EVALUATION OF THE PSYCHOLOGICAL AND IMMUNE EFFECT OF LONG TERM YOGA PRACTICE ON BREAST CANCER SURVIVORS: A CROSS SECTIONAL EXPLORATIVE STUDY

Thesis Submitted for the Award of
DOCTOR OF PHILOSOPHY (YOGA)

By

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Further it is declared that the subject matter of this thesis has not formed the basis for the award of any degree, diploma, associate-ship, fellowship or similar titles previously.

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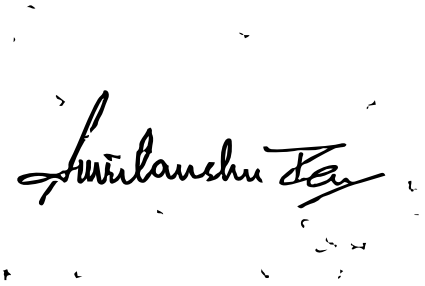
I hereby declare that this study was conducted by me at Swami Vivekananda Yoga Anusandhana Samsthana (S-VYASA), Bangalore, under the guidance of Dr Manjunath N K, and Dr Raghavendra Rao, Visiting Faculty, Division of Yoga and Life Sciences, Swami Vivekananda Yoga Anusandhana Samsthana, Deemed University, Bengaluru, India.

I also declare that the subject matter of my thesis entitled "**EVALUATION OF THE PSYCHOLOGICAL AND IMMUNE EFFECT OF LONG TERM YOGA PRACTICE ON BREAST CANCER SURVIVORS: A CROSS SECTIONAL EXPLORATIVE STUDY"** has not formed the basis of the award of any degree, diploma, associate-ship, fellowship or similar titles previously.



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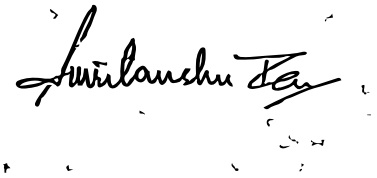

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STANDARD INTERNATIONAL TRANSLITERATION CODE USED TO TRANSLITERATE SANSKRIT WORDS

a	अ	**Ka**	क	**ḍa**	ड	**ma**	म
ā	आ	**Kha**	ख	**ḍha**	ढ	**ya**	य
i	इ	**Ga**	ग	**ṇa**	ण	**ra**	र
ī	ई	**Gha**	घ	**ta**	त	**la**	ल
u	उ	**Ṅa**	ङ	**tha**	थ	**va**	व
ū	ऊ	**Ca**	च	**da**	द	**sa**	स
e	ए	**Cha**	छ	**dha**	ध	**śa**	श
ai	ऐ	**Ja**	ज	**na**	न	**ṣa**	ष
o	ओ	**Jha**	झ	**pa**	प	**ha**	ह
au	औ	**Ñ**	ञ	**pha**	फ	**kṣa**	क्ष
m	अं	**Ṭa**	ट	**ba**	ब	**tra**	Ś
ḥ	अः	**Ṭha**	ठ	**bha**	भ	**jña**	ज्ञ

K+a	क	**K+ ī**	की	**K+e**	के	**K+au**	कौ
K+ā	का	**K+u**	कु	**K+ai**	कै	**K+m**	कं
K+i	कि	**K+ ū**	कू	**K+o**	को	**K+ḥ**	कः

SUBJECT INDEX AND COMMON ABBREVIATIONS USED

CBY	**Carcinoma of Breast Survivors with Yoga experience**
CBN	**Carcinoma of Breast Survivors who are Yoga Naïve**
NHY	**Normal Healthy Volunteers with Yoga Experience**
NHN	**Normal Healthy Volunteers who are Yoga Naïve**
CABS	**Carcinoma of Breast Survivors**
STAI	**Spielberg's State and Trait Anxiety Inventory**
BDI	**Beck's Depression Inventory**
PSS	**Perceived Stress Scale**
PANAS	**Positive Affect and Negative affect Scale**
WHOQOL	**World Health Organization Quality of life**
GHQ	**General Health Questionnaire**
NF-κB	**Nuclear Factor Kappa B**
IL1α	**Interleukin-1 alpha**
IL1β	**Interleukin-1 beta**
IL2	**Interleukin-2**
IL4	**Interleukin-4**
IL6	**Interleukin-6**
IL8	**Interleukin-8**
IL10	**Interleukin-10**
TNF-α	**Tumor necrosis Factor - alpha**
IFN-γ	**Interferon gamma**
VEGF	**Vascular Endothelial Growth factor**
EGF	**Epidermal Growth Factor**
MCP-1	**Monocyte Chemo-attractant Protein -1**
SKYM	**Sukshma Vyayama**
SMET	**Self-Management of Excessive Tension**
PET	**Prana Energizing Technique**
MSRT	**Mind Sound Resonance Technique**
MIRT	**Mind Imagery Technique**
VISAK	**Vijnana Sadhana Kausala**
ANAMS	**Ananda Amrita Sinchana**

KEYWORDS

Yoga; Breast cancer survivors; Cytokines; NF-κB; Psychological profile; Etiopathogenesis of cancer; Psychoneuro-oncology;

Contents

Abstract

Cancer is the leading cause of death worldwide with Breast Cancer being a major health burden amongst women. Research to eradicate the tumor burden without harming the host has progressed with many success stories that have resulted in successful elimination of the tumor (in a few cancers), improved longevity and better quality life. Increasing incidence of breast cancer, coupled with, better medical strategies to detect and destroy the cancerous cells, has resulted in a large number of cancer survivors. Although the inclusions differ between, a cancer survivor is one who has 'beaten the cancer' having completed the active treatment phase. (Twombly, 2004)

Evaluating the health status and needs of these survivors, based on their cancer history is very essential. Evidence seems to point to the beneficial effects of Mind body interventions with changes in lifestyle as a useful tool in improving the quality of life by tackling some of the delayed and long term side effects of cancer treatment; and may also contribute to prevention of recurrence. Administering mind body techniques as an add-on to conventional medicine however needs to be achieved in a systematic and scientific manner so as to move towards its maximum acceptability.

Yoga, as an ancient Indian science that emphasizes a healthy lifestyle, is one such mind-body strategy that could be easily applied in both high and low resource settings of breast cancer survivors. Interpreting the concepts discussed in yoga texts, translating it into modules that can be administered to cancer patients is an essential component of collecting evidence apart from demonstrating its efficacy in clinical settings.

The literary research that forms a part of this thesis has attempted to propose a psycho-neuro-immunological model of the etiopathogenesis of this disease by combining the concepts from yoga scriptures and modern scientific literature.

The experimental part of the work was aimed at evaluating the effects of yoga amongst breast cancer survivors. This process of evaluating the health benefits of yoga in breast cancer survivors is achieved by a cross sectional pilot study looking at four cohorts of individuals. Breast cancer survivors who were > six months post-treatment were recruited from out-patient departments of three major cancer hospitals in Bengaluru. Healthy volunteers also were included. All subjects who were part of the study were between 27 years to 69 years of age and were presently healthy. The four groups were cancer survivors with (CBY, n=27) or without yoga experience (CBN, n=25), normal healthy individuals with (NHY, n=28) or without (NHY, n=28) prior experience of yoga. Stage II and III Carcinoma of breast women between the ages of 25 and 70, who had completed cancer related treatment more than six months prior to the date of recruitment and were presently healthy were included in the study. The healthy groups included women of the same age groups who did not have an acute infection in the past two months and who do not have chronic illness. Individuals in the two yoga groups completed a questionnaire on the duration, regularity, contents of the yoga practices that they had been practicing. Standard Psychometric questionnaires to assess psychological outcomes of stress, quality of life, depressions, affect and general health, along with a blood sample to evaluate immune outcomes of cytokine profiles and nuclear transcription factors provided an opportunity to compare a multitude of physical and psychological effects. Data were analyzed to look for difference between groups by the analysis of variance (ANOVA) or Kruskall Wallis tests depending on the distribution of data. Results showed significant differences between the four groups in IL-6 ($p=0.019$), IL8 (0.022), IL10 ($p=0.005$) and VEGF ($p=0.033$) amongst the immune outcomes.

Among the psychological variables, yoga group was significantly better in General Health ($p<0.001$), all domains of QoL ($p<0.001$), State and Trait Anxiety ($p<0.001$), Depression ($p<0.001$) and perceived stress ($p<0.001$).

Conclusion: These results forms preliminary evidence to indicate that yoga and lifestyle modification have the potential to improve the psychological profiles and improve the immune status with lesser pro-inflammatory activity in breast cancer survivors.

In the future, controlled interventional studies in larger groups are imperative in order to generate stronger evidence of these effects.

1. INTRODUCTION

Cancer has been on the increase over the past decade and better treatment options have enabled patients to manage cancer more efficiently. This has led to an increase it the numbers of cancer survivors. Many survivors take to healthy lifestyle changes, like yoga and other alternative therapies, in order to prevent the recurrence, improve quality of life and increase the disease free survival. Thus there is an urgent need to understand cancer as described in the yoga literature and to standardize yoga techniques that are beneficial and feasible for cancer patients. Part of this study attempts to develop a modified psycho-neuro-immunological model for the etiology of cancer using knowledge from traditional yoga based literature and modern empirical evidence. Based on this, modules of yoga practices are designed that can be easily practiced by patients living with cancer.

Till date, there has been extensive evidence generated for the effects of Yoga on the breast cancer patients during the various treatment phases. A spectrum of benefits, ranging from the psychological (anxiety, depressions, stress), psychosocial (functional QoL, Health Related QoL), Physical, Immune, to molecular levels have been shown. Studies on breast cancer survivors (Banasik, Williams, Haberman, Blank, & Bendel, 2011; Bower, Garet, & Sternlieb, 2011; Carson, Carson, Porter, Keefe, & Seewaldt, 2009; Culos-Reed, Carlson, Daroux, & Hately-Aldous, 2006) have evaluated psychological, physical, menopausal changes brought about by yoga. The present thesis is an attempt to explore and compare psychological, physiological and immune parameters between yoga practitioners and yoga-naïve cancer survivors which has not been attempted before.

1.1.Definition

1.1.1. Cancer

Cancer is a generic term for a large group of diseases affecting any part of the body. It is the rapid creation of abnormal cells, typically originating from a single anomalous cell that grow beyond their usual boundaries, capable of invading adjoining parts of the body and re-establish in other organs (metastasis). The transformation from a normal cell into a tumor cell is a multistage process, typically a progression from a pre-cancerous lesion with cellular hyperplasia to malignant tumors with advanced dysplasia and angiogenesis.

1.2.Epidemiology

1.2.1. World Scenario

Cancer is a leading cause of death worldwide, accounting for 7.6 million deaths (around 13% of all deaths) in 2008.(Bray, Ren, Masuyer, & Ferlay, 2012) The main types of cancer around the globe are: lung cancer with a prevalence of 1.37million, stomach cancer (0.7 million), liver cancer (0.695 million), colorectal cancer (0.6 million), breast cancer (0.458 million) and cervical cancer (0.275 million). About 30% of cancer deaths are due to lifestyle related risk factors i.e. high BMI, Low fruit and vegetable intake, lack of physical activity and tobacco & alcohol abuse (World Health Organization, 2012) and are modifiable.

Other non-modifiable causes of cancer are viral infections such as Hepatitis B Virus, Hepatitis C Virus and Human Papilloma Virus account for 20% of cancer deaths in low and middle income countries.(World Health Organization, 2012) Deaths from cancer are projected to continue rising worldwide, with an estimated 13.1 million deaths in 2030. (World Health Organization, 2012)

Breast Cancer is a major health burden amongst women and was responsible for about 375,000 deaths, worldwide, in the year 2000 (Ferlay, Shin, et al., 2010). It is responsible for over 10% of the estimated 10 million cancers diagnosed each year in both sexes (Ferlay, Shin, et al., 2010). According to International Agency for Research in 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 (Ferlay, Parkin, et al., 2010). In 2009 alone, USA reported 192,370 new breast cancer cases and 40,170 deaths due to breast cancer with the age adjusted incidence of cancer being 124.3 per 100,000 women (SEER, 2009). It is the most common cancer in women, accounting for 16% of cancer–related deaths (Landis, Murray, Bolden, & Wingo, 1998). Table 1 shows the rates of prevalence and mortality in different countries for the year 2008.

Table 1: Prevalence and mortality of breast cancer worldwide for the year 2008

	PREVALENCE			DEATHS		
	Cases	Age Std Rate	Crude Rate	Deaths	Age Std Rate	Crude 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
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
Western Asia	20155	21.96	27.87	8459	9.22	11.82
China	106014	17.09	16.39	28787	4.64	4.51
India	79124	16.13	19.10	40607	8.28	9.91
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 takes the 2000 US population distribution and applies it to other time periods under consideration.

(Ferlay, Shin, et al., 2010)

1.2.2. 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 in all registries except Barshi with the relative proportion ranging from 19.3% to 27.5%.

According to data from the National Cancer registry Program, every year 80,000 new cases of Breast Cancer are detected in Indian cities.(NCRP & Report, 1996) Breast cancer disease claims 35,000 lives every year, and is increasing by 8 per cent since 1990.(NCRP, 2008) In 1970, for instance, the incidence of Breast Cancer in India was barely 20 per 100,000 urban women. Today, that number has shot up to 29.3 nearly a 50% increase. Among the Parsis in Mumbai, a relatively westernized community in which few women have children and fewer

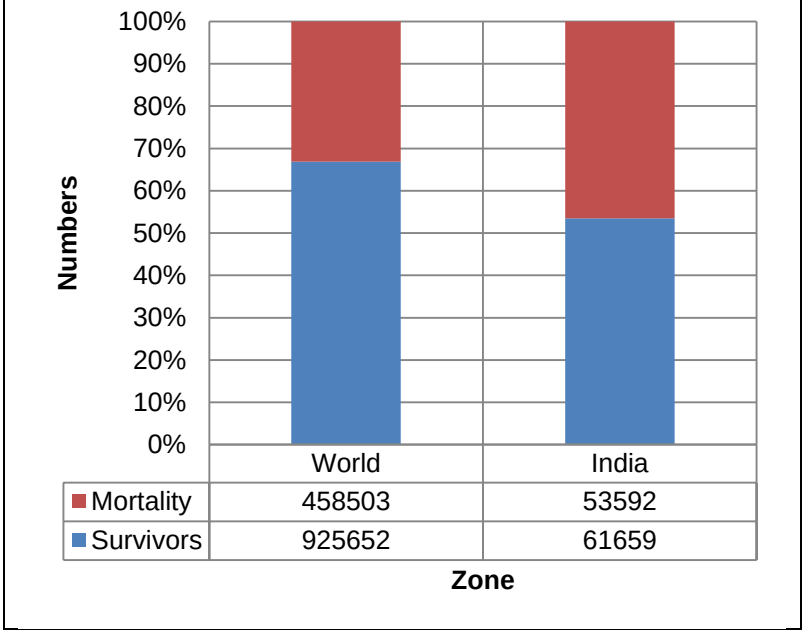
breast–feed them, the incidence rate is higher at 43.8 per 1,00,000 women.(International Association for Cancer Research, 2004) Comparatively, in rural areas the incidence is only 8.5. This is still far less than the West, where one out of nine women gets the disease. But urban India is not far behind; the incidence of Breast Cancer is likely to double in the next 10 years (Indian Council for Medical Research, 2000). Table 2 shows the incidence and the mortality of breast cancer in India for the year 2008.

Table 2: Incidence and Mortality of Breast Cancer Cases in India in 2008	
Incidence (Number of Cases)	Mortality
1,15,251	53,592
(Ferlay, Shin, et al., 2010)	

1.2.3. Scenario in Bangalore

Data from 2001–2004 show that the Age Adjusted Incidence Rate (AAR) varied between 39.8 to 116.5/100,000 among females, breast being the leading site of cancer followed by cervix, esophagus, ovary, mouth, stomach and others in Bangalore.

Figure 1 Survival and Mortality in Breast Cancer (2008)



According to a latest report in 2008 by the Bangalore population based cancer registry [Kidwai memorial Institute of Oncology], Karnataka has about 150,000 cancer cases at a given time with around 35,000 being added each year. During the year 2001– 2003, a total number of 6112 male and 7247 female cases were registered at this registry alone. Similar to the trend seen worldwide, Bangalore also has seen a

gradual increase in the total number of breast cases compared to the previous years (Reddy, 2009).

1.2.4. Increasing prevalence due to reducing mortality

The world statistics indicates that the prevalence of the disease has not reduced, which is intriguing, given that research to understand the etiology and eradicate the tumor burden without harming the host has progressed greatly over several decades. In India alone, 22.2% of women presently suffer from cancer which is expected to increase to almost 30% in the next five years (Ferlay, Shin, et al., 2010). On the other hand mortality amongst people living with cancer is reducing in industrialized countries due to increased utilization of mammographic screening, early detection of disease, and availability of improved therapies. As a result of these two effects there is a large body of people who have survived cancer. The Age Adjusted Ten year Relative Survival for breast cancer is a standard measure of how many individual would survive for ten years post-treatment. This number has increased from 61.1% (1990) to 77.0% (2007) in the United Kingdom. Figure 1 shows the comparison of the breast cancers in the world with India indicating a 67% and 53% survival rate respectively. The latest available survival rates reported by Jemal et al (Siegel, Naishadham, & Jemal, 2013) indicate that in the year 2012 there were an estimated 232,340 new cases of breast cancer of which 192720 (~83%) survived.

1.3.Causes and risk factors of breast cancer

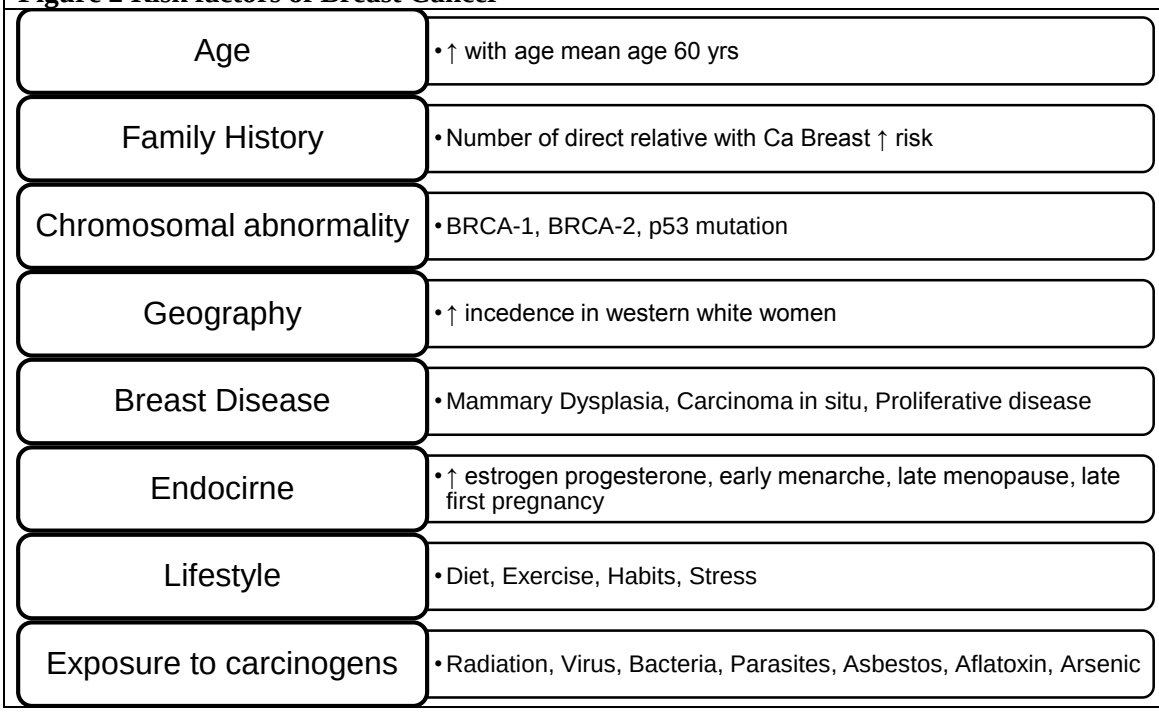
Knowledge about the causes of breast cancer, and interventions to prevent and manage the disease is extensive. The cellular changes seen are the result of the interaction between several factors, as can be seen in Figure 2.

Ageing is one of the fundamental factors for cancer development. The incidence of cancer rises dramatically with age, most likely due to a buildup of risks for specific cancers that increase

with age. The overall risk accumulation is combined with the tendency for cellular repair mechanisms to be less effective as a person grows older.

Exposure to known physical and chemical carcinogens like γ-radiation, asbestos etc. could prove to be a major risk factor. Chronic infections from hepatitis B (HBV), hepatitis C virus (HCV) and some types of Human Papilloma Virus (HPV) could be risk factors for cancer and is seen in low and middle-income countries. Unhealthy habits such as tobacco, alcohol, improper diet and inadequate physical inactivity are the main cancer risk factors worldwide. More recent understanding has indicated that psychological stress could also increase the risk of developing

Figure 2 Risk factors of Breast Cancer



cancers. All these lifestyle practices induce the accumulation of toxins, which stimulate cells to become cancerous. Understanding and reversing these lifestyle habits might hold value in prevention, better prognosis and improved quality of life in individuals living with cancer.

1.4.Prevention and Treatment of cancer

1.4.1. Prevention of cancer

Knowledge of these risk factors is crucial in reducing the risks and would help to prevent cells from becoming cancerous. It is known today that 90% of risk factors are lifestyle related which can be modified or controlled. Regular exercise, diet with high anti-oxidants, smoking and alcohol cessation, and low stress conditions would lower the risk of cancer by 30%. As with studies of obesity, epidemiologic studies have shown that diabetes and chronically elevated insulin levels are associated with a variety of cancers (Calle, Murphy, Rodriguez, Thun, & Heath, 1998; Coughlin, Calle, Teras, Petrelli, & Thun, 2004; Giovannucci, 1995; Stoll, 2002; Will, Galuska, Vinicor, & Calle, 1998). Being overweight, sexually transmitted HPV infections, urban air pollution and indoor smoke from solid fuels are modifiable factors that could increase cancer risks

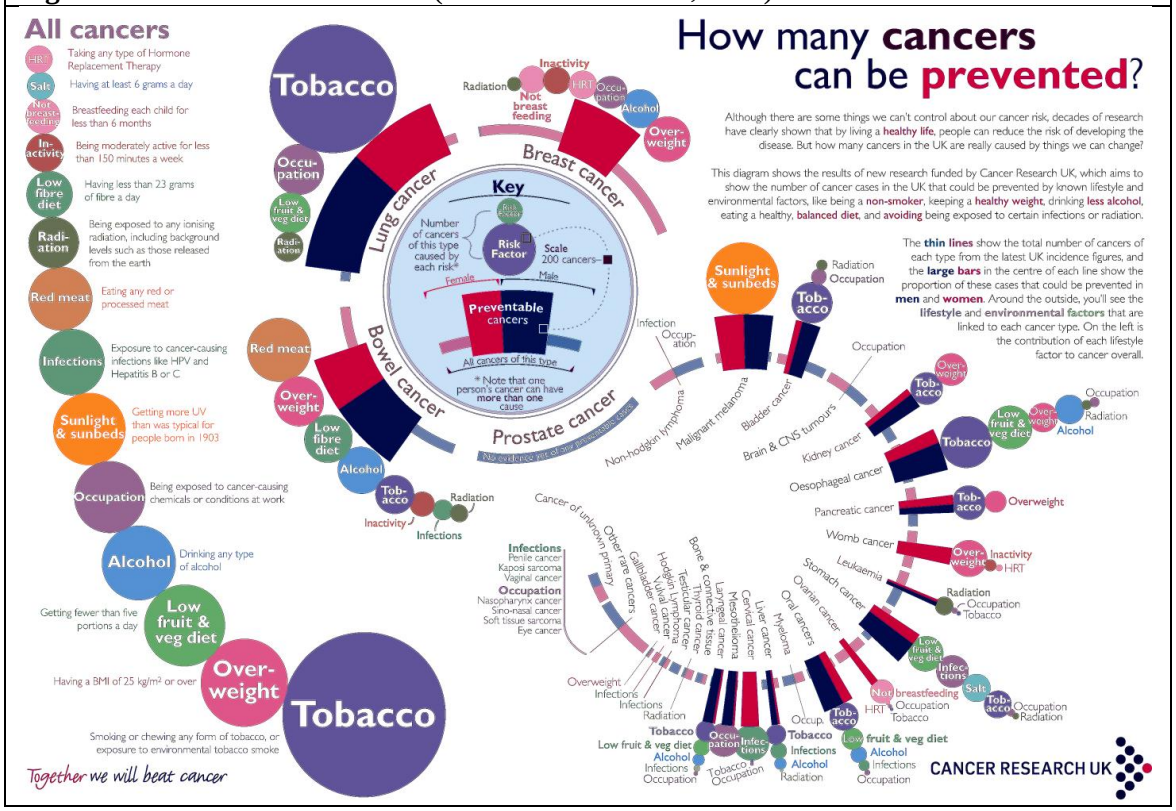
Cancer can be efficiently handled by adopting lifestyle strategies for cancer prevention, early detection through regular screening, vaccination against human papilloma virus (HPV) and hepatitis B virus (HBV), control of occupational hazards, reduction in the exposure to sunlight and better allopathic treatment and care. Many cancers have a high chance of cure if detected early and treated adequately. (Bonadonna, Hortobagyi, & Valagussa, 2006)

Early Detection has two components:(World Health Organization, 2013)

a. **Screening:** Screening is defined as ‘the systematic application of a test in an asymptomatic population’. It aims to identify individuals with abnormalities suggestive of specific cancers or pre-cancers and refer them promptly for diagnosis and treatment. Screening programs are especially effective for frequent cancer types for which a cost-effective, affordable, acceptable and accessible screening test to detect the disease in the

majority of the population at risk is available. Monthly breast self-examination is a simple but efficient way of screening for breast nodules and changes. Genetic screening is also done in the case of breast cancer to look for genetic mutation of BRCA-1 and BRCA-2 genes. Mutations in the BRCA1 gene could lead to 65% of women developing breast cancer before the age of 70. Correspondingly BRCA2 mutations lead to 45% of women developing breast cancer before the age of 70years. (Antoniou et al., 2003)

Figure 3 Risk factors for Cancer (Cancer Research UK, 2012)



b. **Early diagnosis:** The awareness of early signs and symptoms (for cancer types such as cervical, breast colorectal and oral) in order to get them diagnosed and treated early before the disease becomes advanced. Early diagnosis programs are particularly relevant in low-resource settings where the majority of patients are diagnosed in very late stages and where there is no screening.

c.

1.4.2. Treatment of cancer

Cancer treatment requires a careful selection of one or more intervention, such as surgery, radiotherapy and chemotherapy amongst others. The goal is to cure the disease by eliminating the majority of cancerous cells or considerably prolong life while improving the patient's quality of life. Cancer diagnosis and treatment is complemented by psychological support which has shown to improve treatment response and prognosis.

Surgical intervention is often the most effective option for the removal of solid tumors and results in reduction of the tumor burden considerably.(Bonadonna et al., 2006) The aim of the surgery is to excise the tumor completely with an adequate margin of normal tissue touching the tumor to prevent vascular and lymphatic spread. In breast cancer, surgical methods aim to conserve as much of the normal tissue as possible but many times a complete mastectomy is necessary, in which case reconstruction of the breast is possible through a cosmetic procedure. Radiotherapy is the use of high energy ionizing radiation to destroy the cancerous tissue. Different sources of radiation (X-rays, γ-rays, β particles) are chosen depending on its charge, penetrability, and relative biologic effect. Radiation is used in the case of inoperable breast lesions and brain and bone metastasis. Chemicals that are anti-neoplastic are used as chemotherapeutic drugs in the treatment of cancer. These drugs could be conventional drugs that act on rapidly multiplying cells and destroy them. Advancements in this field have resulted in molecular targeting by these drugs. Anticancer antibodies help to target, specifically, the cancerous cells. Many gynecological cancers result in the dysregulation of the hormonal levels and replacement of these hormones (antiestrogsen, estrogen, aromatase blocker) could result in reversal of tumors or delayed recurrence. Many other modalities of treatment like immune therapy, gene therapy are used in combination, based on the type of cancer and its' stage. All these treatment modalities are robust and aggressive methods that help to remove the cancerous

cells but at the same time cause multitude of side effects and tax the body and mind significantly. Usually an oncologist has to weigh the advantages of the treatment with its side effects. (Bonadonna et al., 2006)

Some of the most common cancer types, such as breast cancer, cervical cancer, oral cancer and colorectal cancer have much better prognosis when detected early and treated according to best practices. On the other hand, even other cancer types that are more disseminated, such as leukemias and lymphomas in children, and testicular seminoma, have high cure rates if appropriate treatment is provided. (Battista & Grover, 1988)

Palliative care

In advanced disease, the treatment is aimed at relieving the symptoms of the patient rather than to cure the cancer enabling the patients to live more comfortably. Palliative care is an urgent humanitarian need for people worldwide with cancer and other chronic fatal diseases and is particularly applicable in places with a high proportion of patients in advanced stages where there is little chance of cure. This treatment options include relief strategies from not just physical but also psychosocial and spiritual levels. Effective public health strategies, comprising of community- and home-based care are essential to provide pain relief and palliative care for patients and their families in low-resource settings. For example, improved access to oral morphine is mandatory for the treatment of severe cancer pain, suffered by over 80% of cancer patients in terminal phase. (World Health Organization, 2013)

Today oncologists agree that cancer is a lifestyle related inflammatory disorder that needs lifelong management and complete cure is almost not possible. The goal of the treatment is to reduce the cancer burden and to prevent recurrence. Once the active treatment phase is complete, the cancer survivor would require adopting practices that would help prevent re-adhesion of the

remaining cancer cells and a better immune system to detect and destroy the cancerous cells. This is partially achieved through medication, hormonal rebalancing and immunotherapies but significant lifestyle changes along with conventional management would add a great advantage in the fight against cancer recurrence.

1.5. Breast Cancer Survivors

The national Coalition for Cancer Survivorship has tried, over the past few decades to define the phrase 'cancer survivor' with much difficulty due to varied interpretations. In early days (1986) it was suggested that patients who were 'post-treatment' were considered survivors. This evolved (2003) to include those who are diagnosed with cancer. According to this, a person is considered to be a survivor from the time of diagnosis until the end of life. This definition further was modified to include the family and caregivers of cancer patients whose life has been affected. (Twombly, 2004) ("Life After Cancer," 2012). These effects are speculated to be fear, illness related stress, concerns of adequate and accurate medical aid received, economic and psychosocial concerns amongst other. A systematic study to evaluate to the concerns of the cancer caregivers are needed to accurately define factors that are affected.

For our present research purpose , we planned to include only those who completed the initial active treatment phase of breast cancer as per the definition suggested by the national cancer institute ("Cancer Survivor: Definition," 2012). Breast Cancer survivorship focuses on the health and life of a person with cancer post-treatment until the end of life. It covers the physical, psychological, psychosocial and economic issues of cancer, beyond the diagnosis and treatment phases. Survivorship includes issues related to the ability to get health care and follow-up treatment, late effects of treatment, second cancers, and quality of life. Although family members, friends, and caregivers are also considered part of the survivorship experience, they are not included in the definition of a 'breast cancer survivor' for this study.

1.5.1. Symptoms in breast cancer survivors

People living with breast cancer; experience a plethora of morbidities that are a result of treatment related side effects and compromised immune functioning which are further aggravated by psychological disturbance. Side effects are essentially classified into short-term side effects (showing up during the treatment phase and lasting for a couple of months), long-term side effects (showing up during the treatment phase and lasting for an extended duration) and late side effects (showing up after active treatment phase has been over for a couple of months). These can also be classified as physical and psychological symptoms or based on the treatment that causes it. Below is a description of some of the side effects

Physical and Physiological Side Effects

Effects of Radiation Therapy

Radiation therapy can cause side effects by damaging normal, healthy cells near the cancer. Many people who get radiation therapy have skin changes including dryness, itching, peeling, or blistering. Fatigue is often described by patients undergoing radiotherapy, as feeling worn out or exhausted. Depending on the part of the body being treated and the dosage of the radiation that is administered, patients may also have diarrhea, hair loss in the treatment area, mouth dryness and ulcers, nausea and vomiting, sexual changes, swelling, trouble swallowing, urinary and bladder changes. Most of these side effects go away within 2 months after radiation therapy is finished.(National Cancer Institute, n.d.; Shapiro & Recht, 2001)

Late-side effects occurring 6 or more months after radiation therapy again vary by the dose and location of radiation received. These may include infertility, joint problems, lymphedema, mouth problems, and radiation induced secondary cancers. (Siegel et al., 2012)

Effects of Chemotherapy

Chemotherapy drugs are powerful anti-neoplastic medicines that can cause side effects. Some of these side effects are anemia, appetite changes, bleeding, constipation, diarrhea, fatigue, hair loss, infection, infertility, mouth and throat changes, nausea and vomiting, nervous system changes, pain, sexual changes, skin and nail changes, urinary, kidney, and bladder changes, flu-like symptoms, fluid retention and eye changes.(World Health Organization, 2013)

Effects of Surgery

Side effects of breast cancer surgery can include pain, temporary swelling, tenderness, and hard scar tissue that form in the surgical site. As with all operations, bleeding and infection at the surgery site are also possible. Late side effects could present in the form of lymphedema.

Common side effects

Pain can be caused by cancer itself or by certain treatments, such as surgery. Nausea and vomiting are among the most feared side effects of cancer treatment. While many people treated for cancer have bouts of nausea and vomiting, there are medicines that effective to control these side effects. Fatigue is another most common and distressing side effects of cancer and its treatment. Fatigue from cancer treatment is often more intense than the feelings of being tired we all have from time to time. Anemia, which is also seen in patients, can result in feeling weak, tired, or short of breath. Lymphedema is a build-up of lymph fluid in the fatty tissues just under your skin. This build-up causes swelling (or edema), most often in the arms or legs. Lymphedema can result from surgery or radiation therapy to treat certain cancers. Infections in people who have cancer or are getting cancer treatment can be more serious than those in other people due to a compromised immune function. They can also be harder to treat. Sexual health alteration, infertility, ostomosis could also present themselves as side effects during and after cancer treatment. (Bonadonna et al., 2006)

Breast Cancer Recurrence

Cancer recurrence is the return of cancer after a period of time in which no cancer could be detected which itself could be a side effect of the treatment. The site of recurrence could be the same or the cancer could manifest at a new location. Base on this it is termed as local, regional or distant recurrence. Recurrence depends on a number of factors like the type and site of cancer that was treated, the quantity of treatment received, age of the patient, duration since the previous treatment was completed etc. It is essential to understand that every individual case of unique and there are several steps one can take to reduce the risk of recurrence. A healthy lifestyle with regular exercise, proper diet rich in fiber and anti-oxidants and low in cholesterologenic substances is an easy modification that can go a long way in preventing recurrence (Bonadonna et al., 2006). Psychologically, the fear of recurrence can be very debilitating for the day-to-day functioning and it has been suggested that the psychological profile of the patient can influence the disease (Lewis, O'Brien, & Barraclough, 2002), hence battling the fear and anxiety is very essential. Regular follow up with the oncologist helps to detect recurrence very early that can ensure more treatment options and better prognosis.

