using baseline Global Quality of life as a covariate showed significant difference between groups with better increase in self-report Global Quality of life in yoga compared to control group [F(1,63) = 33.07, $p < 0.001$, ES-0.004,-7.02%]. Paired-samples *t*-test done to assess within group showed a significant increase in Global Quality of life

scores with in yoga group (t = -5.32, p< 0.001) and not in the control group (t = -0.94, p = 0.35) following intervention (Table 6.2.3.1).

Table 6.2.3.1: Comparison of scores for functional scales and Global quality of life of EORTC QoLC30 scores between yoga and control groups.

	Yoga (n=35)			Control (n=31)				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size, (Cohen's f)**	**(Y-C) % Change**
Physical Function	70.09 (22.42)	78.29 (29.65)	-11.70	51.61 (22.38)	49.03 (28.68)	5.00	1.0	-16.70
Role Function	68.57 (34.48)	91.43**† (19.12)	-33.34	51.61 (32.87)	53.23 (40.69)	-3.14	1.3	-30.20

Emotional Function	70.90 (17.70)	84.03**† (22.67)	-18.52	62.92 (20.74)	59.16 (29.24)	5.98	0.9	-24.49
Cognitive Function	81.97 (22.20)	95.23** (10.33)	-16.18	72.06 (27.62)	68.87 (28.99)	4.43	1.2	-20.60
Social Function	55.29 (29.14)	73.34** (20.23)	-32.65	48.39 (27.75)	52.23 (26.20)	-7.94	0.9	-24.71
Global Quality of Life	54.09 (23.20)	73.00**†† (15.64)	-34.96	46.03 (15.48)	49.23 (16.08)	-6.95	1.5	-28.01

* *p* values < 0.05, ** *p* values < 0.01 for within group change using Wilcoxon test

† *p* values < 0.05, †† *p* values < 0.01 for between group change using Mann Whitney test.

6.2.3.3 EORTC QLC30 –Symptom scale:

Non Parametric Mann-Whitney test done to assess between group change showed significant improvement in Fatigue (z = -1.95, *p* =0.05), Pain (z = -2.05, *p* <0.05), Insomnia (z = -3.03, *p* <0.01) in yoga group compared to control group. Non Parametric Wilcoxon test done to assess within group change showed significant improvement in Fatigue (z = -3.40, *p* <0.01), Nausea & Vomiting (z = -2.47, *p* <0.05), Pain (z = -3.19, *p* <0.01), Dyspnoea (z = -2.62, *p* <0.01), Insomnia (z = -3.64, *p* <0.01), Appetite loss (z = -3.89, *p* <0.01) and Constipation (z = -1.98, *p* <0.05) in Yoga group alone. Similar changes were not observed in control group (Table 6.2.3.2).

Table 6.2.3.2: Comparison of scores for symptom scale of EORTC QoLC30 scores between yoga and control groups.

	Yoga (n=35)			Control (n=31)				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size, (Cohen's d)**	**(Y-C) % Change**
Fatigue	40.46 (26.78)	20.49**† (18.66)	49.36	56.68 (19.55)	51.90 (26.21)	8.43	1.4	40.92
Nausea &Vomiting	8.57 (16.84)	0.97* (4.00)	88.68	21.00 (19.68)	16.71 (25.42)	20.43	0.8	68.25
Pain	33.40 (24.98)	17.17**† (17.31)	48.59	46.26 (25.77)	48.81 (29.21)	-5.51	1.3	54.11
Dyspnoea	20.89 (24.40)	10.37** (15.54)	50.36	30.23 (24.75)	29.13 (23.81)	3.64	0.9	46.72
Insomnia	35.14 (25.60)	9.46**†† (17.21)	73.08	36.65 (27.55)	38.77 (30.99)	-5.78	1.2	78.86
Appetite Loss	25.71 (29.24)	5.69** (15.06)	77.87	31.37 (28.26)	28.03 (28.51)	10.65	1.0	67.22
Constipation	10.46 (23.95)	2.83* (9.37)	72.94	11.97 (26.48)	20.45 (33.04)	-70.84	0.7	143.79
Diarrhea	5.69 (18.89)	1.89 (7.77)	66.78	18.19 (25.56)	14.33 (18.85)	21.22	0.8	45.56

* *p* values < 0.05, ** *p* values < 0.01 for within group change using Wilcoxon test

† *p* values < 0.05, †† *p* values < 0.01 for between group change using Mann Whitney test.

6.2.4 Fatigue Symptom Inventory

Fatigue Severity:

Analysis of covariance on post measures using baseline fatigue severity score as a covariate showed a significant difference between groups with better decrease in fatigue severity in yoga compared to control group [F(1,61)=32.55, *p* <0.001, ES-1.4, PC-61.15%]. Paired-sample t-test done to assess within group change showed a significant decrease in fatigue severity in yoga group only (*t* = 6.7, *p* < 0.001) and not in the control group (*t* = -0.05, *p* = 0.96) (Table 6.2.4).

Fatigue Frequency:

Analysis of covariance on post measures using baseline fatigue frequency score as a covariate showed a significant difference between groups with better decrease in fatigue frequency in yoga compared to control group [F(1,61)=17.81, *p* <0.001, ES-1.1, PC-52.64%].Paired-sample t-test done to assess within group change showed a significant decrease in fatigue frequency in yoga group only (*t* = 5.8, *p* < 0.001) and not in the control group (*t* = 0.33, *p* = 0.74) (Table 6.2.4).

Fatigue Interference:

Analysis of covariance on post measures using baseline fatigue interference score as a covariate showed a significant difference between groups with better decrease in fatigue interference in yoga compared to control group [F(1,61)=28.36, *p* <0.001, ES-1.3, PC-72.6%]. Paired-sample t-

test done to assess within group change showed a significant decrease in fatigue interference in yoga group only (t = 5.5, p < 0.001) and not in the control group (t = -0.36, p = 0.72) (Table 6.2.4).

Fatigue diurnal variation:

Analysis of covariance on post measures using baseline fatigue diurnal variation score as a covariate showed a significant difference between groups with better decrease in fatigue diurnal variation in yoga compared to control group [F(1,61)=13.65, p <0.001, ES-0.9,PC-52.33%].Paired-sample t-test done to assess within group change showed a significant decrease in fatigue diurnal variation in yoga group only (t = 3.8, p < 0.001) and not in the control group (t = -1.18, p = 0.24) (Table 6.2.4).

Table 6.2.4: Comparison of Fatigue Symptom Inventory scores using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga (n=33)			Control (n=31)				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size (Cohen's d)**	**(Y-C) % Change**
Fatigue Severity	17.18 (9.14)	6.76***††† (7.13)	60.65	17.94 (6.95)	18.03 (9.05)	-0.50	1.4	61.15
Fatigue	8.70	3.70***†††	57.47	9.52	9.06	4.83	1.1	52.64

Frequency	(4.83)	(4.07)		(3.96)	(5.78)			
Interferance	23.27 (16.90)	7.64***††† (9.47)	67.17	25.61 (16.06)	27.0 (18.34)	-5.43	1.3	72.60
Diurnal variation	3.00 (1.35)	1.82**††† (1.74)	39.33	2.77 (1.12)	3.13 (1.20)	-13.00	0.9	52.33

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ for between group change using ANCOVA.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using paired t test

6.2.5 Insomnia Rating Scale (IRS)

IRS Symptom Distress: Analysis of covariance on post measures using baseline symptom distress scores as a covariate showed a significant difference between groups with better decrease in symptom distress scores in yoga compared to control group [F(1,61)=21.23, p <0.001, ES-1.2, PC-91.31%].Paired-sample t-test done to assess within group change showed a significant decrease in symptom distress scores in yoga group only (t = 3.1, p = 0.004) and not in the control group (t = -1.32, p = 0.19) (Table 6.2.5).

