

**A Comprehensive Yoga Program (SKY) as an Adjunct Therapy for Prostate Cancer –
A Randomized Pilot Study**

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Study Protocol and Statistical Analysis Plan
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Background and Significance

A rapidly growing body of research now robustly links psychological and behavioral factors to physiological parameters and to the incidence and biology of a broad spectrum of diseases, ranging from coronary heart disease, to asthma, HIV-1 infection, and cancer (e.g. Levy et al., 1987; Redd et al., 1991; Kiecolt-Glaser et al., 2002; Antoni, 2003). For example, evidence exists which links psychological factors to the incidence and progression of cancer (Lewis et al., 2002; Thomas et al., 2002).

It is known that being diagnosed with cancer and receiving treatment is associated with high emotional distress that lowers psychological and physiological wellbeing (Patrick et al., 2003). Cancer patients commonly experience pain, anxiety, depression, and fatigue which often continue even after the end of treatment (e.g. Patrick et al., 2003; Kangas et al., 2008). There is thus a need for research to find the treatments that best can address such symptoms.

Psychosocial stress has also been suggested to potentiate cancer development and possibly tumor progression by promoting alterations in normal DNA repair capabilities (e.g. Kiecolt-Glaser et al., 2002). Chronic distress, such as having a chronically ill child, or caring for a relative with a life threatening disease, has been shown to lead to shortened telomeres and thereby possibly promote earlier onset of age-related diseases (Epel et al 2004). These and other findings suggest that psychosocial stress can affect physiological parameters which in turn can affect quality of life as well as disease progression/outcome in cancer patients. Consistently, a life-style change program that included diet, exercise, and stress reduction methods had favorable effects in PCa and breast cancer patients in terms of clinical events, cancer related gene expression, telomerase levels and activity, and biochemical markers (e.g. Ornish et al., 2008, 2013).

The findings summarized above have been the rationale for the use of psychosocial interventions in the rehabilitation of cancer. Recent meta-analysis findings suggest that psychosocial treatment can be effective in improving quality of life parameters after primary cancer treatment (Fors et al., 2010). Furthermore, psychosocial support treatment decreased disease recurrence and increased life expectancy in a cohort of cancer survivors (n=227, 11-year followup) (Andersen et al., 2008). In a study involving both PCa and breast cancer patients, a mindfulness based program enhanced quality of life and decreased stress symptoms, altered cortisol and immune patterns consistent with less stress and mood disturbance (Carlson et al., 2007). In addition, it was also shown in a randomized clinical trial that chronic inflammation, negative mood, and fatigue were alleviated by a yoga based program in breast cancer survivors (Kiecolt-Glaser et al., 2014). Similarly, another randomized trial showed that a yoga program improved quality of life and physiological effects associated with radiotherapy in breast cancer survivors (Chandwani et al., 2014).

Prostate cancer (PCa) is the most prevalent cancer in men (Desantis et al., 2014). PCa has the highest Medicare expenditure than any other cancer that affects older men. Modern tailored

treatment regimens have resulted in longer life expectancy, but also longer treatment periods, which lead to treatment related morbidity, as well as adverse side effects, including psychological distress and pain (e.g. Penson and Chan, 2007; Bhoojani et al., 2008)). For example, depression has serious implications for outcomes and recovery from PCa as reflected in debilitating effects on health related quality of life, functional status, health resource utilization and cost (Bhoojani et al., 2008; Pirl et al., 2008; Reeve et al., 2009, Weber et al., 2008). Consistently, a recent National Cancer Institute based evaluation recommended four patient-reported outcomes to be routinely incorporated into clinical trials: pain, fatigue, mental well-being, and physical well-being (Chen et al., 2014).

As indicated in some of the examples above, many patients with cancer turn to integrative medicine (IM) modalities to help manage their symptoms (for a review, see Dobos et al., 2013). In addition to best standard of care from western perspective, IM encompasses a broad array of heterogeneous treatments, ranging from herbal medicine to yoga. Yoga has recently undergone empirical investigation, as exemplified above, as a potentially beneficial intervention for patients with cancer. An ancient Eastern tradition estimated to be a 5000-year-old discipline originating from India (Udapa and Singh, 1972), a yoga program encompasses various domains, including ethical disciplines (e.g. non-harm in actions and words), physical postures (asanas), and spiritual practices, with the goal of uniting the mind, body, and spirit for health and self-awareness. Hatha-yoga, the classical form of yoga, is considered to improve bodily functions through the manipulation of cardiovascular, respiratory, metabolic, and other control mechanisms. Whereas asanas are generally familiar, the pranayama, the breathing practices, and the central role that they have in yoga, are not usually sufficiently emphasized.