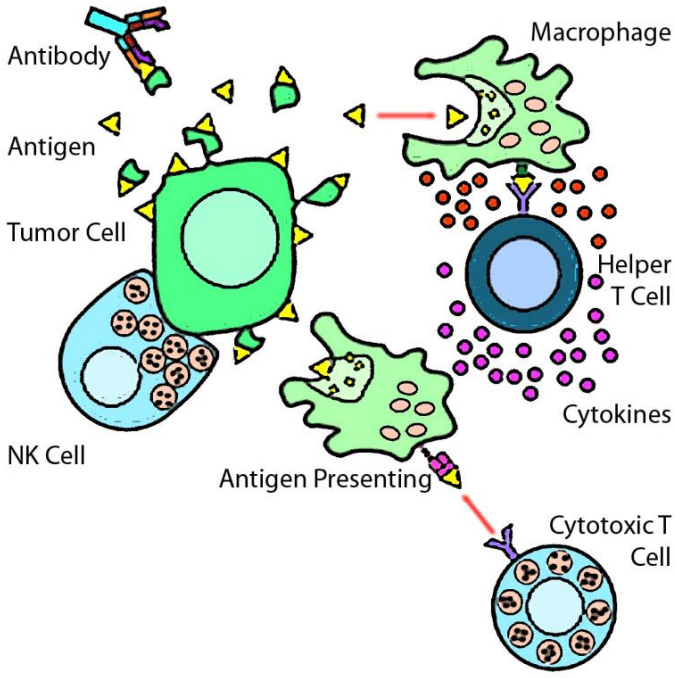
Psychological Side Effects

Apart from the insult on the body by the physical side effects, there is significant impact on the state of mind starting from the time of diagnosis, through the treatment and may persist for many years after all treatment is completed. This plays a vital role in determinants of treatment response, prognosis, quality of life and disease free survival.(Ganz et al., 1996) From the time of diagnosis, considerable amount of fear, anxiety and distress emerges that lasts for a significant duration. Depressions, mood changes, disturbance of positive and negative feelings also are common in cancer patients and survivors. Often, the attitude towards cancer can play a significant role in treatment adherence, treatment response and outcome and prognosis. Studies

have shown that those who are capable of taking the disease in their stride and readying themselves to fight the cancer have a much better chance of the fighting the disease than those who give up hope on the news that they have cancer.(Burris, Jacobsen, Loftus, & Andrykowski, 2012) Fear of death is a major factor in psyche of cancer patients. These psychological disturbances last not just for the duration of the treatment but for many years after and influence general health and quality of life of breast cancer survivors whereby they can increase the risk of regression and reduce disease free survival.

Psycho-oncology is the study of the oncologic pathways that are influenced by the psychology of an individual.(N. Smith, Fuhrmann, & Tausk, 2009) This field of study has made progress is identifying the role of the mind is modulating several cancer related determinants including Inflammation, anemia, nausea (N. Smith et al., 2009)

Figure 4 Immune Recognition of Cancer Cells (Kelly, 2006)



1.6. Role of Immune System in Cancer

Both specific and non-specific immune responses are known to act against both prevention and progression of cancer cells. Various types of immune effector cells are known to play an active role in this anti-tumor defense. In brief, we illustrate the cells and mechanisms of immune defense against cancer in Figure 4.

According to the non-specific immunosurveillance theory, the immune system is capable of protecting against newly formed tumor cells and tumor growth (Vile, Cong, & Dorudi, 2010).

The clinical relevance of immuno-surveillance in cancer has been questioned off late as immune recognition of tumor cells and cytotoxic responses against cancer are only mildly effective. It is now generally believed that anti-cancer immune defenses although modest in its ability to control disease employ both specific and non-specific killing mechanisms.(Lewis et al., 2002)

Clinical observations have also indicated immune activity responsible for cancer defense in cases of spontaneous regression of tumors. (Rosenberg, 1991) Immuno suppressant drugs have a side effect of increasing the incidence of tumor (Oliver & Nouri, 1992) and immunization by killed tumor cells have conferred subsequent tumor resistance in mouse models. (Beverly, 2003)

Rarely tumor cell have unique proteins that can be recognized as antigens which makes it difficult for the immune system to detect the threat. Virus induced cancers however do have these proteins and are more susceptible to detection. Tumor protein uniqueness could be a structural, qualitative or quantitative difference from normal cells that makes it vulnerable to the immune system.

Tumor specific immune responses could be cell mediated or anti-body-complement-mediated.(King & Robins, 2006) Cancer cells that have major histocompatibility complexes are easier to recognize and destroy, but sometimes Cytotoxic –T-Lymphocytes may also recognize tumor antigens.(Shu, Plautz, Krauss, & Chang, 1997)

1.6.1. Cancer as an inflammatory Disease

Ayurveda (the science of long life) postulates that continuous irritation over long periods of time can lead to cancer (*arbuda*). Whether this irritation is the same as that Rudolf Virchow referred to as inflammation in the nineteenth century is uncertain. The observable consequences of irritation were first described by Aulus Cornelius Celsus, a Roman medical writer and possibly a physician in the first century (ca 25BC-50 AD), who characterized inflammation as

“redness (rubor) and swelling (tumor) with heat (calor) and pain (dolor)”. Virchow postulated that micro inflammation that results from irritation leads to the development of most chronic diseases including cancer. This inflammation is now regarded as a “secret killer” for diseases such as atherosclerosis, rheumatoid arthritis, multiple sclerosis, asthma, Alzheimer's, depression, fatigue, neuropathic pain, lack of appetite, and cancer(Heidland, Klassen, Rutkowski, & Bahner, 2006).

1.6.2. The biomarkers of the Immune System (Cytokines and NF-κB)

1.6.2.1. Definition of cytokines and NFKB

Transcription factors are proteins that bind to specific DNA sequences and control which genes are to be transcribed or how much it should be expressed thereby controlling a plethora of protein profiles of the cells. All transcription factors consists of a DNA biding site that attaches to the target genes and can promote or repress the protein expression from that gene.(T. I. Lee & Young, 2000; Nikolov & Burley, 1997; Roeder, 1996) The transcription factors can bring about differential enhancement of transcription that could impart several functions to the cell like responding to intracellular and environmental signals, controlling the cell cycle, initiating pathogenesis and modulate embryonic development.

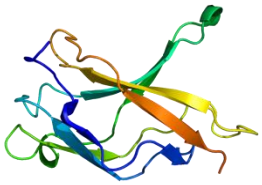
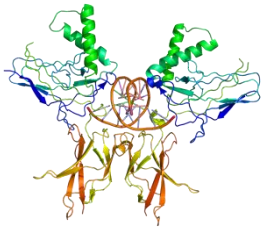
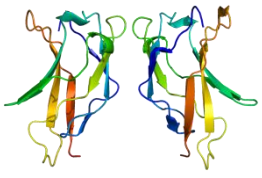
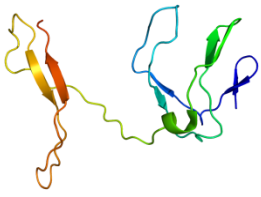
One important transcription factor associated with inflammation in general and cancer in particular is Nuclear Factor-kappa-B. This transcription factor is found in almost all animal cell types and is expressed at low levels in normal cells whereas it has a key role in regulating the immune response to infection (inflammation) by monitoring and regulating the cytokine profile of the body and hence is produced at higher levels during an immune reaction. Clinically, high levels of NF-κB for a long period (chronic inflammation) is implicated in cancers. This is due to the fact that NF-κB influences the genes responsible for cell proliferations and prevents cellular

vulnerability to apoptosis.(Sheikh & Huang, 2003) NF-κB is seen to be chronically active in several other diseases that are related to impair immune functioning like autoimmune disorders.(Monaco et al., 2004)

Cytokines are small cell-signaling protein molecules (immunomodulating agents) that are secreted by numerous cells and are a category of signaling molecules used extensively in intercellular communication. They can be classified as proteins, peptides, or glycoproteins and are a diverse family of regulators produced throughout the body by cells of diverse embryological origin. Cytokines are diverse group of intercellular signaling low molecular weight proteins that provide a network controlling local and systemic immune and inflammatory responses but also wound healing, hematopoiesis and other biologic process. (Hardman, Limbird, & Gilman, 2001) Virtually all nucleated cells produce such immunomodulating agents, but especially endo/epithelial cells and resident macrophages (many near the interface with the external environment) are potent producers of cytokines that could present systemic or localized immune responses. (Cannon, 2000)

1.6.2.2. Classification of Cytokines and NF-κB

Table 3 Classification of NF-κB

Class I		Class II		
NF-κB 1	NF-κB 2	Rel A	Rel B	c-Rel
p105-p50	p100-p52	p65		
				

Nuclear Factor Kappa B is a family of five proteins that share a Rel homology resulting in their classification. The NF-κB is divided into Class I and Class II proteins with structural

differences between them. (Nabel & Verma, 1993) The table below shows the five types of NF-κB that result from structural classification.

Cytokines are downstream cascade signal proteins that are activated or suppressed by the action of NF-κB. These further form negative or positive feedback loops in order to ensure a coordinated immune response.

Cytokines have historically been classified into 'families' based on their apparent activity and/or impact on a given cell type, system, or tissue but lately effort to establish categories based on receptors have been made since cytokines and receptors are highly conserved. (Fries, 2009)

The table below provides an overview of key cytokine and growth factor groups by receptor family as well as by classical family names and demonstrates the present characteristics and functionality at the family level.

Table 4 Classification of Cytokines based on cytokine receptors

Receptor Family	Receptor Characteristics	Members	Common Activity	Cytokine Characteristics
Hematopoietin – type 1	Cytosolic box 1 / 2	IL-6R G-CSFR gp130 **IL-12R**	T/B cell activation	4 α-helical bundles
	WSXWS extracellular sequence	LIFR IL-2Rβ IL-2Rγ **IL-4R** IL-3Rα IL-9R GM-CSFR IL-5R	Hematopoiesis	4 α-helical bundles
Interferon – type 2	Cytosolic box 1 / 2, Extracellular Fibronectin domain	IFN-α/βR IFN-R-α/β **IL-10R**	Anti-viral (not IL-10)	4 α-helical bundles
Tumor Necrosis Factor	Cytosolic death domain Four Cys-rich extracellular regions	P55 **TNFR** P75 TNRR (no death domain) LTβR NGFR CD40 CD30 CD27 4-1BB OX40 TRAMP (DR3) TRAILR (DR4)	Proinflammatory	Jelly roll motif
Interleukin-1 / Toll-like	Cytosolic Toll / IL- 1R (TIR) domain Ig domains (IL-1R) Leucine-rich repeats (extracellular	**IL-1RI IL-1RII**(no TIR) IL-1RacP IL018R α/β- chains T1/ST2 IL-1RAPL SIGIRR TLR1-TLR10	Proinflammatory	β-trefoil

	TLR subgroup)			
Tyrosine Kinase	Cytosolic tyrosine kinase domain	M-CSFR **EGFR** TGF IGFs FGF's	Growth Factors	β-sheet
Chemokine	7 trans-membrane regions	**IL-8 MCP's** RANTES Eotaxin	Chemotaxis	Triple-stranded antiparallel β-sheet Greek key motif
(Fitzgerald, O'Neill, Gearing, & Callard, 2001)				

1.6.3. Psychosocial effects on anti-tumor immune mechanisms

Over the past two decades there has been considerable increase in the evidence available to attest the psychosocial effects on immunity. Some of these studies having have also looked at psychosocial imbalance and cancer related immunity. Any psychological factor that has the potential to improve the immune system also, when disturbed may be detrimental to varieties of cancers. Although it is imperative to understand the mechanisms and the pathways that connect psychology and immunology, it is almost impossible to understand changes of individual parameters without looking at a network on influencing variables and thus incorrect to apply a purely reductionist approach to either fields. However, various attempts have been made to draw correlates of stress appraisal and cancer immunology.(Carlson, Speca, Faris, & Patel, 2007; Glaser & Kiecolt-Glaser, 1994; Reiche, Nunes, & Morimoto, 2004; Thornton & Andersen, 2006) Differences in how chronic stress can change immuno outcomes as opposed to the effects of acute stressors are also explored.(Aggarwal & Gehlot, 2009; Aggarwal, Shishodia, Sandur, Pandey, & Sethi, 2006) The manner in which an individual responds to stress (Depression and anxiety) is also a factor that influences NK cell activity and cortisol levels, although the results are inconclusive.(Herbert & Cohen, 1993a, 1993b) Social support is also a very important in determining the quality of life and related immune parameters. The overall social support and quality of life in the case of cancer is a function of the interpersonal relationships between the cancer patients, friends and family and the doctor. Levy and her colleagues showed that NK Cell

Activity was associated with the perceived support from the physician, as well as active coping strategies and active social support seeking activities.(Levy et al., 1990)

1.7.Need for Complementary and Alternative Therapies

Increase in the incidence of cancer and the inability of conventional medicine to tackle side effects and quality of life are salient reasons that have led patients to resort to complementary and alternative medicine (CAM). According to a survey, approximately 21% of leukemia survivors in the United States had engaged in CAM practices.(M. Gupta, Shafiq, Kumari, & Pandhi, 2002) In India, approximately 56% of the cancer patients took recourse to alternative therapies. (M. Gupta et al., 2002) Among these, yoga was the third most commonly accepted therapy.(M. Gupta et al., 2002) This survey also compiled the reasons for resorting to CAM. They were: management of side effects, reduction of costs involved, avoiding poor quality of life, minimizing psychological ill-health and hope of reducing the chances of recurrence that was not assured after undergoing such traumatic conventional treatments.

The reasons (those related to the psyche, side effects, cost, amongst others) quoted in this survey are given little attention by the treating oncologist as these appeared to be non-consequential as the therapy had to be aggressive to remove the tumor burden with minimal damage to healthy tissues. It is only in the last decade that the role of the mind has emerged to be a key factor in determining the health of a cancer survivor. Conventional treatment has concentrated on dealing with pathophysiology at physical, physiological and molecular levels, but in reality the human system is governed by a more powerful subtle entity called the mind.(Hirayama, 1979) Thus, mind-body techniques like yoga are powerful complementary healing systems that can change the approach to cancer care.

1.8. Yoga as a Complementary Therapeutic Strategy

Among the various CAM treatments available, yoga offers a holistic model, using an entirely different concept of understanding human body in health and disease states; it also offers self-corrective techniques to restore normalcy. The very definition of health (swastha), according to yoga, is a self-aware state of mind, which is little understood in health and healing. Yoga as a way of life suggests that the mind is the root cause for all maladies and that the malfunction at the mental level percolates as abnormal functioning of the body, mediated through abnormal redistribution of the vital energy. Understanding the intricacies of the mechanisms enables an individual to target corrective and restorative practices at the root of the problem rather than tackle its symptoms. Thus, yoga seems to offer interventions that may hold self-corrective answers to problems that are more subtle and basic, and bring about a more comprehensive restoration of health.

1.9. Need for the Study

Yoga as prescribed in traditional texts offer lifestyle mechanisms to restore health and evolve towards a state of positive health. These suggestions are to be systematically scrutinized in order to custom-fit for the case of cancer. Hence, a detailed review of traditional and empirical literature is necessary. This further needs to be clarified and a holistic model to understand cancer needs to be brought about. This would help to provide cancer care comprehensively. Further, yoga practices need to be aligned to this new, amalgamated understanding of cancer etiology and progression. Yoga as an intervention, on one hand, needs to adhere to the scriptural authenticity, yet be customized based on the needs of the patients. The efficacy of an intervention, thus developed could stand the robust tests of scientific validity.

The ever increasing number of cancer survivors, coupled with a plethora of cancer and cancer treatment related morbidities have necessitated the exploration of alternative methods of

management strategies. Studies, till date, have found beneficial effects of yoga at various phases of treatment but few studies are to provide substantial evidence for its effects in the post-treatment phase. A positive psychological profile, healthy practices and immune upkeep of an individual are important aspects of successful cancer survival. It is to be seen if, yoga provides psychological, immune and lifestyle benefits in breast cancer survivors parallel to the effects demonstrated during various treatment phases. Hence, a pilot initiative, in the form of a multi-cohort study is undertaken, which looks at the effect of prior exposure to yoga on several health and quality of life related outcomes in breast cancer survivors.

2. AIMS AND OBJECTIVES

2.1.Aims:

To find evidence for a holistic yoga interpretation of the psycho-neuro-immunological model of cancer; develop a need based yoga module for cancer survivors and evaluate the efficacy of prior yoga experience on health, immune and psychological profiles of breast cancer survivors.

2.2.Objectives

1. To develop conceptual model for the etiopathogenesis of cancer that is based on traditional yoga literature and scientific evidence on the lines of the psycho-neuro-immunological (PNI) pathway.
2. To develop modules of yoga practices based on the scriptural prescriptions of yoga techniques, needs of the cancer patient at different treatment phases and modern scientific evidence of the effects of mindful practices on cancer related outcomes.
3. To explore the effects of long term yoga practice in breast cancer survivors by means of a cross sectional study.
4. To study differences in immune and psychological profiles between four cohorts i.e. Breast Cancer survivors with prior yoga experience (CBY); Breast Cancer Survivors who are naïve to yoga (CBN); Healthy Volunteers who have prior yoga experience (NHY) and; Healthy Volunteers who are naïve to Yoga (NHN) in order to understand distinct strata of the health spectrum. (ill health to positive health)

2.3.Research questions

- Does Vedic literature contain the understanding of cancer homologous to the modern knowledge which could be helpful to complement conventional treatment?

- Could there be differences in anxiety, depression, quality of life and stress perception, between breast cancer survivors with or without a history of yoga practice?
- Could there be differences in pro-inflammatory and anti-inflammatory cytokine levels and cellular transcription factors, between breast cancer survivors with or without a history of yoga practice?

2.4. Hypothesis

- Vedic literature contains mentions of cancer that are homologous to modern science yet have several differences in the way that cancer is understood.
- Literature and empirical evidence of yoga literature suggests that yoga could be used to complement conventional medicine in the management of cancer.
- Trait anxiety$_{(CBY)}$ ≠ Trait anxiety$_{(CBN)}$ ≠ Trait anxiety$_{(NHY)}$ ≠ Trait anxiety$_{(NHN)}$
- Depression$_{(CBY)}$ ≠ Depression$_{(CBN)}$ ≠ Depression$_{(NHY)}$ ≠ Depression$_{(NHN)}$
- QOL$_{(CBY)}$ ≠ QOL$_{(CBN)}$ ≠ QOL$_{(NHY)}$ ≠ QOL$_{(NHN)}$
- Pro-Inflammatory Activity$_{(CBY)}$ ≠ Pro-Inflammatory Acitivty$_{(CBN)}$ ≠ Pro-Inflammatory Activity$_{(NHY)}$ ≠ Pro-Inflammatory Activity$_{(NHN)}$
- Anti-Inflammatory Activity$_{(CBY)}$ ≠ Anti-Inflammatory Activity$_{(CBN)}$ ≠ Anti-Inflammatory Activity$_{(NHY)}$ ≠ Anti -Inflammatory Activity$_{(NHN)}$
- NF-κβ$_{(CBY)}$ ≠ NF-κβ$_{(CBN)}$ ≠ NF-κβ$_{(NHY)}$ ≠ NF-κβ$_{(NHN)}$

* All hypotheses test would be two-tailed with an α level of 0.05

2.5.Null hypotheses

Literary hypotheses would not be subjected to testing. The empirical hypotheses would be tested using inferential statistics, the null hypotheses for which are listed below.

- Trait anxiety$_{(CBY)}$ = Trait anxiety$_{(CBN)}$ = Trait anxiety$_{(NHY)}$ = Trait anxiety$_{(NHN)}$
- Depression$_{(CBY)}$ = Depression$_{(CBN)}$ = Depression$_{(NHY)}$ = Depression$_{(NHN)}$
- QOL$_{(CBY)}$ = QOL$_{(CBN)}$ = QOL$_{(NHY)}$ = QOL$_{(NHN)}$
- Pro-Inflammatory Activity$_{(CBY)}$ = Pro-Inflammatory Acitivty$_{(CBN)}$ = Pro-Inflammatory Activity$_{(NHY)}$ = Pro-Inflammatory Activity$_{(NHN)}$
- Anti-Inflammatory Activity$_{(CBY)}$ = Anti-Inflammatory Activity$_{(CBN)}$ = Anti-Inflammatory Activity$_{(NHY)}$ = Anti -Inflammatory Activity$_{(NHN)}$
- NF-κβ$_{(CBY)}$ = NF-κβ$_{(CBN)}$ = NF-κβ$_{(NHY)}$ = NF-κβ$_{(NHN)}$

3. LITERATURE SURVEY

This chapter presents an overview of the published literature over the past decade, providing evidence for the interplay between the mind and the body. This also presents the details of the methods used to propose a novel, yoga based psycho-neuro-immunological model for cancer to bridge the gap in the understanding of the causes of cancer and etiology between scientific and vedic texts and validate need based yoga modules for breast cancer.

This deep-rooted interplay between stress and disease has been explored for centuries both in western and eastern cultures. Though traditional eastern systems of medicine have considered mind and body as inherently intertwined for over 50 centuries, it is only in the 20th century that western society stated recognizing that cancer is more commonly observed in depressed (melancholic) individuals rather than happy (sanguine) individuals.(Dunn, 1996) In the past three decades there has been an explosion in the area of the effects of stress on disease which has led to enough evidence for the role of stress in various disorders like asthma, metabolic syndromes, diabetes, heart disease and cancer. (Adler & Matthews, 1994; S Cohen & Herbert, 1996; DeLongis, Folkman, & Lazarus, 1988; Frasure-Smith, 1991; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; McEwen & Stellar, 1993; Young & Welsh, 2005). The first part of this chapter (3.1) tabulates the available scientific literature on stress and immune functions in general, goes on the tabulate (3.2) the evidence for the role of the effects of yoga on immune system in general and finally (3.4) the published literature on the effects of yoga on immune system in cancer survivors. Nine publications from Swami Vivekananda Yoga Anusandhana Samsthana were all based on integrated approach of yoga therapy for cancer (IAYT) as complimentary during the conventional therapy (surgery, radation and chemotherapies) that evolved after formulating the yoga based etiopatholigcal model and the therapeutic modules which is tabulated at the end of the chapter.

3.1.Stress and immune functions

One of the first published article in the field of PNI that guided research interest in the field was the work of Solomon et al that suggested a link between emotions and immunity.(Solomon & Moos, 1964) Animal studies also confirmed this effect, where mice subjected to chronic stressors reduced their NK cell activity.(Aarstad, Gaudernack, & Seljelid, 1983) Theories that have emerged recently have proposed that stressors induce cognitive and affective responses triggering sympathetic nervous system and endocrine changes (Corticotropin releasing hormone, epinephrine, nor-epinephrine, adrenaline amongst other) which could result in an impaired immune function through the Hypothalamic-Pituitary-Adrenal and Sympatho-Adrenal-Medullary axes.(Chrousos & Gold, 1992; S Cohen & Herbert, 1996; Glaser & Kiecolt-Glaser, 1994; McEwen et al., 1997; Olff, 1999) Studies have shown that acute stressors, may have a stimulating effect on the immune system, while in the case of chronic stress (and in particular in depression), the immune system may be down-regulated. (Olff, 1999; Segerstrom & Miller, 2004) It is presumed that the stress-triggered neuroendocrine hormones lead to immune dysregulation, which also could result in autoimmune disease, by altering or amplifying cytokine production. (Stojanovich & Marisavljevich, 2008) A study in 2001 also showed that chronic depression causes increased IL-6, CD4/CD8 ratio and decreased NK cell cytotoxicity and nonproliferative responses. (Zorrilla et al., 2001) Biondi M noted that physical stress like exercise, relaxation and biofeedback brings about changes in psychological stress related immune changes.(Biondi, 2001)

3.2.Cancer and immunity

Though several environmental/dietary carcinogens have been shown to facilitate carcinogenesis, psychological stress has been shown to enhance the progression of carcinogenesis though not involved in its direct causation.(Sood & Lutgendorf, 2011) The

relationship between psychological profiles and cancer symptomatology and prognosis are well established but the immune implications of these are now being understood. A cross sectional study involving fatigued cancer patients showed increased levels of NF-κB and reduced glucocorticoid expression implying that increased pro-inflammatory transcription factors contribute to persistent fatigue. (Bower, Ganz, Irwin, Arevalo, & Cole, 2011).

3.3.Immune and cellular effects of yoga

The effect of yoga on the immune system has been studied for a decade looking at various aspects of natural and innate immunity, the overview of which is presented in the table below.

	Author, Year	**Design (n, Design, Intervention)**	**Result**	**Conclusion**
1	(Vedamurthachar et al., 2006)	Sudarshan Kriya Yoga (n=30), control (n=30) alcoholics 60 minutes sessions, alternate days for two-weeks Depression (BDI) and morning plasma cortisol, ACTH and prolactin measured	SKY group reduced depression more than control. SKY group reduced plasma cortisol & ACTH more than control. Depression correlated with cortisol in SKY group.	Reduction in stress-hormone levels (cortisol and ACTH)
2	(Solberg, Halvorsen, Sundgot-Borgen, Ingjer, & Holen, 1995)	meditating (n-6), non-meditating (n=6) male runners 6 months intervention CD8+, CD2+ measured after VO2max	CD8+ T cells increased less in the meditation group & CD2+ cells doubled after VO2max	Meditation reduce immuno-suppressive influence of physical stress
3	(Jiang, Li, & Zhang, 2009)	Yoga [3 times weekly] (n=30), Yoga [once weekly] (n=30, control (n=30) female college students 8 week intervention lgG level measured	Yoga increases IgG levels More Prominent in 3 times/week group	Yoga influence the immunity (IgG levels)
4	(Gopal, Mondal, Gandhi, Arora, & Bhattacharjee, 2011)	Yoga (n=30), control (n=30) 1st –year medical students 12 weeks Heart rate, respiratory rate, blood pressure, Stress, anxiety, Serum	Physiological measures increased in control but did not in yoga group. Psychological stress was very high in control but moderately high in yoga group	Yoga resists autonomic changes and impairment of cellular immunity seen during exam

		cortisol, IL-4, IFN-γ measured	serum cortisol increased & IFN-γ decreased less in yoga group than in the control Both groups increased IL-4	stress
5	(Kiecolt-Glaser et al., 1986)	Relaxation (n=17), control (n=17) 1 month percentage helper/inducer T- lymphocytes, helper/inducer-suppressor/cytotoxic-cell ratio & NK-cell activity measured	Both groups reduced percentage helper/inducer T- lymphocytes, helper/inducer-suppressor/cytotoxic-cell ratio & NK-cell activity Frequency of relaxation was significant predictor of % of helper/inducer cells Increased self-rated distress	Relaxation influences psychosocial modulation of cellular immunity during exam stress
6	(Kariya, Yook, Yang, Lee, & No, 2010)	Yoga (n=255) 16 weeks Symptoms checklist, physical self-perception, serum immunoglobulin measured	Somatization, personal relationship, hostility decreased Compulsion, anxiety, depression, fear, psychosis decreased Serum IgM decreased	Yoga improves social health & promotes immune (IgM) changes
7	(Kumar & Pandya, 2012)	Yoga (n=80), Control (n=30) PG students 30 min/day for 6months ESR measured	ESR was lower in yoga group for both males and females.	Yoga nidra helps to reduce non-specific inflammation
8	(Yadav, Magan, Mehta, Sharma, & Mahapatra, 2012)	Yoga (n=86) patients with Chronic inflammatory disease 10 days Plasma cortisol, β-endorphins, IL-6, TNF-α measured	Plasma cortisol reduced, β-endorphins increased and inflammatory cytokines (IL-6, TNF-α) reduced	Yoga reduces stress and inflammation in chronic diseases

Studies over the past decade have indicated that yoga practices have brought about lowering of sympathetic and inflammatory activity in different samples. (IL-6, TNF, IFN-γ, Serum IgM levels, % helper/inducer T-lymphocytes, NK-cell activity, and CD8+ T cells, Eosinphil Sedimentation Rate, serum cortisol, plasma cortisol & ACTH) and increased anti-inflammatory activity (IL-4). These studies have been conducted systematically (many of which are randomized control trials) and hence provide a strong evidence for the immune effects of yoga.

3.4. Yoga and Cancer Survivors

There has been a substantial increase in the evidence of the effects of yoga for cancer during the treatment phase over the past decade, but little has been done to evaluate the effects on cancer survivors. Below is an overview of the published literature available for yoga and its effects on cancer survivors.

	Author, Year	**Design (n, Design, Intervention)**	**Result**	**Conclusion**
1	(Bower et al., 2012)	Yoga (n=16), Health Education (n=15) fatigued CABS 12 weeks RCT Fatigue, vigor, depressive symptoms, sleep, perceived stress, physical performance measured	Fatigue declined in yoga group Vigor increased in yoga group Depressive symptoms and stress decreased in both groups	Iyengar yoga helps to reduce fatigue and improve vigor
2	(Mustian et al., 2010)	Yoga (n=205), Std Care (n=205) CABS Phase II RCT 75min/session, twice/week for 4 weeks Sleep Quality, Fatigue, Quality of Life, sleep medication measured	Sleep Quality, Fatigue, QoL improved in yoga group Sleep medication use reduced in yoga group but increased in controls.	Yoga reduces impaired sleep, fatigue and sleep medication.
3	(Littman et al., 2012)	Yoga (n=32), WLC (n=31), RCT 5 sessions/week for 6 months QoL, Fatigue, weight, WHR measured	QoL, fatigue improved trend in yoga group compared to control	Yoga may help WHR and QoL
4	(Van Puymbroeck, Burk, Shinew, Kuhlenschmidt, & Schmid, 2013)	Yoga (n=18) CABS after yoga 8 weeks of yoga One-group pre-post Semi structured interview for interpretative phenomenological analysis of subjects' experience	physical, mental and social health and healing benefits after yoga	Yoga is important tool in healing process
5	(Ojha, 2012)	Yoga (n=63), Control (n=31) CABS Case control study 5 days/week for 8weeks Depression,	Depressive symptoms Decreased in yoga group QoL improved for in yoga group for ages <50	Yoga helps overcome depression and increases QoL
6	(Levine & Balk, 2012)	Yoga (n=25) CABS One group pre-post	Physical, emotional, functional, breast	Yoga feasible and clinically useful for

		6 weeks of yoga 5 QOL categories measured	cancer specific well-being, Trial Outcome Index, FACT-G, and FACT-B showed improvement Emotional and functional Wellbeing better for those below average Physical Wellbeing better for those above average	CABS with low QoL

The above studies indicate that yoga has several psychological, psychosocial and physical benefits for cancer survivors. The yoga intervention ranging from 4 to 12 weeks have been implemented in controlled studies to observe the outcomes. In the study by Bower et al. health education has been used as a control intervention to compare the effects of Iyengar yoga that primarily relies on stretches. Stretching and relaxation has been shown to decrease fatigue,(Fulcher & White, 1997) and reduce depressive symptoms in cancer subjects and hence this could have been used as an active control intervention instead. Mustian et al. in their randomized control study on CAB survivors documented reduction in impaired sleep, fatigue and sleep medication in the yoga group that provided a standardized 'UR Yoga for Cancer Survivors'. But, not all subjects of the study had sleep dysregulation at baseline, more over population was heterogeneous with respect to age and treatment status. The results would have been more reliable if they had used a standard sleep questionnaire instead of a check list of the subjective symptoms of disturbance in sleep. The secondary analysis presented in the study stating reduction in sleep medication might be questionable as all subjects in the study did not use sleep medication to start with or had impaired sleep. The study by Littman et al. is methodologically stronger with a longer follow up (6 months) that has shown, non-significant trends of improvement in QoL and reduction in WHR with viniyoga. Participants in this study completed only 45% of the classes during this intervention period that could have had an impact on the results. Van Puymbroeck et al have reported a subjective narrative of the observations and

hence is hard to make inferences from the qualitative data generated by a small representative sample of breast cancer patients. The report of Ojha et al is a case study and hence is a narrative of individual unique cases where yoga has been shown to influence cancer survival. Levine et al. has shown an improvement in QoL domains amongst breast cancer patients who have low QoL. However this study lacks controls and has a low sample size of 25 patients. Though most of the above studies reported have methodological problems, they are all equivocal in suggesting benefit finding with Yoga intervention. Most of the above studies have shown subjective improvements and improvements in quality of life and have not evaluated any biological markers of inflammation and immune response

3.5. Yoga, cancer and immune functions

	Author, Year	**Design (n, Design, Intervention)**	**Result**	**Conclusion**
1	(Banerjee et al., 2007)	RCT, Integrated Yoga (n=34) control n=34) CAB undergoing radiotherapy Anxiety & Depression (HADS), Stress (PSS), DNA damage measured	Decreased anxiety, depression & stress in yoga group Radiation-induced DNA damage increased less in yoga group.	yoga modulates stress and susceptibility to DNA damage
2	(Ram, Raghuram, Banerjee, Vadiraja, & Rao, 2013)	Cross sectional, Breast cancer patients(n=9) Yoga Practitioners (n-9)	Qualitative DNA Damage, Percentage Apoptosis	Yoga practitioners need less apoptosis due to less DNA damage
3	(Rao et al., 2008a)	RCT, Yoga (n=33), supportive therapy +exercise rehabilitation (n=36) CAB 60 min/per for 4 weeks anxiety, depression, treatment- distress, QoL, T lymphocyte subsets, immunoglobulins measured	state and trait anxiety, depression, symptom severity, distress decreased QoL improved lesser decrease in CD 56% and lower serum IgA levels	Yoga reduces post-operative distress, prevents immune suppression.
4	(Banasik et al., 2011)	RCT, Yoga (n=9) , WLC (n=9) stage II-IV CABS 90minutes/2days/weeks for 8 weeks cortisol, emotional wellbeing and fatigue measured	lower 5am cortisol and fatigue, better emotional wellbeing in yoga group	yoga is low risk way to improve psychosocial health and regulate cortisol levels
5	(Vadiraja, Rao, Raghuram, et al., 2009)	RCT, Yoga (n = 44) supportive therapy (n = 44) CAB	Anxiety, depression, stress decrease in yoga group 6 a.m. salivary cortisol,	Yoga manages distress Modulates stress

		6 weeks Diurnal salivary cortisol, anxiety, depression, stress measured	pooled cortisol decreased in yoga group Morning cortisol, anxiety, depression positively correlated.	hormones

All these studies have displayed the effect of yoga in improving the immune functions amongst breast cancer survivors during the treatment phase. Systematic studies exploring the immune effects of yoga have demonstrated cortisol rhythmicity restoration, lower serum IgA levels, lesser decrease in CD56%, and better resilience to radiation induced DNA damage, thereby providing the evidence for including yoga as an add-on to clinical management of breast cancer.