IRS Sleep Parameters:

Analysis of covariance on post measures using baseline sleep distress parameter scores as a covariate showed a significant difference between groups with better decrease in sleep distress parameter scores in yoga compared to control group [F(1,61)=5.75, p =0.02, ES-0.6, PC-

111.43%]. Paired-sample t-test done to assess within group change showed a significant decrease in sleep distress parameter scores in yoga group only (t = 2.5, p = 0.01) and not in the control group (t = -1.30, p = 0.20) (Table 6.2.5).

IRS Quality of life:

Analysis of covariance on post measures using baseline sleep quality of life scores as a covariate showed a significant difference between groups with better decrease in sleep quality of life scores in yoga compared to control group [F(1,61)=13.03, p =0.001, ES-0.9, PC-20.25%]. Paired-sample t-test done to assess within group change showed a significant decrease in sleep quality of life scores in yoga group only (t = 2.9, p = 0.006) and not in the control group (t = 0.78, p = 0.44) (Table 6.2.5).

IRS Total Scores:

Analysis of covariance on post measures using baseline sleep total distress scores as a covariate showed a significant difference between groups with better decrease in sleep total distress scores in yoga compared to control group [F(1,61)=22.40, p =0.001, ES-1.2, PC--70.77%].Paired-sample t-test done to assess within group change showed a significant decrease in sleep total distress scores in yoga group only (t = 3.3, p = 0.002) and not in the control group (t = -1.33, p = 0.19) (Table 6.2.5).

Table 6.2.5: Comparison of Insomnia Rating Scale scores using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga (n=33)			Control (n=31)				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size (Cohen's d)**	**(Y-C) % Change**
IRS Symptom distress	20.97 (20.48)	7.88**††† (14.29)	62.42	32.16 (31.86)	41.45 (35.56)	-28.89	1.2	91.31
IRS Sleep Parameter	6.91 (6.81)	3.18*† (5.67)	53.98	7.52 (6.67)	11.84 (19.57)	-57.45	0.6	-3.47
IRS QOL	14.06 (6.44)	10.36**†† (4.10)	26.32	16.00 (6.13)	15.03 (5.50)	6.06	0.9	20.25
IRS Total Scores	43.03 (34.03)	21.42**††† (22.3)	50.22	55.77 (41.32)	67.23 (47.17)	-20.55	1.2	70.77

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for within group change using paired t test

† $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ for between group change using ANCOVA.

6.2.6 Diurnal salivary cortisol levels:

Analysis of covariance (ANCOVA) was used to assess between group differences using baseline cortisol value (for the corresponding time) as a covariate did not show any significant change. A

liner mixed effects model using R software showed no difference in pre cortisol slopes (p = 0.67, t = 0.41) and post cortisol slopes (Post: p = 0.42, t = 0.8) between groups. Paired-samples t-test to assess within group change following intervention showed a significant decrease in 0600 hrs cortisol (t = 2.28, p = 0.031) in yoga group alone but not in the control group (t = -0.31, p = 0.76) (Table 6.2.6).

Table 6.2.6: Results of diurnal cortisol levels after intervention using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga (n=25)			Control (n=21)				
Outcome Variables	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size, (Cohen's d)**	**(Y-C) % Change**
0600 hrs cortisol	0.22 (0.15)	0.15* (0.13)	31.82	0.22 (0.26)	0.24 (0.22)	-9.09	0.5	40.91
0900 hrs cortisol	0.11 (0.06)	0.07 (0.08)	36.36	0.14 (0.15)	0.19 (0.29)	-35.71	0.6	72.08
2100 hrs cortisol	0.09 (0.08)	0.10 (0.24)	-11.11	0.12 (0.15)	0.12 (0.14)	0.00	0.1	-11.11
Mean cortisol	0.15 (0.11)	0.11 (0.13)	26.67	0.19 (0.25)	0.18 (0.20)	5.26	0.4	21.40

* $p < 0.05$ for within group change using paired't' test.

† $p < 0.05$ for between group change using ANCOVA.

6.2.7 NK Cell count and percentage:

Analysis of covariance (ANCOVA) was used to assess between group differences using baseline NK Cell % value as a covariate showed significant improvement in NK Cell % in yoga group compared to control group [F (1, 31) =5.43, p = 0.03, ES-0.5, PC--32.43%]. Other parameters like NK Cell Count did not show any significant difference between groups. Paired-samples t-test to assess within group change following intervention showed a significant increase in NK Cell% (t = -3.10, $p < 0.01$) in yoga group alone but not in the control group (t = 1.03, p = 0.32) (Table 6.2.7).

6.2.8 Absolute Lymphocyte count:

The baseline values of ALC were different in the two groups. There was no significant change within or between groups in ALC (Table 6.2.7).

Table 6.2.7: Comparison of Mean values of NK Cell and ALC levels using ANCOVA between yoga and control groups and paired't' test within groups.

	Yoga (n=19)			Control (n=15)				
Outcome Variable	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Pre Mean (SD)**	**Post Mean (SD)**	**% Change**	**Effect Size (Cohen's d)**	**(Y-C) % Change**
NK Cell	209.21 (123.12)	213.16 (125.31)	1.89	192.73 (130.39)	181.47 (109.07)	-5.84	0.3	-7.73

Count								
NK %	9.68 (4.28)	11.32*† (4.92)	16.94	10.33 (5.61)	8.73 (5.55)	-15.49	0.5	-32.43†
ALC	2016.05 (768.18)	2041.26 (853.73)	1.25	1792.93 (997.22)	1829.93 (797.73)	2.06	0.3	0.81

NK= Natural Killer, ALC: Absolute Lymphocyte count * $p < 0.05$ for within group change using paired 't' test.† $p < 0.05$ for between group change using ANCOVA.

6.2.9 Bivariate relationships:

Bivariate Relationships between affective states, perceived stress and fatigue on quality of life subscales were determined using Pearson's Correlations analysis. There was a significant negative correlation of emotional function with anxiety states ($p = 0.04$) and perceived stress ($p = 0.05$) and cognitive function with depression ($p = 0.02$) (Table 6.2.9.1).

Table 6.2.9.1 Bivariate relationships between changes in scores for anxiety, depression, perceived stress, fatigue, functional Scales and Global quality of life scores following intervention in yoga group using Pearson correlation analysis.

Variables	Physical Function	Role Function	Emotional Function	Cognitive Function	Social Function	Global Quality of Life
Anxiety	-0.10	-0.11	-0.34*	-0.32	0.02	0.08
Depression	-0.15	-0.11	-0.26	-0.40*	-0.18	-0.19

Perceived stress	0.05	0.10	-0.34*	-0.29	-0.02	-0.23
Fatigue Severity	0.19	-0.01	0.04	-0.21	0.04	-0.27
Fatigue Interference	-0.06	-0.09	-0.12	-0.27	-0.22	-0.30
Fatigue Frequency	0.03	0.03	0.02	-0.18	-0.15	-0.24
Fatigue Diurnal Variation	0.08	0.22	0.07	0.15	-0.07	0.26

* *p* values < 0.05, ** *p* values < 0.01 for Pearson correlation.

There was a significant positive correlation between changes in anxiety states (p = 0.04), depression (p = 0.03) and perceived stress (p = 0.02) with changes in insomnia rating scale sleep scores and significant positive correlation of changes in perceived stress with changes in symptom distress (p = 0.02) and quality of life (p =0.01). However, there was no effect of fatigue on sleep scores (see table 6.2.9.2). There was a positive correlation between changes in fatigue severity with 9 am salivary cortisol levels (p = 0.004) (see tables 6.2.9.2 and 6.2.9.3).

