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# Stress management for cancer survivors using a technologically adapted psychosocial intervention: A randomized trial determining the effect of expressive writing on psychoneuroimmunology based outcomes

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# Stress management for cancer survivors using a technologically adapted psychosocial intervention: A randomized trial determining the effect of expressive writing on psychoneuroimmunology based outcomes

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy (Ph.D.) in Social and Behavioral Health at the School of Medicine, Virginia Commonwealth University, Medical College of Virginia (MCV) Campus

by

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## List of Abbreviations

| | |
|---|---|
| ACS | American Cancer Society |
| AMSTAR | Assessment of Multiple Systematic Reviews |
| AUC | Area Under the Curve |
| BOM | Baseline Outcome Measures |
| BSCI | Brief Screen for Cognitive Impairment |
| CAR | Cortisol Awakening Response |
| CAM | Complementary and Alternative |
| CBI-B | Cancer Behavior Inventory-Brief version |
| CBSM | Cognitive Behavioral Stress Management |
| CDC | Centers of Disease Control and Prevention |
| CRP | C- Reactive Protein |
| CS | Cancer Survivors |
| DCS | Diurnal Cortisol Slope |
| ELISA | Enzyme Linked Immune Sorbent Assay |
| EW | Expressive Writing |
| FCRI-S | Fear of Cancer Recurrence Inventory– Severity subscale |
| GLM | General Linear Model |
| HPA | Hypothalamic-Pituitary-Adrenocortical |
| IOM | Institute of Medicine |
| LIWC | Linguistic Inquiry and Word Count |
| LCSW | Licensed Clinical Social Worker |

| | |
|---|---|
| MANOVA | Multivariate Analysis of Variance |
| NCI | National Cancer Institute |
| PHQ | Patient Health Questionnaire |
| POM | Post-intervention Outcome Measures |
| PNI | Psychoneuroimmunology |
| PSS | Perceived Stress Scale |
| RCT | Randomized Controlled Trial |
| SNS | Sympathetic Nervous System |
| WHO | World Health Organization |

**Abstract**

STRESS MANAGEMENT FOR CANCER SURVIVORS USING A TECHNOLOGICALLY ADAPTED PSYCHOSOCIAL INTERVENTION: A RANDOMIZED TRIAL DETERMINING THE EFFECT OF EXPRESSIVE WRITING ON PSYCHONEUROIMMUNOLOGY BASED OUTCOMES

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Patients with cancer transitioning from completing their final cancer treatments to survivorship are particularly at risk for experiencing psychosocial stress, and the Institute of Medicine (IOM) has referred to these cancer patients as "lost in transition." In this study, patients with cancer in their transition phase after completing their final radiation treatment were defined

as cancer survivors (CS). CS must deal with chronic stressors such as the fear of cancer recurrence as well as the resumption of their roles in their family and work lives. Chronic stress impacts the nervous system and increases secretion of stress hormones (e.g. cortisol) from the endocrine system, which in turn influences immune function. These systems are particularly relevant for CS since research has shown associations between abnormal cortisol patterns and increased mortality in breast CS and immune dysfunction in CS can increase susceptibility to infections. The theoretical framework of psychoneuroimmunology (PNI), which describes the interactions between the psychosocial, neuroendocrine and immune systems, guided the choice of outcomes for this study. The IOM has identified a lack of theory-driven interventions for managing psychosocial stress in CS. We reviewed the literature and identified two major types of PNI-based psychosocial interventions for cancer patients, namely cognitive-behavioral and complementary medical. One promising brief and inexpensive psychosocial intervention was expressive writing, which involved participants disclosing their deepest thoughts and feelings regarding their cancer in four 20-30 minute writing sessions over four consecutive days. We conducted a two-arm randomized controlled trial to determine the efficacy of an online expressive writing (EW) intervention delivered to CS who were 2-12 months post-radiation treatment completion. The results of this study revealed that EW was effective in regulating stress in our sample of CS over a period of six weeks as measured by lowered salivary cortisol levels and lowered self-reported fear of cancer recurrence. Online EW is a low-cost and convenient approach for delivering stress-management interventions for CS during survivorship. However, coordinated efforts are needed from health researchers, professionals and policy makers to define standardized approaches for testing psychosocial interventions and using PNI biomarkers to help develop evidence-based psychosocial cancer-care for CS during survivorship.