The above literature are all randomized controlled studies that have been conducted systematically and therefore provide strong evidence that yoga is beneficial to cancer patients during the treatment phase. However, there is a need to evaluate the effects (immune and psychological) that yoga could have during the phase of cancer survival. The reduced DNA damage demonstrated by Banerjee et al. could have been confounded by inherent changes in cellular susceptibility to radiation, further modulated by a heterogeneity of prior treatment (Surgery, medications, CT). The study by Ram et al. is a cross sectional study comparing women with breast cancer and healthy advanced yoga practitioner of both genders. This might be a source of numerous confounding factors that could reduce the validity of results obtained. Also, the sample size of this cross sectional study was too small to make much meaningful inferences. Rao et al. in 2008 showed that yoga prevents immune suppression as observed by lesser decrease in CD 56% and lower serum IgA levels. But they measured CD56 by Immuno-histo-chemistry as opposed to Flow Cytometry which is a more accurate and reliable tool. Also, this study also looked at IgA levels in the serum instead of secretory IgA levels which is a better marker for tumor load. In the same study, although the beneficial effects of yoga on stress and other psychological measures were documented, the subjects were not included based on their high

stress levels or abnormal psychological profiles. In the study by Banasik et al., the sample size was small and the intervention provided was only for 180 minutes for the entire week (2, ninety minute sessions per week). This study also has shown a change only in 5am cortisol levels which might not be directly indicative of the HPA axis dysregulation which is dependent on other factors like the diurnal cortisol slope and the pooled cortisol levels. These factors make it difficult to provide robust evidence for the effects of yoga on cancer related outcomes. Similar to this, the study by Vadiraj et al., also has not been able to detect a significant effect on pooled cortisol levels and also the diagonal cortisol slope which would have provided more information on the HPA axis dysregulation. Many of the above mentioned studies, had low sample sizes, and provided short durations of yoga practices that could have limited the detectability of the true effects. Even though all these were conducted in breast cancer patients, heterogeneity of cancer histopathology, stage/grade, genotypes and prior cancer treatment regimens could have confounded the outcomes. Moreover the results show a relative improvement in immune measures in cancer patients following yoga, but don't answer the question if these results were indeed different from the normal population. Hence we planned an explorative controlled systematic comparison between several populations (cancer and healthy volunteers) with or without exposure to yoga in order to generate hypotheses for the possible mechanisms and applications that yoga might have in cancer patients and healthy individuals.

3.6 Proposition of a novel, yoga based psycho-neuro-immunological model for cancer etiology and validation of need based yoga modules for breast cancer.

The modern medicine until recently understood the causes of cancer to be limited to the physical realm and mainly organic, only now acknowledging the role of the psyche in cancer manifestation.(Dalton, Boesen, Ross, Schapiro, & Johansen, 2002) Yoga on the other hand describes in great detail the aspects of how, wrong knowledge results in misplaced emotions,

further causing wrong systemic processes ultimately resulting in psychosomatic ailments. Yoga texts however fall short in the knowhow of the physical aspects of cancer, like the immunology, the genetics and the metastasis of the tumor tissue to name a few. Though we don't know for sure that psychologic stress can cause cancer, we now know that it can hasten its progression. This study explores the philosophical concepts of yoga in cancer causation similar to the biopsychosocial model of disease propounded by western psychologists and draws similarities in both these approaches. Thus is it not the intention to either exclude or isolate the causes from each other but to form a comprehensive understanding based on both sciences (science and yoga). Thus, the aim of the present work was to point out that it is important to take into account the interplay of physical factors, lifestyle, and psyche in terms of cancer etiopathogenesis.

This part of the exploratory study attempts to compile concepts from both these systems of science was undertaken in order to eventually merge concepts and bring about a holistic pathway for the etiology of cancer. The next phase was to explore the needs of the cancer patients at different phases of treatment and survival which could be addressed by complementing conventional medicine with yoga. This was done with the help of experts in the field of cancer and yoga so as to preserve the validity of the concepts being proposed and the yoga practices being prescribed.

3.6.Background

Life style and psychosocial stresses were recognized to be contributory to sickness, by a few researchers, as early as nineteen seventies(Hirayama, 1979), but it is only recently that the modern biomedicine has been able to accumulate enough data to propose a psycho-neuro-immunological model for cancer (N. Smith et al., 2009). During recent decades, numerous clinical and basic laboratory studies have provided evidence in support of the concept that bio-psycho-social factors can influence malignant disease in animal models as well as in humans.

This has helped to create an awareness of the role of mind body relationship in the etiology (Godbout & Glaser, 2006) and progression of cancer. Anderson et al proposed a model in 1994 that pointed to a relationship between mind and cancer. By 2006 a model that portrayed a linear progressive causal relationship between psychological stress, immune disturbance and cancer was created. Further, in 2010 Ao, P, et al (Ao, Galas, Hood, Yin, & Zhu, 2010) proposed a non-linear mathematical model of the interaction of the caspase-3 molecules in the etiology of cancer based on inputs from several genetic research laboratories. Based on these and other studies, (N. Smith et al., 2009) it is now understood that the mind plays a crucial role in not just the etiology of the disease but also the treatment outcome prognosis and recurrence.

Ancient Indian texts dating back to about 5000 years (Rig Veda, Patanjali Yoga Sutra and ayurveda) provide a highly evolved conceptual basis for the aetiopathogenesis of disease and its management.

The 'Integrated Yoga Therapy (IYT) for Cancer', used as complimentary to conventional medicine in all studies conducted by Swami Vivekānanda Yoga Anusandana Samsthana (S-VYASA) consisted of practices that were based on this model. The objective of this part of the research was to develop a psycho-neuro-immmunological pathway for the etiopathogenesis of cancer and also to present the logical steps used to compile IAYT based modules for cancer, using both ancient yoga concepts and modern scientific knowledge.

3.7.Methodology of literary research

This was a retrospective exploratory study which was qualitative in nature with the objective of understanding of the etiology of cancer and developing Integrated Yoga Therapy (IAYT) modules for cancer. This was achieved through a review of relevant literature including empirical evidence, review articles and scriptural references that have contributed significantly to

the field of mind body medicine and evolve the schematic diagram based on the concepts described during the discussions. This retrospective scientific narrative has been classified under four phases [Table 5]

Table 5 – Stages in the development of yogic model for the etiopathogenesis of cancer

1. Content Generation
   - Review of traditional texts
   - Review of scientific literature on cancer pathology
   - Interactions and discussions with experienced yoga gurus
2. Model Development
   - Focused Group Discussions and semi structured interviews
   - 8 experts from yoga or oncology field
   - preparation of yogic model for cancer management
3. Yoga Module Preparation
   - List of practices based on etiopathology and need
   - Validation of yoga modules
4. Field Testing
   - Pilot studies on patients with cancer in stages 2-4 in sites such as breast, cervix, stomach, colon cancers included
   - Randomized controlled studies on patients with breast cancer(stage 2-3)

3.7.1. Content Generation

3.7.1.1. Review of traditional Indian literature

Research scholars reviewed traditional yoga and Ayurveda texts and found references to disease etiology in general and mentions of cancer specific pathology and progression. (Easwaran, 1973; Swahananda, 2010; Tapasyananda, 2011; Venkatesananda & Chappel, 1984) A comprehensive list of all attributes and treatment modalities were compiled for further discussion.

Senior yoga teachers and scriptural experts were consulted to elicit interpretations of the yoga texts in order to disambiguate various concepts suggested in the scriptures that further led to development of the model and the modules.

3.7.1.2. Review of modern scientific literature

Scientific literature including empirical evidence and review articles were also scrutinized. The search was limited to peer reviewed articles from the past decade in order to preserve relevance. Hypothesized cancer etiology models(Ao et al., 2010) were noted apart from accumulating information regarding latest clinical evidence that had been generated in the field of mind body medicine as a disease management strategy.(Helyer et al., 2006; Kiecolt-Glaser et al., 2010; Ledesma & Kumano, 2009; Moadel et al., 2007; Speck, Courneya, Mâsse, Duval, & Schmitz, 2010a)

3.7.2. Model Development

A master list of all the theories in the literature, proposed pathways for the etiology of breast cancer and practices that have been suggested were compiled and presented to a group of experts (brief bio-data of expert provided in Appendix V) for deliberations.

These focus group discussions (FGD) were exploratory and qualitative in nature, and this flexibility facilitated the process of research to become a more humanized method than a restricted questionnaire method. Detailed notes were maintained during the discussions so that they could be referred to at a later time. Despite its time consuming characteristic, these exploratory discussions helped the researchers to interact as contributors to the model. The probing questions and in-depth discussions that were part of the FGD facilitated the development of the model by a process of sharing each other's' experiences and know-how. This also aided in the development of the modules that evolved.

For each item on the list, the experts were also asked to mark 'useful', or 'not relevant' for understanding cancer etiology. Each questions also provided the opportunity for the experts to provide suggestions and corrections. The group was also asked to suggest references regarding

cancer and its etiopathology that were not part of the checklist. These discussions and suggestions thereof were noted and were added to the pre-existing list.

All the suggestions offered by the members of the FGD were deemed equally important and taken into consideration for designing the model. This was done by the research scholars under the guidance of the yoga experts.

This exercise provided an opportunity to find common patterns and to fill the gaps in the understanding of the etiopathology of breast cancer. The major theories that made an attempt to explain the etiology of cancer, and suggest suitable remedies for the cancer were studied. The gamut of therapeutic modalities described in ayurveda and yoga including yoga postures, breathing practices (pranayama), mind modulation techniques (meditation), and lifestyle advice was considered as relevant to the objectives of the focus group discussion (FGD).

3.7.2.1. Participants of Focused group

The Participants of the focus group discussions included eight members. The constitution of the members of the FGD is given in the table below.

Table 6 Members of the Focus Group

Member	**Description**	**Numbers**
Yoga Experts	Yoga scholar with in-depth knowledge and extensive experience of yoga techniques	3
Post Graduate Physician	Physician with strong medical background (also with yoga experience)	1
Oncologist	Expertise in conventional cancer treatment, specific morbidities and patient needs	2
Research Scholar	Doctoral scholars in the field of the yoga	2
A brief bio data of the members has been provided in appendix V	**Total**	**8**

The objective for diversifying the constitution of the FGD was aimed at eliciting different viewpoints of cancer etiology, treatment and patient needs.

3.7.3. Module Preparation

A second part of the check list consisted of questions that assessed the psychological and physical needs of the cancer patients and suggestions for the yoga related practices at different stages of Conventional therapies (surgery, chemotherapy or radiation). This was administered as part of the above FGDs. Apart from the members of the FGD, this checklist was also provided to cancer patients and caregivers of cancer patients to elicit their opinion. Inputs regarding feasibility, need, relevance, of several yoga techniques were elicited, which helped to construct a need based yoga module to be incorporated as adjunct to conventional treatment.

Once the modules were designed using both, the model for the etiopathology and the needs of the cancer patients, they were presented to the group of experts for the third time in order to take it forward to the field testing phase.

3.7.4. Field Testing

3.7.4.1. Pilot studies

The modules that evolved were initially administered to patients with different cancers as part of the pilot study. These studies were conducted from year 2000 to 2005 on several cancer patients. (Breast, stomach, esophagus, uterine cervix, colon, brain etc.) These subjects were recruited from the residential health home (Arogyadhama) of Swami Vivekananda Yoga Anusandhana Samsthana. These subjects were admitted for two to three weeks to undergo integrated yoga therapy program as part of the pilot study. These modules (details of which are given in appendix V were administered to them for the period of their stay by trained experts (two of the senior faculty who were involved in the FGD). During the intervention, daily follow-up and clinical assessments were taken, apart from feedback from these patients, which were recorded immediately after each session. These assessments included blood pressure, heart rate, breath rate, medication scores and feedback regarding the difficulty level, feasibility, experience

of the session. The clinical data obtained and the responses collected were re-circulated amongst the same group experts to finalize the modules based on the feedback.

3.7.4.2. Randomized control trials

The final yoga modules including inputs from the pilot study were tested through randomized control trials. The two randomized controlled studies that followed used the IAYT module for cancer as an add-on during the entire course of conventional management of breast cancer (stages 2 and 3). These studies on breast cancer conducted from 2005 to 2010 formed the data for the eight publications on the complimentary role of IYT in breast cancer.(Banerjee et al., 2007; Rao et al., 2006, 2008a, 2008b, 2009; Vadiraja et al., 2010; Vadiraja, Rao, Nagendra, et al., 2009; Vadiraja, Rao, Raghuram, et al., 2009)

3.8. Outcome of literary research

Traditional Yoga and Ayurveda texts were reviewed and references found for disease etiology in general and mentions of cancer and cancer specific pathology and progression. A comprehensive list of all attributes and treatment modalities were compiled for further discussion. Efforts were also made to compile the needs of the cancer patients during different treatment phases and suggest alternative interventions that could influence cancer progression negatively and treatment, prognosis and quality of life positively.

The concepts that emerged as a result of these discussions are presented in detail below. Also, eight yoga modules that were generated keeping in mind the needs of the cancer patient, expected cancer treatment related side effects, the patients' energy levels and psychological states are described.

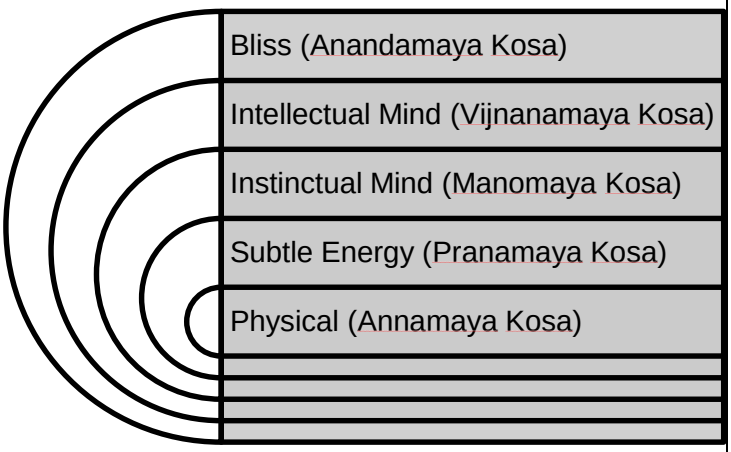
3.8.1. Etiopathology of cancer according to yoga scriptures

To be able to understand and appreciate the yoga scriptures and its interpretation of disease etiology it is imperative to first understand some on the basic concepts put forth by the literature. These concepts essentially presented themselves with the broader objective of understanding the true nature of the self and hence they all talk about bliss (ananda), bramhan and silence as the goal to remain stress and disease free. Below is an effort to understand some of the basic concepts of yoga literature in order to better appreciate the model that would be proposed later.

3.8.1.1. Panchakośa Viveka (the five components of human being)

According to one of the major Upanishads called the taittiriya Upanishad (Gambhirananda, 2010), the human system consists of five components [panca kośa] comprised of the physical body (Annamaya Kośa), subtle snergy or Prāṇa (Prāṇamaya kośa), instinctual mind (Manomaya kośa), intellectual or discriminative mind (Vignānamaya kośa) and bliss-full silent state (Ānandamaya kośa) [Figure 5].

Figure 5: The five layers of the human system



अन्नं ब्रह्मेतिव्यजनात्। अन्नाध्येव खल्विमानि भूतानि जायन्ते। अन्नेन जातानि जीवन्ति। अन्नं प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।२॥
annaṁ brahmetivyajanāt। annādhyeva khalvimāni bhūtāni jāyante। annena jātāni jīvanti। annaṁ prayantyabhisamviṣantīti।। tai upa। 3।2।।
I have come to realize that the physical is the ultimate truth. It is the physical that is responsible for all the elements of the universe to be born; The world is sustained because of the phsycial and finally it is into the physical that the entire world dissolves and is destroyed thereby.

प्राणो ब्रह्मेतिव्यजनात्। प्राणाध्येव खल्विमानि भूतानि जायन्ते। प्राणेन जातानि जीवन्ति। प्राणं प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।३॥
prāṇo brahmetivyajanāt। prāṇādhyeva khalvimāni bhūtāni jāyante। prāṇena jātāni jīvanti। prāṇaṁ prayantyabhisamviṣantīti।। tai upa। 3।3।।
I have realized that the vital energy is the truth. The vital energy is the cause for the birth of the all the elements in the universe; the vital energy is what sustains the universe and the same vital energy is responsible for the dissolution of the Universe.
मनो ब्रह्मेतिव्यजनात्। मनसोह्येव खल्विमानि भूतानि जायन्ते। मनसा जातानि जीवन्ति। मनः प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।४॥
mano brahmetivyajanāt। manasohyeva khalvimāni bhūtāni jāyante। manasā jātāni jīvanti। manaḥ prayantyabhisamviṣantīti।। tai upa। 3।4।।
I have realized that the mind is the truth. The mind is the reason for the origin of the universe; the mind is what sustains the universe and the same mind is responsible for the dissolution of the Universe.
विज्ञानं ब्रह्मेतिव्यजनात्। विज्ञानाध्येव खल्विमानि भूतानि जायन्ते। विज्ञनेन जातानि जीवन्ति। विज्ञानं प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।५॥
vijñānaṁ brahmetivyajanāt। vijñānādhyeva khalvimāni bhūtāni jāyante। vijñanena jātāni jīvanti। vijñānaṁ prayantyabhisamviṣantīti।। tai upa। 3।5।।
I have come to realize that the intellect is the supreme truth. It is the intellect that is capable of creating the elements of the universe; The intellect keep the universe sustained and the same intellect can destroy the entire universe.

आनन्दो ब्रह्मेतिव्यजनात्। आनन्दाध्येव खल्विमानि भूतानि जायन्ते। आनन्देन जातानि जीवन्ति। आनन्दं प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।६॥
ānando brahmetivyajanāt। ānandādhyeva khalvimāni bhūtāni jāyante। ānandena jātāni jīvanti। ānandaṁ prayantyabhisamviṣantīti।। tai upa। 3।6।।
I have come to realize that the happiness is supreme. It is the bliss that is responsible for the birth, sustenance and destruction of the universe.

Shvetashvatara Upanishad (Easwaran, 1973) describes that a human being is in perfect harmony with nature and healthy when he is established in Ānandamaya kośa which is the unchanging state of being, the self (called Brahman) and the causal state of being from where all other (ever changing) Kośas emerge. (Gambhirananda, 2010)

पृथ्व्यप्तेजोऽनिलखे समुत्थिते पञ्चात्मके योगागुरो प्रवृत्ते
न तस्य रोगो न जरा न मृत्युः प्राप्तस्य योगाग्निमयं शरीरम्॥ श्वेत उप ।२ ।१२ ॥
लघुत्वमारोग्यमलोलुपत्वं वर्णप्रस्सदं स्वरसौष्ठवं च
गन्धः शुभो मूत्रपुरीषमल्पं योगप्रवृत्तिं प्रथमां वदन्ति ॥श्वेत उप ।३ ।१३ ॥
यथैव बिम्बं मृदयोपलिप्तं तेजोमयं भ्राजते तत्सुधान्तम्
तद्वात्मतत्त्वं प्रसमीक्ष्य देहि एकः कृतार्थो भवते वीतशोकः ॥श्वेत उप ॥२ ।१४ ॥
यदात्मतत्त्वेन तु ब्रह्मतत्त्वं दीपोपमेनेह युक्तः प्रपश्येत्
अजं ध्रुवं सर्वतत्त्वैर्विशुद्धं ज्ञात्वा देवं मुच्यते सर्वपाशौ ॥श्वेत उप ।२ ।१५ ॥
pṛthvyaptejo'nilakhe samutthite pañcātmake yogāguro pravṛtte na tasya rogo na jarā na mṛtyuḥ prāptasya yogāgnimayaṁ śarīram ।।śveta upa।2।12।। laghutvamārogyamalolupatvaṁ varṇaprassadaṁ svarasauṣṭhavaṁ ca gandhaḥ śubho mūtrapurīṣamalpaṁ yogapravṛttiṁ prathamāṁ vadanti ।।śveta upa।3।13।। yathaiva bimbaṁ mṛdayopaliptaṁ tejomayaṁ bhrājate tatsudhāntam tadvātmatattvaṁ prasamīkṣya dehi ekaḥ kṛtārtho bhavate vītaśokaḥ ।।śveta upa।।2।14।। yadātmatattvena tu brahmatattvaṁ dīpopameneha yuktaḥ prapaśyet ajaṁ dhruvaṁ sarvatattvairviśuddhaṁ jñātvā devaṁ mucyate sarvapāśau ।।śveta upa।2।15।।
When (in the Yogi's body) composed of earth, water, light, air and ether, the five-fold qualities which mark concentration are manifest, then there is no disease, or age, or pain for him, who has obtained the body burning with the fire of concentration ।।śveta upa।2।12।। When the body is light and without disease, the mind without desire, when the colour is shining, sweet the voice and pleasant the smell, when the excrements are few, they say, the first degree of concentration is gained ।।śveta upa।2।13।। As a piece (of gold or silver) covered with earth, when cleansed, shines like light, so the embodied soul, when beholding the true nature of the soul (of itself) becomes one, obtaines its true end, and every pain ceases ।।śveta upa।।2।14।। When absorbed in this concentration (the Yogi) sees by the true nature of his own self, which manifests like a light, the true nature Bramha, which is not born, eternal and free from all the effects of nature, he gets released from all bonds ।।śveta upa।2।15।।

आनन्दाध्येव खल्विमानि भूतानि जायन्ते ॥ तै उप ।३ ।६ ॥
ānandādhyeva khalvimāni bhūtāni jāyante ।। tai upa। 3।6।।
From bliss is born entire universe.

Analogies to explain that Ānanda or perfect health is the unchanging core of one's personality are found in abundance in the scriptures. Some describe it as the string in a necklace of beads (Chapter7, Verse7)(Tapasyananda, 2011) which indicates that although the beads might vary in shape size color etc., the underlying common factor is the string that hold them together; gold in all jewels (Chapter6, Section1, Verse6)(Swahananda, 2010) or the clay in different shaped pots (Chapter6, Section1, Verse3)(Swahananda, 2010) are other analogies given that describe it as the essential material that makes up any object irrespective of the shape of that object.

मत्तः परतरं नान्यत् किञ्चिदस्ति धनंजय । मयि सर्वमिदं प्रोतं सूत्रे मणिगणा इव ॥ भ गी । ७ ।७ ॥
mattaḥ parataraṁ nānyat kiñcidasti dhanañjaya। mayi sarvamidaṁ protaṁ sūtre maṇigaṇā iva।। bha gī । 7।7।।
Oh Arjuna, there is nothing superior to consciousness (bliss). Very similar to the pearls that have a common thread, everything in existence is connected to consciousness..

यथा सौम्य एकेन नख-निकृन्तनेन सर्वम् काष्णायसं विज्नातम् स्यात् वाचारम्भणं विकारो नामधेयं काष्णायसम् इत्येव सत्यम् एवम् सौम्य स आदेशो भवतीति ।छा उप । ६ ।१ ।६ ॥
yathā saumya ekena nakha-nikṛntanena sarvam kārṣṇayasaṁ vijnātam syāt vācārambhaṇaṁ vikāro nāmadheyaṁ kārṣṇāyasam ityeva satyam evam saumya sa ādeśo bhavatīti।chā upa। 6।1।6।।
Just as a scissors that is made of iron but is called a scissors. For the one who knows the truth, it is the iron only that has taken up the form of a scissors. Similarly, the knowledge of bliss is the truth which can take up different form in the world and understanding bliss in its causal form is right knowledge.

येनाश्रुतम् श्रुतम् भवति अमतम् मतम् अविज्नातम् विज्नातम् इति कथं नु भगवः स आदेशो भवतीति ॥छा उप । ६ ।१ ।३ ॥
yenāśrutam śrutam bhavati amatam matam avijnātam vijnātam iti kathaṁ nu bhagavaḥ sa ādeśo bhavatīti।।chā upa। 6।1।3।।
Sir, please teach me the right knowledge which enables one to hear what cannot be heard, think what is beyond thought and know that which is unknowable.

This state of blissfulness is experienced as a state wherein one reaches a state of inner quietude with awareness and the knowledge that 'I am made of the same universal consciousness and bliss that forms the base material of the entire creation'.(Verse2)(Nikhilananda, 2006)

सर्वं हि एतद् ब्रह्म । अयमात्मा ब्रह्म । सोऽयम् आत्मा चतुष्पात् ॥ मा उप ।२ ॥
sarvaṁ hi etad brahma। ayamātmā brahma। so'yam ātmā catuṣpāt।। mā upa।2।।
All is verily the universal consciousness, the self, which is also part of the universal consciousness is comprised of four quarters.

As an analogy, Sri Ramakrishna Paramahamsa's anecdotes presents an incident when a salt doll dives into the ocean to understand the depth of the ocean but gets the joy of becoming the ocean itself by losing its individual entity (Nikhilananda, 2000).

3.8.1.2. The process of Prasava (Downward Causation)

Waves of thoughts begin in this ocean of blissful quietude and become grosser and grosser to form the other four components of the body. (Chapter3 Verse3-6)(Gambhirananda, 2010)

प्राणो ब्रह्मेतिव्यजनात्। प्राणाध्येव खल्विमानि भूतानि जायन्ते। प्राणेन जातानि जीवन्ति। प्राणं प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।३॥
prāṇo brahmetivyajanāt। prāṇādhyeva khalvimāni bhūtāni jāyante। prāṇena jātāni jīvanti। prāṇaṁ prayantyabhisamviṣantīti।। tai upa। 3।3।।
I have realized that the vital energy is the truth. The vital energy is the cause for the birth of the all the elements in the universe; the vital energy is what sustains the universe and the same vital energy is responsible for the dissolution of the Universe.

मनो ब्रह्मेतिव्यजनात्। मनसोह्येव खल्विमानि भूतानि जायन्ते। मनसा जातानि जीवन्ति। मनः प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।४॥
mano brahmetivyajanāt। manasohyeva khalvimāni bhūtāni jāyante। manasā jātāni jīvanti। manaḥ prayantyabhisamviṣantīti।। tai upa। 3।4।।
I have realized that the mind is the truth. The mind is the reason for the origin of the universe; the mind is what sustains the universe and the same mind is responsible for the dissolution of the Universe.

विज्ञानं ब्रह्मेतिव्यजनात्। विज्ञानाध्येव खल्विमानि भूतानि जायन्ते। विज्ञनेन जातानि जीवन्ति। विज्ञानं प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।५॥
vijñānaṁ brahmetivyajanāt। vijñānādhyeva khalvimāni bhūtāni jāyante। vijñanena jātāni jīvanti। vijñānaṁ prayantyabhisamviṣantīti।। tai upa। 3।5।।
I have come to realize that the intellect is the supreme truth. It is the intellect that is capable of creating the elements of the universe; The intellect keep the universe sustained and the same intellect can destroy the entire universe.

आनन्दो ब्रह्मेतिव्यजनात्। आनन्दाध्येव खल्विमानि भूतानि जायन्ते। आनन्देन जातानि जीवन्ति। आनन्दं प्रयंत्यभिसम्विषन्तीति॥ तै उप।३।६॥
ānando brahmetivyajanāt। ānandādhyeva khalvimāni bhūtāni jāyante। ānandena jātāni jīvanti। ānandaṁ prayantyabhisamviṣantīti।। tai upa। 3।6।।
I have come to realize that the happiness is supreme. It is the bliss that is responsible for the birth, sustenance and destruction of the universe.

The first wave (spandana) that appears is the 'I' (self-awareness) followed by several varieties of waves that form a template of right knowledge the gamut of which is called the Vignānamaya kośa. In this state man is in perfect health as he is in tune with nature (Gambhirananda, 2010) and leads a healthy life style with complete mastery over his mind (Chapter1 Verse3)(Taimni, 1999)

तदा द्रष्टुः स्वरूपे अवस्थानम्॥प यो सू।१।३॥
tadā draṣṭuḥ svarūpe avasthānam ।।pa yo sū।1।3।।
Then the self gets established in its natural state.

As these waves of thoughts gather speed and intensify due to repetition (momentum, higher amplitude and repetitions), [Chapter5 Verse26)(Tapasyananda, 2011), (Chapter8 Verse88)(Venkatesananda & Chappel, 1984)] it gathers energy to become the Manomaya kośa.

कामक्रोधविमुकानां यतीनां यतचेतसाम्। अभितो ब्रह्मनिर्वाणं वर्तते विदितात्मनाम्॥भ गी।५।२६॥
kāmakrodhavimukānāṁ yatīnāṁ yatacetasām। abhito brahmanirvāṇaṁ vartate viditātmanām ।।bha gī।5।26।।

Those who are aware of the self and who have overcome lust and anger enjoy complete freedom in this life and the next.

This phase is where likes and dislikes begin.(Verse21.1)(Sankaracharya, 1986)

एतेषां पंचत वानां समष्टिसाविकांशान्मनो बुद्ध्यहंकारचित्तन्तःकरणानि सम्भुतानि ॥तत्त्व ।२१ ।१ ॥
eteṣāṁ pañcata vānāṁ samaṣṭisāvikāṁśānmano buddhyahaṅkāracittantaḥkaraṇāni sambhutāni।।tattva।21।1।।
From the total sattvik contents of these five elements, antahkarana is formed, the five components of which are manas, buddhi, ahankara and citta.

As the energy in these thoughts increase it gradually becomes capable of influencing the physiology of the body. This process of becoming gross continues it goes on to become the vital energy (prāṇamaya kośa) which in fluences breathing and other physiological capabilities. Based on the normal functioning of the body, characteristic physical molecules are evolved that define structural fitness and functioning.(Annamaya kośa) (Chapter3 Verse2)(Gambhirananda, 2010).

अन्नं ब्रह्मेतिव्यजनात्। अन्नाध्येव खल्विमानि भूतानि जायन्ते। अन्नेन जातानि जीवन्ति। अन्नं प्रयंत्यभिसम्विषन्तीति॥ तै उप ।३ ।२ ॥
annaṁ brahmetivyajanāt। annādhyeva khalvimāni bhūtāni jāyante। annena jātāni jīvanti। annaṁ prayantyabhisamviṣantīti।। tai upa। 3।2।।
I have come to realize that the physical is the ultimate truth. It is the physical that is responsible for all the elements of the universe to be born; The world is sustained because of the phsycial and finally it is into the physical that the entire world dissolves and is destroyed thereby.

3.8.1.3. Prati prasava (reversal of downward causation)

Yoga practices offer techniques of mastering the gross (Venkatesananda & Chappel, 1984) to reach the subtle layers of one's existence by introspective slowing down of thoughts.

यत्कृपालेशमात्रेण तीर्णोस्मि भवसागरम् श्रीमद्वङ्गधरेन्द्राख्यान्श्रीगुरूंस्तान्सदा भजे ॥यो वा ।१ ।१७ ॥

yatkṛpāleśamātreṇa tīrṇosmi bhavasāgaram śrīmadgaṅgadharendrākhyānśrīgurūṁstānsadā bhaje||yo vā|1|17|| Even the slightest thought immerses a man in sorrow; when devoid of all thoughts he enjoys imperishable bliss ||yo vā|1|17||

By controlling the gross physical body one is able to bring about changes in the physiology as well as the mind. For example when one wants to be attentive, it is preferred to stand or to sit up straight. One the other hand, when the body is required to rest, one lies down to enable relaxation of the mind. The reverse is also true where the subtle controls the gross. If one masters his breathing (prāṇa) he can manipulate the functions of physical body; the subtler mind can manipulate prāṇa and vignāna, in turn can master the mind. (Chapter1 Verse40) (Taimni, 1999)

परमाणुप्रममहत्वान्तोऽस्य वशीकारः ॥प यो सू।१।४० ॥ paramāṇupramamahatvānto'sya vaśīkāraḥ|pa yo sū|1|40||
The mastery of the psyche results in control of the relationship with the smallest atom or to cosmic proportions.

The goal of this is to establish in a state of complete mastery and happiness by remaining in a state of Ānandamaya kośa which in turn influences Vignāna. This is a state of complete contentment and freedom from all distress and disease (Chapter2 Verse12)(Easwaran, 1973).

पृथ्व्यप्तेजोऽनिलखे समुत्थिते पञ्चात्मके योगागुरो प्रवृत्ते न तस्य रोगो न जरा न मृत्युः प्राप्तस्य योगाग्निमयं शरीरम्॥श्वे उप।२।१२॥ pṛthvyaptejo'nilakhe samutthite pañcātmake yogāguro pravṛtte na tasya rogo na jarā na mṛtyuḥ prāptasya yogāgnimayaṁ śarīram||śve upa|2|12||
When (in the Yogi's body) composed of earth, water, light, air and ether, the five-fold qualities which mark concentration are manifest, then there is no disease, or age, or pain for him, who has obtained the body burning with the fire of concentration ||śveta upa|2|12||

By this practice of being established in blissfulness accompanied by right knowledge or awareness is a state where one develops the ability to manipulate the laws of nature within the body and outside the body (Chapter1 Verse4)(Taimni, 1999).

वृत्ति सारूप्यंमितरत्र ॥प यो सू ।१ ।४ ॥
vṛtti sārūpyammitaratra ।pa yo sū ।1 ।4 ।।
At other times, there is conformity with the mento-emotional energy

3.8.1.4. The model for cancer causation

The ability to manipulate the laws of nature, indicates the ability to master the programming of the cell cycle using the mind, which is the most highly evolved and the most powerful entity in the manifest universe. A living human body is a flux of continuous changes that is programmed to live a full lifespan of about a century in perfect health. As man goes through the ups and downs of life (be it exposure to external onslaughts like injury or infection, or emotionally challenging situations or internal changes), it sets off an imbalance. The scriptures are very emphatic while elucidating this imbalance and explain that imbalance occurs due to lack of mastery over mind which is the beginning of any mind-body disease. Sage Vasistha describes the progression of this imbalance that results in cancer (and/or other lifestyle related disorder) in the text Yoga Vasistha (Chapter9 Verse82-117)(Venkatesananda & Chappel, 1984).