Table 6.2.9.2 Bivariate relationships between changes in Stress, Fatigue and Measures of Sleep scores using Pearson correlation analysis in yoga group after intervention.

Insomnia Rating Scale				
Variable	**Symptom Distress**	**Sleep**	**QOL**	**Total**
Anxiety	0.30	0.36*	0.32	0.34*
Depression	0.27	0.39*	0.38*	0.34*
Perceived Stress	0.41*	0.41*	0.46**	0.48**
Fatigue Severity	0.29	0.22	0.15	0.27
Fatigue Interference	0.33	0.29	0.28	0.31
Fatigue Frequency	0.29	0.13	0.12	0.24
Fatigue Diurnal Variation	-0.10	0.17	-0.23	-0.03

* *p* values < 0.05, ** *p* values < 0.01 for Pearson correlation.

Table 6.2.9.3 Bivariate relationships between changes in measures of Stress, Fatigue, Salivary Cortisol and NK Cell Counts following intervention in yoga group using Pearson correlation analysis

Outcome Variable	0600 cortisol level	0900 cortisol level	2100 cortisol level	Mean diurnal cortisol level	NK Cell Count	NK Cell %	ALC
Anxiety	0.22	0.14	0.25	0.33	0.10	0.16	0.23
Depression	-0.11	0.09	0.29	0.13	0.34	0.29	0.09
Perceived stress	-0.09	0.09	0.29	0.20	0.22	0.34	-0.06
Fatigue Severity	-0.28	0.53**	-0.19	-0.38	-0.02	-0.12	0.21
Fatigue Interference	0.26	-0.24	0.08	-0.14	-0.02	-0.01	-0.21
Fatigue Frequency	0.22	-0.36	-0.06	-0.27	-0.12	-0.13	-0.03
Fatigue Diurnal Variation	-0.14	-0.06	0.21	-0.08	0.01	0.12	0.34

* *p* values < 0.05, ** *p* values < 0.01 for Pearson correlation. NK-Natural Killer ALC-Absolute Lymphocyte Count

6.2.10 Adherence to intervention

In the advanced breast cancer study too the adherence was good with 80% attending 24 supervised sessions. There was a significant improvement in global quality of life (t=3, p= 0.005) and significant decrease in 9 am salivary cortisol levels (t=-3.6, p= 0.001) in those who attended greater than 20 classes as compared to those attending less than 20 classes on independent samples 't' test (6.2.10a and 6.2.10b).

Table 6.2.10a: Comparison of change scores on Rotterdam symptom checklist, EORTC Qol subscales using independent samples t test between those attending yoga classes (>20/<20 classes) in yoga group.

	Change Score							
Attendance Category	**Psychological distress**	**Physical distress**	**Physical function**	**Role function**	**Emotional function**	**Cognitive function**	**Social function**	**Quality of life**
<20 classes Mean (SD) (n=10)	9.8 (9.1)	3.8 (7.5)	-4 (29.5)	-10 (31.6)	-10.7 (34.9)	-4.9 (22.4)	-19.9 (25.9)	8.9 (7.6)**
>20 classes Mean (SD) (n=24)	8.4 (6.7)	5.4 (10.1)	-8.33 (26.3)	-25 (32.9)	-12.2 (25.9)	-16.6 (19.6)	-18.1 (32.6)	1.5 (5.9)

* *p* values < 0.05 ** *p* values < 0.01

Table 6.2.10b: Comparison of change scores on fatigue, perceived stress, anxiety, depression, salivary cortisol and Nk cell counts using independent samples 't' test between those attending yoga classes (>20/<20 classes) in yoga group.

	Change Score											
Attendance Category	**Fatigue**	**Fatigue severity**	**PSS**	**Anxiety**	**Depression**	**6am cortisol**	**9am cortisol**	**9pm cortisol**	**Mean cortisol**	**Nk cell counts**	**Nk cell %**	**ALC**
<20 classes Mean (SD) (n=10)	11 (34.8)	12.3 (10.4)	7 (10.6)	3.1 (4.4)	4.6 (4.8)	0.10 (0.16)	-0.05 (0.09)	-0.06 (0.54)**	-0.00 (0.54)	43 (71.8)	-0.74 (1.6)	670.8 (120.2)
>20 classes Mean (SD) (n=24)	20.1 (25.4)	9.4 (8.5)	6.6 (7.7)	3.2 (2.7)	3.4 (3.1)	0.05 (0.15)	0.07 (0.07)	0.07 (0.08)	0.06 (0.08)	-22.7 (129.8)	-2.1 (2.4)	321.3 (687.8)

* *p* values < 0.05 ** *p* values < 0.01 ALC- Absolute Leukocyte Count

7. DISCUSSION

Two different RCTs were carried out to study the efficacy of yoga in patients with breast cancer. In (BCS2/3) study, 88 recently diagnosed early breast cancer patients (stage 1-3) undergoing radiotherapy was randomly allocated to yoga and control (supportive therapy) groups. In BCS 4 study 91 patients with stage IV breast cancers were randomized to receive either yoga therapy or supportive therapy for 3 months. Mood, affect, stress, symptoms, sleep, quality of life, salivary cortisol and immune measures (NK cells and absolute lymphocyte count) were measured before and after the intervention. There was significantly better reduction in yoga group than control group in anxiety, depression, perceived stress and morning salivary cortisol levels in both studies following intervention. There was significantly better improvement in QoL (emotional, cognitive functions), positive affect, negative affect, distressful symptoms and 0600 and 2100 hrs cortisol in early breast cancer patients. In Metastatic breast cancer patients there was significantly better improvement in QoL (role function, emotional function and global QoL), fatigue, symptoms, distressful sleep parameters, 0600 hrs cortisol and NK cell % . However, there was a significant decrease in diurnal cortisol slope in first study only following intervention.

7.1. Baseline assessments: Comparison with normative data:

Baseline assessments on mood states, affect, quality of life, treatment related symptoms and cortisol measures were done prior to primary treatment. The baseline values on HADS- A scale were above the normal cut off scores (Crawford JR, Henry JD et al. 2001) with the means falling under the category of mild anxiety in both early breast and metastatic breast cancer population. The test's authors recommended that, for the Anxiety and Depression scales alike, raw scores

between 8 and 10 identify mild cases, 11–15 moderate cases, and 16 or above, severe cases (Zigmond & Snaith, 1994). The scores in our population ranged from -10 in both study groups. While self reported anxiety was lesser in advanced breast cancer group as compared to early breast cancer group, self reported depression score was more in the advanced breast cancer group as compared to early breast cancer group.

The normative data for perceived stress scores in US population between 30-65 years is similar to that of ours study sample. Since PSS is not a diagnostic instrument, so there are no cut-offs. There are only comparisons between people in a given sample (Cohen S & Williamson G, 1998; Cohen S, Kamarck T et al. 1983).

Positive affect in our study population had lower values (mean of 23 vs. 31) as compared to the norms in a community sample of normal females. Negative affect was higher (23 vs. 17) than the norms. This would mean that stressors that breast cancer patients experience would have contributed to higher negative affect and lower positive affect (Crawford JR, Henry JD et al. 2004; Watson D, Clark LA et al. 1988).

The salivary cortisol levels at 6 am was lower in our study population (mean of 0.25 in early cancer group and 0.12 in Metastatic group) as compared to normal healthy subjects (mean of 0.56).The evening salivary cortisol levels were similar to the norms. (Luda MH, Cerdas S et al. 1988).