**Keywords:** Cancer, Survivors, Stress management intervention, Expressive writing, Randomized trial, Psychoneuroimmunology, Neuroendocrine-immune biomarkers

## Chapter I. Introduction

Cancer remains a significant cause of death and suffering for individuals on physical, mental and social levels, the world over. In the United States, 41% of individuals are faced with the possibility of a cancer diagnoses in their lifetime, and more than a million new cancer diagnoses are projected to occur this year. Advances in early detection and treatments have led to a consistent increase in individuals that have survived their cancer, currently estimated to be more than 13 million individuals in the US alone[2]. Cancer patients experience high levels of psychosocial stress across the cancer-care continuum, i.e. from diagnosis through survivorship care and palliative care[3]. Chronic psychosocial stress in cancer patients can have serious negative health consequences by impeding patient's psychosocial functions (e.g. lowered ability to cope with cancer) as well as biological functions (e.g. increased susceptibility to infection due immune suppression), and represents a serious public health problem. In this study we describe psychosocial stressors faced by cancer patients, identify interventions to remediate psychosocial stress in cancer patients and conduct a randomized trial of psychosocial intervention called expressive writing for cancer patients who were transitioning off their last radiation treatment.

### What Psychosocial Stressors Exist in Patients Diagnosed With Cancer?

Cancer patients are susceptible to mental health problems such as depression and anxiety. A recent meta-analysis suggest that the prevalence of depression in cancer patients is 16.3%; of which 14.9% of cancer patients are suffering major depression and 19.2% minor depression, as defined by DSM criteria[4]. The same study found the prevalence of adjustment disorder to be 19.4%, anxiety 10.3%, and dysthymia 2.7% in their sample of cancer patients[4]. In addition to mental health issues, cancer patients are also faced with a great amount of emotional distress, and four in ten patients with cancer report experiencing significant distress[5]. Cancer patients are

commonly faced with issues such as fear of death and the associated fear of losing close interpersonal relationships (e.g. family and friends) due to death. Other socio-emotional issues in cancer patients include interruption of life plans, chronic uncertainty, changes in body image and self-esteem, fear of cancer recurrence, and hopelessness[3]. These psychosocial problems affect the cancer patient's ability to function productively at work and result in difficulty in maintaining employment and hence, a decrease in income[1,6] A survey study revealed that more than one third of cancer patients and their family members reported that they were unable to perform at their job, and 19% lost or changed jobs or needed to work fewer hours because of the illness, while 22% reported a lower income[6].

Medical expenses incurred due to cancer can exhaust patients and their families financial resources, and it is has been established in the United States that 62% of bankruptcies in Americans are medically related[7]. These financial problems lead to more stress in cancer patients and further exacerbate the existing psychosocial problems. Furthermore, physical and mental impairments (e.g. chronic fatigue and cognitive dysfunction) due to cancer related treatment regimens also add to the cancer patient's psychosocial problems[8]. Treatment-related adverse effects can impact cancer patients several years after all treatments are completed. For example, a recent study demonstrated that survivors of breast cancer treated with adjuvant chemotherapy more than 20 years ago performed worse on neuropsychological tests of immediate and delayed verbal memory, processing speed, executive functioning and psychomotor speed, when compared to random population controls [9]. Hence, patients with cancer are faced with range of unmet psychosocial needs depending on where they lie along the continuum of cancer care[1].

**The Cancer Care Trajectory: Defining Cancer Survivors**

The NCI considers the cancer care trajectory to begin "from the time of diagnosis through

the balance of his or her life,"[1][p. 29] and a patient can be considered to lie in one of the phases of this continuum, see Figure 1. The major phases of this trajectory are 1) diagnosis and staging, 2) treatment, i.e., intended to cure or palliative treatment, 3) survivorship care, 4) recurrence (or secondary cancers), and 5) death. The Institute of Medicine (IOM) has identified a considerable deficiency of cancer care specifically for the psychosocial issues faced by cancer patients in the survivorship care phase [1]. Moreover, there are a growing number of cancer survivors, with figures from the NCI and CDC reporting that more than 11 million people are currently living with a history of cancer in the United States[10]. The numbers of cancer survivors are expected to increase even more due to advances in early detection and effective treatments along with an aging population. The office of survivorship at the NCI considers patients to be cancer survivors after a definitive initial diagnosis of cancer until the end of life, and this definition also includes family members, caregivers and friends, since they are affected by the cancer experience as well[11]. However, the NCI's definition lacks specificity for defining cancer survivors for research protocols. This study directed its research focus towards cancer patients who were in the cancer-free survival phase. Specifically, we defined our target population as cancer patients who had completed their cancer treatments (intended to cure) and were declared disease-free (no recurrence or secondary cancers), and these cancer patients are hereafter referred to as cancer survivors (CS).