राम उवाच ॥

किंविनाशाः किमुत्पादाः शरीरेस्मिन्मुनीश्वर ।

आधयो व्याधयश्चैव यथावत्कथयाशु मे ॥यो वा ।६ ।९ ।८२ ॥

वसिष्ठ उवाच ॥

देहदुःखं विदुर्व्याधिमाध्याख्यं वासनामयम् ।

मौख्र्यमूले हि ते विध्यात्तत्वज्ञानपरिक्षये ॥यो वा ।६ ।९ ।८३ ॥

अतत्त्वज्ञानवशतस्त्विन्द्रियाक्रमणं विना ।

हृदि तानवमुत्सृज्य रागद्वेषेष्वनारतम् ॥यो वा ।६ ।९ ।८४ ॥

इदं प्राप्तमिदं नेति जाड्यात्सुधनमोहदाः । आधयः संप्रवर्तन्ते वर्षासु मिहिका यथा ॥यो वा ।६ ।९ ।८५ ॥

भूशं स्फुरन्तीष्विच्छासु मौख्र्ये च धनतां गते । दुरन्ताभ्यवहारेण दुर्देशाक्रमणेन च ॥यो वा ।६ ।९ ।८६ ॥

दुःकालव्यवहारेण दुःक्रियास्फुरणेन च । दुर्जनासङ्गदिषेण दुर्भावोद्भावनेन च ॥यो वा ।६ ।९ ।८७ ॥

क्षीणत्वाद्वातिपूर्णत्वान्नडीनां रन्ध्रसंततौ । प्राणे विधुरतां याते काये च विकलीकृते ॥यो वा ।६ ।९ ।८८ ॥

द्विविधो ह्याधिरस्तीह सामान्यम् सार एव च । व्यवहारश्च सामान्यः सारो जन्मनि यः स्मृतः ॥यो वा ।६ ।९ ।९२ ॥

प्राप्तेनाभिमतेनैव नश्यन्ति व्यावहारिकाःव्। आधिक्षये चाधिभावाः क्षीयन्ते व्याधयोऽप्यलम्॥यो वा।६।९।९३॥ आत्मज्ञानं विना सारो नाधिर्नाश्यति राघव। यथा रज्ज्ववबोधेन विना सर्पो न नश्यति॥यो वा।६।९।९४॥
rāma uvāca।। kiṁvināśāḥ kimutpādāḥ śarīresminmunīśvara। ādhayo vyādhayaścaiva yathāvatkathayāśu me।।yo vā।6।9।82।। vasiṣṭha uvāca।। dehaduḥkhaṁ vidurvyādhimādhyākhyaṁ vāsanāmayam। maurkhyamūle hi te vidhyāttatvajñānaparikṣaye।।yo vā।6।9।83।। atattvajñānavaśatastvindriyākramaṇaṁ vinā। hṛdi tānavamutsṛjya rāgadveṣeṣvanāratam।।yo vā।6।9।84।। idaṁ prāptamidaṁ neti jāḍyātsudhanamohadāḥ। ādhayaḥ sampravartante varṣāsu mihikā yathā।।yo vā।6।9।85।। bhūśaṁ sphurantīṣvicchāsu maurkhye ca dhanatāṁ gate। durantābhyavahāreeṇa durdeśākramaṇena ca।।yo vā।6।9।86।। duḥkālavyavahāreṇa duḥkriyāsphuraṇeena ca। durjanāsaṅgadiṣeṇa durbhāvodbhāvanena ca।।yo vā।6।9।87।। kṣīṇatvādvātipūrṇatvānnaḍīnāṁ randhrasantatau। prāṇe vidhuratāṁ yāte kāye ca vikalīkṛte।।yo vā।6।9।88।। dvividho hyādhirastīha sāmānyam sāra eva ca। vyavahāraśca sāmānyaḥ sāro janmani yaḥ smṛtaḥ।।yo vā।6।9।92।। prāptenābhimatenaiva naśyanti vyāvahārikāû। ādhikṣaye cādhibhāvāḥ kṣīyante vyādhayo'pyalam।।yo vā।6।9।93।। ātmajñānaṁ vinā sāro nādhirnāśyati rāghava। yathā rajjvavabodhena vinā sarpo na naśyati।।yo vā।6।9।94।।
Rama asked, what are vyadhi (illnesses), what are adhi (psychic disorders) and what are the degenerative conditions of the body? Please enlighten me on these .yo va,6,9,82. The teacher explained that going against what is right causes imbalances. These imbalances amplify themselves resulting in mental illnesses called Ádhis'. At this stage there are no symptoms at the physical level. Prompted by the perpetual growth of desires, these mental diseases concealed in us, begin to manifest themselves as wrong actions such as eating of unwholesome food, living in unhealthy dwellings, doing things at untimely hours, association with the wicked, evil thoughts, inflict injuries, etc. These breed physical diseases called Vyādhis or the secondary diseases. These persistent agitations cause violent fluctuations in the flow of pana in the nadi. The prana flows in wrong paths flying from one to the other without rhythm and harmony. The nadis can no longer, in this condition, maintain stability and steadiness, but quiver. Due to these disturbances of the prana and unsteadiness in the nadi, the food does not get properly digested. This is the first physical manifestation of a disturbed mind.

The search for happiness in outside objects continues with unresolved conflicts due to wrong notion about the meaning of life and nature of happiness. The nature of this conflict or distress is described as 'uncontrolled recycling of sentences in the mind' (yogic definition of stress)(Chapter5 Verse23)(Tapasyananda, 2011) in the Manomaya kośa.

शन्कोतिहैव यः सोढुं प्राक्शरीरविमोक्षणात्। कामक्रोधोद्भवं वेगं स युक्तः स सुखी नरः ॥भ गी ।५।२३॥
śankotihaiva yaḥ soḍhuṁ prākśarīravimokṣaṇāt। kāmakrodhoodbhavaṁ vegaṁ sa yuktaḥ sa sukhī naraḥ।।bha gī।5।23।।
He alone, who is able to withstand, in this very life before casting off this body, the urges of lust and anger, is a Yogi, and he alone is a happy man ।।bha gī।5।23।।

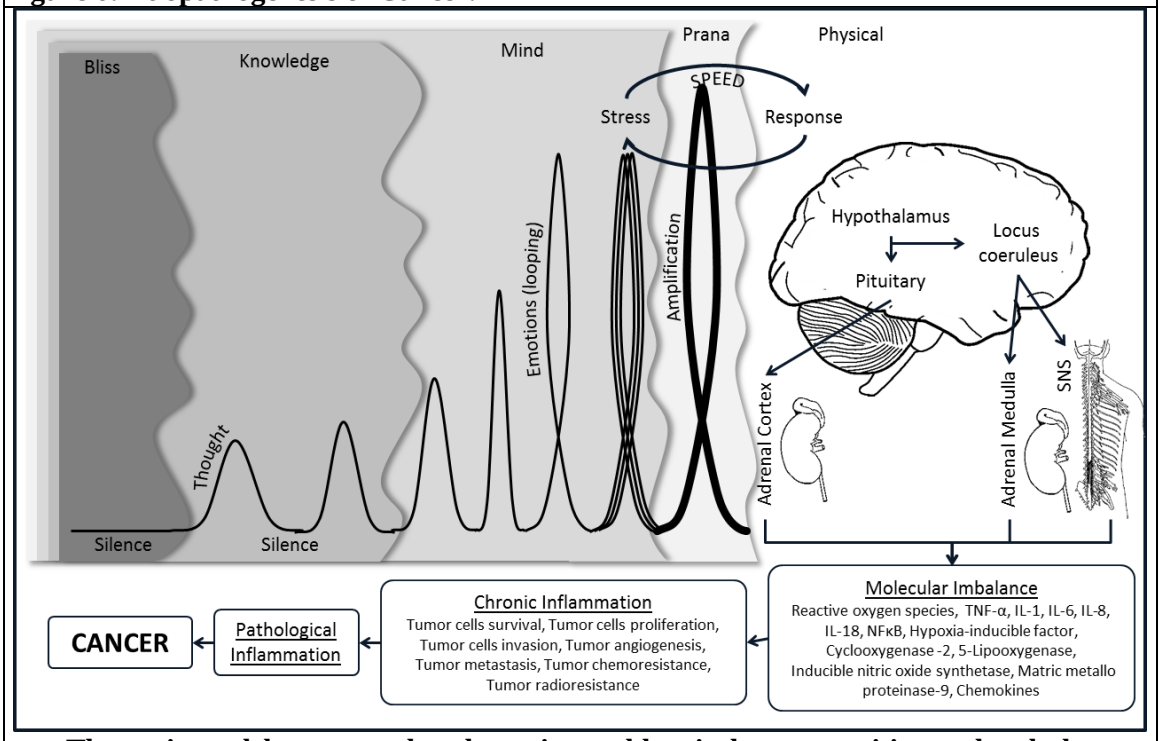
This imbalance due to uncontrolled speed (udvega) of suppressed emotions when unchecked results in an imbalance and percolates into prāṇamaya kośa. This is detectable as disturbed pattern of breathing (increased rate and irregular rhythm) and poor digestion. As this imbalance and loss of mastery goes on for some time it becomes an involuntary habit, a reflex. Chronic constipation or irritable bowel (constipation and diarrhea), fatigue and generalized body aches are the other general (non-specific) manifestations at this level. When unattended by correcting the imbalance at the root cause (the Manomaya and Vignānamaya kośas) the process continues and localizes to a specific zone in the physical body (Annamaya kośa).

Thus, the uncontrolled rush of prāṇa (vital energy), results in uncontrolled electro-chemical process in the physical body, the annamaya kośa. This appears to mean that the physical fight (tissue inflammation) is a reflection of the violence or fight in the mind. We know today that inflammation is a feature of cancer. Thus, the uncontrolled excessive prāṇa (subtle energy) flow seems to cause the changes in the molecular level that goes on to alter the apoptotic programming resulting in immortal cells and perpetuation of cancer cells [Figure 6]. Further, the

texts go on to describe that the localization of the disease (cancer) depends on external (insult by carcinogenic agents, trauma, toxins, and infections) or internal (genetic) factors.

In summary, the yogic model proposes that the entire problem is due to repetitive onslaught by uncontrolled thoughts (suppressed emotions) at the mind level (Manomaya kośa) which causes excessive prāṇa activity and manifests as violence (inflammation) at annamaya kośa to show up as cancer. Although cancer can occur from external factors alone, knowledge from yoga texts suggests that the mind could also play are role, either in oncogenesis, or reducing the body's resilience, thereby resulting in illness, cancer being one of the possibilities.

Figure 6: Etiopathogenesis of Cancer.



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3.8.2. Integrated Yoga Therapy for Cancer

The integrated approach of yoga offers a comprehensive means to overcome the damage by achieving mastery at all levels through deep cellular rest (reducing the speed, imbalance and

inflammation). At the physical level (Annamaya kośa) there are practices that include: cleansing the body (yogic kriya) of the endotoxins (Aama, as portrayed in ayurveda) both at the gross (fecal matter) and subtle (molecular toxins e.g. free radicals) levels (Tripathi & Singh, 1999); correcting the life style through yogic diet and injunctions for healthy behavior (sleep, activity, speech, righteousness); and providing deep rest (reduce the speed) to the damaged/sick tissues through physical postures (asanas). Prāṇayama or breathing techniques corrects the imbalances in prāṇamaya kośa through voluntary reduction in the rate of breathing. (Vivekananda, 1999) Of these practices, yoga based system of dies relies on moderation of the components of food as well and the quantity is prescribed (Yuktahara). Unlike any other system of diet and nutrition, yoga and Ayurveda agree that it is not just what one eats that matters but, why one eats, how one eats, and what is the objective of consuming food is important. In yoga it is understood that all activities like work, eating, resting are to sub-serve the higher goal of mastery over the mind. In Ayurveda system, food is considered medicinal and the right quantity, at the right time, in the right manner is capable of having detoxification and healing characteristics.

Meditation techniques (Dharana, Dhyana, Samadhi and Sanyama), the Manomaya kośa practices are the most important as they aim at direct mastery over the mind, the root cause of the problem by establishing in an introspective state of blissful awareness (dhyana = effortless flow of a single thought. (Chapter2 Verse2)(Taimni, 1999) (Chapter3, Verse2)(Vivekananda, 1999).

समाधि भावनार्थः क्लेशतनूकरणार्थश्च ॥प यो सू।२।२॥
samādhi bhāvanārthaḥ kleśtanūkaraṇārthaśca।pa yo sū।2।2।।
It is for the purpose of producing continuous effortless linkages of the attention to a higher concentration for and for causing the reduction of the mental and emotional afflictions.

Devotion (bhakti yoga or emotional culture) is another important component that helps in harnessing the uncontrolled surge of violent suppressed emotions through using ‘pure love’, a

positive strong emotion. At the vignānamaya kośa level (intellectual), correction of the false notion is achieved through understanding that 'I am (the self is) made of the universal consciousness and bliss (Ānanda) which is independent of the mind'. At Ānandamaya kośa level, karma yoga helps in achieving blissful awareness free from all fears (including fear of death). Thus the highlight of this model is the possibility of the practitioner to de-identify and dissolve oneself in the universal consciousness that is described as existence (sat), consciousness (chit) and bliss (Ānanda), through right knowledge and awareness. All practices including yogic diet, kriya (cleansing), asana, prāṇayama, dhārana, dhyāna, devotion and self-analysis prepare the system to stop the turbulent fluctuations (superficial and deep seated subconscious activities) and allow the mind to rest in a state of inner quietude (wakeful sleep). A single positive thought (a resolve) introduced to this blissful quietude (sanyamah) has the ability to reverse the imbalances at all levels. (Taimni, 1999) Thus the process of reversing the structural and functional abnormalities at the tissue level is described through this model.

3.8.3. The needs of cancer patients

The opinion from three major contributors to the health of the cancer patients was sought regarding the various needs of the patient at different phases of treatment and survival. These inputs were valuable determinants to define the focus and the contents of the yoga module that was to follow. Firstly the needs of the cancer patient were enlisted and regarded as the primary focus. Secondary to this, were the inputs given by the clinician, and finally, the concerns of the patient caregivers were enlisted. This enabled us to identify the domains in which yoga could contribute as a complementary therapy to conventional treatment. The salient concerns of the three stakeholders are listed below. [Table 7]. This list of concerns are the primary focus while developing IAYT modules for cancer and yoga can assist reducing all these concerns either directly or indirectly.

Table 7: Needs of a cancer patient			
Treatment phase	**Patients' concerns**	**Clinician's needs**	**Caregivers' feedback**
Surgery	Fear, anxiety, success of surgery, fear of complications.	Wound healing, drain retention, better prognosis	Hospital stay, follow up visits, functional, independence, reduce economic burden
Radiation Therapy	Fatigue, pain, nausea, physical appearance, Fear of complications	Efficiency of RT, Prevent fibrosis, Lymph edema, Superficial tissue damage Tolerance to scheduled dose	Quality of life, vomiting
Chemo-therapy	Fear of side effects, fatigue, pain, nausea, physical appearance, problems of repeated venipuncture, maintenance of chemo port.	Completion of treatment and adherence, anemia (Hb), immune suppression, energy level	Functional independence, negative emotions depression, Nausea /vomiting
Hormone Therapy	Side effects Loss of reproductive functions.	Treatment adherence	Hospital visits, Mood
Post-treatment	Supportive medication, Long-term side effects	Immune status, Long-term side effects	Functional independence, quality of life

3.8.4. IAYT modules for Cancer

Modules that evolved based on the understanding of the modern and ancient interpretations of the etiology of cancer, combined with the needs of the patient as opined by patients, clinicians and caregivers, served the purpose of providing a comprehensive and need based yoga intervention to be administered as complementary to conventional treatment.

Eight modules of yoga interventions evolved that consisted of practices most applicable to the complementary management of cancer. In the below table [Table 8] these practices are listed and further categorized based on their applicability to the five phases of cancer treatment. A detailed description of the these modules are found in Appendix V

Table 8: Eight modules of the IAYTC grouped into five categories							
Personality Aspects	Modules	Phase of cancer					
		Surgery	RT	CT	HT	Survival	
Annamaya	Sukshmavyayamas [SKYM]		✓		✓	✓	Physical, Functional Domain
	Self-Management of Excessive Tension [SMET]	✓			✓	✓	
Prānamaya	Pranic Energization Technique [PET]		✓	✓	✓		Psychological, Functional Domain
Manomaya	Mind Sound Resonance Technique [MSRT]		✓			✓	Psychological, Social Domain
	Mind Emotions Management Technique [MEMT]		✓	✓	✓	✓	
	Mind Imagery Technique [MIRT]	✓		✓			
Vignānamaya	Vignana Sadhana Kaushala [VISAK]			✓		✓	Psychological, Social Domain
Ānandamaya	Ananda Amrta Sinchana [ANAMS]			✓		✓	Spiritual Domain
RT: Radiotherapy; CT: Chemotherapy; HT: Hormone Therapy							

All these modules have the common purpose of correcting the imbalances at five aspects of the personality (Panca Kosa), through alert rest to the mind-body-complex in general and to the effected organ in particular. Each module in turn consisted of eight steps and took about 30 minutes to perform. All modules began with a selected prayer, followed by steps to progressively develop the faculties of perception/introspection to finally culminate in a process where participants took a resolve. These ‘resolves’ were positive statements like “I am healthy”; “I am not afraid of my disease” or “my immune system is capable of destroying the cancer in my body” which helped to reinforce healing mechanisms to percolate from the mind to the body. The combination of progressive relaxation techniques and a strong positive resolve brought about proactive healing. It was suggested by the focus group that the practices were to be taught in ten sessions of one and half hours (90 minutes) each. The structure of the 90 minutes session was divided into an initial 30 minute discussion to understand the principle and back ground of the techniques. In the next 50 minute, the participants learnt the module under guided

instructions which was then followed by 10 minutes of interaction to check the experience and clarify questions.

3.8.5. Pilot studies

The pilot studies conducted at a residential set up to elicit feedback from cancer patients provided crucial indications as to how the module could be made more 'user friendly'. All participants started with basic modules based on the abilities and needs. The yoga therapist and the clinician assessed the experiences of the participants using a check list before moving on to more advanced levels as prescribed for a yoga intervention.(Nagarathna & Nagendra, 1997) Questions regarding the feasibility, duration and experiences of the modules were put forth to the patients. Changes suggested was systematically documented and applied after discussions with experts.

There were three major changes that were suggested based on these pilot experiments and were incorporated into the final modules.

1. The duration of each module had to be reduced from 90 minutes to 60 minutes with 30 minutes for theory and 30 minutes for practice.
2. There was a need for recorded audio CDs to help them continue the practice at their convenience.
3. Some of the imageries used during the practice (Mind Imagery Technique) had to be replaced with more suitable images. (Example: Learning how not to fear the "The experience of death" had to be replaced by a more subtle concept of "Surrender to the divine lord" which gave much more confidence to overcome fear and face the disease.)

3.8.6. Efficacy of IAYT for cancer

In our first RCT (Rao et al., 2008b), 69 women with stage II or III breast cancer were recruited to study the effect of different modules of yoga during different stages of conventional treatment starting from the first day of diagnosis until the treatment was completed. During the period of 2005-2008 when all our RCTs were planned, the protocol of management at Bangalore institute of oncology where the studies were conducted, the standard conventional protocol was surgery, followed by radiation therapy and chemotherapy (six cycles at an interval of three weeks with changes depending on the side effects) which changed by the end of the study. The summary of the observed changes are divided into four categories and presented in Table 9.

3.8.6.1. Effects of IAYTC during surgery

All participants were taught SKYM (in part) and SMET in two days before surgery either as inpatients or outpatient. They practiced DRT (ten minutes) component of SMET four times a day for two days in the immediate post-operative period in the hospital; SKYM practice was revised with a few additions during their stay. They were asked to continue the full practice (SKYM and SMET) daily for 30 minutes at home. The results showed lesser number of days of drain retention which resulted in lesser duration of hospital stay after surgery implying economic advantages.(Rao et al., 2008b) They also showed significant reduction in the number and severity of other distressful symptoms after surgery.(Rao et al., 2008a)

3.8.6.2. Effects of IAYTC during radiation therapy

As they moved on to radiation therapy when the wound had healed they went on to learn PET and MSRT. During radiation therapy, the level of perceived stress ,anxiety and depression were lesser in the yoga group;(Banerjee et al., 2007) the DNA damage as measured by comet assay was significantly lesser in the yoga group as compared to the control group.(Banerjee et al., 2007)

3.8.6.3. Effects of IAYTC during and after chemotherapy

As they prepared for chemotherapy (CT) they went on to learn MIRT and MEMT; they were given prerecorded audio CDs for home practice; they were made to listen and practice MSRT followed by PET during the hour long chemotherapy infusion. As the CT progressed (six cycles at an interval of three weeks between the intravenous infusion therapy), the patients were taught the other practices of VISAK and ANAMS which are meant to allay the fear at subtler levels.

The results of the study where all patients received the same type and duration of chemotherapy showed significant reduction in both State and Trait anxiety (STAI); the CT related distressful symptoms were significantly lower in the yoga group (Rao et al., 2009); the frequency and severity of post-chemotherapy nausea and the anticipatory nausea reduced significantly. There were significant correlations between nausea, vomiting and psychological variables such as anxiety, depression, symptom distress, quality of life and toxicity(Rao et al., 2006). There was also reduction in depression and increase in quality of life during the course of treatment.

3.8.6.4. Effects after completing the therapy

At the end of the entire therapy perceived stress level was lower with better emotional and cognitive functions of quality of life, and positive affect in the yoga group (Vadiraja et al., 2010).

A comprehensive table containing, chronologically, the results of the RCTs are presented below.[Table 9] All these below randomized control trials had substantial sample sizes and made use of accurate statistical tests to isolate treatment effect and thereby indicate generalizable results.

Table 9: Results of efficacy trials conducted with IAYTC as intervention				
	BENEFITS			
Author	**PHYSICAL (Annamaya kosha)**	**VITAL ENERGY (Pranamaya kosha)**	**PSYCHOLOGICAL (Manomaya and vijnanamaya kosha)**	**QUALITY OF LIFE (anadamaya kosha)**
Rao 2006 EJCC	↓Emesis intensity ↓Nausea frequency ↓Symptom Numbers ↓Symptom Severity	↓Emesis and intensity ↓Nausea intensity ↓Symptom distress	↓ Anticipatory Nausea frequency ↓ Anticipatory Nausea Intensity ↓Anxiety ↓Depression	
Banerjee 2007 ICT	↓DNA Damage	↓Perceived Stress	↓Anxiety ↓Depression	↑Overall QOL
Rao 2008 IJOY	↑CD8+ ↑CD56+	↓Symptom Severity	↓Trait anxiety ↓Depression	General QOL ↑
Rao 2008 IJOY	↓Drain Retention Suture Removal: ↓Duration ↓Hospital Stay			
Rao 2009 CTIM		↓Symptom Distress	↓ State Anxiety ↓ Trait Anxiety	
Vadiraj 2009 IJOY	↓Physical Distress ↓Pain	↑Physical Activity ↓Appetite Loss ↓Fatigue	↓ Distress ↓Insomnia	
Vadiraj 2009 ICT	↓6am cortisol ↓ Pooled cortisol		Anxiety ↓ Depression ↓	
Vadiraj 2010 CTIM			↓Negative Affect ↑ Emotional QOL	Positive Affect↑ QOL: Cognitive ↑
EJCC: European Journal of Cancer Care; ICT: Integrative Cancer Therapies; IJOY: International Journal of Yoga; CTIM: Complementary Therapies in Medicine; ↑: Increase; ↓: Decrease				

3.9. Summary

3.9.1. Evidence for the yoga based etiology model for cancer

3.9.1.1. Psycho-hormonal pathway

Significant decrease in the psychological and physical distress, fatigue, pain, insomnia, appetite loss and negative affect with improved activity levels and positive affect (Vadiraja, Rao, Nagendra, et al., 2009) in patients with stage 2 and 3 breast cancer after IAYTC was observed. There were positive correlations between the physical and psychological symptoms. The activity levels were correlated with fatigue, nausea and vomiting, constipation and diarrhea. The perceived stress (PSS), anxiety and depression (HADS) were also significantly lower ($p<0.001$) in the yoga group.

Corresponding to this, the salivary cortisol collected at 6am and the overall pooled cortisol levels were significantly lower in the yoga group of patients with stage II and III breast cancer; and the scores for anxiety and depression were correlated with 6am cortisol levels.(Vadiraja, Rao, Raghuram, et al., 2009). This provides support for the mind influencing the stress hormones and thereby resulting in changes on stress physiology.

3.9.1.2. Psycho-immune pathway

Measurement of serum IgA, CD8+ and CD56+ counts and TNF-α were undertaken which provided evidence to the immune system normalizing effects of the integrated yoga modules (Rao et al., 2008a). The Plasma TNF-α levels were significantly lower in the immediate post-operative period (7th day) in yoga group as compared to control group (Mann-Whitney $p<0.001$) indicating lower pro-inflammatory activity which could explain faster healing.(Rao et al., 2008b) Serum IgA were significantly lower, %CD8+ and %CD56 counts were significantly higher in yoga group pointing to better immune adaptability towards the stressor.(Rao et al., 2008a)

Rao et al in 2008, also went on to show a predictive relationship between the emotional states (anxiety and depression) and the outcome of surgery. The yoga intervention played an important role in predicting the number of days for drain retention, suture removal interval, duration of hospital stay and post-surgery and TNF-α levels (Rao et al., 2008b).There were also significant correlations between nausea, vomiting and psychological variables such as anxiety, depression, symptom distress, quality of life and toxicity(Rao et al., 2006).

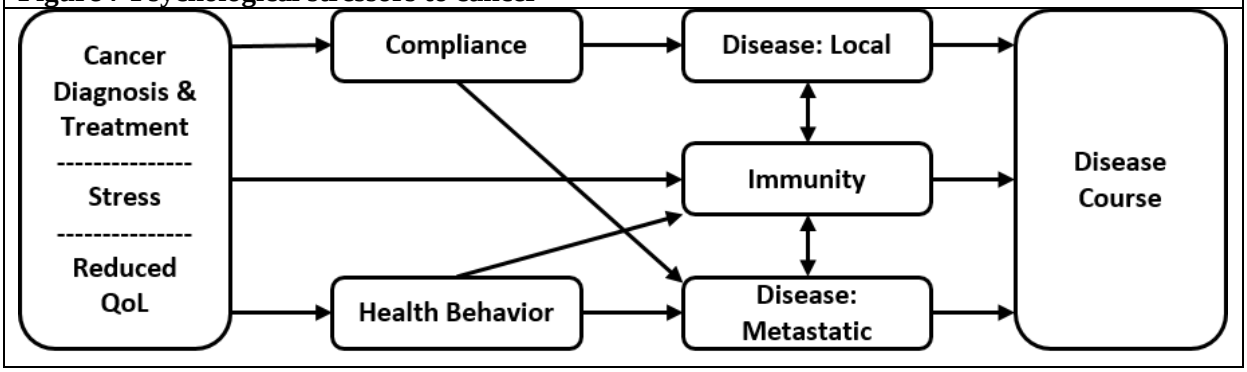
Reduced susceptibility to DNA damage was another outcome studied through the course of these RCTs that could indicate that corrective changes in the mind could percolate into basic cellular functioning.

These results provide support to the theory of downward causation that postulates that the disturbance in the mind is the root cause of cancer. Focus on psychological correction, along with conventional remedies may be considered for a better therapeutic strategy.

3.9.2. Comparisons with other psycho-oncological models

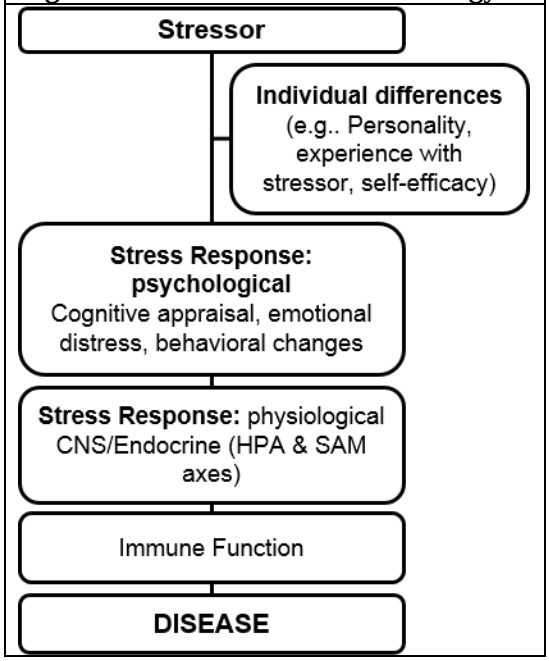
Anderson et al, in 1994, proposed a bio-behavioral model of the relationship between stresses of cancer based on several publications up until then. (Andersen, Kiecolt-Glaser, & Glaser, 1994) Her study highlighted the mechanisms by which psychological and behavioral responses may influence biological processes and the health outcomes and gave insights into the role of mind in compliance to standard therapies. (Figure 7) Further, based on a decade long (between 1995 and 2005) explosive discoveries on the relationship between psyche and the immune modulation the same researchers (Thornton and Anderson 2006) presented a psycho-neuro-immunological model of cancer.(Figure 8)

Figure 7 Psychological stressors to cancer



This model, for the first time, hypothesized a causal linear relationship between the chain of events starting from stressors, psychological stress response that may lead to physiological stress response going on to immune changes and the disease processes which could also include many molecular mediators and moderators to the model. Rao et al in 2008 has shown a predictive relationship between yoga and immune parameters. However, the present cross sectional study did not detect sequential relationship between psychological and immune parameters.

Figure 8 PNI model of disease etiology



Research in the last decade identified several mediators involved in the genetics of cancer that has led to successful drug discoveries. Based on these Ao P, et al., in 2010, proposed a nonlinear mathematical physical (stochastic dynamic) model of the genesis and progression of cancer depicting the complexity of the interplay between these molecules.

Similar to these, basic discoveries at molecular level that led to safer drugs to scavenge the cancer cells, the eastern yoga model offers a sound conceptual basis for psycho-oncological processes that leads to techniques of yoga with the potential of returning to normalcy.

3.10. Conclusion

This model of the etiopathogenesis of cancer is the combination of scriptural knowledge that has evolved over 5000 years of research in the east by yoga masters as an introspective science with modern scientific evidence and understanding. This model of the origin and progression of cancer takes into account the existence of subtle aspects of the personality such as prāṇa, mind, and the self (the soul). The holistic model proposes that the root cause of the disease is the wrong mindset or incorrect notion viz 'the source of happiness is the external agents of enjoyment'. The life's ambitions and plans are all based on this notion. Frustrations occur when these are not fulfilled. Emotional suppressions become mandatory to carry on with life. This results in chronic imbalance that disturbs homeostasis and culminates to cancer. This analysis provides the logical basis for using corrective techniques that are used in yoga practices and forms the scriptural basis of the integrated approach of yoga therapy for cancer. The model incorporates all aspects of the personality, with mind as the starting point and cancer as the end point of the process.

Eight modules of practices, to correct mental and physical imbalances, evolved through focused group discussions. Corrections in the modules were implemented after getting feedback from cancer patients through pilot studies. Randomized control studies provided more evidence to the value of these IAYTC modules as add-on therapy. Predictive and correlational relationship between psychological with immunological and humoral variables as shown by Rao et al in 2008 was considered as supportive evidence for the scriptural basis for the modules. This study had demonstrated that yoga was a strong predictor for TNF-α levels.

Among the various CAM treatments available, yoga has proved to be useful in management of cancer. Eight modules of IAYTC to be introduced systematically as add-on to conventional therapies (surgery, radiation, and chemo) of cancer with additional benefits of improved quality

of life, stress reduction, correction of HPA axis and immune system imbalances offers many more tools to the existing protocols of cancer management.

This study also demonstrates the steps in the development of a yoga intervention for clinical evaluation of efficacy. Future studies that use yoga as an intervention, would benefit from systematic development of the module and pilot studies in order to evaluate the feasibility prior to undertaking efficacy trials for specific settings and populations. Also it is imperative to understand the roles of the individual components of the module through studies on the mechanisms of action.

4. MATERIALS AND METHODS

This chapter presents the details of design, subjects, outcome variables, data extraction, and data analyses.

4.1. Design of the study

This study was a cross-sectional study involving four cohorts as shown in table. The first group was Breast cancer survivors with prior experience of yoga (CBY); the second group comprised of breast cancer survivors who had no prior exposure to yoga (CBN). The third and the fourth groups consisted of healthy individuals who have done yoga (NHY) and those who had no prior yoga experience (NHN) respectively.

Table 10:Four groups of the study

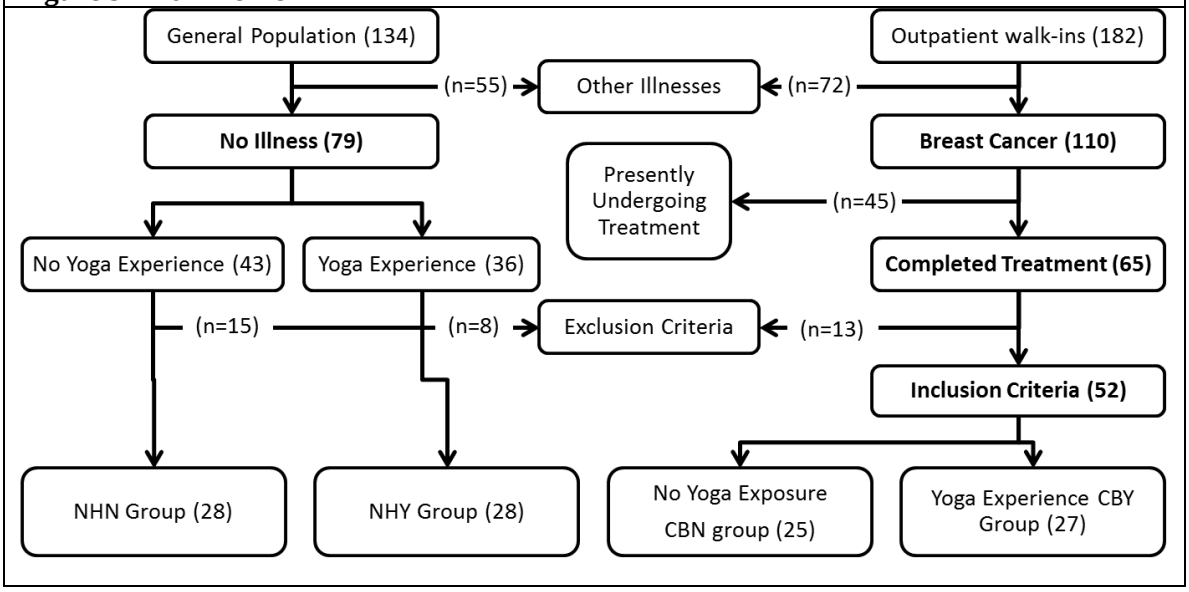
Group	**Description**	**Code**
Group 1	Breast cancer Survivors with yoga experience	CBY
Group 2	Breast cancer Survivors with no yoga experience	CBN
Group 3	Healthy volunteers with yoga experience	NHY
Group 4	Healthy volunteers with no yoga experience	NHN

Details of all yoga techniques practiced by the yoga group (NHY and CBY) were documented at the time of recruitment. Yoga experience included various practices ranging from physical postures (asana), breathing techniques (pranayama), meditation, repetitive chanting (japa).