Baseline assessments: Comparison with other studies:

Subjects in our study reported mild to moderate levels of anxiety at baseline prior to radiotherapy consistent with earlier observations (Chaturvedi SK, Prabha Chandra S et al. 1996).

We have used a modified version of PSS with ten questions as compared to fourteen questions used by West et al in their study comparing hatha yoga with African dance in college students. The mean baseline values of PSS were 40 points lower compared to earlier study (West J et al. 2004) as this study used 14 item PSS as against our 10 item PSS. HADS data are similar to earlier observations in Indian Cancer Population (Chaturvedi SK, Prabha Chandra S et al. 1996). PANAS is 10 points lower than that reported for breast cancer patients in United Kingdom (24 vs. 34.7 for positive affect and 22 vs. 15.8 for negative affect) (Danhaeur et al. 2008). Lower scores for positive affect and higher scores in negative affect seen in our population could be because of the cross cultural differences in their perception to diagnosis of breast cancer, treatment toxicity, fear of recurrence or death that could affect mood in these patients. The data on fatigue and Rotterdam Symptom checklist and EORTC Quality of life are comparable to earlier observations (Moadel A et al.2007, Michaelson et al.1996). The normative values of these scales are not available as most of these have been designed for use in clinical settings. High levels of anxiety and depression also correlated positively with distressful symptoms and inversely with quality of life (Bukberg J, Penman D et al. 1984; Umesh SB 1998). The low salivary cortisol levels indicate attenuated diurnal salivary cortisol responses indicating HPA axes Dysregulation in these groups. A flat rhythm seen in advanced breast cancer patients is similar to earlier observations in similar populations that have depression (Sephton SE, Sapolsky RM et al. 2000).

7.2 Changes in Mood States after the Intervention

7.2.1 Anxiety:

The results suggest an overall decrease in anxiety with time in both early and advanced BCS cases in both yoga and control groups. In the early breast cancer study yoga intervention significantly reduced self reported anxiety on HADS- A by 26.22% compared to control group.

The effect size for reduction in anxiety was 0.31, whereas in advanced breast cancer study, reduction in anxiety following yoga intervention was 56 % (ES= 1.9) compared to control group. This could be for the fact that patients with advanced breast cancer reported higher anxiety at start of treatment than those with early breast cancers. Our results are in consonance with earlier findings that have shown better anxiolytic effects with mind body interventions in patients with higher anxiety and distress. Further our results are bolstered by other studies in non-cancer population using yoga intervention that have clearly demonstrated both change in anxiety following ten days to six months of intervention. (Kabat-Zinn J, Massion AO et al. 1992; Malathi A and Damodaran A 1999; Bijlani RL 2004; Taneja I, Deepak KK et al. 2004; Woolery A, Myers H et al. 2004; Khalsa SB and Cope S 2006). The effect size for reduction of anxiety in our BCS 2/3 was 0.31 which is similar to an earlier study in similar population (0.33) using the same supportive therapy as control intervention (Raghavendra Rao M, Nagarathna Raghuram et al. 2009).The percent decrease in self report anxiety is nearly similar to earlier studies using Mindfulness based stress reduction interventions in breast and prostate cancer patients (41.9%) using profile of moods scale (Speca M, Carlson LE et al. 2000)and using hatha yoga in distressed women with State Anxiety Inventory (25.9%)(Michalsen A, Grossman P et al. 2005).

The anxiolytic effects of yoga intervention could be explained by reduction in the levels of psycho physiological arousal such as decrease in sympathetic activity (Telles S, Joshi M et al. 2004) and balance in the autonomic nervous system responses (Telles S and Desiraju T 1993) and ushering in a hypo metabolic state as seen earlier in healthy populations (Telles S, Reddy SK et al. 2000; Chaya MS, Kurpad AV et al. 2006). Overall, the anxiolytic effects of yoga program could be attributed to stress reduction rather than mere social support and education. This is consistent with earlier studies that have shown better results with stress reduction than purely supportive interventions (Deberry S, Davis S et al. 1989; Spiegel D, Bloom JR et al. 1989).

7.2.2 Depression:

The results suggest an overall decrease in depression with time in both the groups. In the early breast cancer study yoga intervention reduced self reported depression on HADS-D by 26.9% compared to control group. The effect size for reduction in depression was 0.31.Whereas in advanced breast cancer study yoga intervention significantly reduced depression on HADS-D by 53.6% compared to control group. The effect size for reduction in self reported depression was 1.6. This could be for the fact that patients with advanced breast cancers reported greater self reported depression than patients with stage 2/3 breast cancers at the start of intervention. Our results are similar to earlier studies that have shown reductions in self reported depression in CESD scale following Mindfulness based stress reduction intervention in breast and prostate cancer patients (38.1%) (Speca M, Carlson LE et al. 2000) and hatha yoga intervention in distressed women (41.9%) (Michalsen A, Grossman P et al. 2005). Our results are consistent with other studies using relaxation techniques and adjuvant psychological therapy which have shown a similar decrease in depression in these populations (Greer S, Moorey S et al. 1992). Yoga has been found useful in subjects with subclinical depression in non cancer subjects (Woolery A, Myers H et al. 2004) as well as in those with major depressive disorders (Wood C 1993; Malathi A and Damodaran A 1999; Ray US, Mukhopadhyaya S et al. 2001; Lavey R, Sherman T et al. 2005). Earlier studies using behavioral therapy (Hopko DR, Bell JL et al. 2005) and yoga (Vedamurthachar A, Janakiramaiah N et al. 2006) have reported large effect sizes (>1) for their respective interventions similar to ours.

Stress has been implicated in the pathogenesis of depression (Meyer SE, Chrousos GP et al. 2001) and an extensive literature has documented the association of depression with elevated cortisol levels (Stokes PE 1995). Various conceptual models have been proposed such as the allostatic load model and post traumatic phenomenology to explain the relationships between

stress and neuroendocrine dysregulation (Ronson A 2006). Numerous studies have reported beneficial antidepressant effects with similar stress reduction interventions such as relaxation training in cancer patients (Luebbert K, Dahme B et al. 2001).

Overall, the antidepressant effects of yoga program could be attributed to stress reduction rather than mere social support and education. This is consistent with earlier studies that have shown better results with stress reduction than purely supportive interventions (Deberry S, Davis S et al. 1989; Spiegel D, Bloom JR et al. 1989). The antidepressant effects of yoga intervention could be explained by reduction in the levels of psychophysiological arousal such as decrease in sympathetic activity (Ray US, Mukhopadhyaya S et al. 2001), balance in the autonomic nervous system responses (Telles S, Nagarathna R et al. 1993), alterations in neuroendocrine arousal (Harte JL, Eifert GH et al. 1995; West J, Otte C et al. 2004) and decrease in morning cortisol (Vedamurthachar A, Janakiramaiah N et al. 2006).

Scores on self-reported symptoms of depression correlated positively with Negative affect, symptoms and distress, and correlated negatively with positive affect, functional domain aspect of quality of life and activity level prior to radiation treatment further supporting the idea that reductions in depression could contribute to decrements in treatment related distress, improved mood and outcomes (Carey M and Burish TG 1988) and also improved activity and quality of life.

Subjects in yoga group reported greater reductions in depression scores than controls. It may be argued that yoga group received more attention than the supportive therapy group and this could have contributed towards a placebo effect. However, unlike other studies using wait listed controls the control group here also received psychodynamic supportive therapy sessions. These sessions were used only with an intention of negating the confounding variables such as social

support, instructor- patient interaction, education, and attention that are known to improve the psychological and social functioning in cancer patients (Telch CF and Telch MJ 1986). Another objective of using social support as a control was with a view of analyzing and identifying the effects of stress reduction conferred by yoga intervention versus a purely supportive intervention on outcome measures. Moreover, earlier studies have also demonstrated that placebo effects caused due to attention is unfounded in subjects with melancholia (Nelson JC, Mazure SM et al. 1990). We chose to have individual therapy sessions as against group practice, as individual sessions also helped to understand the specific needs and concerns of participants and monitor individual progress in practice thereby reducing the confounding effects of being in a group (Reissman F 1965).