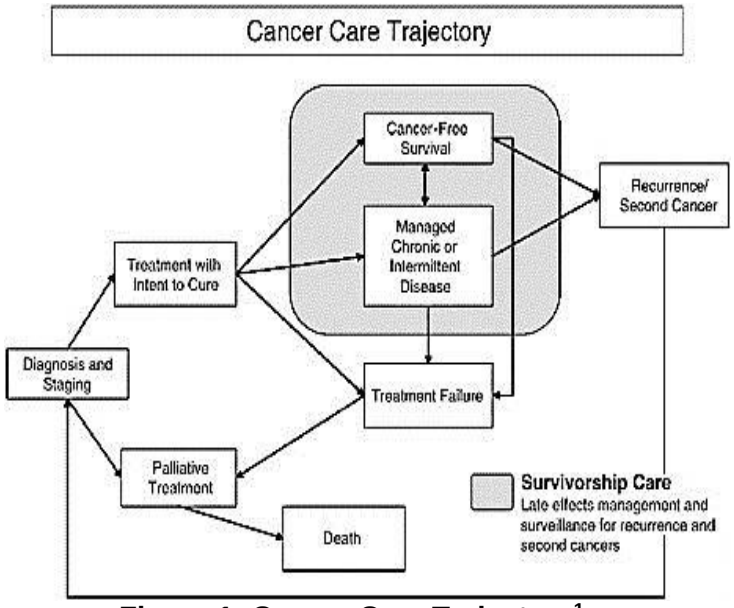



**Figure 1: Cancer Care Trajectory[1]**

**Phases of Cancer Survivorship from a Psychosocial Perspective**

From a psychosocial perspective, the period of cancer-free survival can be assumed to have two phases, called re-entry and long-term survival, which were initially suggested by a physician who was diagnosed and treated for cancer[12,13], and have been subsequently adopted by some psycho-oncology researchers[14-16]. The re-entry phase of survivorship is considered to start from immediately after treatment completion up to approximately 12-18 months of cancer-free survivorship. Patients beyond 18-24 months of remission are considered to be in the long-term survivorship phase. Researchers have identified that that the re-entry phase is a period of heightened distress for CS and patients have many unmet psychosocial needs during this phase[16,17]. For example, a longitudinal study of distress in breast CS described that 15% of women reported experiencing heightened distress beginning at treatment completion until six months after treatment completion[18]. Moreover, psychosocial interventions have not been designed to meet the needs of CS in the re-entry phase. This may be due to the assumption that individuals in the re-entry survival phase experience relief after completing their treatment and from being free of their cancer diagnosis. However, these patients are faced with myriad of psychosocial stressors which includes the fear of cancer recurrence [12].

**Stressors Experienced by Cancer Survivors (CS) in the Re-Entry Phase**

CS in the re-entry phase experience stress due psychosocial problems and treatment related adverse effects. Research indicates that some pronounced psychosocial problems for CS during the re-entry phase include the fear of cancer recurrence, uncertainty about the future, interruption of life plans, impaired body image and self-esteem, and fear of death [1,3]. Another source of stress for CS in the re-entry phase is the late and long-term adverse effects of cancer treatment regimens. Late effects of treatment regimens refer to unrecognized toxicities that were

absent or subclinical at the end of therapy[1,19]. These late effects manifest during survivorship subsequent to unseen injury because of any one or more of the following, a) developmental processes, b) the failure of compensatory mechanisms to act in due course, or c) organ aging[1,19]. Late effects can appear anytime, ranging from a few months to years after the completion of treatment. Long-term effects are side effects or complications of treatment that are recognized during treatment that continue beyond the end of treatment[1,19]. Common late and long-term effects of treatment for CS in re-entry phase include fatigue/ sleep disturbance, pain, sexual dysfunction, urinary/bowel problems, and cognitive problems[1,16] Neuropsychological impairments such as memory problems and impairments in executive function are also common in CS[9]. Cancer treatments involving extensive surgery or radiation can also result in a range of impairments in physical function in CS, such as restrictions in movement of limbs, chronic pain and fatigue[19]. These functional impairments can lead to a decrease in daily activities and performance, which in turn leads to frustration and chronic stress in survivors.