One of the most widely used breathing techniques derived from yoga is Sudarshan Kriya (SK) (Murthy et al, 1998; Janakiramaiah et al., 2000) that is used in conjunction with other central aspects of yoga. SK is traditionally understood to use specific rhythms of the breath to eliminate stress, support the various organs and systems within the body, transform overpowering emotions and restore peace of mind. Recent medical research on SK and related practices (SK&P), also referred to as SK yoga or SKY, has indicated significant effects on various aspects of the physiology and the psychology of the participants.

For example, studies demonstrated that SKY has important antidepressant effects in clinical settings (Murthy et al, 1998; Janakiramaiah et al., 2000) and is comparable to the antidepressant drug Imipramine in its efficacy. Effect of SKY on psychological health is not limited to clinical patients. **Saatcioglu** and co-workers conducted a controlled study and found that participants in the SKY group, but not the control group, significantly lowered their degree of anxiety, depression and stress, and also increased their degree of optimism (Kjellgren et al., 2007).

Another study found significantly lower levels of blood lactate in practitioners of SKY compared with the control group. Conversely, the levels of superoxide dismutase (SOD), catalase, and glutathione, three major defenses against oxidative stress, were all found to be significantly higher in SKY practitioners compared with the control group (Sharma et al., 2003). These data suggest that people who practice SKY have an improved antioxidant status and defense against oxidative stress.

Various additional studies indicate that SKY results in improved physical and psychological health. For example, there are interesting findings on the effects of SKY on brain function, indicative of a state of wakeful alertness (Bhatia et al., 2003). In addition, there appears to be strengthening of the immune system, as measured by increases in natural killer (NK) cell number, in both healthy people, but also in cancer patients (Kochupillai et al., 2005). Furthermore, SKY has been shown to be effective in post-traumatic stress disorder (Carter et al., 2013) and in a randomized trial **Saatcioglu** and co-workers found that it affected the circulating immune cells at the level of gene expression (Qu et al., 2013).

The goal of this proposal is to systematically study the possible impact of SKY on PCa patients. The studies will include not only psychological assessment through self-report questionnaires on pain, fatigue and psychological well-being, but also objective measures on basic physiological parameters, including the stress hormone cortisol and cytokine IL-6. **Our hypothesis** is that there would be a measurable effect of SKY on psychological distress in PCa patients on the

parameters to be tested, and that this will correlate with favorable changes in physiological parameters that may impact disease progression.

Our preliminary data from two clinical trials we conducted in students (Kjellgren et al, 2007) and healthy volunteers (Qu et al, 2013) support our hypothesis (see above, studies by Saatcioglu and co-workers, as referenced in Kjellgren and Qu papers). There was decreased anxiety, depression and stress in one study, and improved physiologic changes in the other. These preliminary results give us confidence that the proposed study will show the hypothesized improvements in the health status and physiological parameters of patients with PCa.

Specific Aims:

This study will have two parts:

1. Determine any change in pain, fatigue and psychological well-being as a result of SKY in PCa patients.
2. Assess changes in some physiological parameters in response to SKY in the same subjects, compare these with those from Part 1, and assess whether these translate into clinical effects.

Subjects:

PCa patients that have been treated with radiotherapy will be recruited to the study (Winship Cancer Institute Clinic, contact person Dr. Omer Kucuk).

Inclusion criteria: Age \geq 45 years; having finished radiotherapy at least two months ago; ability to speak/read English and give informed consent; having an interest in being part of a study to evaluate yoga-derived exercises and eager to practice some kind of relaxation exercise daily for 3 months.

Exclusion criteria: Having a diagnosis of psychiatric illness or other major illness in addition to PCa, such as other cancers, uncontrolled hypertension, lung disease, liver disease or heart disease.