7.2.3 Perceived stress:

The results suggest an overall decrease in perceived stress scores with time in both the studies. In the early breast cancer study yoga intervention reduced perceived stress by 21 % (ES=0.36) compared to control group. Whereas in advanced breast cancer study yoga intervention significantly reduced perceived stress by 32.6% (ES=1.4) compared to control group. Our results are similar to other studies in non-cancer populations using yoga intervention that have clearly demonstrated decrease in perceived stress (West J, Otte C et al. 2004; Michalsen A, Grossman P et al. 2005; Chattha R, Raghuram N et al. 2008; Satyapriya M, Nagendra HR et al. 2009). In the study by West J et al comparing effects of yoga with biology class there was a decrease in perceived stress by 17.2% compared to controls. In a study by Chatta R et al on climacteric syndrome in menopausal women and by Satyapriya et al in pregnant women the decrease in perceived stress was 24.2% and 19.3% following integrated yoga program respectively. The effect size for reduction of perceived stress in our studies ranged between 0.36 to 1.4 (Cohen's

f), which is similar to the study by Ritu et al using similar kind of intervention assessed by same perceived stress scale on perimenopausal women which showed a Cohen's 'd' value of 0.66 and by Michaelson et al with ES=1.1 in women with psychological distress.

There is growing evidence that perceived stress has a major impact on the initiation and progression of disease, i.e. cardiovascular disease and chronic pain syndromes (Chapman CR and Gavrin J 1999; Rosengren A, Hawken S et al. 2004) by down regulating the immune system, it is observed that greater perceived stress prospectively predicted lower NK cell activity 15–18 months later among caregivers with a cancer history (Vitaliano PP, Scanlan JM et al. 1998) and perceived stress was related to decreased antibody titers to influenza vaccine and decreased IL-2 response to in vitro stimulation by influenza virus (Kohut ML, Cooper MM et al. 2002) in a community sample of older adults who had recently received influenza vaccination. Perceived stress has also been found to be positively related to salivary cortisol levels (Granath J, Ingvarsson S et al. 2006).

Scores on self reported perceived stress scores correlated positively with negative affect, symptoms, distress, and correlated negatively with positive affect, functional domain aspect of quality of life, activity level prior to radiation treatment further supporting the idea that reductions in perceived stress could contribute to decrements in treatment related distress, improved mood and outcomes (Carey MP and Burish TG 1985) and also improved activity and quality of life.

7.2.4 Positive affect and negative affect:

The results suggest an overall Increase in positive affect and decrease in negative affect scores with time in both the groups. In the early breast cancer study, yoga intervention increased

positive affect by 15.86% (ES=0.11) compared to control group and decreased negative affect by 33.69% (ES=0.16) compared to control group.

Studies using yoga as an intervention also showed similar effects where 10 weekly 75 minutes restorative yoga among women with breast and ovarian cancer showed significant decrease in negative affect (10.7%) but no change in positive affect 4.3%) (Danhauer SC, Tooze JA et al. 2008). Another study on healthy volunteers following three 90 minute sessions of Hatha yoga showed significant decrease in negative affect (18.4%) and improvement in positive affect (4.6%) (West J, Otte C et al. 2004; Danhauer SC, Tooze JA et al. 2008). The effect size for increase in positive affect in our study is 0.26 (Cohen's f) and for negative affect is 0.39 (Cohen's f). Our study showed a significant increase in positive affect which is contrary to earlier yoga study on breast and ovarian cancer (Danhauer SC, Tooze JA et al. 2008). This difference may be because of type and intensity of intervention. We choose individual therapy compared to earlier group therapy sessions as individual sessions would have helped to understand the specific needs and concerns of participants and monitor individual progress in practice thereby contributing to positive affect (Reissman F, 1965). Our results are similar to other studies in cancer population where in supervised group exercise has shown a similar increase in positive affect (17.5%) (Mohr DC, Hart SL et al. 2005) and decrease in negative affect (9.8%) (Mutrie N, Campbell AM et al. 2007).

Decrease in negative affect and increase in positive affect could be explained by reduction in the levels of psychological distress such as anxiety, depression and perceived stress as these were found to be significantly related to affect. Earlier studies have shown negative affect to be related to both anxiety and depression, while the absence of positive affect is related more strongly to depression (Boon MT and Peeters FP 1999).

Scores on self reported positive affect correlated positively with functional scales of quality of life, global quality of life, activity level and correlated negatively with anxiety, depression, perceived stress, distress and symptom scale. Whereas Negative affect correlated directly with anxiety, depression, perceived stress, symptom scale and correlated inversely with functional scales of quality of life, global quality of life and activity level prior to radiation treatment which is similar to an earlier study (Voogt E, van der Heide A et al. 2005). Various yoga interventions have shown to reduce psychological distress such as anxiety and depression, perceived stress (Michalsen A, Grossman P et al. 2005; Raghavendra Rao M, Nagarathna Raghuram et al. 2009) further supporting the idea that reductions in perceived stress could contribute to decrements in treatment related distress, improved mood and outcomes (Carey M and Burish TG 1988) and also improved activity and quality of life.

7.2.5 Quality of life

7.2.5.1 Functional aspect of Quality of life:

In early breast cancer study there was a significant improvement in emotional function (22.2%, ES= 0.14) and cognitive function (8.61%, ES=0.09) in the intervention group compared to control group. Where as in advanced breast cancer study there was a significant improvement in physical function (16.71%, ES= 1), role function (30.2%, ES=1.3), emotional function (24.5%, ES=0.9), cognitive function (20.6%, ES=1.2), social function (24.7%, ES=0.9) and overall quality of life (28%, ES=1.5) in yoga group compared to controls. This suggests that advanced breast cancer patients had worse quality of life compared to early breast cancer patients and effects with yoga intervention were better on Quality of life outcomes in advanced breast cancer patients compared to early breast cancer patients. Another reason could also be a longer intervention period (12 weeks) in advanced breast cancer patients compared to 6 weeks in early

breast cancers. In another study with similar yoga intervention in a cohort of early breast cancer patients undergoing radiation therapy, there was an improvement in physical functioning after one week of yoga intervention but not at one and three months following intervention (Chandwani KD et al, 2010). Assessments in our study were done 6 weeks following intervention comparable to one month following intervention in this study. It may be argued that physical activity improvements could be one of the earliest changes one would expect following yoga intervention. Our results in early breast cancer study are in tune with earlier findings using MBSR intervention in early breast and prostate cancer patients where emotional function improved by 8.3%, cognitive function by 6.1%, social function by 6.6% and global quality of life improved significantly by 8.3% (Carlson LE, Speca M et al. 2004). An earlier study using restorative yoga showed a significant improvement in functional quality of life on FACT G scale (4.6%), emotional function (1.4%), and social function (3.3.%) further offering support to our findings(Danhauer SC, Tooze JA et al. 2008). However our results are in contrast to psychological intervention that has shown decrease in physical function by 9.0%, role function by 9.3%, cognitive function by 4.1%, and social function by 4.7% and improvement in emotional function by 4.0 % (Bordeleau L, Szalai JP et al. 2003). This could be for the fact that unlike behavioral interventions these mind body therapies are more active form of interventions that command a greater degree of involvement by the patients. These interventions also help sustain interest and assume control unlike behavioral interventions.