**Why is the Re-Entry Phase a Particularly Stressful Period of Cancer Survivorship?**

One reason for increased stress in the re-entry phase is the loss of interaction with health care providers and caregivers[14,16]. During the treatment phase, cancer patients are continuously interacting with their oncology care team, and therefore experience a sense of protection [17,19]. There is also more interpersonal social support from caregivers for cancer patients during the treatment phase which decreases after completing treatment [20]. After treatment regimens are completed, many patients perceive a decrease in social support because they are no longer in regular contact with the oncology team[16,21]. Therefore, the transition from active treatment to the re-entry phase becomes a particularly stressful period for patients. In addition, there is very little preparation for the re-entry phase by health care professionals or others, which results in unmet

needs for information and psychosocial health services[1,14,22]. During this transition phase, CS are often confronted with making sense of their identity and learning to cope with the stressful experiences during their diagnosis and treatment[23]. Concurrently, CS are expected to return to life as usual and reassume their original family and work roles and responsibilities. Therefore CS in the re-entry phase often face multiple stressors related to their cancer diagnosis and learning how to cope after treatment while perceiving a loss of social support and resources[14]. CS who are in the re-entry phase after completing their radiation treatments are particularly at risk for being distressed and having psychosocial problems.

**Psychosocial Stress Experienced by Cancer Survivors after Radiation Therapy**

Numerous studies of CS populations have focused on the physical and psychosocial problems created by chemotherapy (e.g. fatigue and depression) and surgery (e.g. loss of organ(s) and impaired body image); very few studies have directed their attention to psychosocial effects of radiation treatments[24]. There is a growing body of evidence indicating that CS encounter many psychosocial stressors after completing radiation treatment[25]. A comparative study consisting of CS (5 years after initial treatment for cervical cancer, N=114) that had either received surgery (n=37) or radiation (n=37) and a control group (healthy patients with no cancer treatment, n=40), found that compared with CS of surgical treatments and the control group, radiation CS had significantly lower health-related quality of life (physical and mental health), increased psychosocial distress, and problems in sexual functioning[26]. Furthermore, longitudinal studies with cancer patients receiving radiation treatments suggest that depression and impairment in psychological well-being increase significantly after treatment[27-30]. Another longitudinal study found that negative perceptions of the survivorship experience and worry about the future increased significantly 6 months after completion of radiation therapy[31].

This suggests that CS post-radiation have numerous unmet psychosocial needs that make them susceptible to chronic stress, which has very serious implications for CS since chronic stress impacts human biology, e.g. by influencing the nervous, endocrine and immune systems.

**How Does Psychosocial Stress Affect Biological Outcomes?**

Researchers across a variety of disciplines have investigated the nature versus nurture explanation for health outcomes in human beings. Advances in health and social sciences have established the field of bio-behavioral clinical research which investigates interactions between psychosocial factors and biological outcomes[32]. Over the past three decades scientists have specifically explored how chronic psychological stress affects physiological systems, specifically, the neuroendocrine and immune systems[33-35]. Chronic stress affects the functioning of the nervous system, which initiates secretion of glucocorticoids (e.g. cortisol) from the endocrine system[36]. Continued exposure to high concentrations of stress mediators causes decreased expression of glucocorticoid receptors, thereby leading to cortisol resistance[37]. Thus, normal cortisol regulation of the immune system is lost, leading to a pro-inflammatory state and immune system dysregulation[37,38].

These systems are particularly relevant for cancer populations because previous research has demonstrated that abnormal patterns of cortisol secretions (cortisol rhythms) are associated with increased mortality in breast cancer patients[39]. Dysfunction of the immune system also has critical consequences for cancer populations, such as increasing susceptibility to infection, and impacting the progression of cancer, thereby increasing the likelihood of cancer recurrence and development of secondary cancers[3,40,41]. Therefore, neuro-hormonal (e.g. cortisol) and immune functioning are very critical biological health outcomes for CS. The study of interactions between the psychological, neuroendocrine and immune systems has given rise to the inter-

disciplinary field of psychoneuroimmunology (PNI).

**Psychoneuroimmunology (PNI) and Immune Function**

Studies suggesting the psychosomatic influence of mental disorders on biologic outcome measures were being published since the 1940s, however substantial progress in PNI research occurred only after 1980[42]. The term psychoneuroimmunology (PNI) was coined in 1981[43,44], and in the subsequent 30 years, science has witnessed major advances in understanding how psychological factors affect the brain and central nervous system, which influence the production and release of certain hormones, e.g. glucocorticoids, which in turn affect the function of the immune system[44-46]. Two physiological pathways have been studied to understand how chronic stress exerts influence on immune function.

The first is the hypothalamic-pituitary-adrenocortical (HPA) axis, which is also called the limbic-hypothalamamic-pituitary-adrenocortical axis (LHPA), due to the role of the limbic system of the brain (i.e. amygdala and hippocampus) in the human stress response[47]. Multiple hormones are involved the HPA axis pathway, which are released from different organ systems in the body. Acute and chronic psychological stress initiates the release of corticotropin-releasing hormone (CRH) from the hypothalamus[47]. CRH then causes the release of adreno-corticotropin releasing hormone (ACTH) from the pituitary gland.