4.2. Subjects

The trial profile (Figure 9) shows the details of subject recruitment process. The first and the second cohorts consisted of breast cancer survivors who did yoga during their cancer treatment for at least 3 months and those who had no prior exposure to yoga respectively. Healthy women without any chronic or acute phase illnesses formed the third and fourth group; the third group consisting of healthy women with at least 6 months of regular yoga experience and the fourth without any exposure to yoga.

Figure 9 Trial Profile



4.2.1. Sample size

The primary outcome variable of the present study was the pro and anti-inflammatory cytokine profiles. Till date, there are no cross sectional or interventional studies using yoga as an intervention for breast cancer survivors that have measured cytokine profiles. Thus the closest study by Carlson L E (Carlson, 2003) that looked at the effects of a mindfulness based stress reduction program in breast and prostate cancer patients on cytokine profile was chosen. Using data from this study, we derived that the effect size was 0.63 which further yielded an optimum sample size of n=23 in each arm. Considering the secondary outcome variable which was psychological wellbeing, we selected the study by Gielissen, M F M, et al (Gielissen, Verhagen, & Bleijenberg, 2007) that provided cognitive behavioral therapy to fatigued cancer survivors. The data from this study yielded an effect size of 0.78 and an optimum sample size of 15 in arm, thereby. All the above calculation considered that the probability of Type-1 error would not exceed 0.05 with a statistical power of 0.8. For these calculations we used the noncommercial statistical power analysis program G*Power version 3.1.5.(Faul, Erdfelder, Lang, & Buchner, 2007)

The resultant cohorts had n=27 in the CBY group; n=25 in the CBN group; n=28 in the NHY group; and n=28 in the NHN group taking into consideration the wide variability in values of the primary outcome variables.

4.2.2. Source of subjects

Breast cancer survivors were screened from several outpatient cancer clinics and hospitals in the city. Recruitment was done from HCG hospital, HCG Bangalore Institute of Oncology, Rangadore Memorial Hospital and Ambuja Health Clinic, after explaining the study and obtaining consent from them and their respective oncologists. Breast cancer patients were screened when they came for their routine 6-monthly checkup. Also subjects from a previous randomized control study conducted by SVYASA University involving breast cancer patients were contacted and requested to participate.

Normal healthy individuals with experience of yoga were screened from yoga classes conducted in the city of Bangalore. The yoga practitioners were asked to provide information regarding relatives and friends who had no prior experience of yoga and were healthy. This group of individuals formed the yoga naïve group.

The selection criteria laid out for each of the categories were strictly followed and subjects were matched between groups.

4.3.Selection Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
BREAST CANCER YOGA GROUP (CBY)	
• Female Carcinoma Breast Survivors • Age: 30–65 years • > 6 months from completing the Ca treatment • Yoga practice (> 6 months regular practice in the past one year) • Must have undergone chemotherapy	• Neutropenia – Grade III and IV or thrombocytopenia • Chronic illnesses: asthma, diabetes, hypertension, hypo/hyperthyroidism, arthritis, heart conditions, psychiatric problems etc • Morbid Obesity (BMI > 40)

• Eosinophil Sedimentation Rate (ESR) in normal ranges	• Present Anticancer oral chemotherapy-therapeutic or palliative or maintenance • Those on Ayurveda, homeopathy, siddha medications (other CAM) • Presence of infection
BREAST CANCER YOGA NAÏVE GROUP (CBN)	
• Female Carcinoma Breast Survivors • Age: 30–65 years • > 6 months from completing the Ca treatment • Yoga naïve (< 3 yoga sessions in the past one year) • Must have undergone chemotherapy • ESR in normal ranges	• Same exclusions as previous group
HEALTHY YOGA PRACTITIONER GROUP (NHY)	
• Female • Age: 30–65 years • Healthy (self-reported symptom checklist) • Yoga practice (>6 months regular yoga practice in the past one year) • ESR in normal ranges	• Chronic illnesses: asthma, diabetes, hypertension, hypo/hyperthyroidism, arthritis, heart conditions, psychiatric problems etc • Morbid Obesity (BMI > 40) • Those on Ayurveda, homeopathy, siddha medications (other CAM) • Presence of infection
HEALTHY YOGA NAÏVE GROUP (NHN)	
• Female • Age: 30–65 years • Healthy (self-reported symptom checklist) • No prior Yoga practice (< 3 yoga sessions in the past one year) • ESR in normal ranges	• Chronic illnesses: asthma, diabetes, hypertension, hypo/hyperthyroidism, arthritis, heart conditions, psychiatric problems etc • Morbid Obesity (BMI > 40) • Those on Ayurveda, homeopathy, siddha medications (other CAM) • Presence of infection

4.4.Screening and Recruitment

To maintain uniformity in data collection for this one-time study, all subjects were requested to come to Health Care Global Cancer Hospital. Transportation was provided for the commute, to and from the hospital and refreshments was provided after data was collected. The subjects who satisfied the selection criteria were accommodated in a quiet room in the out-patient annex where the study was explained by the researcher and the consent was sought. The participants then completed a screening questionnaire that determined whether they could be included into the study. Once the researcher ascertained that they could be included, subjects were provided with a patient information checklist to be completed. This comprised of information related to

demography and lifestyle practices including diet, exercise, and yoga, amongst others. The researcher assisted the subjects fill the section on cancer history with the help of the medical records. Along with this was a battery of psychological questionnaires evaluating Perceived Stress (PSS), State and Trait Anxiety (STAI X1, X2), affect (PANAS), quality of Life (WHO QoL Bref) and General Health (GHQ-28) were administered. A trained researcher was present during this entire time and provided assistance if required. Once this was completed the researcher escorted the subject to the phlebotomy department of the hospital where an expert technician collected 20 ml of venous blood using a BD eclipse^{TM} blood collection needle (Cat#) and a BD Pronto^{TM} needle holder (Cat #) through venipuncture at antecubital vein. The samples were drawn into two 10ml BD heparinized vacutainer^{TM} and one 3ml BD serum separation vacutainer. Those who did not satisfy the criteria were explained the reasons why they could not be recruited and duly thanked for their time. Subjects who wanted to enroll for yoga sessions were brought in touch with a yoga therapist for further follow-up.

4.5. Subject matching and minimization of confounders

The variables that were predicted to influence the outcome of the immune and psychological measures were enlisted. These were then weighted according to how much influence would be exerted by them on the primary outcomes. Based on this, subjects were recruited into two of the breast cancer groups using the process of minimization. Minimization is a process of matching for predicted confounding variables using their respective influence on the primary dependent variable. Using a mathematical algorithm, minimization protocol systematically allocates subjects across all groups in a manner that these confounding variables distribute themselves evenly. For the present study, the entire age range defined by the inclusion criteria was distributed into five-year intervals. The numbers of the subjects in each of these age intervals were matched across the four groups. Between yoga and yoga naïve breast cancer survivors,

other confounders like stage and grade of the tumor at the time of diagnosis, histopathology type, treatment regimens received, surgery type, number of years since treatment was taken into consideration for minimization.

4.6. Randomization

Since this study used a cross sectional design comprising of four distinct cohorts there was no randomization involved.

4.7. Blinding and Masking

The statistician who subsequently analyzed the data was blinded to the attributes of the groups and the subjects contained in them. The demographic datasheet, psychological questionnaires and blood samples of all subjects were removed of personal identifiers, coded and numbered. A table that contained the details of coding was kept confidential by the researcher.

4.8. Ethical clearance and consent

The study was cleared by the institutional review board and the ethical committee of the university (SVYASA) [(SVYASAIEC/2010/Jan/04) (14 January 2010)] and an assent from the hospitals that participated, (Health care global, Rangadore Memorial Hospital) was obtained. Signed informed consent of the patients was elicited. The consent form had a description of the study objectives and design in simple language. Separate informed consent forms were created for Cancer survivors and Healthy individuals that were independently approved by the ethics committees. The forms also contained clear instructions about the responsibilities and rights of the subjects. Cancer survivors who were interested to join yoga classes were assisted and information regarding the same was provided to them by the researcher. A Copy of both the informed consent forms used for this study are presented in appendix X.

4.9. Variables

The primary outcome variables used in the present study comprised of psychological as well as immunological observations. Psychological measures aimed at looking at stress, its response and effects on quality of life. Below is a list of psychometric tools used for this purpose.

4.9.1. Primary Outcome Variables – Psychological

Psychological profiles included standardized psychometric inventories that evaluated the following measures.

Table 11 List of Psychological Outcome Measures

Measure	Instrument Used	Reliability	Validity
General Health	General Health Questionnaire – 28	0.78	**0.9**
Percieved Stress	Perceived Stress Scale	0.85	0.85
Anxiety	State and Trait Anxiety Inventory X1/X2	0.54 – 0.86	0.73 – 0.85
Depression	Beck's Depression Inventory II	0.93	0.8
Quality of Life	WHO Quality of Life Questionnaire	-	-

These psychometric inventories coincided with different cancer related psychological domains that are affected as a result of diagnosis, treatment and survival. General health is affected when an environmental situation (like cancer survival) is perceived to be stressful, resulting in a stress response that expresses as anxiety or depression. This in turn impairs the quality of life in physical, psychological, social and functional domains. Elevated stress, anxiety, depression, and reduced quality of life are common concerns among cancer patients and previous research has shown yoga to be helpful in these domains. (Banerjee et al., 2007; Rao et al., 2008a, 2009; Vadiraja et al., 2010; Vadiraja, Rao, Raghuram, et al., 2009)

4.9.1.1. General Health Questionnaire – 28

The general health questionnaire – 28 is a valid and reliable (0.78-0.9)(Robinson & Price, 1982) measure of the general health of an individual and is useful for screening cases of possible psychological ill-health. Values of GHQ above 24 are considered "possible psychiatric cases". (Goldberg, 1978)

4.9.1.2. Perceived Stress Scale

The Perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. The questions in the PSS ask about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way. Coefficient alpha reliability reported for the PSS-10 version is 0.85. (Sheldon Cohen, Janicki-Deverts, & Miller, 2007)

4.9.1.3. State and Trait Anxiety Inventory X1 and X2

The State-Trait Anxiety Inventory Form X (STAI) is the definitive instrument for measuring anxiety in adults. The STAI clearly differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." The essential qualities evaluated by the STAI are feelings of apprehension, tension, nervousness, and worry. Reliability scores for the STAI-X scale are 0.54 for state and 0.86 for trait anxiety. Validity is in between 0.73 to 0.85. (Gorsuch, Luchene, & Spielberger, 1970)

4.9.1.4. Beck's Depression Inventory – II

BDI has been used for 35 years to identify and assess depressive symptoms, and has been reported to be highly reliable regardless of the population to which it is administered. It has a high coefficient alpha, (.80) its construct validity has been established, and it is able to differentiate depressed from non-depressed patients. Test-retest reliability was studied using the responses of 26 outpatients who were tested at first and second therapy sessions one week apart. There was a correlation of .93, which was significant at $p < .001$. (Beck & Steer, 1984)

4.9.1.5. WHO Quality of Life Questionnaire – BREF

The WHOQOL-100 quality of life assessment was developed by the WHOQOL Group in an attempt to develop a quality of life assessment that would be applicable cross-culturally. The WHOQOL—BREF is a shorter form adhering to the four domains of the original tool. The domains that the WHOQOL-BREF assesses are the physical, Psychological, social and environmental (functional) domains along with Overall Quality of Life. (World Health Organization, 1996) The Authors of the WHOQOL-BREF instrument have reported excellent psychometric properties of reliability and validity and have concluded that it is an instrument that is valid across cultures.(Skevington, Lotfy, & O'Connell, 2004)

4.9.2. Primary Outcome Variables – Immune

The Eosinophil Sedimentation Rate (ESR), measured by the manual method, was used as an index for determining the latent inflammatory levels and subjects with higher than normal levels were excluded from further processing of the sample as this would yield confounding levels of immune measures.

Immune measures included 12 cytokines and 1 transcription factor that would provide an indication of both pro- and anti-inflammatory activities. The outcome variables are listed in the table below

Table 12 List of Immune Outcome Measures

	Symbol	Detail	Range (pg/ml)	Sensitivity (pg/ml)
1	*NFκ-B*	Nuclear Factor κ-B		
2	*IL1 α*	Interleukin 1 – α	0-500	0.8
3	*IL1 β*	Interleukin 1 – β	0-250	1.6
4	*IL2*	Interleukin 2	0-3000	4.8
5	*IL4*	Interleukin 4	0-900	6.6
6	*IL6*	Interleukin 6	0-900	1.2
7	*IL8*	Interleukin 8	0-3000	4.9
8	*IL10*	Interleukin 10	0-1000	1.8
9	*VEGF*	Vascular Endothelial Growth Factor	0-3000	14.6
10	*IFNγ*	Interferon γ	0-1500	3.5
11	*TNFα*	Tumor Necrosis Factor α	0-1500	4.4
12	*MCP1*	Monocyte Chemotactic Protein 1	0-1500	13.2
13	*EGF*	Epidermal Growth Factor	0-900	2.9

This battery of cytokines provided information regarding both humoral and adaptive immune responses, apart from specific cancer related markers. These cytokines were selected in order to determine cancer related pro- and anti-inflammatory activity. The Cytometric Beads Assay protocol (Randox, Cat# EV3513) that uses a single serum sample of 0.3mlto estimate all 12 cytokines was used. The core technology is the Biochip, a solid-state device containing an array of discrete test regions of immobilized antibodies specific to different cytokines and growth factors. A sandwich chemiluminescent immunoassay is employed for the cytokine array. Increased levels of cytokine in a specimen will lead to increased binding of antibody labelled with horseradish peroxidase (HRP) and thus an increase in the chemiluminescence signal emitted. The light signal generated from each of the test regions on the biochip is detected using digital imaging technology and compared to that from a stored calibration curve. The concentration of analyte present in the sample is calculated from the calibration curve. Detailed protocol for serum separation and cytometric beads array assay are available in appendix XI.

Nuclear Factor-κB is the first responder for inflammation and results in a cascade of cytokine regulation that results in a controlled immune response. The AlphaScreen® SureFire® assay (Perkin Elmer, cat# TGRNFS500) was used to evaluate the activated nuclear NF-κB p65 (p-ser536 epitope). The assay protocol uses 11µl of the peripheral blood mono-nucleated cell (PBMC) lysate and generates signals recorded as alphascreen signal (counts). AlphaScreen® SureFire® technology allows the detection of phosphorylated proteins in cellular lysates in a highly sensitive, quantitative and user friendly assay. In these assays, sandwich antibody complexes, which are only formed in the presence of analyte, are captured by alpha screen donor and acceptor beads, bringing them into close proximity. The excitation of the donor bead provokes the release of singlet oxygen molecules that triggers a cascade of energy transfer in the

Acceptor beads, resulting in the emission of light at 520-620nm. Details of the protocol for isolation of PBMC, storage and the surefire assay are available in appendix XI.

4.9.3. Secondary Outcome Variables

Secondary outcome variables were exploratory in nature and included variables that could confound the outcome of the primary outcomes. These data were also collected with the intent to explore if any of these variables mediated the relationship between the core independent (yoga, cancer) and dependent variables (psychological and immune). Secondary variables were elicited in the form of a researcher administered checklist and hematological and biochemical parameters from the sample of blood, details of which is given below.

4.9.3.1. Patient information checklist

This was a checklist developed specifically for the present study in order to obtain details such as clinical data, personal and family history. This information was elicited in order to match the baseline characteristics of the subjects across groups to the extent possible. All responses were recorded by the researcher in the form of an interview. The checklist was divided into headings that are listed below.

(a) Demography (Name, Address, contact information, Income, Parity)

(b) Anthropometry (Age, Height, Weight)

(c) Medical History (past chronic/acute illness, medication)

(d) Cancer History (diagnosis, stage/grade, histopathology, treatment received, date of treatment completion, present medication, present symptoms)

(e) Lifestyle practices (habits, work hours, etc.)

(f) Yoga practices (duration, regularity, school of yoga, session details, etc.)

(g) Other spiritual practices (temple visits, etc.)

Details of the patient information checklist can be found in the appendix X.

4.9.3.2. Biochemical Measures

Blood samples that were drawn from the subjects were also subjected to basic biochemical analyses of blood grouping, albumin to globulin ratio, hemoglobin percentage eosinophil sedimentation rate and differential counts. Blood pressure was noted just before the blood draw to indicate if blood draw related anxiety existed. If so, subjects were asked to rest for five minutes with guided deep breathing before then next attempt. These variables were measured, primarily to ensure that ESR levels were in range, there was no latent infection indicated by abnormal differential counts and that subjects did not have anemia, hyper or hypotension, abnormal lipid and sugar levels. These variables were used purely for excluding outliers.

4.10. Data Extraction

The battery of self-reported questionnaires completed by the study subjects were scored as per the procedures described in each of their manuals respectively and the final scores were entered into a Microsoft Excel Sheet and coded prior to analyses. The data were then scrutinized for accuracy and completeness in reporting and those that were incomplete were excluded from further analyses. Group names were assigned numbers and subjects were assigned codes for preserving confidentiality and preventing bias during analyses.

The blood samples (23ml) collected were coded and labeled according to the study code and were removed of any information that could identify the subject. All samples were immediately processed. 3ml of whole blood collected in the serum separation tube was immediately centrifuged at 2000rpm for 20 minutes at room temperature. ~1.5ml of the supernatant serum was separated and stored as three 0.5ml aliquots. One aliquot was used for the immediate biochemical and hematological investigations and the other two aliquots were preserved at -80^{o}C immediately. The remaining 20 ml whole blood was processed by the researcher for isolating the

lymphocytes by Ficoll gradient method. The protocol for the ficoll gradient method is found in the appendix XI. Cellular viability assay using Trypan blue exclusion assay helped to identify and count the PBMCs. The resulting viable PBMCs in the suspension were counted using a hemocytometer and adjusted to a cell density of 50 million cells per milliliter. Aliquots of 100µl were then made and stored at -80^{0}C. The protocol for cryopreservation can be found in Appendix XI. It was ensured that the duration from blood draw to cryopreservation would not exceed 4 hours and that the samples were always maintained at laboratory temperatures (22^{o}C) and sterile conditions. All aliquots were labeled with only the date of collection and the sample code and all samples were processed by the same researcher. The process of blood collection was done by a phlebotomist at the hospital/clinic following which samples were transport to the laboratory facility, processed and stored by the PhD Candidate.

Once the recruitment phase was complete and all the samples had been collected, which took about one year, the aliquots were batch thawed prior to analyses. Serum samples were subjected to the cytometric beads assay protocol and the mono-nucleated cell suspensions were analyzed for NF-κB by the alphascreen surefire assay. Detailed protocols used for the estimation of molecular parameters are found in Appendix XI.

4.11. Data analysis

All data obtained were entered into a data-processing-software (Microsift Excel). This included columns consisting of the outcome measures of one row per subject. This datasheet consisted only of subject codes and recoded group information in order to avoid bias during analyses.

The intent of the analyses was to establish if there were significant differences between the four cohorts. For this purpose, the Statistical Package for Social Studies version 17 was made use of.

4.11.1.Descriptive Analyses

The measures of central tendency (mean or median) and dispersion (standard deviation/ Interquartile range) were calculated. Each group was evaluated for conformity to a normal distribution that would decide which tests would be used for the comparisons to be made and thereby the inferences that could be drawn.

4.11.2.Inferential Analyses

If the datasets to be compared were normally distributed, multiple group comparisons were made using a One-Way-ANOVA, else the non-parametric Kruskall Wallis test was applied. Probability values <0.05 were considered as a significant outcome and post-hoc analyses ensued. In cases where a One-Way ANOVA was used, pair-wise comparisons were made using t-tests with the corrected alpha for 6 pair-wise comparisons (Bonferroni correction p=0.0083). One the other hand, non-parametric pair-wise comparisons were made using the Mann-Whitney-U tests for two independent samples with the corrected Bonferroni alpha. Categorical variable were cross-tabulated with groups and the Chi-Square tests was conducted in order to infer about the distribution. Alpha levels for the Chi-Square tests were kept at 0.05, probability values below which were considered significant.

5. RESULTS

5.1. Demography and Baseline Matching

Descriptive Characteristics of the four groups are presented in the table below. The data are divided into anthropometric, biochemical occupational, socio-demographic, lifestyle, and spiritual practices. Comparisons of age between cancer survivors with (CBY) and without (CBN) yoga experience and between healthy volunteers with (NHY) and without (NHN) yoga experience showed no significant differences (p=0.538, p=0.065). CBN group had the highest mean age (53.08 ± 10.38) and NHY group with the lowest (41.18 ± 8.29). Comparing age between all four groups however showed significant differences (p=0.001). This was probably because of the difficulty in finding and recruiting healthy individuals conforming to the selection criteria in the higher age ranges (>60years). The four groups were comparable for height (p=0.555), weight (p=0.825) and BMI (p=0.704), showing no significant differences between groups.

Table 13 Comparison of Anthropometric variables between the four groups

ANTHROPOMETRY	CBY (n=27)	CBN (n=25)	NHY (n=28)	NHN (n=28)	Sig.
AGE (Mean±SD)	51.22 ± 11.02	53.08 ± 10.38	46.86 ± 10.17	42.36 ± 7.48	***0.001‡***
	(Independent t-test p=0.538)		(Independent t-test p=0.065)		
Height (cm)	157.85 ± 5.70	156.92 ± 9.26	156.39 ± 5.09	158.21 ± 8.87	0.555‡
Weight (kg)	63.41 ± 9.15	61.76 ± 6.66	61.79 ± 6.52	62.54 ±12.92	0.825‡
BMI(Mean±SD)	25.43 ± 3.38	25.17 ± 2.70	25.33 ± 3.04	25.10 ± 5.46	0.704‡

‡: p-value of Kruskal- Wallis Test
p-values <0.05 are considered significant

Biochemical parameters were assessed to exclude subjects with values outside normal ranges. On comparing the four groups, there was no significant between the four group for eosinophil sedimentation rate, total protein, albumin, globulin, and albumin globulin ratio. Significant differences were observed for hemoglobin (p=0.025) and total blood counts (p=0.020). Hemoglobim was not significantly correlated with any of the primary outcome measures and total blood counts were standardized to 50 million cells/ml for evaluation of NF-κB using peripheral blood mono-nucleated cells.

Table 14 Comparison of Anthropometric variables between the four groups					
ANTHROPOMETRY	**CBY (n=27)**	**CBN (n=25)**	**NHY (n=28)**	**NHN (n=28)**	**Sig.**
Hemoglobin (Mean±SD)	11.35 ± .75	11.81 ± .55	11.88 ± .70	11.86 ± .65	***0.025‡***
Eosinophil Sedimentation Rate	11.52 ± 5.98	10.32 ± 6.16	10.07 ± 5.73	11.75 ± 5.92	0.629
Total Blood count	8393.33 ± 2421.50	8713.60 ± 2868.32	10192.86 ± 2843.31	8550.00 ± 1445.94	***0.020‡***
Total Protein*	6.51 ± .35	6.74 ± .23	6.48 ± .45	6.60 ± .44	0.071
Albumin	3.96 ± .26	4.16 ± .18	4.01 ± .31	4.00 ± .28	0.080
Globulin	2.54 ± .24	2.58 ± .19	2.47 ± .28	2.59 ± .23	0.303
Albumin : Globulin	1.57 ± .19	1.62 ± .15	1.64 ± .22	1.55 ± .14	0.212
‡: p-value of Kruskal- Wallis Test *: Test for group differences with One-Way ANOVA p-values <0.05 are considered significant					

The occupation of the subjects varied significantly (p<0.001) with the highest number of employed subjects in the NHN group (89.29%) and lowest in the CBN group (32.00%). Daily working hours amongst subjects who were employed were also significantly different (p=0.027) with annual income varying significantly (p=0.027). There was a highly significant (rho=0.812, p<0.001) correlation between the working hours and annual income as expected, however there were no significant correlation between work hours or income and yoga practice or the primary outcome measures.

Table 15 Comparison of Occupational variables between the four groups						
OCCUPATIONAL		**CBY (n=27)**	**CBN (n=25)**	**NHY (n=28)**	**NHN (n=28)**	
Occupation	Housewife	10 (37.04%)	15 (60.00%)	16 (57.14%)	03 (10.71%)	***<0.001†***
	Employed	14 (51.85%)	08 (32.00%)	12 (42.86%)	25 (89.29%)	
	Retired	03 (11.10%)	02 (08.00%)	00 (00.00%)	00 (00.00%)	
Working Hours (mean±SD) [amongst employed]		7.36 ± 3.18	6.19 ± 3.87	5.75 ± 3.75	8.64 ± 1.71	***0.027‡***
Annual Income (X100,000)		47.21 ± 39.20	31.75 ± 90.36	15.00 ± 18.41	46.51 ± 71.51	***0.027‡***
†: p-value of Chi-Square Test ‡: p-value of Kruskal- Wallis Test p-values <0.05 are considered significant						

The marital status (p=0.797) and the parity (p=0.177) was similar with no significant differences between the four groups.

Table 16 Comparison of Socio-Demographic variables between the four groups						
SOCIODEMOGRAPHIC		**CBY (n=27)**	**CBN (n=25)**	**NHY (n=28)**	**NHN (n=28)**	
Marital status	Married	25 (92.59%)	23 (92.00%)	27 (96.43%)	26 (92.86%)	0.797†
	Unmarried	02 (07.41%)	02 (08.00%)	01 (03.57%)	02 (07.14%)	
Number of Children		1.67±0.83	1.88 ± 1.13	1.57 ± 0.74	1.29 ± 0.94	0.177‡
†: p-value of Kruskal- Wallis Test ‡: p-value of Chi-Square Test p-values <0.05 are considered significant						

Comparison of lifestyle variables indicated that the appetite was significantly better ($p<0.001$) in the NHY group but the CBY group reported to consuming significantly more ($p<0.001$) number of meals in a day. The numbers of vegetarians although similar across groups, the NHY group consisted of the largest number of vegetarians (89.29%). The frequency of non-vegetarian food consumed per month was notably lower in the NHY (2.33 ± 1.53) and NHN (2.89 ± 1.76) groups although it was non-significant.

Sleep duration ($p=0.046$) and sleep quality was significantly better in the NHY group with maximum percentage (75%) of the group reporting good sleep.

Table 17 Comparison of Lifestyle variables between the four groups						
LIFESTYLE		**CBY (n=27)**	**CBN (n=25)**	**NHY (n=28)**	**NHN (n=28)**	
Appetite	Poor	02 (07.41%)	02 (08.00%)	00 (00.00%)	00 (00.00%)	***<0.001†***
	Normal	16 (59.26%)	19 (76.00%)	11 (39.29%)	28 (100.0%)	
	Good	09 (33.33%)	04 (16.00%)	17 (60.71%)	00 (00.00%)	
Meals per day		3.15 ± 0.456	2.96 ± 0.200	2.86 ± 0.356	2.64 ± 0.488	***<0.001‡***
Diet	Non-Vegetarian	10 (37.04%)	10 (04.00%)	03 (10.71%)	09 (32.14%)	0.076†
Freq of Non-Veg/month [amongst non-veg]		7.50 ± 8.46	7.00 ± 9.02	2.33 ± 1.53	2.89 ± 1.76	0.134‡
Hours of Sleep		6.78 ± 0.93	6.84 ± 1.18	7.21 ± 0.96	6.29 ± 1.01	***0.046‡***
Quality of Sleep	Poor	07 (25.93%)	15 (06.00%)	02 (07.14%)	04 (14.29%)	***<0.001†***
	Normal	06 (22.22%)	06 (24.00%)	05 (17.86%)	05 (17.86%)	
	Good	14 (51.85%)	04 (16.00%)	21 (75.00%)	19 (67.86%)	
†: p-value of Kruskal- Wallis Test ‡: p-value of Chi-Square Test p-values <0.05 are considered significant						

Yoga experience was compared between the two groups (CBY & NHY). The number of months of yoga experience was similar ($p=0.220$) between the two groups but a larger percentage of the NHY group practiced yoga 3-4 times (57.14%) a week or 7 days per week

(17.86%). Other than yoga, subjects reported as having tried other CAM modalities in the past year. Although this was significantly different between the four groups, it did not correlate with any of the primary outcome measures. The CAM modality used was Ayurveda, for across all groups, except for two subjects in the NHN group, reporting Pranic Healing and Homeopathy.

Table 18 Comparison of Yoga experience between the four groups

YOGA EXPERIENCE		**CBY (n=27)**	**CBN (n=25)**	**NHY (n=28)**	**NHN (n=28)**	
Yoga Experience (months)		74.06 ± 96.05	-	74.39 ± 85.53	-	0.220‡
Regularity	Irregular	02 (07.41%)		00 (00.00%)		0.242†
	1-2 / week	01 (03.70%)	-	00 (00.00%)	-	
	3-4 / week	09 (33.33%)	-	16 (57.14%)	-	
	5-6 / week	10 (37.04%)	-	07 (25.00%)	-	
	7 / week	02 (07.41%)	-	05 (17.86%)	-	
Past CAM Use		11 (40.74%)	01 (04.00%)	01 (03.57%)	04 (14.29%)	***<0.001†***

†: p-value of Kruskal- Wallis Test
‡: p-value of Chi-Square Test
p-values <0.05 are considered significant

Between the two groups of cancer survivors, baseline comparisons showed that age of cancer diagnosis was matched (p=0.600) along with the post treatment duration (p=0.789). Stage and the present hormone therapy treatment were also comparable ((p=0.999, p=0.766) between the two groups. The above mentioned comparisons are presented in Table 19 below.

Table 19 Comparison of Cancer History between the four groups

		CBY (n=27)	**CBN (n=25)**	**NHY (n=28)**	**NHN (n=28)**	
Age at Diagnosis		49.33 ± 11.06	47.76 ± 10.36	-	-	0.600†
Years of Survival		4.07 ± 0.87	3.84 ± 1.38	-	-	0.789†
Stage	I	9 (33.33%)	8 (32%)	-	-	0.999‡
	II	13 (48.15%)	12 (48%)	-	-	
	III	4 (14.81%)	4 (16%)	-	-	
	IV	1 (3.7%)	1 (4%)	-	-	
Present Hormone therapy		4	3	-	-	0.766‡

†: p-value of independent samples t-Test
‡: p-value of Chi-Square Test
p-values <0.05 are considered significant

5.2. Psychological Variables

5.2.1. General Health

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly higher values as compared to CBY ($p<0.001$), NHY ($p<0.001$), and NHN ($p<0.001$) groups. Also NHY group had significantly better general health scores ($p<0.001$) as compared to NHN group. CBY group and NHY group did not show any significant differences.

Table 20 Results of General Health

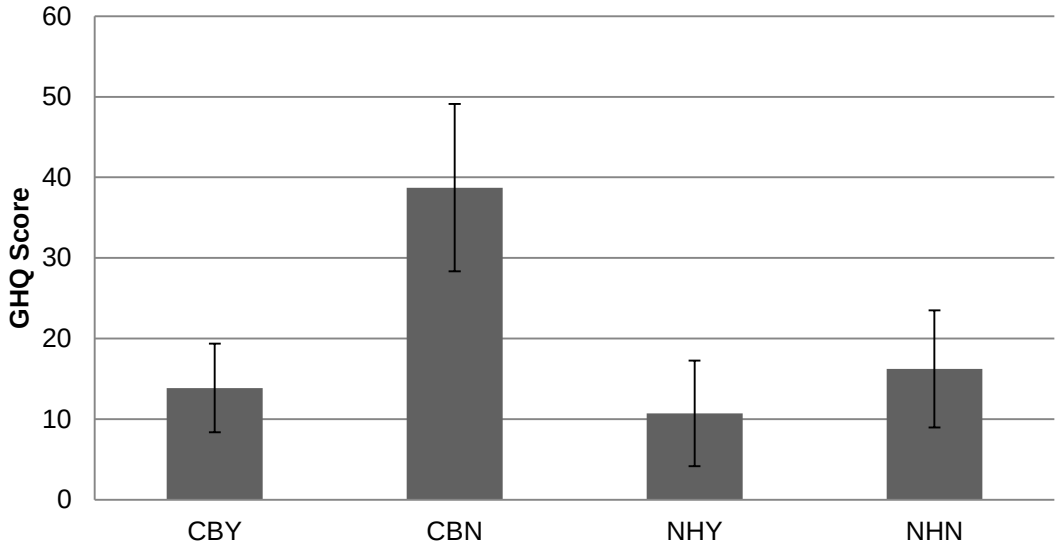
	CBY	CBN	NHY	NHN	Sig.
Mean ± SD	13.85 ± 5.50	38.72 ± 10.39	10.71 ± 6.54	16.21 ± 7.27	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Sig.
CBY	CBN	<0.001 *
NHY	NHN	<0.001 *
CBY	NHY	0.033
CBN	NHN	<0.001 *

†: Kruskal Wallis test for comparing multiple groups ($\alpha = 0.05$)
‡: Mann-Whitney-U test for pairwise comparisons ($\alpha = 0.008$)
*: Significant outcome

Figure 10 Results of General Health



5.2.2. Perceived Stress

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly higher values as compared to CBY ($p<0.001$) and NHN ($p<0.001$) groups. Also NHY group showed a trend of lower stress scores ($p<0.001$) as compared to NHN group. CBY group and NHY group did not show any significant differences.