7.2.5.2 Global quality of life:

The results suggest an Increase in global quality of life after yoga. Yoga intervention in early breast cancer (BCS2/3) increased the global quality of life by 7.6 % which is not significant and supportive therapy increased 0.57%. In metastatic BCS4 study Yoga increased significantly the

global quality of life by 34.96%, and supportive therapy increased it by 6.95%. This non significant improvement of 7.6 % in global quality of life on EORTC-QOL in early breast cancer is not very different from an 8.26% change in Carlson's study which had reached significant p values following 8-weeks of MBSR program in early stage breast and prostate cancer (Carlson LE, Speca M et al. 2004). This improvement in physical function and non significant improvement in global quality of life in our early breast cancer study is in contrast to another earlier study that has shown improvements in quality of life (2.0%), emotional function (11.2%), and decrease in social function (1.4%) and spiritual well being (2.7%), although there was poor adherence to yoga intervention. This could be due to the fact that Moadel's study (Moadel AB, Shah C et al. 2007) differed from ours with respect to the scale used for measuring Qol (Functional Assessment of Cancer Treatment-Breast) and heterogeneity in conventional cancer treatments.

Several studies have shown that both psychological and treatment related distress affect quality of life concerns in cancer patients (Visser MRM and Smets EMA 1998; Courneya KS and Friedenreich CM 1999; Stark D, Kiely M et al. 2002; Perry S, Kowalski TL et al. 2007). Cancer patients have to constantly make lifestyle changes to adjust and cope with these treatment related distress and seek supportive care (Umesh SB 1998). Yoga and exercise as a lifestyle and stress reduction intervention has shown to decrease negative affect and improve positive affect (West J, Otte C et al. 2004; Mutrie N, Campbell AM et al. 2007; Danhauer SC, Tooze JA et al. 2008). This change in affect could have contributed to improvement in quality of life concerns in these patients. This is further corroborated by our results with decrease in negative affect being related to improvement in physical function, emotional function and social function and improvement in positive affect being related to improvement in role function.

Yoga commands a therapeutic appeal in India, and is being increasingly used in the management of various chronic illnesses including cancer. Possible threat perceptions and intrusive thoughts could motivate cancer patients to pursue health care behaviors that offer spiritual solace (Chaturvedi S 2003). It is here that yoga as a psycho spiritual intervention could offer the much needed support. However in our study we were not able to assess this spiritual component in quality of life, nevertheless it could be one of the possible mechanisms by which yoga could have influenced other quality of life domains.

7.2.6 Symptom and Distress:

Distressful symptoms were measured using Rotterdam Symptom checklist and Symptom items on the EORTC QOL30 scale in BCS2/3 study and only the latter in advanced breast cancer study. In the early breast cancer study yoga intervention significantly reduced fatigue by 33.15% (ES=0.33), insomnia by 58.37% (ES=0.47) loss of appetite by 94.9% (ES=0.38) as compared to control group. In advanced breast cancer study yoga intervention reduced fatigue (40.9%, ES=1.4), nausea and vomiting (40.9%, ES=1.4), pain (54.1%, ES=1.3), dyspnoea (46.7%, ES=0.9), insomnia (78.9%, ES=1.2) loss of appetite (67.2%, ES=1.0) and constipation (143.8%, ES= 0.7) as compared to control group.

This is in contrast to earlier interventions with MBSR that has shown similar decrease in loss of appetite (61.2%) but lesser decrease in fatigue (9.3%) and insomnia (2.2%) (Carlson LE, Speca M et al. 2003). Another study by the same group has shown decrease in fatigue on profile of moods score by 22.3% and decrease in gastrointestinal symptoms by 33.7% on symptoms of stress inventory (Carlson LE and Garland SN 2005). These contrasting findings could therefore be attributed to differences in the intervention, heterogeneity in study samples and stages of cancers.

In the early breast cancer study yoga intervention significantly reduced psychological distress (33.98%, ES=0.39), physical distress (30.82:%, ES=0.33) and improved activity level (6.89%, ES=0.14) as compared to control group.

These results offer further support to other preliminary findings that have shown beneficial effects of yoga intervention in reducing distressful symptoms such as fatigue, pain, loss of appetite, insomnia and improving mood and quality of life concerns in cancer patients (Speca M, Carlson LE et al. 2000; Moadel AB, Shah C et al. 2007). Though beneficial effects are seen with yoga on symptom management it should be noted that subjects in these studies were in various stages of treatment, disease and had varied diagnosis contributing to generalizability of findings (Bower JE, Alison Woolery MA et al. 2005). In our study the cohort sample were patients with stage II and III breast cancer receiving adjuvant therapy as well as advanced breast cancer patients and our results support benefit finding of yoga in modulating distressful symptoms in both these populations. The effect size was high (Cohen's f >3) for fatigue, insomnia, psychological distress and physical distress and moderate for pain and activity.

There was a significant positive correlation between symptoms with physical and psychological distress and negative correlation of these with activity. The results indicate that yoga intervention was helpful in reducing these distressing symptoms and that reduction in these could have reduced physical and psychological distress and improved activity. Patients with cancer often have multiple symptoms and symptoms can often cluster together in a systematic way whereby treatment of one can influence the treatment of other symptoms as well (Barsevick AM 2007). Though effects of intervention on symptom clusters is not the main aim of this study, its effects on a multitude of symptoms such as pain, fatigue, nausea, insomnia, loss of appetite could have nevertheless contributed to improvement in health outcomes. Moreover,

most of these symptoms persist throughout the course of disease and effective treatment of these in initial stages is known to affect health outcomes later even after completion of treatment (Shimozuma K, Ganz PA et al. 1999). It may be hypothesized that yoga could serve to be prophylactic intervention in the initial stages of treatment affecting quality of life outcomes in future. This is important in today's scenario where in efforts are being directed at producing new insights into the causes of and cures for cancer, rather than managing the symptoms due to disease and its treatment.

Evidence suggests that pain, fatigue and depression are frequently under treated. Patients and health care providers have reported depression and persistent lack of energy as the aggressiveness of therapy has been increased and/or the underlying malignancy has worsened (Patrick DL, Ferketich SL et al. 2003). Cancer symptom management would benefit if an integrated intervention plan existed for a cluster of symptoms based on a clear understanding of which symptoms are likely to cluster, when clustering is likely to occur, and how a symptom cluster affects patient outcomes at different stages of treatment. Most of these symptom clusters are influenced by patients' perception, awareness, education, mood states and can be explained through various biologic, psychological, behavioral, and sociocultural mechanisms that constitute a symptom interaction network and symptom experience (Parker KP, Kimble LP et al. 2005). The experience of multiple simultaneous symptoms has a synergistic effect on symptom distress (Lenz ER, Pugh LC et al. 1997).

Management of symptoms therefore requires a holistic approach that integrates behavioral and mind body strategies, this is more so emphasized in earlier studies that have shown several stress reduction and mind body approaches to reduce distressful symptoms and mood states in cancer patients. The results of our study reinforce findings of our earlier study that has shown

beneficial effects of yoga intervention in managing chemotherapy related nausea and vomiting (Raghavendra RM, Nagarathna R et al. 2007). This simple intervention can be imparted to nurses and cancer care givers especially in developing countries where access and resources for supportive care rarely exist.