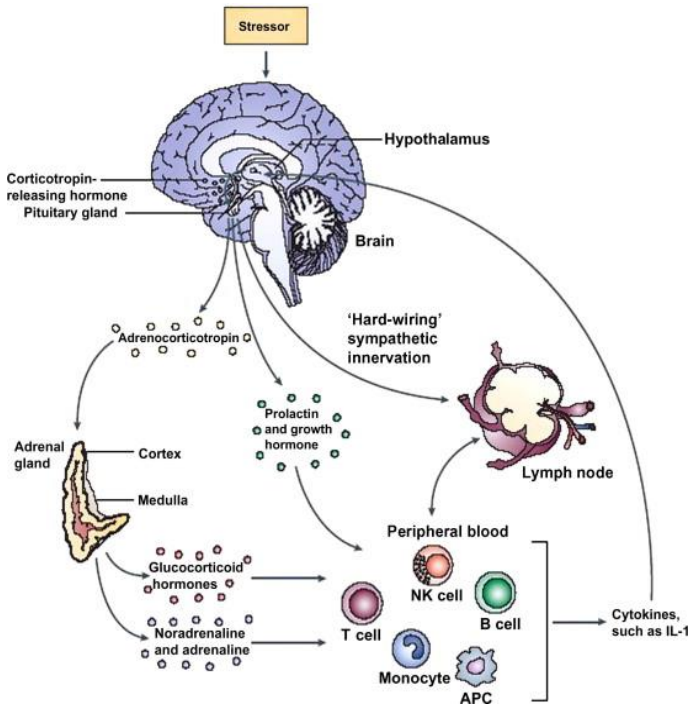



**Figure 2: Stress, HPA axis and immunity[46]**

Subsequently, ACTH activates the release of cortisol and adrenaline from the adrenal gland[47], see Figure 2. The immune system is affected by change in the levels of hormones secreted by the adrenal gland. Dysregulation of cortisol levels can give rise to persistent inflammation which alters the capacity of immune cells to combat infections and disease. Glucocorticoid/cortisol dysregulation causes immune suppression by inhibiting certain transcription factors (NF-κB) involved in the production of cytokines (e.g. Interleukins), which are cellular signaling molecules involved in modulating the immune response, see Figure 2.

Another relevant physiologic pathway involved in the human stress response is the sympathetic nervous system (SNS)[47]. The SNS affects various systems (e.g. cardiovascular system) and glands (e.g. lymph nodes, salivary glands) in the body through direct innervation, which refers to a hardwiring of the body through a network of nerves. Stress causes the SNS to initiate the fight-or-flight response and releases the hormones epinephrine and norepinephrine. These hormones have a wide-ranging effect on the body, and also influence immune function, for example, a reduction in the cytotoxic activity of natural killer (NK) cells. The SNS is known to initiate secretion of salivary enzyme α-Amylase. This system of interrelated interactions between psycho-social factors and physiological systems comprises the PNI framework. This PNI framework views psychosocial factors as moderators of the neuroendocrine system that together influence immune function[48,49]. Further evidence in favor of PNI mechanisms is established through psychosocial intervention research, wherein interventions that were designed to reduce stress have demonstrated a decrease in cortisol secretion and have improved functional measures of the immune system such as cytokines [50,51]. Studying the neuroendocrine and immunological effects of psychosocial stress management interventions for CS using the PNI framework is a needed area of research, since CS are predisposed to have immunosuppression.

**Immune Suppression in Cancer Survivors**

It can be posited that the immune systems of cancer survivors are compromised by the combined impact of 1) late and long-term effects of treatment regimens such as surgery, chemotherapy and radiation, 2) negative immunologic effects due to the cancer itself and 3) chronic psychosocial stressors described above. Late effects of chemotherapeutic drugs such as methotrexate have been implicated to cause a reduction in all types of immune cells and insidiously affect bone-marrow production of immune cells in cancer survivors many years after treatment[1]. Long-term effects, i.e. side-effects or complications of treatment, on immune function are common in patients that are treated with immunosuppressive agents (e.g. cyclophosphamide treatment in transplant recipients), or hormonal therapy (e.g. corticosteroid therapy)[1]. All the treatment modalities for cancer, which includes surgery, chemotherapy and radiation, have the potential to cause varying degrees of immune suppression.