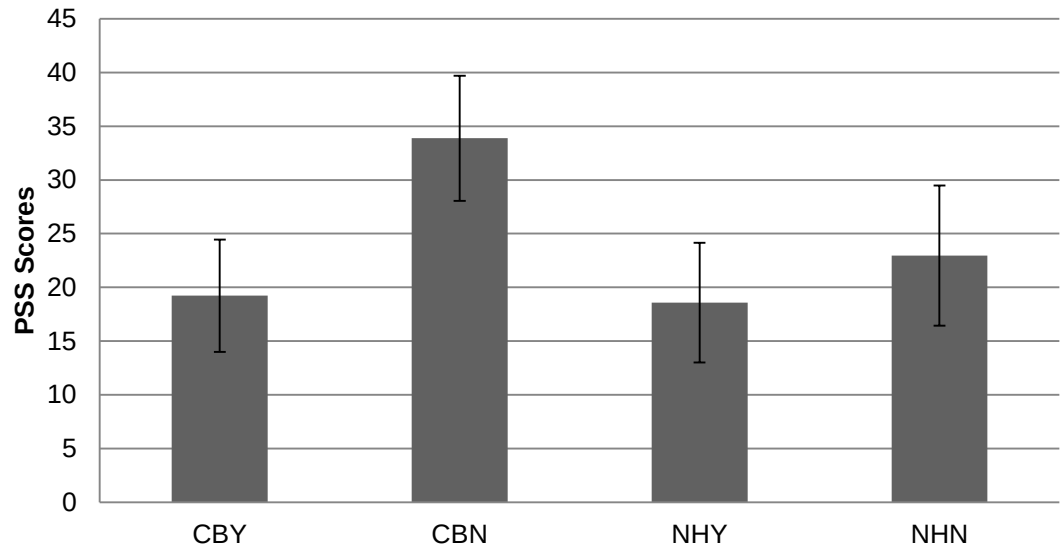
Table 21 Results of Perceived Stress

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	19.22 ± 5.24	33.88 ± 5.82	18.57 ± 5.57	22.96 ± 6.52	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	<0.001 *
NHY	NHN	0.010
CBY	NHY	0.813
CBN	NHN	<0.001 *

Figure 11 Results of Perceived Stress



5.2.3. Anxiety

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly higher values as compared to CBY ($p<0.001$) and NHN ($p<0.001$) groups. Also NHY group had significantly lower state anxiety scores ($p=0.005$) as compared to NHN group. CBY group and NHY group did not show any significant differences.

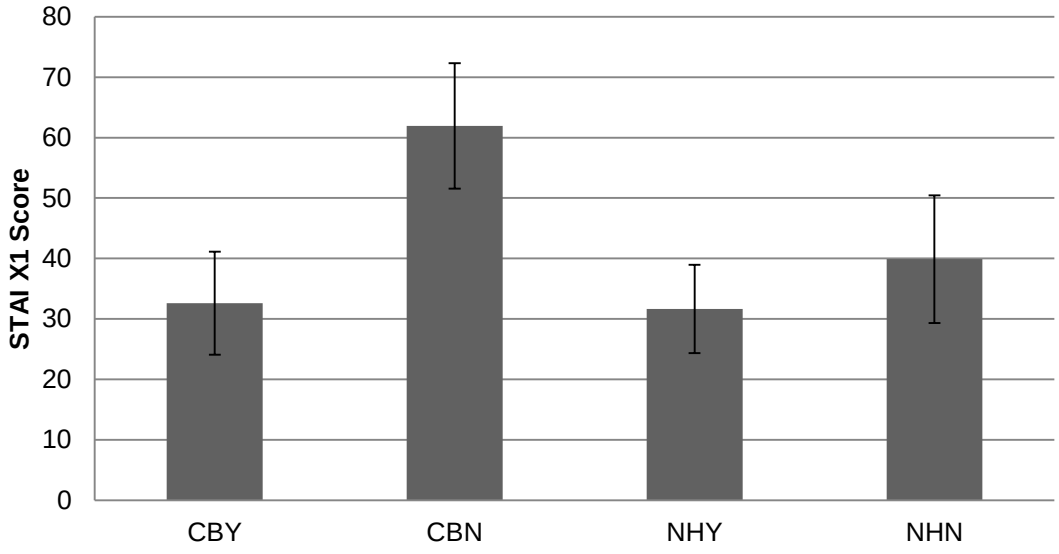
Table 22 Results of State Anxiety

	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	32.59 ± 8.53	61.96 ± 10.38	31.64 ± 7.30	39.89 ± 10.55	<0.001 *

Pairwise Comparisons

Group 1	**Group 2**	**Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]**
CBY	CBN	<0.001 *
NHY	NHN	0.005 *
CBY	NHY	0.846
CBN	NHN	<0.001 *

Figure 12 Results of State Anxiety



Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly higher values as compared to CBY ($p<0.001$) and NHN ($p<0.001$) groups. Also NHY group had significantly lower trait anxiety scores ($p<0.001$) as compared to NHN group. CBY group and NHY group did not show any significant differences.

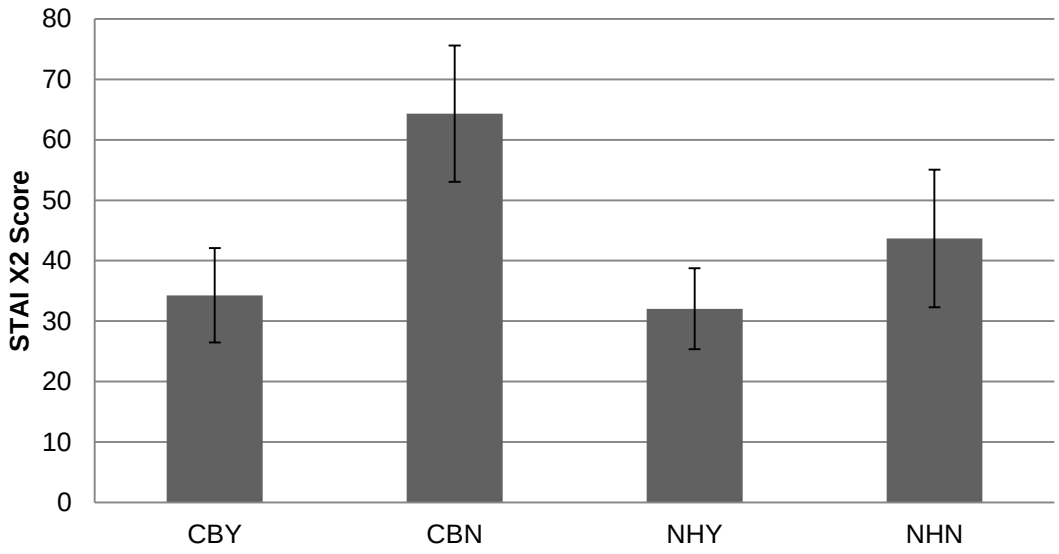
Table 23 Results of Trait Anxiety

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	34.26 ± 7.81	64.32 ± 11.29	32.04 ± 6.7	43.68 ± 11.39	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	<0.001 *
NHY	NHN	<0.001 *
CBY	NHY	0.438
CBN	NHN	<0.001 *

Figure 13 Results of Trait Anxiety



5.2.4. Depression

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly higher values as compared to CBY ($p<0.001$) and NHN ($p<0.001$) groups. CBY group and NHY group did not show any significant differences.

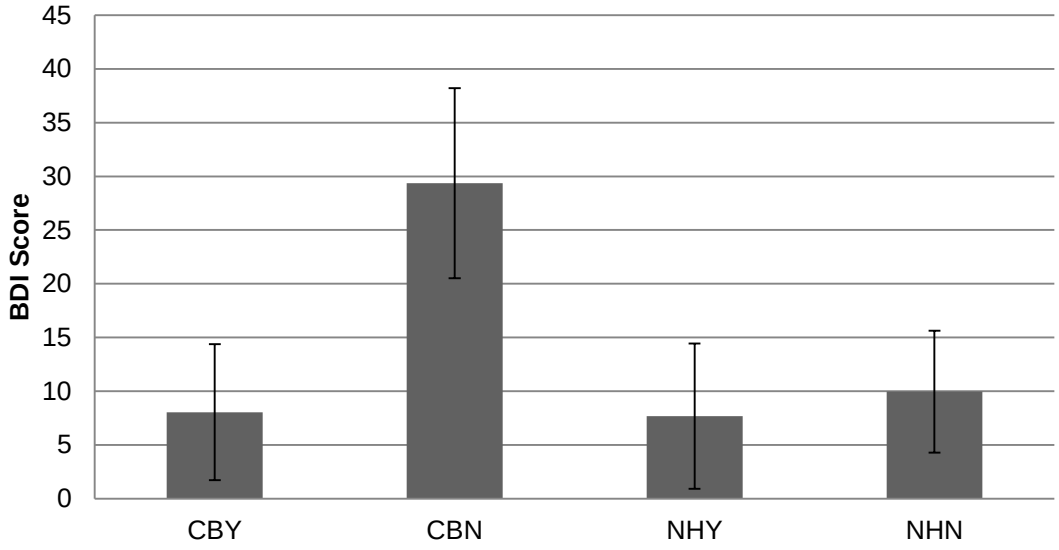
Table 24 Results of Depression

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	8.04 ± 6.33	29.36 ± 8.84	7.68 ± 6.77	9.96 ± 5.68	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	<0.001 *
NHY	NHN	0.099
CBY	NHY	0.774
CBN	NHN	<0.001 *

Figure 14 Results of Depression



5.2.5. Quality of Life

Kruskall-Wallis Test to compare the four groups indicated Significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons yielded significant difference between all pairs of comparisons ($p<0.001$) with physical quality of life being lowest in the CBN group.

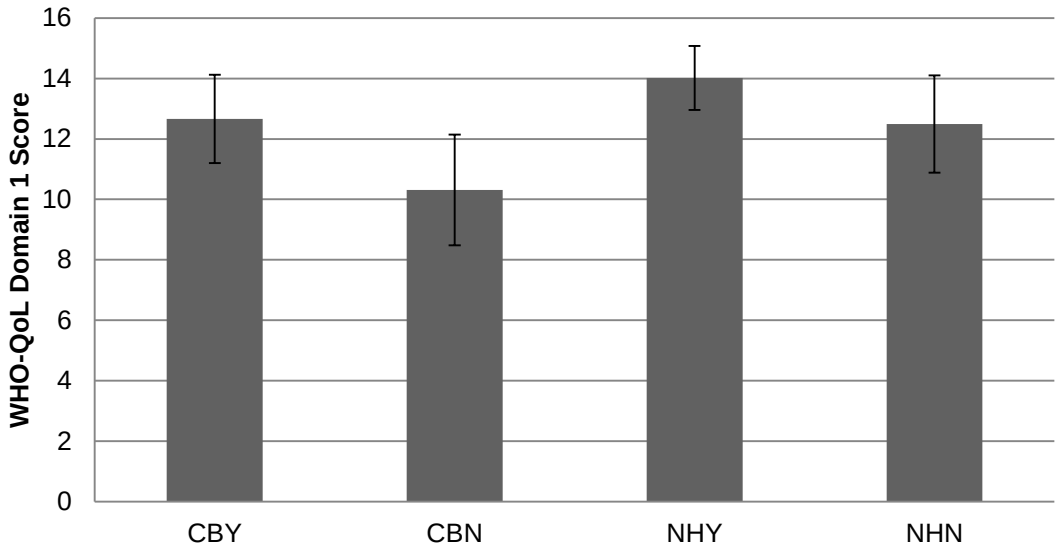
Table 25 Results of Quality of Life (Physical Domain)

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	12.66 ± 1.46	10.31 ± 1.83	14.02 ± 1.06	12.49 ± 1.61	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	<0.001 *
NHY	NHN	<0.001 *
CBY	NHY	<0.001 *
CBN	NHN	<0.001 *

Figure 15 Results of Quality of Life (Physical Domain)



Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly lower values as compared to CBY ($p<0.001$) and NHN ($p<0.001$) groups. CBY group and NHY group did not show any significant differences.

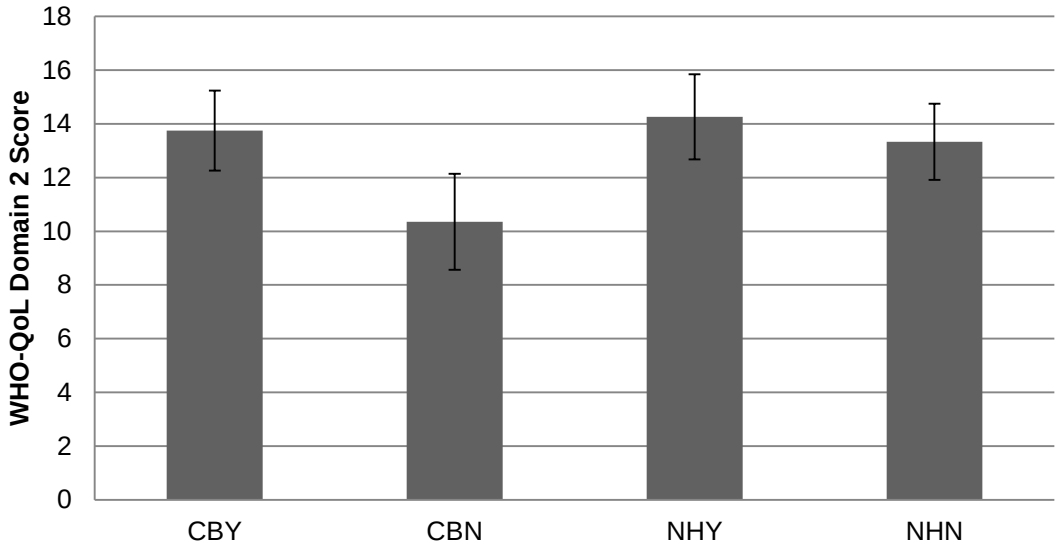
Table 26 Results of Quality of Life (Psychological Domain)

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	13.75 ± 1.49	10.35 ± 1.79	14.26 ± 1.58	13.33 ± 1.42	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni $\alpha = 0.00833$]
CBY	CBN	<0.001 *
NHY	NHN	0.041
CBY	NHY	0.275
CBN	NHN	<0.001 *

Figure 16 Results of Quality of Life (Psychological Domain)



Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly lower values as compared to CBY ($p<0.001$) and NHN ($p<0.001$) groups. Also NHY group had significantly better social quality of life scores ($p=0.001$) as compared to NHN group. CBY group and NHY group did not show any significant differences.

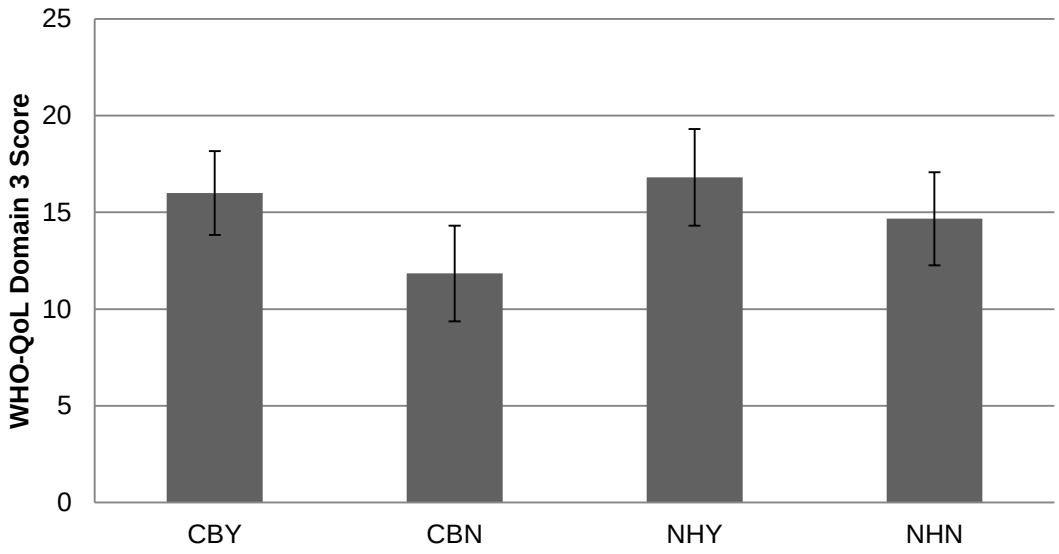
Table 27 Results of Quality of Life (Social Domain)

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	16.00 ± 2.16	11.84 ± 2.47	16.81 ± 2.50	14.67 ± 2.41	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	<0.001 *
NHY	NHN	0.001 *
CBY	NHY	0.056
CBN	NHN	<0.001 *

Figure 17 Results of Quality of Life (Social Domain)



Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups ($p<0.001$). Further analyses by pairwise comparisons showed that CBN group had significantly lower values as compared to CBY ($p<0.001$) and NHN ($p<0.001$) groups. Also NHY group had significantly better functional quality of life scores ($p<0.001$) as compared to NHN group. CBY group and NHY group did not show any significant differences.

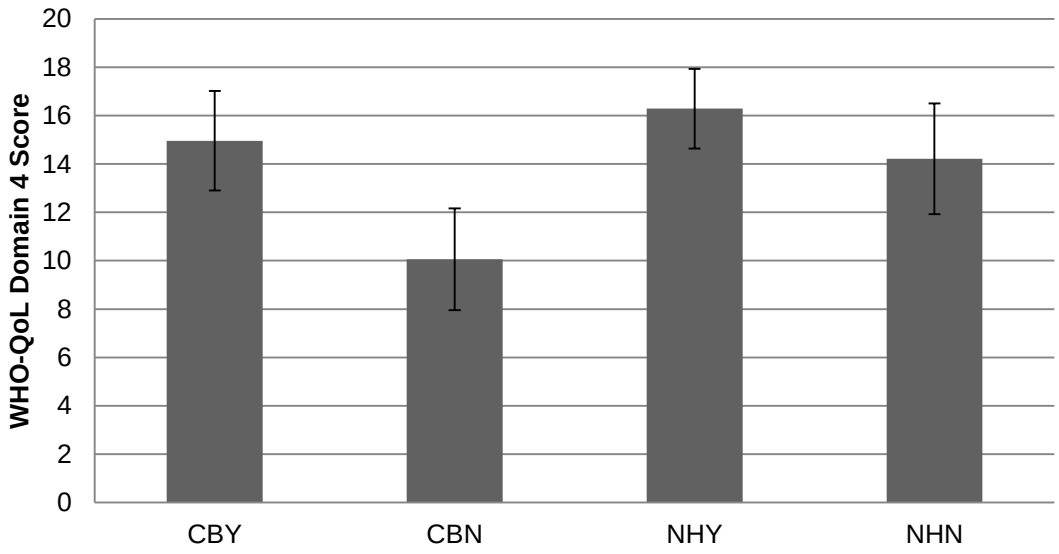
Table 28 Results of Quality of Life (Functional Domain)

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	14.96 ± 2.06	10.06 ± 2.11	16.29 ± 1.65	14.21 ± 2.29	<0.001 *

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	<0.001 *
NHY	NHN	<0.001 *
CBY	NHY	0.018
CBN	NHN	<0.001 *

Figure 18 Results of Quality of Life (Functional Domain)



5.3.Immunological Variables

The immune measures were included from three broad categories of cellular indicators of inflammation. They were Th1 and Th2 cytokines and NF-κB.

5.3.1. Nuclear Factor κ –B

NF-κB levels indicated significant differences between all four groups (p=0.012), whereas pairwise comparisons showed no significant differences between groups. Higher values were recorded in the NHY group in comparison with the NHN group (p=0.058) and also the CBY group (p=0.094) although non-significant.

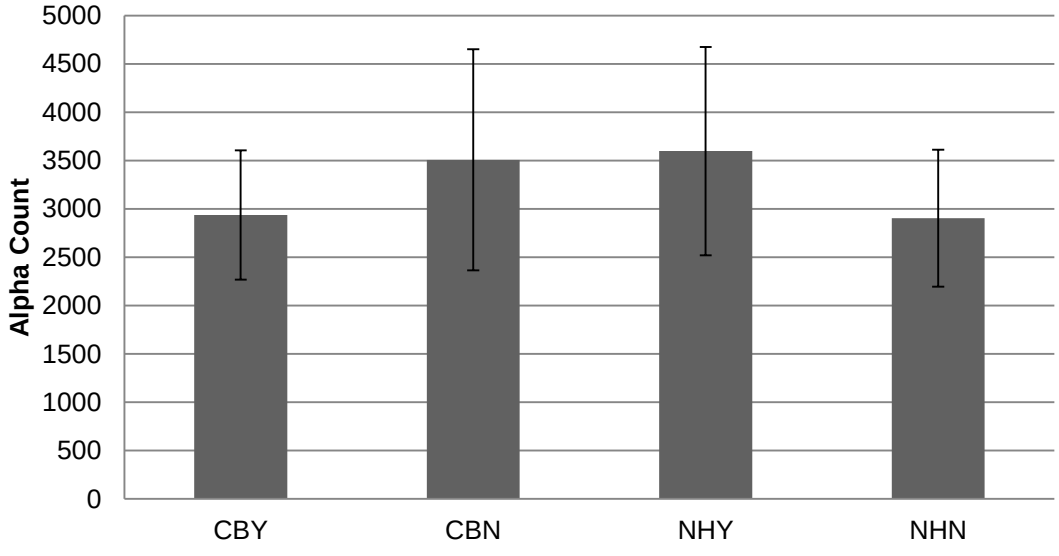
Table 29 Results of Nuclear Factor κ - B

	CBY (n=26)	CBN (n=22)	NHY (n=25	NHN (n=24)	ANOVA (sig.)
Mean ± SD	2936.73 ± 667.56	3507.93 ± 1142.28	3597.41 ± 1077.98	2904.83 ± 708.71	0.012 *

Pairwise Comparisons

Group 1	Group 2	Post-Hoc Tests (Sig.)
CBY	CBN	0.225
NHY	NHN	0.058
CBY	NHY	0.094
CBN	NHN	0.149
CBY	NHN	1.000
CBN	NHY	1.000

Figure 19 Results of Nuclear Factor κ – B



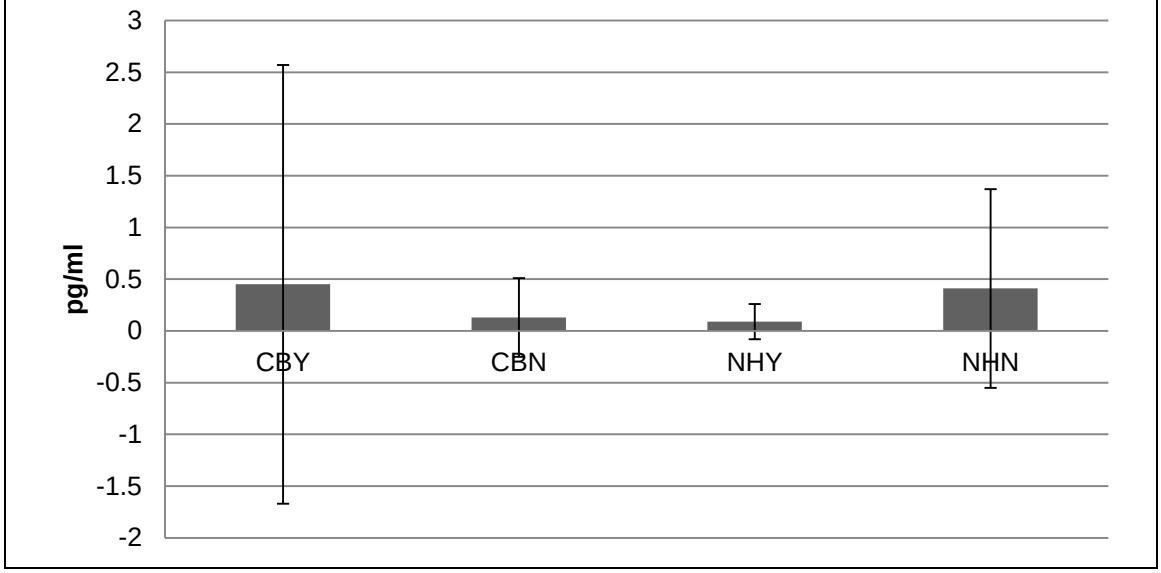
5.3.2. Interleukin 1 – α

Kruskall-Wallis Test to compare the four groups indicated **no significant differences** between the groups (p=0.128). Data were not subjected to further analyses.

Table 30 Results of Interleukin 1 – α					
	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	0.45 ± 2.12	0.13 ± 0.38	0.09 ± 0.17	0.41 ± 0.96	0.128

Pairwise Comparisons not done as no significant difference between groups

Figure 20 Results of Interleukin 1 – α



5.3.3. Interleukin 1 – β

Kruskall-Wallis Test to compare the four groups indicated a significant differences between the groups (p=0.040). However, further analyses by pairwise comparisons showed no significant difference but noted lower values in the NHY group as compared to NHN group (p=0.017) and CBN group (p=0.016).

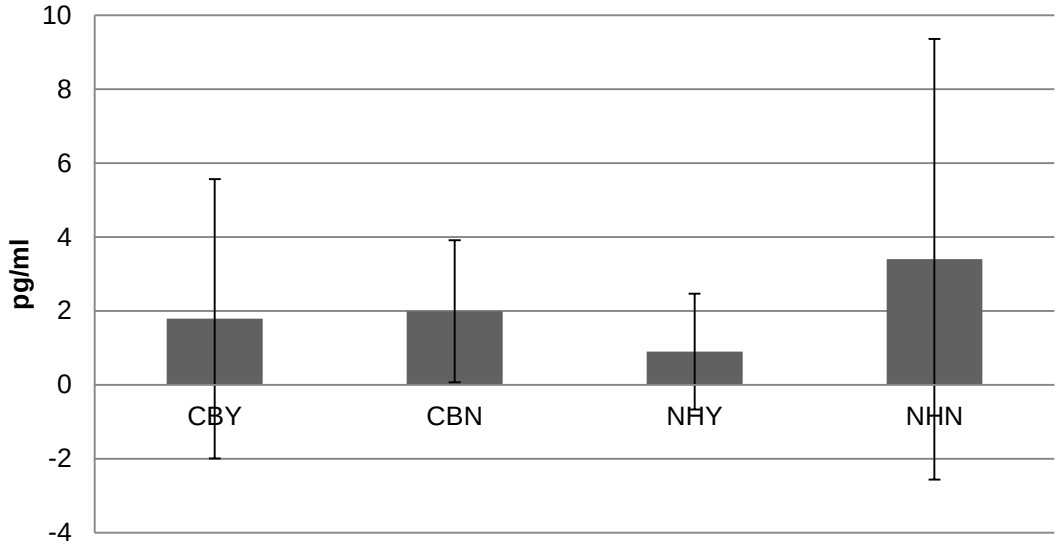
Table 31 Results of Interleukin 1 – β

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	1.79 ± 3.78	1.99 ± 1.92	0.90 ± 1.57	3.40 ± 5.96	0.040

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	0.142
NHY	NHN	0.017
CBY	NHY	0.329
CBN	NHN	0.918
CBY	NHN	0.151
CBN	NHY	0.016

Figure 21 Results of Interleukin 1 – β



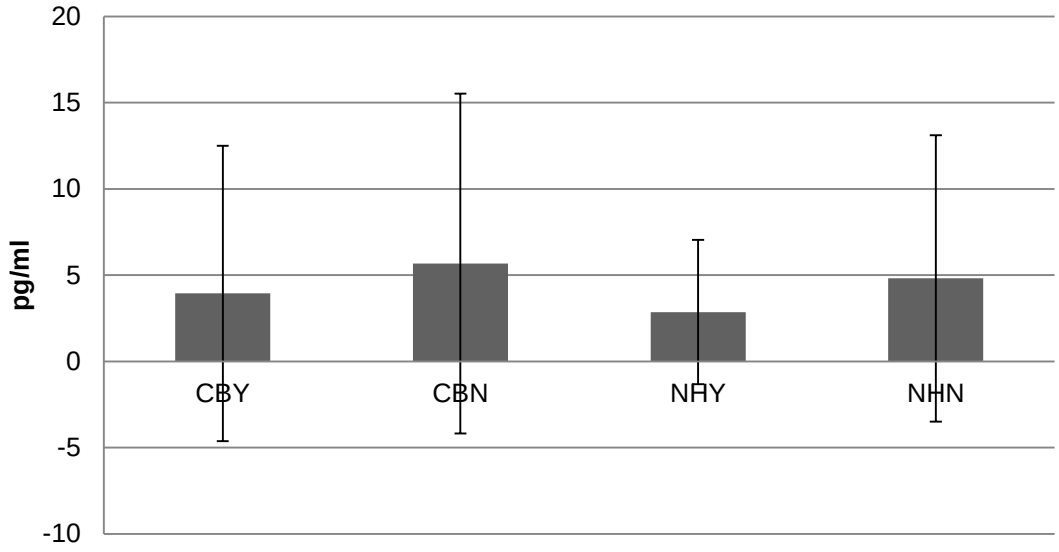
5.3.4. Interleukin 2

Kruskall-Wallis Test to compare the four groups indicated **no significant differences** between the groups (p=0.424). Data were not subjected to further analyses.

Table 32 Results of Interleukin 2					
	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	3.94 ± 8.56	5.67 ± 9.86	2.86 ± 4.18	4.81 ± 8.30	0.424

Pairwise Comparisons not done as no significant difference between groups

Figure 22 Results of IL-2



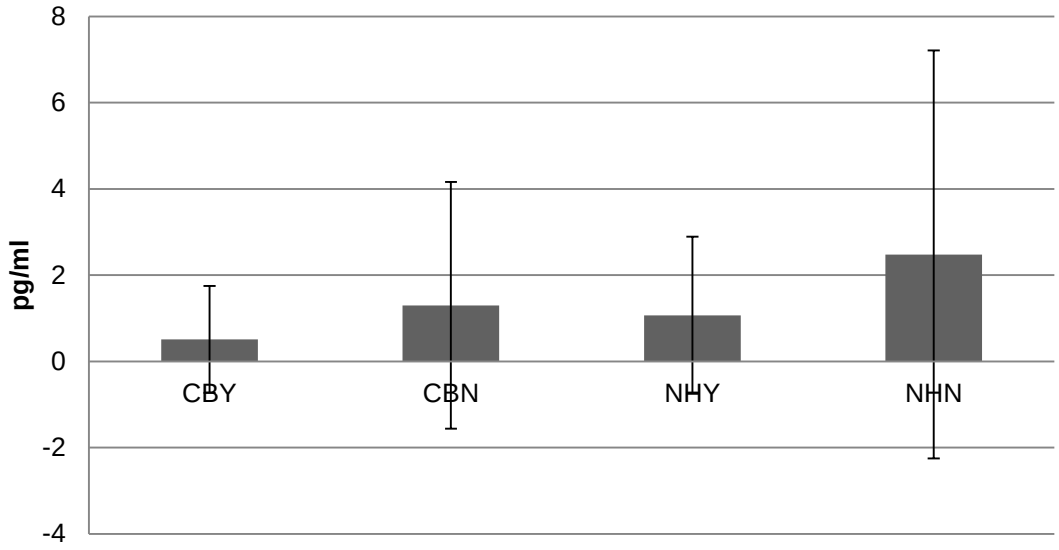
5.3.5. Interleukin 4

Kruskall-Wallis Test to compare the four groups indicated **no significant differences** between the groups (p=0.138). Data were not subjected to further analyses.

Table 33 Results of Interleukin 4					
	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	0.51 ± 1.24	1.30 ± 2.86	1.07 ± 1.82	2.48 ± 4.73	0.138

Pairwise Comparisons not done as no significant difference between groups

Figure 23 Results of IL-4



5.3.6. Interleukin 6

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups (p=0.019). Pairwise comparisons showed significantly higher values in NHN group (p=0.005) in comparison to the CBY group. NHN group had highest values of IL-6 amongst all four groups. Higher values of IL-6 were noted in the NHY group (p=0.010) as compared to CBY group, although it was not significant.

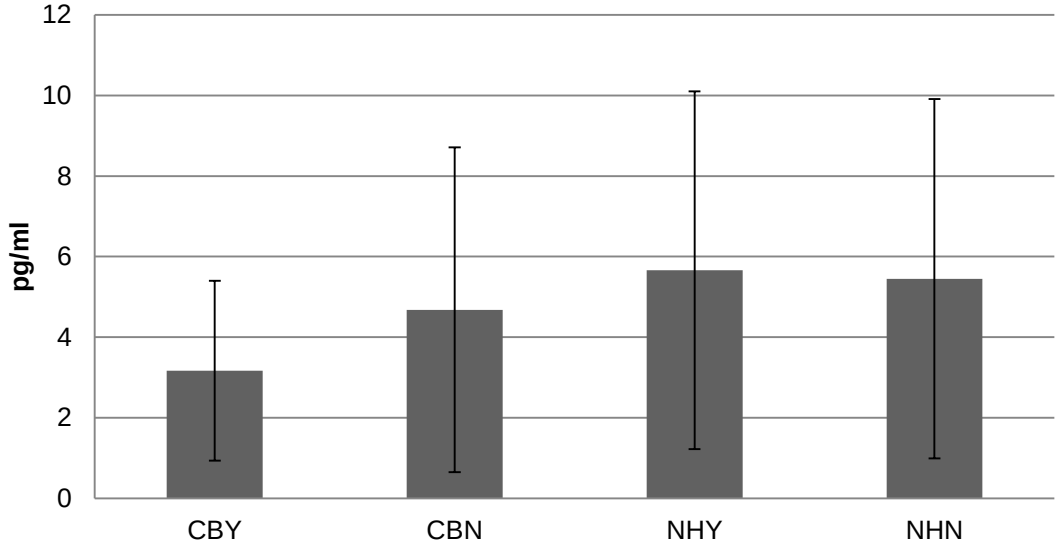
Table 34 Results of Interleukin 6

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	3.17 ± 2.23	4.68 ± 4.03	5.66 ± 4.44	5.45 ± 4.46	0.019

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]
CBY	CBN	0.087
NHY	NHN	0.851
CBY	NHY	0.010
CBN	NHN	0.384
CBY	NHN	***0.005****
CBN	NHY	0.289

Figure 24 Results of IL-6



5.3.7. Interleukin 8

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups (p=0.022). Pairwise comparisons showed significantly lower values in the CBY group as compared to NHN group (p=0.003). Comparison of CBY and CBN groups did not show any significant differences. The reasons for the observed differences have been elaborated in the discussion.

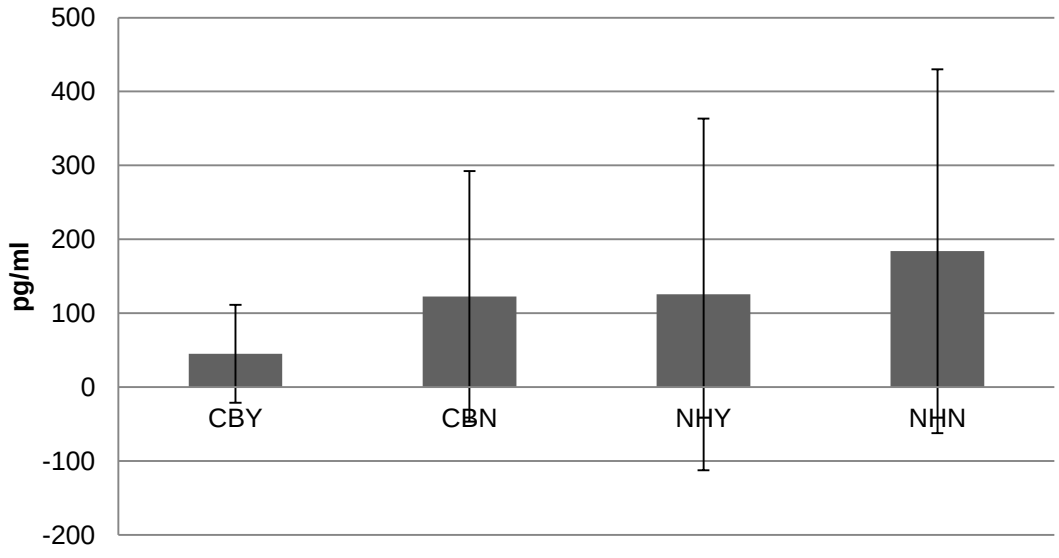
Table 35 Results of Interleukin 8

	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	45.12 ± 66.39	122.82 ± 169.51	125.50 ± 237.83	183.96 ± 246.14	0.022

Pairwise Comparisons

Group 1	**Group 2**	**Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]**
CBY	CBN	0.062
NHY	NHN	0.091
CBY	NHY	0.182
CBN	NHN	0.193
CBY	NHN	***0.003****
CBN	NHY	0.627

Figure 25 Results of IL-8



5.3.8. Interleukin 10

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups (p=0.005). Further analyses by pairwise comparisons showed that CBN group had significantly higher values as compared to NHY (p=0.012). The values for IL-10 in the CBY group were a constant 0.00 and hence could not be utilized for the comparison with other groups but it could indicate that the entire group had values lower than the detectable ranges. .