7.2.7 Sleep on Pittsburg Insomnia Rating Scale:

In advanced breast cancer study there was a significant decrease in symptom distress (91.3%, ES=1.2), sleep parameters (111.4%, ES=0.6), quality of life (20.3%, ES=0.9), and overall insomnia score (70.8%, ES=1.2). Our results are consistent with earlier findings with Mindfulness Based Stress Reduction Intervention that has shown improvement in overall sleep quality by 20.4% (Carlson LE and Garland SN 2005). Insomnia has been related to poor NK cell function, higher morning cortisol levels and abnormal diurnal rhythms in breast cancer patients (Sephton SE, Sapolsky RM et al. 2000). This is an important problem as it seems to worsen with age and psychological distress (Fetveit A 2009). This is also one of the important symptoms in the cancer care continuum expressed often by patients (Berger AM 2009). Improving sleep duration, quality and restoring the normal sleep rhythms is important to preserve immune homeostasis and quality of life. The improvements seen with our intervention suggests that yoga could be used as an adjunct to manage sleep disorders in cancer patients.

7.2.8 Fatigue symptom inventory:

In advanced breast cancer study there was a significant decrease in fatigue (61.2%, ES=1.4), fatigue frequency (52.6%, ES=1.5), Fatigue interference (72.6%, ES=1.3), diurnal variation (52.3%, ES=0.9) in yoga group compared to controls on fatigue symptom inventory. Our results are in contrast to earlier studies that have shown a modest decrease in fatigue (5.7% following

MBSR intervention on POMS –Fatigue subscale(Carlson LE, Speca M et al. 2004) and 6.4% on FACIT Fatigue scale in a study by Alyson Moadel (Moadel AB, Shah C et al. 2007). This could be because of inadequacy of the subscale to measure various dimensions of fatigue (Speca M, Carlson LE et al. 2000) and use of yoga intervention in early stage cancer patients where fatigue would not have been a main concern (Moadel AB, Shah C et al. 2007) contrary to our study where fatigue was measured in advanced breast cancer patients using a specific fatigue symptom inventory. Fatigue is an important symptom in cancer patients that directly affects functional quality of life. Apart from clinical conditions that affect fatigue such as infections, anemia and pain, progressive disease itself causes fatigue as a part of cancer cachexia through release of inflammatory cytokines. Therefore managing fatigue is also an indication that the disease is also managed. The decrease in fatigue seen with our study and consequent reductions in morning salivary cortisol and improvement in NK cell counts support this understanding.

7.2.9 Adherence to intervention and outcomes:

Adherence to intervention was good in our study with 56.7% attending 20-25 supervised sessions and 13.7% attending >25/30supervised sessions over a six week period in the early breast cancer study. This was primarily due to the fact that all patients were undergoing adjuvant radiotherapy and were visiting the hospital five days a week for six consecutive weeks and this could have contributed to the beneficial results. However adherence did not seem to influence significant changes in outcome measures in early breast cancer study. This perhaps created a floor effect where in dose response relationship could not be established. In the advanced breast cancer study too the adherence was good with 80% attending 24 supervised

sessions. There was a significant improvement in quality of life and decrease in 9 pm cortisol in subjects with good adherence to intervention (attending >20 classes). Adherence to intervention in control group was 100% as they had to invariably meet the counselors before appointment with their oncologists. This also explains why earlier studies did not have similar effects as number of sessions was very limited (9 – 12 sessions) (Carlson LE, Speca M et al. 2003; West J, Otte C et al. 2004).

7.2.10 Diurnal salivary cortisol level:

In the early breast cancer study yoga intervention significantly reduced the early morning salivary cortisol levels (28.07%, ES=0.24) significantly better than the control group. There was also a significant decrease in early morning salivary cortisol levels in the advanced breast cancer study in yoga group only (40.9%, ES=0.5). The decrease in morning salivary cortisol levels suggests possible stress reducing benefits of yoga intervention. Our results are similar to earlier studies that have shown similar decreases in cortisol following Sudarshan Kriya Yoga in alcoholics (56.6%) (Vedamurthachar A, Janakiramaiah N et al. 2006) and Hatha yoga (46.6%) vs. Cognitive Behaviour Therapy (22.7%) in distressed women (Granath J, Ingvarsson S et al. 2006), and Hatha Yoga in college students (17.4%) (West J, Otte C et al. 2004). Our results are also similar to changes (16% to 45%) in cortisol seen with behavioural interventions in cancer populations (Schedlowski M, Jung C et al. 1994; Van der Pompe G, Duivenvoorrden HJ et al. 1997; Cruess DG, Antoni MH et al. 2000). While these earlier studies have measured one time plasma cortisol, we chose to assess both morning and evening levels of free salivary cortisol as changes in the rate of cortisol secretion over a day (diurnal cortisol rhythm) is considered as a robust measure compared to onetime cortisol assessment (Sephton SE, Sapolsky RM et al. 2000; Turner-Cobb JM, Sephton SE et al. 2000). Earlier studies with similar stress reduction

interventions such as MBSR have also shown decrements in cortisol in breast cancer patients who had initially high cortisol levels suggesting that more distressed patients tend to benefit with stress reduction intervention (Carlson LE, Speca M et al. 2004). Similarly we subdivided our patients into those with values higher and lower than the baseline mean cortisol value and computed the degree of changes after the intervention in both early and advanced breast cancer cohorts. We found that those with initially low cortisol levels in early breast cancer study (below initial mean cut off) showed significant decreases in 0600 hrs cortisol and mean diurnal cortisol following intervention compared to those with higher initial levels, who in fact displayed a tendency for decrease in their cortisol levels contrary to earlier findings. However there was no difference in both high and low basal cortisol groups in advanced breast cancer study. Though our intervention showed reduction in anxiety, depression and perceived stress in both subgroups, these decrements in psychological distress did not translate into significant reductions in cortisol in the high cutoff group.

It may be hypothesized from these results that distress decreases with time in cancer patients and use of stress reduction interventions only augments this process and that, patients with initially high distress and high cortisol levels would probably take a longer time for attenuation of such high cortisol levels than those with lesser distress or cortisol profiles. Our observations differ from earlier study by Carlson et al (Carlson LE, Speca M et al. 2004) probably due to the differences in cancer populations being studied, differences in type of interventions (MBSR vs. Yoga), lack of control arm in the former and for the fact that patients in our study were on active treatment throughout the study period (Carlson LE, Speca M et al. 2004).

These observations are important as HPA axes dysregulation in terms of diurnal salivary cortisol rhythm is found to be an important predictor for survival in advanced breast cancer patients

(Sephton SE, Sapolsky RM et al. 2000). Modulating cortisol levels at an earlier stage would help reduce distress in future (Cohen L, de Moor C et al. 2001) and possibly improve survival in these patients. The changes in stress response patterns and appraisal could have contributed to reductions in cortisol and distress seen with our intervention. The reduction in perceived stress seen with our intervention further offers support for this mechanism. An elevated level of cortisol is known to have immuno suppressive effects and is largely responsible for the down regulation of immune function because of stress. Reduction seen in cortisol levels in our study offers further support for improvements in immune functioning (NK cell counts) seen in our earlier study in early breast cancer patients undergoing conventional treatment (surgery, radiotherapy and chemotherapy) (Rao RM, Telles S et al. 2008). The combination of physical postures, breathing exercises, relaxation and meditation could have helped attenuate cortisol levels through stress reduction and exercise effect as earlier studies have documented quality of life and biological benefits in cancer patients after moderate exercise (Courneya KS and Friedenreich CM 1999; Courneya KS 2001). Being physically active (walking and household tasks) have also shown to reduce risk for development of breast cancer (Friedenreich CM, Courneya KS et al. 2001). Various components of yoga intervention are known to have a calming effect and correct the autonomic imbalances (Sugi Y Akutsu K 1968; Telles S, Nagaratna R et al. 1994; Telles S, Nagaratna R et al. 1995; Telles S, Reddy SK et al. 2000) and HPA axes disturbances (Carlson LE, Speca M et al. 2004) that prelude stress responses. Overall, the reduced psychological stress and cortisol following yoga program could be attributed to stress reduction rather than mere social support and education in conformity with earlier studies (Spiegel D, Bloom JR et al. 1989).