Moreover, cancer itself can have immunosuppressive influences on patients. For example, many hematologic cancers (e.g. leukemia, lymphoma), and cancers that are likely to become metastatic, are known to alter the production of immune cells resulting in immature cells entering the blood stream, and this effect can continue into survivorship[1,52] . Considering the evidence for chronic stress impacting immune function, it can be suggested that stress combined with the late and long-term effects of cancer treatments, and the cancer itself, can work synergistically to augment the immune suppression in the CS population, which can lead to very serious health consequences. Therefore, CS need interventions that are designed to regulate psychological and emotional stress, which in turn can alter the response from the HPA axis and SNS and result in beneficial changes to their immune function. However, rigorous empirical research is needed to establish evidence for the efficacy of psychosocial interventions for CS.

**The Need for Psychosocial Intervention Research in Cancer Survivors**

Considerable advances have occurred in medical diagnosis and management for patients with cancer.[3] Breakthrough innovations have occurred in areas such as radio-diagnostic imaging (e.g. positron imaging tomography/PET scan[53]), surgical procedures (e.g. robotic surgery[54]) and chemotherapeutic agents (e.g. targeted chemotherapy[55]) for cancer patients. However, interventions to manage the several unmet psychosocial needs of cancer patients and CS have not witnessed the same advances in their science and technological delivery[3]. Therefore the IOM has recommended that researchers and health practitioners in the oncology setting should work towards enhancing the science and delivery of psychosocial health interventions and generate evidence that can institutionalize the use of theory-driven psychosocial interventions as a part of routine cancer care[3]. Based on the IOM report, "interventions that enable patients, their families, and health care providers to optimize biomedical health care and to manage the psychological/behavioral and social aspects of illness and its consequences so as to promote better health," [3 (p.69)] can be considered to be psychosocial interventions. The PNI theoretical framework guided the choice of outcome measures for this intervention research study. However, the first step towards addressing the need for improving the science and delivery of psychosocial intervention, was identifying gaps in the existing literature pertaining to psychosocial interventions for patients with cancer.

## Chapter II. Literature review

Cancer is a significant global public health problem, which has caused 7.6 million deaths world-wide, as estimated by the World Health Organization (WHO) in 2008[56]. In the United States, the Surveillance, Epidemiology and End Results (SEER) for cancer, published by the National Cancer Institute (NCI), reports that 41% of Americans face a chance of being diagnosed with cancer in their lifetime.[57] Cancer remains the second most common cause of death in the United States and this year alone, iSEER estimates 1,638,910 men and women (848,170 men and 790,740 women) will be diagnosed with cancer (of all sites) and there will be 577,190 deaths due to cancer. This corresponds to 4,490 new diagnoses and a loss of more than 1,500 lives, every day[58]. The estimated cost of cancer care amounted to $124 billion in 2010 and is projected to reach around $158 billion by the year 2020[59]. These data illustrate the public health burden posed by cancer, related to morbidity, mortality and healthcare costs. However, cancer affects every aspect of the health and well-being of individuals, i.e. physical, mental and social well-being.

Patients with cancer experience significant psychosocial-emotional trauma that act as chronic stress stimuli, which negatively impact physical well-being (e.g. immune suppression) as well as psychosocial well-being (e.g. poor coping with cancer), and poses a major public health problem [3]. In every stage of their disease course, patients with cancer are faced with a complex set of psychosocial problems. Researchers have highlighted a deficiency of research evidence related to interventions designed to improve mental and social well-being, i.e. psychosocial well-being, in patients with cancer. In order to address the psychosocial problems in cancer patients, researchers and health practitioners have developed a wide range of therapies and interventions. The first step of this dissertation study was to conduct a comprehensive critical review of the literature to identify the types of psychosocial interventions that have

studied in the cancer population and determine how these interventions have influenced particular health outcomes (specifically PNI-based outcomes) in patients with cancer.

**PNI-Based Psychosocial Interventions**

Although studies supporting a relationship between psychosocial stress and adverse health outcomes have been published since the 1940s, substantial progress in PNI research occurred only after 1980[42]. A study published by Spiegel et al[60]. (1989) drew considerable attention to psychosocial intervention research, as it reported an increased survival rate in breast cancer patients who participated in a group-therapy psychosocial intervention[60]. The effects of group therapy on increased survival rate were later attributed to neuroendocrine-immune mechanisms described in the PNI framework[61]. Though Spiegel et al.'s study was controversial and replication studies of their group-therapy intervention failed to demonstrate increased survival[62,63], researchers became interested to explore the neuroendocrine-immune effects of a variety of psychosocial therapies[64], such as Cognitive-Behavioral-Stress-Management (CBSM) and supportive therapy in persons with cancer[64]. Subsequent systematic reviews of PNI-based psychosocial therapies have been conducted[64,65], but, these reviews have lacked a comprehensive approach towards identifying and appraising eligible studies.