Approval by the IRB Committee will be applied for. All participants will sign consent forms and throughout the study they will be treated according to the ethical guidelines, in addition to standard treatment for PCa. Participants will be informed that the data obtained in this study will be kept in a separate approved password controlled secure database at the Winship Cancer Institute of Emory University, and that the data from this database will be linked to the approved clinical database in the same institution. They will also be told that they participate by their free will and that they are free to leave the study whenever they wish without giving any reason for it and not risking any consequence for the standard treatment that they will receive.

The men will be randomly assigned to one of two groups:

1. No treatment control.
2. Healing Breath Program (SKY).

SKY includes gentle stretches (yoga postures), specific breathing exercises (see below), and cognitive coping and stressor evaluation strategies. SKY is traditionally understood to dissolve emotional distress and create the subjective experience of rest and well-being. The instructors in SKY are trained by the International Art of Living Foundation. The yoga intervention is held over 13 weeks: in Week 1, subjects will receive yoga instruction for approximately 3 hours daily on 5 consecutive weekdays, and in Weeks 2-13, subjects will attend yoga instruction once a week for about 2 hours.

The breathing techniques that are part of SKY are: (a) Three-Stage Pranayama with Ujjayi or "Victory Breath", (b) three sets of Bhastrika or "Bellow's Breath", and (c) SK, and they are practiced in that order. The breathing practices are done in a sitting posture, either in a chair or on the floor. Eyes are kept closed throughout the sessions.

A total of 50 patients will be randomized into the two study arms. 20 subjects are aimed at in each group, but to account for drop-out/exclusion, 25 subjects will be recruited per group (to accommodate drop-out/exclusion rate of 20%). Both groups will be tested at the time of recruitment

to the study as Pretest 1. The SKY intervention will be given in groups of 10-15 patients and the tests will be performed again within 2 weeks of the first week of yoga (Posttest 1). The control group will be tested at the same time. Posttest 2 will be performed within 2 weeks of completing the 13-week yoga program, using the same parameters. **In addition to daily home practice, there will be weekly follow-up sessions for the SKY group** which will last about 2 hours during which exercises will be performed in a group and questions that may arise related to the practice will be answered. Control subjects will be offered 1-week of yoga classes after the end of the study (ie, after post-test-2)

Below is a brief flowchart of the study timeline:

Week --	Recruitment (3 months prior to the start of yoga)
Week --	Pretest 1 (within 2 months prior to starting yoga)
Week 1-13	SKY intervention (13 weeks)
Week 2-3	Posttest 1 (within 2 weeks of the first week of yoga)
Week 14-15	Posttest 2 (within 2 weeks of the last week of yoga)

Research design and methods:

Aim 1. Determine any change in pain, fatigue and psychological well-being as a result of SKY in PCa patients.

We will assess psychological wellness parameters in the PCa subjects at the time points as described above. This will be done by administering standardized questionnaires which are enumerated below:

1. The Hospital Anxiety and Depression Scale (HADS): A 14-item self-rating scale, measuring anxiety and depression (Zigmond and Snaith, 1983).
2. The EORTC Quality-of-life Questionnaire (EORTC QLQ-C30). A cancer-specific 30-item questionnaire (Aaronson et al., 1993) incorporating 5-functioning scales, a global health-status/QOL scale and symptoms assessment. In addition Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire will be utilized.
3. The Life Orientation Test – Revised (LOT-R): A 10-item self-report scale, measuring expectations about positive outcome in general (Scheier et al., 1994)
4. 36-item short-form health survey (SF-36) vitality scale, a reliable and valid measure of energy/fatigue in the past month (Stein et al., 1998).
5. Pain will be assessed with the BPI-SF questionnaire (Cleeland and Ryan, 1994).

Aim 2. Assess changes in some physiological parameters in response to SKY.

In addition to the self-report measures described above, it is important to use objective measures to determine if SKY practice results in physiological effects. As reviewed above, previous studies on SKY have indicated various physiological effects, such as positive influence on the immune system, support of the antioxidants system, and effects of gene expression in the circulating immune cells. To evaluate if similar effects are observed in PCa patients, and whether these correlate with the measures in Part 1, venous blood, saliva, and hair will be collected at the three time points and the following tests will be performed:

1. Enzymes indicative of antioxidant status, i.e. Superoxide Dismutase (SOD) and Glutathione peroxidase (GPX) (based on previous studies by Sharma et al., 2003). We will also measure serum 8-isoprostane level, an indicator of oxidative stress.
2. Inflammatory markers, i.e. Interleukin 1 and 6, Tumor Necrosis Factor alpha (TNF α), and C-reactive protein (since these cytokines are important in carcinogenesis and may be modulated by psychosocial intervention therapies).
3. Saliva cortisol taken between 07 and 09 am, as measure of psychophysiological stress (Levine et al., 2007).