Table 36 Results of Interleukin 10

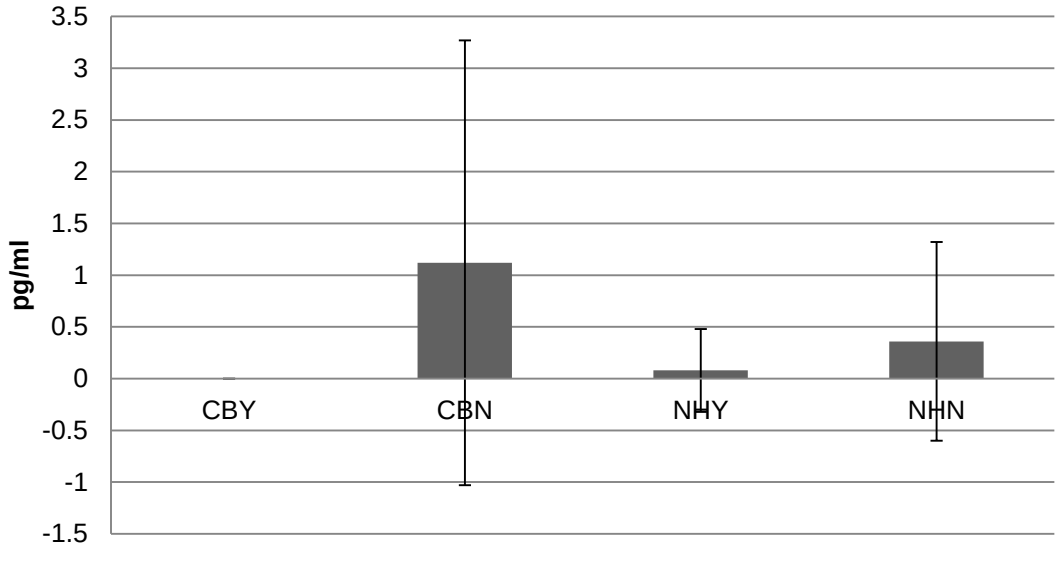
	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	0.00 ± 0.00‡	1.12 ± 2.15	0.08 ± 0.40	0.36 ± 0.96	0.005 *

‡: IL10 values were lower than those detectable by the assay protocol and hence have been considered as 0 values.

Pairwise Comparisons

Group 1	Group 2	Mann-Whitney U (Sig.) [Bonferroni α = 0.016]
NHY	NHN	0.174
CBN	NHN	0.156
CBN	NHY	***0.012****

Figure 26 Results of IL-10



5.3.9. Vascular Endothelial Growth Factor

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups (p=0.033). Further analyses by pairwise comparisons showed that NHN group had significantly lower values as compared to NHY (p=0.001). The possible reasons for the observed values are elaborated in the discussion

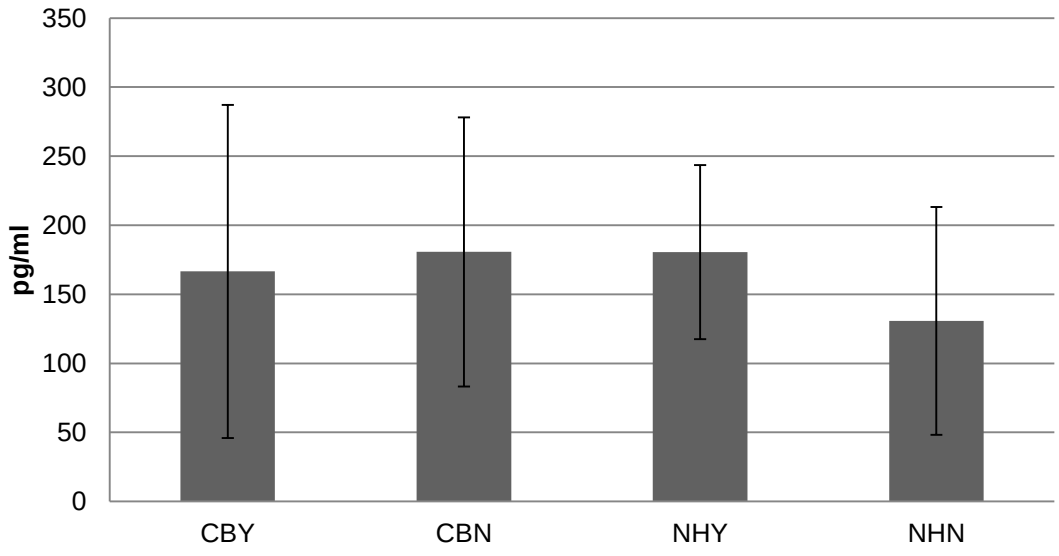
Table 37 Results of Vascular Endothelial Growth Factor

	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	166.56 ± 120.60	180.69 ± 97.39	180.58 ± 63.05	130.74 ± 82.57	0.033 *

Pairwise Comparisons

Group 1	**Group 2**	**Mann-Whitney U (Sig.) [Bonferroni α = 0.00833]**
CBY	CBN	0.422
NHY	NHN	***0.001****
CBY	NHY	0.263
CBN	NHN	0.050
CBY	NHN	0.300
CBN	NHY	0.627

Figure 27 Results of VEGF



5.3.10.Interferon – γ

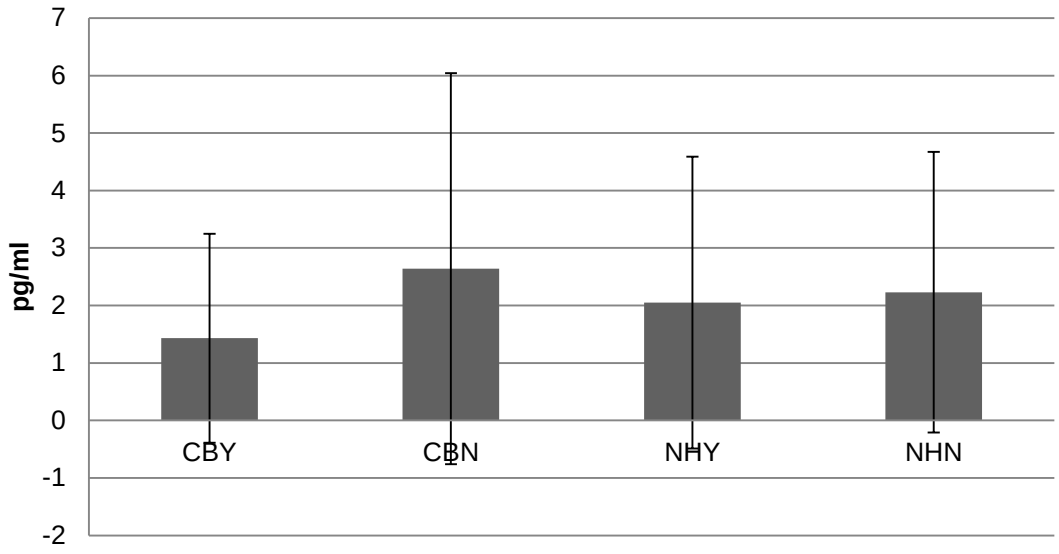
Kruskall-Wallis Test to compare the four groups indicated **no significant differences** between the groups (p=0.612). Data were not subjected to further analyses. Although these values are not significant, it has values similar to other studies.

Table 38 Results of Interferon - γ

	CBY	CBN	NHY	NHN	Kruskal Wallis (sig.)
Mean ± SD	1.43 ± 1.82	2.64 ± 3.40	2.05 ± 2.54	2.23 ± 2.44	0.612

Pairwise Comparisons not done as no significant difference between groups

Figure 28 Results of Interferon - γ



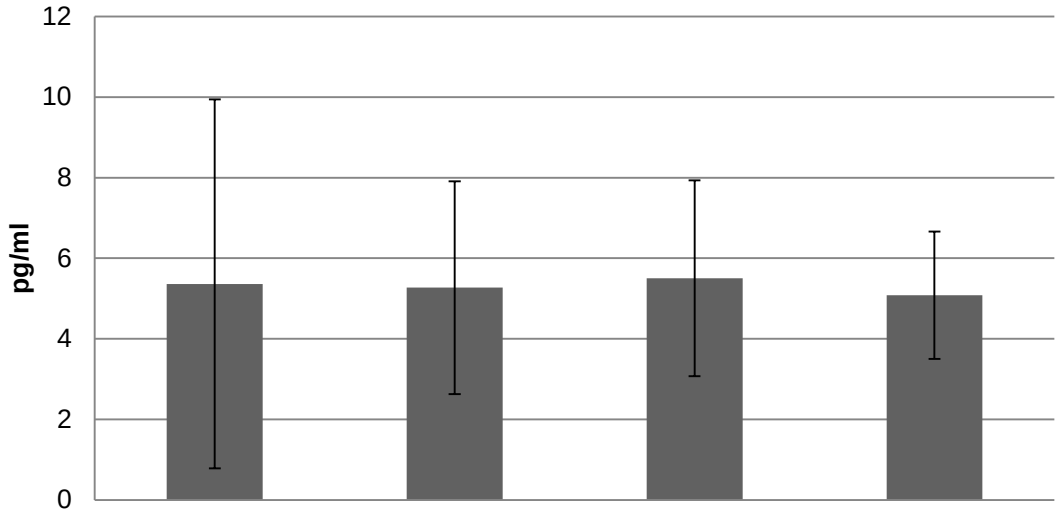
5.3.11. Tumor Necrosis Factor – α

Kruskall-Wallis Test to compare the four groups indicated **no significant differences** between the groups (p=0.264). Data were not subjected to further analyses.

Table 39 Results of Tumor Necrosis Factor - α					
	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	5.36 ± 4.58	5.27 ± 2.64	5.50 ± 2.43	5.08 ± 1.58	0.264

Pairwise Comparisons not done as no significant difference between groups

Figure 29 Results of TNF-α



5.3.12.Monocyte Chemotactic Protein – 1

Kruskall-Wallis Test to compare the four groups indicated significant differences between the groups (p=0.033). Further analyses by pairwise comparisons showed that CBN group had significantly higher values as compared to CBY (p=0.066) and a trend as compared to NHN (p0.084) groups.

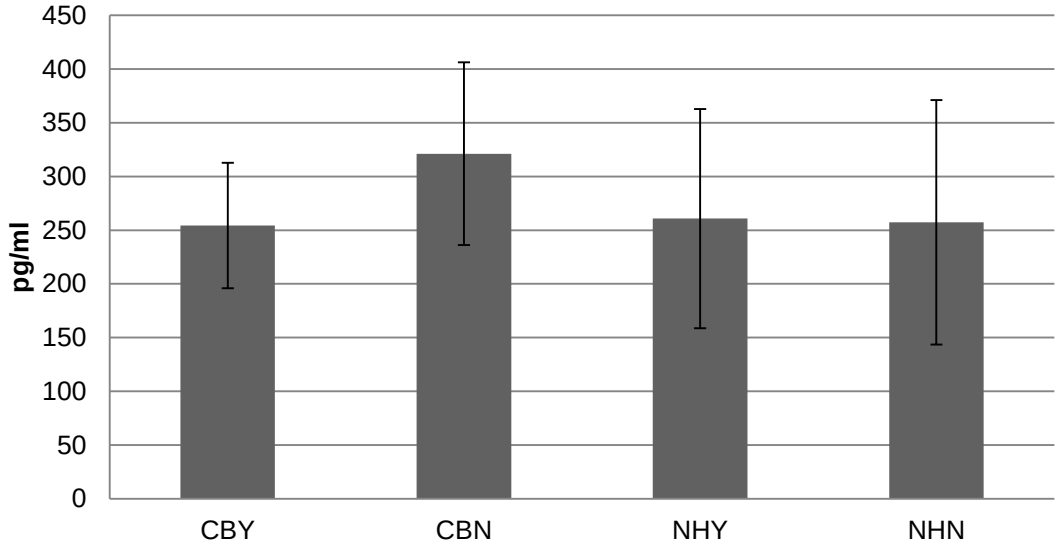
Table 40 Results of Monocyte Chemotactic Protein – 1

	CBY	CBN	NHY	NHN	ANOVA (sig.)
Mean ± SD	254.44 ± 58.36	321.08 ± 85.04	260.81 ± 102.04	257.34 ± 113.88	0.033 *

Pairwise Comparisons

Group 1	Group 2	Post-Hoc Tests (Sig.)
CBY	CBN	0.066
NHY	NHN	1.000
CBY	NHY	1.000
CBN	NHN	0.084
CBY	NHN	1.000
CBN	NHY	0.120

Figure 30 Results of MCP-1



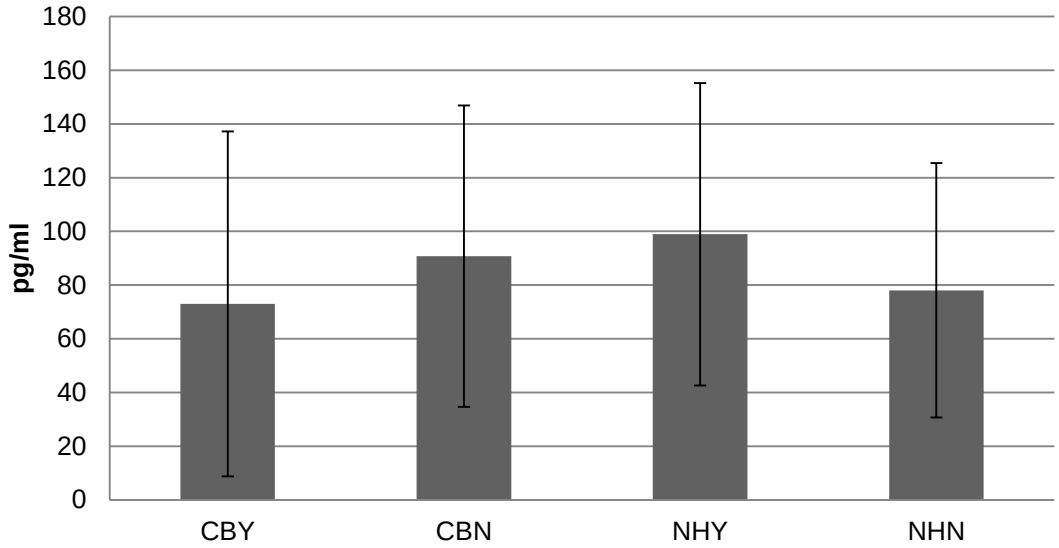
5.3.13.Epidermal Growth Factor

Kruskall-Wallis Test to compare the four groups indicated **no significant differences** between the groups (p=0.320). Data were not subjected to further analyses.

Table 41 Results of Epidermal Growth Factor					
	CBY	**CBN**	**NHY**	**NHN**	**Kruskal Wallis (sig.)**
Mean ± SD	73.02 ± 64.20	90.74 ± 56.09	98.93 ± 56.30	78.06 ± 47.39	0.320

Pairwise Comparisons not done as no significant difference between groups

Figure 31 Results of EGF



5.3.14.Direction of difference in cytokine measures (secondary analyses)

Considering the fact that the cytokine measures did not show much inferential evidence for group differences, a preliminary attempt was made to explore the direction of the group differences irrespective of the magnitude of the difference. [For example, in the cell comparing CBN-CBY for IL1α, the 'up arrow' indicates that the CBY group had higher values than the CBN group although not significant]. Results of a chi square test indicated that a significantly larger number of cytokine measures had lower mean values in the CBY group as compared the CBN groups. (p=0.021) Whereas this was not the case between NHN and NHY group (p=1.000). Also a significantly larger number of variables had lower mean values in the CBY group as compared to the NHY group (p=0.021) which again was not the case when NHN and CBN groups were compared.

Table 42 Relative difference between groups for immune variables

Name	Function	CBN - CBY	NHN - NHY	NHY - CBY	NHN-CBN
IL1α	Pro-inflammatory	↑	↓	↑	↓
IL1β*	Pro-inflammatory	↓	↓	↑	↓
IL2	Pro-inflammatory	↓	↑	↓	↑
IL8*	Pro-inflammatory	↓	↓	↓	↓
VEGF*	Pro-inflammatory	↓	↑	↓	↑
IFNγ	Pro-inflammatory	↓	↓	↓	↑
MCP1*	Pro-inflammatory	↓	↑	↓	↑
EGF	Pro-inflammatory	↓	↑	↓	↑
TNFα	Pro-inflammatory	↑	↑	↓	↑
IL10*	Pleomorphic	↓	↓	↓	↑
IL6*	Pleomorphic	↓	↑	↓	↓
IL4	Anti-Inflammatory	↓	↓	↓	↑
Sig.(X^2 test for goodness of fit)		0.021*	1.000	0.021	1.000

6. DISCUSSION

Since the first published research article evaluating the benefits of a support group therapy(Spiegel, Bloom, & Yalom, 1981) in 1981, several researchers have used techniques like mindfulness-based stress reduction (MBSR), progressive muscle relaxation, Tibetan yoga as alternative forms of mindful and proactive non-pharmacological methodologies in combination with conventional treatment and seen a plethora of benefits in cancer care.

There are many schools of yoga that are being practiced today in the world. These range from simple body postures either with or without the use of props to meditation. Iyengar yoga is one such school of yoga that prescribes simple asanas with supportive aids like pillows, wooden blocks and ropes that assist in reaching final position of difficult postures. Also breath modulation (pranayama) and meditation are practiced in these final postures. Other schools like Sudarshan Kriyā Yoga, Hatha Yoga, and Patanjali yoga have varying proportions of physical, breath and mind activities implemented through diverse techniques. As the premise for calling any practice 'yoga' is clearly defined in ancient Indian literature as *'chitta vritti nirodhah'* (voluntary mastery over the modifications of the mind)(chapter 1 verse2)(Taimni, 1999) and offered practices to achieve this. Researchers have the freedom to select and modify the intervention to suit the desired objectives while maintaining the basic requirement of mind-mastery.

This cross sectional study with four cohorts was an effort to find continuing evidence for the yoga model of PNI of cancer. In order to assess the differences in immunological and psychological profiles of breast cancer survivors who have previously practiced yoga, with age matched yoga naïve survivors. These were also compared with age matched healthy women with and without prior yoga exposure. These groups were chosen with the intent of observing differences between four distinct phases of the health spectrum viz. previous ill-health, previous

ill-health with restorative techniques being practices, normal health, and positive health. The interpretation of the observed difference are presented in the chapter below in detail

6.1. Psychological variables

The psychological state of an individual has been implicated as a factor that influences cancer prognosis, treatment response and several cancer survival health indices. (Buffart et al., 2012; Ganz et al., 1996; Rogers et al., 2012; Simard et al., 2013) In order to assess the state of the mind, the below variables were included.

There was significant differences seen across all psychological variables and have been discussed below.

6.1.1. General Health

The General healthy questionnaire is a screening tool for psychological dysfunction and values of GHQ above 24 are considered an index for psychological ill-health. The present study shows that the CBN group had the highest scores of GHQ that was significantly different from the other three groups. Of the 25 subjects in the CBN group only 3 had scores lesser than the cutoff value of 24. CBY group was similar in scores to the NHN and that NHY group showing no significant differences.

This questionnaire provides a lead that yoga has helped and it is imperative to understand what aspects of psychology are being influenced by the practices of yoga. GHQ is a questionnaire that is inclusive of several domains of psychological health including somatic symptoms, anxiety/insomnia, social dysfunction and depression. Since GHQ is a good screening tool, it has been able to detect higher psychological abnormalities in CBN as compared to CBY group. Also the yoga practitioners have significantly lower scores of GHQ in both the healthy and the cancer survivor populations. It is interesting to note that the CBY and the NHY groups

have no significant difference between them indicating that yoga influences psychological profile irrespective of health or disease. Further test tools help us look into the details of the role of yoga on different components of psychological ill health.

6.1.2. Perceived Stress

It is important to emphasize that psychological stress is defined not solely in terms of the stimulus condition or the response variables, but rather in terms of the transaction between the person and the environment. Psychological stress involves interpretation of the meaning of an event and the interpretation of the adequacy of coping resources. In short, the psychological perspective on stress assumes that stress arises totally out of persons' perceptions (whether accurate or inaccurate) of their relationship to their environment".(S Cohen, Kessler, & Gordon, 1997) When the environmental situation such as cancer survival is appraised as stressful it leads to how the chain of downstream responses causes further psychological abnormalities. This further affects, not just the psychosocial domains but also physiological functioning that modulates several determinants of cancer survival.

The present study showed highest values of perceived stress in the CBN group and was significantly higher than in the NHN group. This showed that cancer survival is still perceived as stressful environment. Further, the CBY group had significantly lower PSS values as compared to CBN group and was not significantly different from the NHY group. This suggested a very important effect of yoga in maintaining a lower perceived stress of cancer survival to the extent of reaching normalcy.

6.1.3. State and Trait Anxiety

Response to a stressor can manifest as anxiety or depression. The psychometric tool used in the present study to assess anxiety levels evaluates two aspects of anxiety, the temporary

condition of “state anxiety” and the more general and long-standing quality of “trait anxiety”. State anxiety is a measure of how the subject is feeling at that present moment and trait anxiety measures the anxiety habit of the individual.

The present study showed highest values of state and trait anxiety in the CBN group and was significantly higher than in the NHN group. This showed that cancer survivors have habituated higher levels of anxiety response which could be triggered by any stimulating circumstances. Further, the CBY group had significantly lower STAI scores as compared to CBN group and was not significantly different from the NHY group. This suggested a very important effect of yoga in lowering the response to the stressor. This could have been achieved by two mechanisms; restoration of autonomic balance where responses towards a perceived stressor are more controlled or by reducing the perception of an event as stressful thereby not requiring an anxiety response.

This effect of lower anxiety scores was observed in the yoga group and non-yoga group of healthy volunteers indicating that there is a progression towards a positive state of psychological health.

6.1.4. Depression

The questionnaire attempts to measure the intensity, severity and depth of depression. It is commonly used in clinical setting as a novel way of diagnosing and categorizing depression in psychiatric settings. The outcome of the BDI scoring, results in categorization of the level of depression. Individuals with scores from 15 to 30 are categorized as moderately depressed; below 15 are mild and above 30 are severely depressed. The outcome in the present study indicated that the CBN group had averages on nearing severe depression (29.36 ± 8.84) and all the other groups had scores less than 10 indicating that they were in the mildly depressed

category. Of the entire study sample only CBN group members were severely depressed with 13 of the 25 CBN group subjects scoring above 30. There were 6 subjects with BDI scores of 0 and all these subjects belonged to either CBY (n=4) or NHY (n=2) groups. Group comparisons indicated similar patterns as anxiety and perceived stress, with CBN group having higher scores of depression than the NHN group, CBY group with lower values than CBN group, and CBY group having values similar to those of the NHY group.

Depression is yet another response to perception of environmental situations as stressful. Depressions fall in the sequence of psychological events that originate from wrong understanding and perception of a situation and culminate in incorrect behavior. The present data reiterates this progression of perceived stress influencing the depressive response similar to that of the anxiety response seen in the previous section.

6.1.5. Quality of Life

The world health organization has developed this scale (WHOQOL BREF) as a quick tool to assess four domains of Quality of Life; physical, psychological, social and functional. Quality of Life has become an important factor in defining the health of an individual. Today, leading oncologists weigh in the quality of life of the patient while planning treatment. The common paradigm is “adding life to years rather than adding years to life” and thus better QoL has become a measure of the success of treatment.

Quality of Life reflects the psychological imbalances that result from amplified responses to incorrectly perceived environmental situations. The higher scores of WHOQOL-BREF indicate a higher quality of life in the specific domains.

The present study showed the lowest scores for all domains in the CBN group and highest scores in the NHY group. Group comparisons indicated similar patterns to previously described

psychometric measures, with CBN group having higher scores than the NHN group, CBY group with lower values than CBN group, and CBY group having values similar to those of the NHY group across all domains. Hence the global quality of life is seen to be higher in cohorts that did yoga. This data also provides preliminary evidence that the deficiency of the quality of life can be reversed and brought back to normalcy by the practice of yoga.

Another pilot study by Littman et al (Littman et al., 2012) indicated an increasing trend in overall quality after yoga, which was similar to the present study. Their study recruited n=63 stage 0-III borderline obese and overweight breast cancer survivors to a 6 month viniyoga intervention and showed that Overall QoL evaluated by the FACT QoL questionnaire improved significantly in the yoga group as compared to the control. In the present study, a different instrument (WHO-QOL), which is applicable for normal individuals, was used for the evaluation of quality of life, as all subjects in the present study were presently healthy.

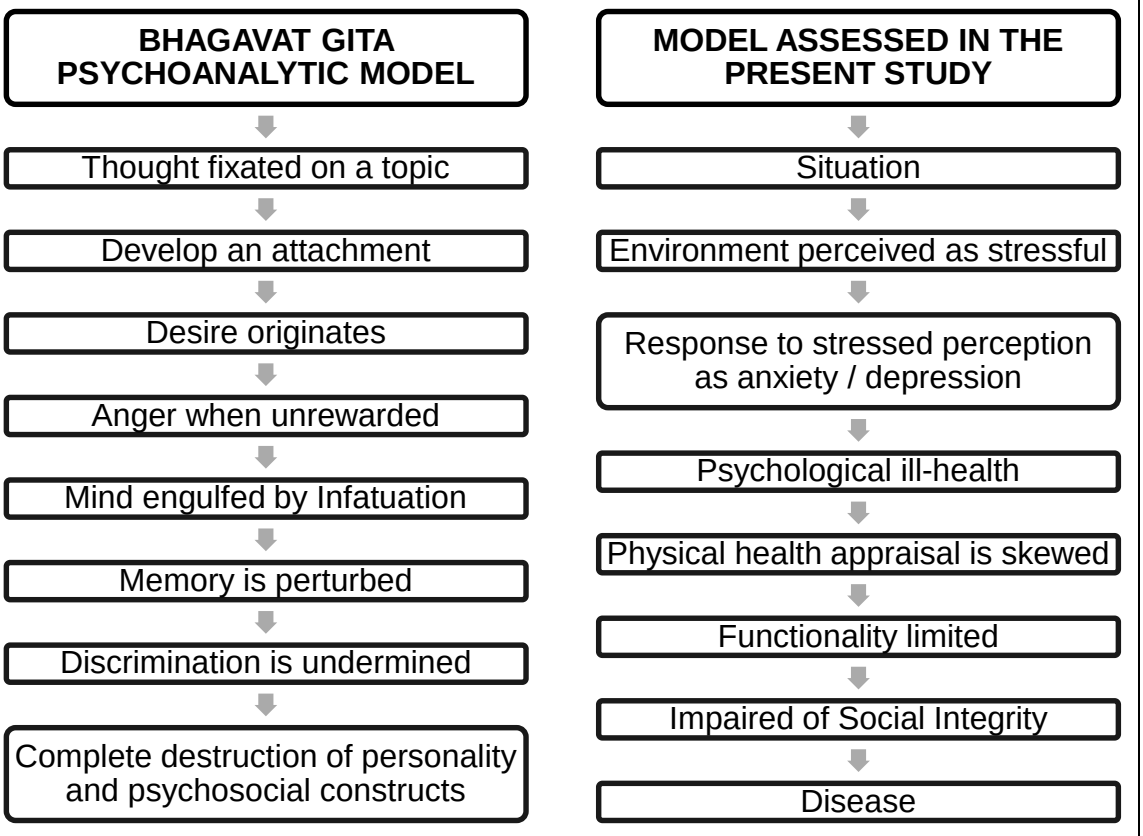
6.1.6. Overview of differences in psychological profiles

To be able to understand the flow of the development of psychological imbalance, it is advisable to look at an overview of differences in the psychological assessments made. Mental imbalance is the product of environmental situations being perceived as stressful. This stress influences how the individual responds to the environment. The major response patterns are those of anxiety or depressed behavior. The severity of these symptoms deteriorates the capability to appraise the psychological state of oneself, impairs physical health that in turn limits functionality, ultimately reducing the quality of social behaviors.

This progression of psychological to social changes are provided in a more organized and accurate manner in texts of yoga (Bhagavat Gita)(Tapasyananda, 2011) where the proponent describes that even a simple thought when converged and amplified can lead to the total

destruction of the personality and psychosocial integrity of an individual. A comparative table describes both these models below.

Figure 32 Comparison of models for psychological progression of disease



Another psychosomatic model as proposed in the yoga literature is the panca kosa as discussed in previous chapters. This postulates that the concept of a healthy individual is one who is a harmonious functioning of the five aspect of his personality i.e. intellectual, psychological, emotional, physiological, and physical. Correlates of this model can be found in other modern literature that is trying to understand this biopsychosicial progression of disease etiology. In this regard a review by Suvinen et al describes that physical pain is a combination of the effects of biological factors, psychological influences and psychosocial norms. These three factors together define the biopsychosocial etiology of pain.(Suvinen, Reade, Kemppainen, Könönen, & Dworkin, 2005)

6.1.7. Comparison with other studies

Studies using Tibetan yoga (L. Cohen, Warneke, Fouladi, Rodriguez, & Chaoul-Reich, 2004), MBSR (Carlson & Garland, 2005; Carlson et al., 2007; Lengacher et al., 2009) and simple awareness (Carson et al., 2009) techniques have shown benefits to cancer patients at physical, psychological, psychosocial levels and consistently reported an improvement in quality of life outcomes. Physical benefits included reduction in fatigue(Carson et al., 2007; Danhauer et al., 2008; Mustian et al., 2007), pain(Carson et al., 2007; TACON, 2006) and symptoms(Duncan, Leis, & Taylor-Brown, 2008; TACON, 2006). Also improvements in sleep measures(L. Cohen et al., 2004) and immune parameters(Carlson et al., 2007) have been reported. Research has also shown that a spectrum of psychological abnormalities like distress(Lin, Hu, Chang, Lin, & Tsauo, 2011; TACON, 2006), stress (Carlson et al., 2007; Lin et al., 2011; Tacón, Caldera, & Ronaghan, 2004), anxiety(Danhauer et al., 2008; Lin et al., 2011; Tacón et al., 2004; TACON, 2006), depression(Danhauer et al., 2008; Lin et al., 2011; TACON, 2006), affect(Danhauer et al., 2008) and mood(Duncan et al., 2008), can be corrected through mind body interventions. Psychosocial variables like mental adjustment(Tacón et al., 2004) and acceptance(Carson et al., 2007) are also affected by inculcating restorative yoga related techniques into the treatment process. Quality of life as measured by several sub scales relating to physical QOL, psychological QOL, Health related QOL and overall QOL have shown consistent improvements(Danhauer et al., 2008; Duijts, Faber, Oldenburg, & Beurden, 2011). A review article suggests that these QOL measures need to play a more important role in planning treatment regimen for cancer patients(Lemieux, Goodwin, Bordeleau, Lauzier, & Théberge, 2011).

6.2.Immune variables

Immunological outcome measures included Th1 and Th2 subset of cytokines that provided an indication of the pro- and anti-inflammatory activities.

6.2.1. Nuclear Factor – kappa B

NF-κB is a transcription factor that regulates the expression of genes responsible for both the innate and adaptive immune responses (cytokines, inducible nitric oxide synthase, cyclo-oxgenase 2, growth factors, and inhibitors of apoptosis and effector enzymes). Cellular responses to bacterial or viral infections and to stress require rapid and accurate transmission of signals from cell-surface receptors to the nucleus. (Viatour, Merville, Bours, & Chariot, 2005) The requirement of transcription factors like NF-κB during this rapid response is crucial as they control cytoplasmic-nuclear shuttling and modulation of transcriptional activity. The family of NF-κB proteins is essential for inflammation, immunity, cell proliferation and apoptosis. Pathological dysregulation of NFkB is linked to inflammatory and autoimmune diseases as well as cancer. Since NF-κB controls cell proliferation and cell survival gene expression, many tumors have constitutively active NF-κB. Activated NF-κB protects the cell apoptosis.(Sheikh & Huang, 2003)

In the present study, group differences were observed between all four group (p=0.012) with highest NF-κB levels observed in the NHY group (3597.41± 10777.98) and the lowest in the NHN group. There was also a higher trend NF-κB levels in the healthy yoga practitioners as compared to the corresponding cancer survivor group although this was not significant. These effects could be attributed to the acute effect of exercise on transcription factor expression. In the cancer survivor population alone there was lower NF-κB level amongst yoga practitioners although this difference was not significant (p=0.225). Since NF-κB is an acute phase transcription factor, its variability is very high and influenced by several factors. The non-significant differences seen between pairs could be attributed to this high variability.

The directional difference seen in the cancer survivor population was in accordance with the anticipated difference although non-significant. On the other hand the direction of difference in the healthy population was not expected.

A thesis work by Crowe in 2004 (Crowe, 2004) attempted to study the changes in NF-κB after yoga in breast cancer survivors, which did not yield significant changes, although the observed direction of change was as anticipated. Till date there are no other studies looking at yoga and its effect on NF-κB and other transcription factors in people living with breast cancer.