**Gaps in Literature: Lack of Comprehensive Reviews**

Previous reviews have lacked breadth and depth in their approach towards evaluating PNI-based psychosocial interventions with regards to a) review methodology, b) limited cancer types evaluated, c) limited descriptions of the types of therapies and d) lack of specificity in reporting PNI-measures

**a) Review methodology.** Although early reviews, published in the 1990s[66-68], of psychosocial therapies indicated that the PNI framework could be used to explain the benefits

(e.g. increased survival) of psychosocial interventions for cancer patients, these reviews did not use statistical methods to assess the PNI effects of psychosocial interventions. A systematic review published in 2002[69] used a more rigorous methodology provided by the evidence-based medicine (EBM) approach, which involved assessing results of rigorous randomized controlled trials[69]. This review concluded that not a single psychosocial intervention strategy could be recommended for improving immune function in cancer patients[69]. However, the review authors, Newell et al. [69], made their conclusion based on a small sample of four qualifying studies that measured PNI outcomes[70-73]. The National Cancer Policy Board (NCPB) criticized this review in a report published in 2004[74], and determined that, due to very narrow methodological specifications, many valuable effects of psychosocial interventions, which includes PNI effects, may have been "missed or undervalued"[74(p97)].Other health researchers have also suggested that the EBM methodology may be too restrictive for evaluating psychosocial therapies and have advocated for reviewers to ensure methodological diversity (described below) in the inclusion of psychosocial interventions[75,76].

**b) Cancer population.** Reviews of PNI-based psychosocial interventions have most commonly reported studies conducted for a specific cancer populations, most often women with breast cancer[64,77-79]. Reviews that adopt this narrow focus eliminate studies conducted in other cancer populations and this limits the reach of psychosocial therapies for persons with cancer.

**c) Types of therapies**. A wide variety of interventions have been developed for addressing the psychosocial aspects of cancer. A meta-review of psychological interventions identified 79 distinct modalities of psychosocial therapies[80], ranging from education to breathing exercises. However, reviewers have not appraised the details of psychosocial interventions in terms of their individual components and activities, methods of delivery or duration of the

interventions[80]. Health researchers have been recommended to pay attention to the aforementioned details of psychosocial therapies in recently provided recommendations for reviewing complex interventions: assessment and trials implementation of services (COMPASS)[80,81].

**d) PNI measures employed**. Reviews of psychosocial interventions that included studies which used PNI biomarkers as outcomes, have not detailed the specifics of the PNI biomarkers and psychometric scales employed[64,79]. Also, researchers in this field have noted that many psychosocial interventions claiming to work through PNI mechanisms have not measured actual PNI biomarkers[68,77,82]. For example, even though the landmark study by Spiegel et al. (1989)[60] alluded to PNI mechanisms[61], it has been noted that biomarkers associated with PNI systems were not obtained as outcome measures in the original study[64]. Recent reviews of research studies designed to determine relationships between psychosocial factors and survival outcomes of patients with cancer continue to suggest psychoneuroimmunologic mechanisms of actions[83,84]. However, these reviews[83,84] have included research that did not use PNI-based biomarkers as outcome measures, and thus calling into question the validity of the claims regarding PNI effects of therapies targeting psychosocial variables in persons with cancer.

**Comprehensive Approach to Literature Review**

Thus, a comprehensive approach to conducting a review of the current literature was undertaken. To this end the directives for conducting evidence reviews of psychosocial interventions provided by the IOM[3,74], the World Health Organization[76] and the COMPASS checklist proposed by Hodges et al[80]. were followed. These directives were operationalized for the current review by a) having methodological diversity in study designs, b) including all cancer populations, c) examining details of the types of psychosocial therapies and d) identifying the

specific PNI outcome measures employed. The aim of the literature review was to assess the current state-of-the-science (studies published after 2001) for PNI-based psychosocial therapies to answer the following questions (Qs):

Q1) Population: In which cancer populations, in terms of type and stage of cancer, have psychosocial interventions using PNI-based measures been conducted?

Q2) Types of interventions: What types of psychosocial interventions (that used PNI-based outcomes measures) have been delivered for cancer patients? Particularly,

a) What activities (e.g., relaxation training) did the therapies employ?
b) What were the method(s) of delivery (e.g., individual/group-based) and personnel involved?
c) What were the durations of the interventions (including length of each session)?

Q3) PNI measures: Which specific measures of PNI subsystems were used as outcomes for psychosocial interventions in the cancer population?