7.2.11 NK Cell counts

In advanced breast cancer study there was a significant improvement in NK Cell % in yoga group (32.4%, ES=0.5) as compared to controls. Our results are similar to an earlier study using Sudarshan kriya yoga in heterogenous cancer populations that have shown similar improvements in NK% (50 %) following intervention (Kochupillai V, Kumar P et al. 2005).These are also in conformity with earlier observations using similar yoga intervention following surgery (22 %) and chemotherapy (21 %) (Rao RM, Telles S et al. 2008). Our findings are consistent with other non yoga stress reduction interventions such as hypnosis (Kiecolt-Glaser JK, Marucha PT et al. 2001; Miller GE and Cohen S 2001). Our observations are further reinforced by studies in both animal models and humans which have shown that stressors suppress NK cell activity (Pollock RE, Lotzova E et al. 1991), reduce lymphocyte proliferative responses to mitogens and bring changes in lymphocyte subpopulations such as NK cell counts (Tonnessen E, Brinklov MM et al. 1987; Ben-Eliyahu S, Yirmiya R et al. 1991). Such immune suppression in cancer patients has also been implicated in the promotion of metastasis via numerous mechanisms, including the suppression of natural killer cell counts and their activity by stress hormones (Ben-Eliyahu S 1998a; Ben-Eliyahu S 1998b). Psychological distress has been associated with activation of stress response mechanisms such as abnormal cortisol levels and rhythms that have been shown to affect NK cell activity and immune cell trafficking (NK cell counts) in breast cancer patients (Sephton SE, Sapolsky RM et al. 2000).

The ability to “unwind” after stressful encounters i.e. the ability to return to ones neuroendocrine baseline influences the total burden that the stressors place on the individual (Frankenhaeuser M 1986). Decrement in NK cell counts has been found to be an important predictor for survival in advanced breast cancer. Catecholamines and glucocorticoids have been shown to rapidly and markedly affect the distribution of NK cells among different immune compartments (e.g., spleen. Liver, lungs, circulating blood, marginating pool of blood etc)

(Benschop RJ, Nieuwenhuis EE et al. 1994; Dhabhar FS, Miller AH et al. 1995) and it may be hypothesized that changes in these hormone levels and NK cell counts could be one of the mechanisms of action of our intervention.

8. SUMMARY AND APPRAISAL OF THE STUDY

8.1 SUMMARY

This thesis is a detailed scientific presentation of two different RCTs. Both BCS2/3 and BCS4 were prospective randomized two armed longitudinal controlled studies. They aim at comparing the effects of an "integrated yoga based stress reduction program" with standard "education and supportive therapy sessions" on mood states, quality of life, conventional treatment related symptoms, Sleep, Cortisol levels, rhythmicity and immune responses such as Natural killer (NK) cell count during the course of their conventional cancer treatment. Subjects satisfying the selection criteria were randomly allocated to receive either integrated yoga based stress reduction program or standard education and supportive therapy before starting their conventional treatment and were followed up with the interventions covering the duration of their adjuvant radiotherapy for BCS2/3 study and for BCS4 or advanced breast cancer study. The assessments were done before and at the end of the study period, i.e. after receiving 25cGy of radiation or 45 days of radiation therapy in BCS2/3 study and after three months of intervention in case of BCS4 study.

In our two studies on patients with early breast cancer (BCS2/3) undergoing radiotherapy and metastatic breast cancer (BCS4), we used integrated yoga program as an intervention and supportive therapy as control. The integrated yoga program comprised techniques such as Mind

Sound Resonance Technique (MSRT), Mind Imagery relaxation techniques (MIRT), Pranic Energisation Technique (PET), Cyclic meditation (CM) and a few asanas and pranayama.

Yoga intervention in both studies showed decrements in stress arousal profiles in terms of decrease in self reported anxiety and depression, perceived stress and morning salivary Cortisol levels. In addition to these, metastatic breast cancer patients showed improvement in NK cell counts. There was a decrease in distressful symptoms and improvement in quality of life in both groups. However, larger randomized controlled trials using structured cognitive behavioral therapy and relaxation interventions are needed to further validate the effects of this intervention.

8.2 CONCLUSIONS

The results from this study indicate that integrated yoga program:

1. Reduces self reported distress such as anxiety and depression symptoms during Radiotherapy in early breast cancers and advanced breast cancer survivors
2. Reduces symptom severity and distress related to conventional treatment in early breast cancer patients.
3. Improves quality of life in both early and advanced breast cancer patients.
4. Improves mood states i.e. decreases negative affect and improves positive affect in early breast cancer patients
5. Decreases morning salivary cortisol levels in both early and advanced breast cancer patients
6. Improves immune status by increasing the NK Cell % in advanced breast cancer patients.

SUMMARY OF CONCLUSIONS

The results of these two RCTs have shown that integrated yoga program can improve mood, affect, quality of life, salivary cortisol rhythm and reduce treatment related symptoms in breast cancer patients in early stage (1-3) undergoing radiotherapy and advanced stage 4 disease. Also this study has shown that yoga can improve the immune status by increasing the NK Cell % in advanced breast cancer patients.

8.3 APPRAISAL

8.3.1 STRENGTH OF THE STUDY

(i) Homogeneous group of patients

One of the main strengths of this study is that it involves a homogenous group of breast cancer populations in both the studies.

(ii) The adherence to intervention has been excellent.

(iii) The stress reduction effects of yoga program with respect to decrements in salivary cortisol and improvement in NK cell % (Carlson LE, Speca M et al. 2004) is a novel finding unlike earlier studies that have not found any significant changes in these measures.

8.3.2 LIMITATIONS OF THE STUDY

(i) No active intervention for control group.

One of the major limitations in both the studies is the inequality in contact duration of interventions. Supportive therapy interventions were used with an intention of negating the

confounding variables such as instructor-patient interaction, education, and attention (Telch CF and Telch MJ 1986). However, inequality in contact duration of this intervention could have affected its effectiveness as successes of such interventions depend mainly on contact duration and content. Similar supportive sessions have been used successfully as a control comparison group to evaluate psychotherapeutic interventions (Telch CF and Telch MJ 1986; Greer S, Moorey S et al. 1992) and have been effective in controlling chemotherapy related side effects.

(ii) Duration of the intervention: The duration of intervention was only for six weeks and we were not able to assess the long term effects of these interventions on cortisol rhythms in BCS2/3 study.

(iii) It was not possible to conduct dexamethasone challenge or measure waking cortisol levels that are used as the standard tests for assessing HPA axes dysregulation.

8.3.3 APPLICATIONS OF THE STUDY

The stress reduction effects of our integrated yoga program offers promising results for integrating this as a part of psychotherapeutic interventions in oncology care. The results from this study support for using these mind body approaches to improve quality of life, mood, and reduced distress, and possibly improve their survival. The results in both early and advanced breast cancer study suggest that yoga can be integrated at any stage in the cancer care continuum.

8.3.4 SUGGESTIONS FOR FUTURE

Future studies should unravel the putative mechanisms and aspects of HPA Axes dysregulations and also assess neuroendocrine responses to artificially induced stressors in the lab. Future

studies should use more sophisticated measurements of immune function such as NK cell cytotoxicity, DNA Repair mechanism etc to understand the psychoneuroimmune mechanisms underlying such interventions. Larger randomized controlled studies using more structured psychiatric and behavioral intervention as controls are needed.

Long term follow up to document the length of survival, recurrence rate would throw more light on the long term efficacy of yoga.

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