A study exploring the effect of meditation the pro-inflammatory activity looked at changes in NF-κB gene expression amongst healthy caregivers (of dementia patients). They concluded that daily meditation reverses the increase in NF-κB expressions thereby reducing pro-inflammatory cytokines activity. (Black et al., 2013)

6.2.2. Interleukin – 1 β

IL-1β is a pro-inflammatory cytokine that mediates cell proliferation, differentiation and apoptosis during inflammation. Secreted by the macrophages as a pro-protein, undergoes activation through the caspase-1 pathway, and helps to promote cancer metastasis along with TNF-α. A high prevalence of IL-1β contributes to tumor re-growth, metastasis and recurrence. (Soria et al., 2011)

The levels of serum IL1B matched with that of normative values (median value of 3.37) of a study conducted by Danis et al.(Danis, Millington, Hyland, & Grennan, 2008). In the present study, IL-1B was highest in the NHN group (3.40±5.96) and the least in the NHY groups. Statistical comparison of the four groups indicated a significant difference (Kruskal Wallis p=0.040). Pairwise comparisons, however showed similar levels of serum IL1B between CBY, CBN and NHN groups suggesting that cancer survivors had reduced pro-inflammatory levels to

normalcy. Although non-significant, there was a pattern of lower values observed between NHN and NHY (Mann-Whitney U p=0.017) and CBN and NHY (Mann-Whitney U p=0.0.016) indicative of the impact of extended yoga practice on low pro-inflammatory immune profile.

6.2.3. Interleukin – 6

Interleukin 6 is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine. IL-6 is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation. IL-6 also plays a role in fighting infection, as IL-6 has been shown in mice to be required for resistance against bacterium Streptococcus pneumonie (Ferguson-Smith et al., 1988)

IL-6 is also considered a myokine, a cytokine produced from muscle, and is elevated in response to muscle contraction.(van der Poll et al., 1997) It is significantly elevated with exercise, and precedes the appearance of other cytokines in the circulation. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates and/or augment substrate delivery.(Febbraio & Pedersen, 2005) Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6's role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10. IL-6 is one of the most important mediators of fever and is secreted by macrophages as part of the acute phase response to specific microbial molecules. It supports the growth of B cells and is antagonistic to regulatory T cells. This induces a cascade of changes leading to intracellular signaling cascades that give rise to inflammatory cytokine production.

In a 2009 study, intra-nasally administered IL-6 was shown to improve sleep-associated consolidation of emotional memories.(Benedict, Scheller, Rose-John, Born, & Marshall, 2009)

IL-6 is relevant to multiple myeloma, (Gadó, Domján, Hegyesi, & Falus, 2000) and prostate cancer, (P. C. Smith, Hobisch, Lin, Culig, & Keller, 2001) and other disorders. Advanced/metastatic cancer patients have higher levels of IL-6 in their blood(American Society of Clinical Oncology, 2006) and anti-IL-6 agents as therapy are studied extensively.(Barton, 2005)

The results of our study showed the CBY group had the least values for IL-6 (3.17±2.23pg/ml). There was a significant difference between the four groups on the Kruskal Wallis test (p=0.019). Pairwise comparisons showed that the CBY group had significantly lower (p=0.005) values than the NHN group. On the other hand, it was interesting to observe that the breast cancer yoga naïve survivors (CBN), who are presently healthy, have similar IL-6 levels as those of healthy controls (NHN). This could indicate that the restoration of normal levels of cytokines responsible for acute inflammatory responses.

In the present study, levels of serum IL-6 were much lower across all groups as compared to in-vitro cultures of normal individuals (median value of 14) observed in the study by Danis et al. (Danis et al., 2008) Studies on cardiac failure patients also observed values of IL-6 much higher than our results which reduced with a yoga intervention.(Pullen et al., 2008, 2010) In contrast to the present study's methodology, all other studies evaluated levels in cytokine secretions of cultured cells. This could be the possible cause for the difference in these values.

In the present study, NHY groups had the highest values of all the four groups. This could be attributed to the myokine function of the IL-6, as blood samples were drawn for the NHY group immediately after their yoga session which could have picked up the exercise effect.(Febbraio & Pedersen, 2005) In the present study the blood was drawn immediately after the yoga session and

hence could have detected immediate myokine effect of IL-6 whereas on the whole, the levels are lower than those presented in either of the cardiac studies.

6.2.4. Interleukin – 8

IL-8 induces chemotaxis in neutrophils and granulocytes, toward the site of infection and initiates phagocytosis. A wide range of cells (endothelial cells, macrophages, mast cells, and keratinocytes) also respond to IL-8 and support chemotactic and angiogenic activities.(Köhidai & Csaba, 1998) A steady emigration of neutrophils from the blood is moderated by IL-8 under physiological conditions.(Baggiolini, Walz, & Kunkel, 1989)

Macrophages are usually the first cells to release IL-8 as they come in contact with the antigens first, although other cells also are recruited for IL-8 release consecutively.

A clinical effect of IL-8 is often mediation of inflammation and is amplified by oxidative stress. This forms a vicious cycle where oxidative stress induced inflammatory changes further increases oxidative stress mediators making it a key parameter in localized inflammation. The fact that Interleukin-8 secretion is increased by oxidative stress, which thereby causes the recruitment of inflammatory cells induces a further increase in oxidant stress mediators, making it a key parameter in localized inflammation.(Vlahopoulos, Boldogh, Casola, & Brasier, 1999)

In cancer IL-8 levels negatively correlated with survival ($P < 0.001$), indicating an association with tumor burden.(Millar, Nemeth, McCabe, Pikounis, & Wickstrom, 2008) and can directly or indirectly promote tumor growth via induction of VEGF expression.(Apte et al., 2006)

In the present study highest values of IL-8 was observed in the NHN group and the lowest in the CBY group which was significant ($p=0.003$). It was an interesting observation that, although

non-significant there was a trend of lower values in the yoga groups of both the healthy and survivor cohorts, pointing to the possibility of lower pro-inflammatory profile amongst those who did yoga.

6.2.5. Interleukin – 10

Interleukin 10 is an anti-inflammatory cytokine but is pleiotropic in immuno-regulation. On the one hand, it down-regulates Th1 cytokines expression (IFN-γ, IL-2, IL-3, TNFα), MHC class II antigens (suppresses capacity of APC), and co-stimulatory molecules on macrophages, but on the other, enhances Th2 cell and mast cells stimulation along with B cell maturation which increases antibody production.

In the present study overall group differences in IL-10 were observed (p=0.005); however, It should be noted that serum levels of IL-10 were very low in the CBY group and fell below the detectable range for the entire group. Highest values of IL-10 were observed in the CBN group (1.12±2.15) and was significantly higher (p=0.012) than the NHY group. The interesting observation was that yoga groups of both healthy and cancer survivors were lower as compared to those of the corresponding non-yoga groups, although it was not significant. Another study by Rogers et al on exercise for breast cancer survivors showed reduced IL-10 levels.(Rogers et al., 2012) The authors however commented that this observation was unexpected. Reduced IL-10 is implicated in several chronic inflammatory and autoimmune disorders.(Correa et al., 2009; Dhabhar et al., 2009; Maurer, Seidel-Guyenot, Metz, Knop, & Steinbrink, 2003; Rogers et al., 2012; Schmulson et al., 2012) Owing to the pleotropic activity if IL-10, reduced levels could indicate that there was a lower pro-inflammatory environment and thus a reduced need for the expression of anti-inflammatory markers amongst yoga practitioners of both healthy and cancer survivor populations.

6.2.6. Vascular Endothelial Growth Factor

Vascular endothelial growth factor is a signal protein that is produced by cells and stimulates vasculogenesis and angiogenesis in order to restore oxygen supply to tissues. Overexpression of VEGF contributes to the growth of solid cancers and cancer cells that can express VEGF are able to grow and metastasize. Poor prognosis in breast cancer with decreased overall survival and disease-free survival and increased metastasis is documented when VEGF is overexpressed.(Patan, 2004)

In the present study, comparison of groups showed that serum VEGF levels are different between the four groups ($p=0.033$) with significantly higher values of VEGF in NHY group as compared to NHN group ($p=0.001$). All other comparisons showed non-significant differences but in contrast to healthy individuals, marginally lower values were observed in CBY group as compared to CBN group. Other studies (Czarkowska-Paczek, Bartlomiejczyk, & Przybylski, 2006) have shown similar concentration of VEGF (91.83pg/ml – 165.61pg/ml) in serum as our study (130.74±82.57pg/ml).

VEGF is implicated with angiogenesisis, and exercise induces the skeletal muscles to stimulate VEGF production, 0 to 2 hours post-exercise, and can be detected in the serum. (Kraus, Stallings, Yeager, & Gavin, 2004; Park et al., 2010) In our study, NHY group had the highest serum VEGF levels. The blood samples were drawn immediately after the yoga session for the NHY group and hence elevated levels of VEGF can be explained. On the other hand, the blood draw for the CBY groups did not happen immediately following a yoga session and hence may have contributed to lower levels of VEGF. This would suggest the reduced tendency for revascularization and angiogenesis.

6.2.7. Overview of differences in immune profiles (Secondary Analysis)

Considering the fact that the cytokine measures did not show much inferential evidence for group differences, a preliminary attempt was made to explore the direction of the group differences irrespective of its magnitude. The table is also divided based on the pro- or anti-inflammatory function of the respective cytokines. Pleomorphic cytokines are those that have both pro-as well as anti-inflammatory activities.

Table 43 Relative difference between groups for immune variables

Name	Function	CBN - CBY	NHN - NHY	NHY - CBY	NHN-CBN
IL1α	Pro-inflammatory	↑	↓	↑	↓
IL1β	Pro-inflammatory	↓	↓	↑	↓
IL2	Pro-inflammatory	↓	↑	↓	↑
IL8	Pro-inflammatory	↓	↓	↓	↓
VEGF	Pro-inflammatory	↓	↑	↓	↑
IFNγ	Pro-inflammatory	↓	↓	↓	↑
MCP1	Pro-inflammatory	↓	↑	↓	↑
EGF	Pro-inflammatory	↓	↑	↓	↑
TNFα	Pro-inflammatory	↑	↑	↓	↑
IL10	Pleomorphic	↓	↓	↓	↑
IL6	Pleomorphic	↓	↑	↓	↓
IL4	Anti-Inflammatory	↓	↓	↓	↑
Sig.(X2 test for goodness of fit)		0.021	1.000	0.021	1.000

Salient Observations of the relative differences are presented below

1. Significantly larger number of pro- and anti-inflammatory cytokine measures had lower mean values in the CBY group as compared to the CBN group. (Except IL1A and TNFα) [10↑; 2↓][p=0.021] This might support our hypotheses that cancer survivors exposed to yoga practice, might lower pro-inflammatory activity.
2. NHY group have no observable pattern in the relative differences as compared to the NHN group. [6↑; 6↓][p=1.000]
3. Comparison of relative differences between NHY and CBY groups indicated that both pro-and anti-inflammatory cytokines are lower amongst the CBY group (except IL1A and IL1B). [10↑; 2↓][p=0.021]

4. Significantly larger number of pro and anti-inflammatory cytokine measures had higher mean values higher in NHN group than those in CBN group (Except IL1A, IL1B, and IL6). [3↑; 9↓]

Looking at the overall differences (whether significant or not), there were some discernible patterns between groups. It appears by careful observation of these patterns that there is a lower pro- and anti-inflammatory profile in the yoga group of cancer survivors. This was in accordance with what was anticipated while conceptualizing the study hypotheses. Literature available indicated that lowered anti-inflammatory cytokines could be a sign of defective restorative mechanisms when pro-inflammatory markers are high during chronic inflammation resulting from psychological distress. (Aggarwal et al., 2006) But a decrease in both pro-and anti-inflammatory cytokines would support the PNI model, where a lifestyle intervention like yoga would reduce the psychosomatic trigger thereby eliciting lesser demand on both pro- and anti-inflammatory responses.

A similar pattern was observed between the NHY and the CBY groups where the CBY group had lower levels of both pro- and anti-inflammatory cytokines. It was unexpected to see that the cancer population doing yoga have better immune profiles as compared to healthy yoga practitioners. This could be explained by the phenomenon of allostatic load that individuals experience due to chronic stress. It is the physiological consequence of heightened neural, neuro-endocrine and immune responses to repeated wear and tear. (Ogden, 2004) The presence of allostatic load initiates allostatic restorative mechanisms in the psychological, neural, and immune axes. Allostatic functions are often capable of not just restoring functionality to normal levels but bringing about an effect where a super-normal conditions sets in.(McEwen, 2000) In the present data, the cytokine levels being lower in the CBY group could have been due to the activation of the allostatic the repair mechanisms thereby having a super-normal cytokine profile

that is lower than the NHY group. This high cytokine levels in the NHY could, however, also be due to the immediate effect of exercise in healthy individuals as the blood sample was drawn after the yoga sessions. This has been dealt with extensively in earlier paragraphs.(van der Poll et al., 1997)

It was noted that amongst non-yoga practitioners, cancer survivors had higher levels of pro- and anti-inflammatory activity. This is probably an evidence to suggest that even after years of cancer treatment, there a latent and chronic inflammatory activity which has not reached normal levels.

6.3.Mechanisms

The model for the etiology of cancer was proposed in the initial phase of this study. This contained major influences from the modern psycho-neuro-immunological understanding of cancer as well as yoga based traditional Indian knowledge of how imbalance of the mind is at the root of disease. The latter part of the study aimed at generating evidence for this mechanism of disease etiology. The tools for both psychological as well and immune evaluations were chosen with the interest of confirming this proposed model. Previous controlled studies looked at the effect of the integrated approach of the yoga therapy for cancer patients and this study used a cross sectional follow-up design to evaluate the effects of long term yoga practice in cancer survivors.

The evidence thus generated needs to be critically observed in order to understand the mechanism of how yoga acts on cancer. Thus, results need to be interpreted under different strata of an individual's personality. These levels proposed (seen in chapter 3) are subtleties of an individual. The approach of yoga is integrative of all levels and thereby differences in level specific variables should be observed. This however was not the case in this study, and this could

be attributed to the fact that the present study included healthy individual in all four groups and was aimed to look at the effects that long term yoga practice would have in different populations. Although the immune parameters do not indicate any direct evidence to this effect, the differences in psychological variables support the concept that cancer is related to the mind. This could indicate the need of mind and body modalities in the management of cancer.

The uniqueness of the proposed yoga based model is that unlike many other models it supposes that there a many more levels to a personality. This forms the clarity for understanding the disease as well as the ability to suggest a solution. Yoga based understanding supposes that the root of any disease is at the mind level where an uncontrolled surge of thoughts can have detrimental effects on the physiology and thereby result in physical level manifestation of the disease. Thus the 'cure' for a disease cannot exist only in the physical domain. The corrective processes, very much like the disease process, have to percolate from the mind into the body. This would result in the much more permanent restoration of health. There is evidence to this mind to body correction that is seen in this study and is detailed below.

6.3.1. Cognitive change

Notional correction is an essential component of mind-body correction and according to the yoga philosophy is a function of the Vignana (intellect). This cognitive or notional transformation is possible by systematic dialogue and presentation of concepts from Upanishads and other yoga texts. Yoga training involves exposure to these dialogues and concepts without which the practices of yoga are deemed incomplete. Imbibing these concepts lead to the understanding that happiness derived from an external source but is an inherent state of existence. The experience of joy is often accompanied by the fulfillment of desire and thus associated with an external object. This however, cannot be further away from the truth which indicates that the experience of joy is when the undulations caused by thoughts cease and the

background silence surfaces. Cessation of thoughts dissolves psychological irregularities and forms a base for notional correction. Regular yoga practice helps to voluntarily reach the inner silence so that pro-active healing can happen. The present study has shown that cancer survivors who practiced yoga did have long term changes in their perception of the stressful situations (lower PSS scores in yoga groups). This perceiving a situation as stressful is a notion that when corrected can percolate as corrective changes through the mind.

6.3.2. Mastery over intrusive thoughts

Meditation, an integral part of the yoga training, is a powerful practice that helps to develop awareness of the mind (self-appraisal) and reverse the direction and speed of thoughts. The wrong direction and high speed of thought are at the helm of uncontrolled responses to the incorrectly perceived environment. These emotional responses are expressed as anxiety or when suppressed result in depression. Both anxiety and depression have shown much lower scores in yoga groups indicating that yoga has achieved this reversal of responding to stress.

6.3.3. Balancing of subtle energies

The model brings in the concept of prana or subtle energy, which connects the body and the mind. Energy as is understood by modern science as an ATP molecule that undergoes phosphorylation in order to release energy. This quantum of energy governs the quantity of activity in a living body that carries out and hence the physiology. According to the yoga based understanding similarities exist where this subtle energy governs the physiology and can bring about changes in the way the body functions. This energy is dependent on the activity of the mind and the magnitude and position of the awareness that the mind is able to muster. Prana has similarities to other oriental systems of healing (qui: Chinese medical concept of subtle energy). (Speck, Courneya, Mâsse, Duval, & Schmitz, 2010b) Long standing imbalances in the functioning of the prana leads to pathological changes; detectable as disturbed rate and rhythm of

breathing. These changes also manifest systemically as physiological changes like altered state of homeostasis, increased or decreased rates of activity of autonomic functions. Yoga texts classify these changes into three categories viz. atijirnatvam (excess functionality), ajirnatvam (reduced functionality) and kujirnatvam (wrong functionality).(Nagarathna & Nagendra, 2009; Venkatesananda & Chappel, 1984) These three types of deviations from normal functionality are a result of the five components of prana presenting in wrong proportion. (Nagarathna & Nagendra, 2009) Since prana is subtler than the physical realm, effects of its abnormalities manifest as non-specific functional deviations from normality such as irregular and shallow breathing patterns, digestive disturbances (excessive or poor appetite, excessive belching or flatulence, irritable bowels or constipation), generalized body aches, fatigue and sleep disturbances. These changes in the subtle energy do not, however, manifest as physical or anatomical changes yet and there is no structural abnormality detectable either at immune system or genetic levels.

To date there are instruments that can only indirectly measure the prana activity by measuring the physiological deviations from normal functioning. Measuring levels of prana directly is still in its infancy. Published literatures using these tools are yet to reach the scientific validity.(Meenakshy, 2009) These tools however are making progress and have a potential when standardized and validated, to be available as methods for detecting several disease prior to their onset.

There are some preliminary studies in evaluating prana based therapies for cancer survivors. In breast cancer, however, there is evidence to show that practices like qui-gong and acupuncture are useful in managing psychological, physical and immune outcomes when complementing conventional treatment. (Deng et al., 2007; Frisk et al., 2008; M. S. Lee, Chen, Sancier, & Ernst, 2007; Speck et al., 2010a; Walker et al., 2010)

6.3.4. Restoration of the Body

Long standing physiological changes further percolate to change the structure of an effected site, anatomical abnormalities and changes in cellular gene expression whereby protein and molecular dysregulation manifests.

6.3.4.1. HPA Axis

This dysregulation is commonly seen as changes in the neurotransmitter levels controlled by the hypothalamus and pituitary. Stressful appraisal of situations, anxiety and depression responses cause these neurotransmitters to be produced at abnormal level. These further signal systemic changes triggering several cascades of changes. The Adrenal Cortex and the medulla (HPA and SAM axes) coordinate the deliberate responses patterns in terms of physical and physiological changes. When these altered conditions are long-standing and chronic, the body adapts to the 'new' baseline. Even the removal of the trigger or the stimulant will not restore normal functionality at this stage. This is seen in several subsystems of bodily dysregulation some of which are listed below

6.3.4.2. Oxidative Stress

Oxidative stress is a condition when generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) exceeds that of cellular adaptive and repair capacities. This affects biological molecules such as nucleic acids, protein, membrane phospholipids to be damaged by oxidation. This results in a failure of normal cellular functioning and can lead to apoptosis. (Chen, Jungsuwadee, Vore, Butterfield, & St Clair, 2007) It is becoming increasingly clear that psychosocial stress can manifest as systemic perturbations of cellular functions, generally increasing oxidative stress (Irie, Asami, Nagata, Miyata, & Kasai, 2002; Yamaguchi, Shioji, Sugimoto, & Yamaoka, 2002; Zheng & Ariizumi, 2007)

Studies have shown that higher oxygen-free-radical production supports breast carcinogenesis.(Tas et al., 2005) Aerobic exercise (Campbell et al., 2010) has reduced oxidative stress significantly and there are several emerging yoga studies that demonstrated a reduction in the amount of reactive oxygen species in diabetic and obese populations.(Gordon et al., 2008; Singh et al., 2001; Vincent, Innes, & Vincent, 2007)

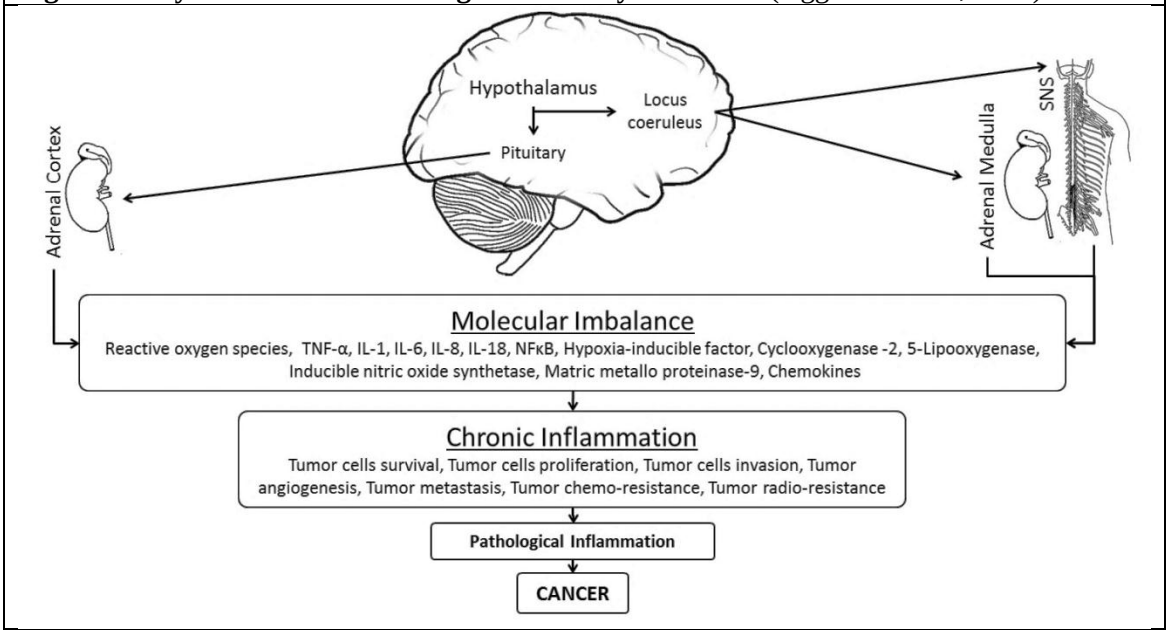
6.3.4.3. Cancer Stem Cells

Recent reports link resistance to conventional therapies and the metastatic potential to a stem-cell-like tumor population, termed cancer stem cells (CSCs)(Bao et al., 2006; Beachy, Karhadkar, & Berman, 2004). CSC population survives injury due to radiations and chemotherapy through their ability to restrict DNA damage by reducing reactive oxygen species and thus, continues to propagate the tumor by preventing DNA damage (Bao et al., 2006). It appears that the elimination of this minority of cancer progenitor cells with stem cell-like properties is essential for the development of more effective curative treatments against cancer. Two factors which facilitate cancer stem cell survival are; aberrant expression of tumor signaling pathways (Bao et al., 2006) and hypoxia (Cipolleschi, Dello Sbarba, & Olivotto, 1993). Hypoxia induced signaling is mediated by Hypoxia-inducible factor (HIF), which is critical for stem cell and tumor cell survival and self-renewal (Heddleston et al., 2010). Apart from balancing the neuro-endocrino-immunological pathways (Bhargav, Nagarathna, Nagendra, Tekur, & Koka, 2010), Yoga practices especially *pranayamas* have been shown to increase blood oxygen saturation levels (R. K. Gupta, Telles, & Balkrishna, 2011)**.** Proposed IAYTC Module thus, may have the potential to make CSCs more susceptible to radiation and chemotherapy induced damage probably by harmonizing tumor signaling pathways and by reducing Hypoxia-induced transcription of HIFs, thereby reducing the progression and recurrence of cancer.

6.3.4.4. Immune dysregulation

Inflammation originates by signal proteins that are induced in specific quantities by control molecules like transcription factors. NF-κB is one such factor that gets activated based on a spectrum of stimulants and in turn regulates a plethora of immune signaling cytokines. This is the bases for the psycho-neuro-immunological pathway. The present study offers a very important evidence to support the PNI pathway and thereby the proposed reversibility model. This could be the cornerstone to understand the etiology, progression, treatment, prognosis and survival of cancer while including the mind of the cancer patient as well. Management and treatment of cancer would greatly benefit from the understanding of how the mind would influence the various inflammatory processes and thereby decide treatment outcomes, prognosis and disease free survival.

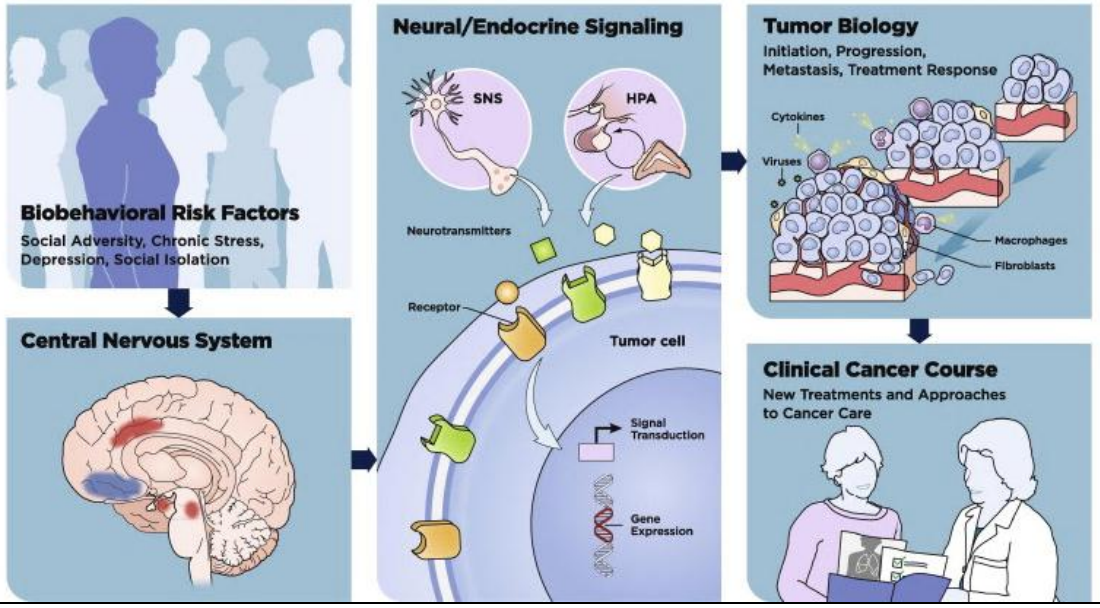
Figure 33 Psycho Neuro Immunological Pathway in Cancer (Aggarwal et al., 2006)



A recent publication containing the heuristic bio-behavioral model to explain the increasing trend in cancer survivors, support the sequence as per the PNI model. (Green McDonald, O'Connell, & Lutgendorf, 2013) Similar to this, the present study also depicted the PNI pathway

along with scriptural yoga based concepts so as to offer a holistic model of the mechanisms involved in cancer.

Figure 34 Bio-behavioral Pathway in Cancer (Andersen et al., 1994)



7. APPRAISAL

7.1.Summary

The first phase of the study was to develop a model for the etiology of cancer using proposed models from modern empirical literature like psycho-neuro-immunology amalgamated with concepts from traditional yoga texts like the Panca Kosa, the Origin of Disease, remedial suggestions offered through systematic yoga practices. The model that emerged suggested that the thoughtless state (which is the true identity) when perturbed by repetitive thoughts get entangled with emotions manifest as physiological abnormalities. This, when ignored, sets into motion the bodily changes, resulting in the creation of abnormal cells thereby reducing the ability of the immune system to detect and destroy imminent threats. This model explains that the root cause of illness is situated much deeper than in the physical realm and curative measures has to reach the mind without which only management of a disease in possible and not its complete cure. Yoga offers techniques that transcend the body and correct the intellect and the constructs of the psyche. This in turn percolates as corrective measures in order to restore health. These techniques are provided in the yoga texts as general suggestions for health and this study also has attempted to formalize yoga modules specific to cancer patients. This was achieved by systematic review of the yoga texts, meetings with yoga experts to understand the interpretations of these prescriptions and finally focus group discussions with oncologists and yoga experts to make it feasible and need based for the specific audience. Eight modules that emerged from these discussions were then administered in a pilot study to elicit feedback from cancer patients. Once the modules were re-modified, full scale randomized control trials were initiated to evaluate the efficacy of these modules.

The second phase of the study was to look at the psychological and immune difference that long term yoga can bring about in cancer patients. The study recruited a total of n=108 (CBY

n=27; CBN n=25; NHY n=28; NHN n=28) presently healthy individuals belonging to four different cohorts with unique properties. Of the four groups, two groups were healthy individuals and the other two had survived stage I-IV breast cancer. One from each of these groups had a history of regular yoga practice (more than six months in the past one year) and the other was never exposed to yoga. This design enabled the comparison of the differences between the four groups in order to yield invaluable information on the long term differences that yoga practice has. The CBN and the NHN groups served as the positive and negative control groups. Psychological and immune profiles were the primary outcome variables and were measured using reliable instruments.

It was observed that cancer survivors who are exposed to the techniques of yoga have much better psychological profiles as seen by reduced stress perception, anxiety, depression and better general health and quality of life. Immune profiles also indicated a reduction in the chronic inflammatory load as well as the requirement for repair mechanisms as seen by reduced pro-and inti-inflammatory cytokines activities respectively. The upstream molecule responsible for the coordination of these cytokines also showed favorable changes in the yoga groups.

7.2.Conclusion

This cross sectional study has shed light on the possibilities that yoga practice can have long term benefits for cancer patients and helps them to maintain better psychological and immune health. Based on the results of this study it is apparent that cancer survivors who resort to healthy lifestyle habits can lead healthier life than normal individual due to the allostatic effect.

7.3.Strengths of the study

Eight published articles that have tested the feasibility, safety and efficacy of the eight integrated yoga modules for cancer have shown beneficial effects in breast cancer patients and hence validates the modules that were created. These modules developed on the basis of time

tested knowledge base of 2000 to 7000 years by the eastern introspective researchers offers many more tools that can be added to conventional cancer treatment. The practices that are offered as part of the yoga regimen consists of breath modulation (pranayama) and mind management (dhyana) techniques that could be added on safely to any of the protocols of management of cancer of different stages at any site. We recommend incorporation of these tested modules in all cancer management protocols to reduce the toxicity and side effects which has been one of the major limitations of most of the therapeutic tools available today. This would add on to better acceptability through improved quality of life.

The cross sectional study is the first study to explore the connection between the psychological constructs and its immune correlates in cancer survivors. Also explorative nature of this study and the exhaustive parameters that have been documented enables further analyses of the various factors that could mediate the relationship of yoga and health of the cancer survivor.

This study has also attempted to evaluate a large number of immune biomarkers that give a comprehensive overview of the immune status of an individual. This has been achieved by using latest technologies that enables rapid analyses of multiple biomarkers using very small quantities of serum samples.

One such unique biomarker that has been studied is the master molecule for inflammatory response (NF-κB). This nuclear factor influences a plethora of molecules that decides how the body responds to inflammatory stressors. NF-κB, in turn is influenced by several other molecular events. Thus this is an extremely important but labile molecule with a very short half-life. Yet the accurate execution of the laboratory protocols have yielded reliable data that can be interpreted meaningfully. This is the first study to evaluate NF-κB that explores the relationships

between breast cancer survivors and yoga. Although the results are not significant, the protocol for evaluating NF-κB levels in unstimulated cells have been executed well and accurate data has been generated. This is has not been reported in many other previous studies which look at stimulating cells with inflammatory agents and then evaluating Nuclear factors and cytokines.

Psychological variables, although extensively used in other settings, have been chosen for this study for applicability to both healthy individual and cancer survivors. These variables have previously documented by other studies during active cancer treatment and have shown psychological dysregulation. These variables also form a basis for evaluating the depth of the correction that yoga brings about. Apart from surface level improvement in general health, physical, psychological and functional quality of life, these variables have also demonstrated deeper effects like reduction in stress appraisal and thereby its response (anxiety, depression). This could indicate the role of yoga in bringing about subtle corrections.

7.4.Limitations of the study

The study is a retrospective presentation of the steps that were followed over the years and not a prospective planned study to assess the validity and reliability of the modules. Statistically acceptable scoring for the check list was not used during all group discussions for ratings as the format was semi structured. This facilitated qualitative exploration of ideas but did not allow for testing of validity and reliability. Not all members of the focused group met during all discussions although efforts were made to include everyone. Statistical calculations of split half reliability were not planned.

The cross sectional study involved immune variable that are known to be influence by a plethora of factors. Although researchers have tried to explore these various factors and documented it, it is important to understand that these variables tend to be extremely dynamic

and responsive to internal and external changes. Thus, there is possibility that the observed effects are due to factors that the authors did not anticipate and take into consideration.

Capturing data quantitatively, relating to yoga practice over the past year, was a challenging task due to the diverse yoga practices, the subject's non-regularity in practice, and reporting errors. The study would have had better value if data regarding how much time had passed since the last yoga session would have been captured.

The protocol for evaluation of cytokines involved the use of serum samples but it was suggested by Dr Selvan S that blood plasma be used instead. This is noted as a drawback of the study. However there are studies that show highly correlations between values cytokines values obtained for both serum and plasma.(Aziz, Nishanian, Mitsuyasu, Detels, & Fahey, 1999)

Since the recruitment process was already underway, a longitudinal study involving yoga on the CBN group could generate more robust evidence for the same hypotheses.

Parameters that were chosen are known to have wide variability and a larger sample size would have provided for a better power to the statistical conclusions.

7.5.Suggestions for future work

More studies to establish the validity and reliability using structured approach is recommended. These modules have to be tested in different races; this is now going on as a NIH funded project at MD Anderson's center for cancer, Houston, USA. Can these techniques replace the existing modalities of management is a major question that has to be addressed by innovative ethically acceptable experimental designs.

Although this study has established a trend that indicates that pro- and anti-inflammatory cytokine levels are lower amongst yoga practitioners, cytokine expression is a highly networked

and coordinated (Soria et al., 2011) and thus there is a need to look at the influence of one variable on the others.

Longitudinal studies to explore the effects of doing yoga on cytokines are necessary to understand the immune level changes. Also, exploring how stimulated blood cells respond, with regards to the expression of nuclear factors like NF-κB, and the changes that yoga could bring about is needed.

To understand the concept of breast cancer etiology, it is suggested to look at cohorts of high risk women and provide them yoga in order to observe its effects in disease onset. Although this has been partially explore through various studies cited in the literature, it would be helpful to conduct long term (from diagnosis to survival) controlled trials with yoga, which would generate support to the proposed PNI model for disease etiology apart from generating evidence for the role of yoga in complementing conventional treatment .

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