4. Hair cortisol, using a 1-inch strand of hair taken from the back of the head, as a measure of psychophysiological stress.
In addition, two epigenetic tests will be performed:
5. RNA will be isolated from the peripheral blood mononuclear cells (PBMCs) and gene expression changes will be assessed as previously done in response to the SKY regimen (Qu et al., 2013).
6. DNA will be isolated from the PBMCs and potential DNA methylation changes in response to SKY regimen.

The levels of these endpoints (1-3) and gene expression profiles will be compared during the different time points as described above.

STUDY FLOW CHART:

Yoga group:

1. **Prestudy evaluations:** Questionnaires, and blood/saliva/hair samples (within 2 months prior to starting Yoga instructions)(Pre-test 1)
2. **Yoga instructions**
Week 1 – Yoga instruction (3 hours daily for 5 days)
Week 2-13 –Yoga instruction (2 hours on one day each week)
3. **Post-study evaluations (1):** Questionnaires, and blood/saliva/hair samples (within 2 weeks of the first week of yoga)(Post-test 1) (Week 2-3)
4. **Post-study evaluations (2):** Questionnaires, and blood/saliva/hair samples (within 2 weeks of the last week of yoga)(Post-test 2) (Week 14-15)

Control group:

- 1) Prestudy evaluations: Questionnaires, and blood/saliva/hair samples (after consenting) (Pre-test 1)
- 2) Post-study evaluations (1): Questionnaires, and blood/saliva/hair samples (within 6-8 weeks from the pre-test 1 evaluations)(Post-test 1)
- 3) Post-study evaluations (2): Questionnaires, and blood/saliva/hair samples (within 2-4 months after Post-test 1 evaluations)(Post-test 2)
- 4) Control subjects will be offered 1-week of yoga classes after the end of the study (ie, after post-test-2)

Statistical Considerations:

Fifty subjects should be a sufficient sample size because in our previous study with a sample size of 14 subjects we were able to observe statistically significant changes (Qu et al, 2013). Comparisons will be made with the Student's t test. A value of $P < 0.05$ will indicate statistical significance.

Research team:

The main coordinator of the project is Dr. Omer Kucuk, Department of Hematology and Medical Oncology, Emory University. The collaborator partners are: Alicia Smith, PhD, Department of Psychiatry; Dr. Ashesh Jani, and Dr. Peter Rossi from Department of Radiation Oncology, Emory University.

Yoga instructions will be provided by Art of Living Center instructors in Atlanta. They have agreed to provide the SKY intervention proposed in this study.

Epigenetic, biochemical and inflammatory marker laboratory tests will be done at Dr. Alicia Smith's Laboratory. Prof. Saatcioglu has conducted research using similar methodology (testing of wellness parameters, cancer related endpoints, and gene expression) (Kjellgren et al., 2007; Qu et al., 2013) which will facilitate the current work.

Ethical considerations: All work will be done in accordance with the ethical principles of human subject use and the rules of the Institutional Review Board (IRB) at Emory University. All

members of the research team have participated in similar studies before involving human subjects and are thus familiar with all the procedures that are necessary.

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Detailed 1-year Budget (see attached Excel file)

\$12,650 study coordinator/nurse/data manager fee

\$4000 SKY instruction and followup (4x16 hr instruction and 24x3 h for followup)

\$1500 IRB fee

\$3350 Biochemical tests

\$4000 Inflammatory biomarkers

\$4500 Pilot epigenetic studies

TOTAL: \$30,000

Budget Justification

Study coordinator (25% effort) will help with subject recruitment, consenting, enrollment on study, follow-up and conduct of the study according to protocol and collecting data and keeping study CRF's and records.

\$12,650

SKY instructors from Art of Living Center (Atlanta) will provide yoga instruction to study subjects.

\$4,000

Biomarker studies (epigenetic, biochemical, inflammatory markers) will be done at Dr. Alicia Smith's laboratory.

\$11,850

IRB fee

\$1,500