**Review Methodology**

Methodology for the review process was based on guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[85]. Authors also reviewed methodological recommendations for conducting literature reviews put forth by the Cochrane collaboration[86], the IOM committee on standards for systematic reviews of comparative effectiveness research[87], and the assessment of multiple systematic reviews (AMSTAR) checklist[88]. Methods involved developing a systematic a) search strategy and b) selection criteria, along with c) screening and identification procedures to eliminate irrelevant studies, which were followed by d) data extraction procedures.

**a) Search Strategy**

The following electronic databases were searched online during November and December of 2013 to identify the studies: PubMed/Medline, EMBASE, PSYCINFO, CINAHL, and Google Scholar. Studies were considered if they were published from January, 2001 to November Week 4, 2013. The search terms (keywords) from a previous systematic review[69] and a meta-analysis[89] of psychological interventions were included in our search strategy.

There were three categories of keywords (described in italics) used in combinations to identify relevant studies related to i) cancer: *cancer, neoplas*, oncolog**; ii) psychosocial intervention: *psych*, psychosoc*, interven*, psychotherapy, psycholog*, cognitive therapy, behav* therapy, self-help-groups, support group*, relax*, hypno*, meditat*, imagery, stress, psychological, counsel*, group therap*, family therapy, depressive disorder therapy, treatment(s), therapy/therapies*; and (iii) PNI measures: *leukocyte, lymphocyte, natural killer cell, interferon, interleukin, tumor necrosis factor, cortisol, neuroendocrine, hormonal, psychoneuroimmunology, immune function*, where * represents wildcard characters. Additionally, the reference sections of all relevant papers were examined to identify any additional relevant studies. This electronic search strategy yielded 403 research records, from which 112 duplicate records were eliminated. The remaining 291 records were screened based on our selection criteria to find eligible studies.

**b) Selection Criteria**

A set of five independent selection criteria related to 1) time-frame and language, 2) study design, 3) cancer population, 4) types of therapies, and 5) PNI-based measures, were used to identify, screen and select eligible studies corresponding with the aims of this review.

**1) Time-frame and language.** Only studies published in peer-reviewed journals after

January, 2001 until November, 2013 were included in our literature review. For a comprehensive review of psychosocial therapies for cancer patients that used PNI-based measures published before 2001, refer to Andersen, 2002[90]. The searches were conducted in English and all the studies included in this review were either published in English or translated into English language by the publishers of the journal.

**2) Study design.** True experimental designs, i.e. randomized controlled trials (RCTs), as well as studies with rigorous quasi-experimental designs[91], such as non-randomized controlled trials (NRCTs) and pretest-posttest measurement designs were included. RCTs had to include the number of cancer patients included in the intervention group and in the control group. Non-experimental designs, such as correlational research studies, were excluded.

Selection criteria relevant to the specific research questions of this review were:

**3) Cancer population.** Interventions conducted with participants diagnosed with cancer at any stage beyond initial diagnosis were included. Since this review aimed to evaluate the impact of psychosocial therapies on the health of patients actually diagnosed with cancer; interventions conducted exclusively with family members or caregivers of cancer patients were excluded.

**4) Types of interventions.** To guide the inclusion of psychosocial therapies, the IOM's definition of psychosocial health interventions, which involved therapies that help patients "to optimize biomedical health care and to manage the psychological/behavioral and social aspects of illness and its consequences so as to promote better health"[3(p69)] was adopted. This IOM definition inherently encompasses therapies employing cognitive and behavioral therapeutic activities, such as coping skills training. However, therapies that emphasized integrative concepts of healing body, mind and spirit, which were classified under complementary medical therapies

by the National Cancer Institute[92,93] were also included. Interventions that exclusively involved behavioral regimens, such as physical exercise, were excluded because the IOM definition required psychosocial therapies to address psychological and or social problems related to illness. Interventions delivered by any health professional, and in any setting, using any method of delivery or duration were included.

**5) PNI-based measures.** Only those psychosocial intervention studies that reported results of at least one neuroendocrine or immune outcome measure, as well as described the PNI framework in the paper's background section were included. Studies that merely referred to the PNI framework but only measured psychological constructs (e.g., depression) or global outcomes (e.g., survival) were excluded.

### c) Screening and Identification Procedures

The 291 research records obtained from the search strategy underwent two stages of screening. Details of the screening and identification process are outlined in Figure 3. In the first stage of screening, the title and abstracts of the research records were evaluated according to the five criteria. In this stage 246/291 records were eliminated leaving us with 45 records. These 45 records entered the second stage of screening, where full text papers were further evaluated for final eligibility. The second screening stage eliminated an additional 23/45 studies leaving 22 studies (Figure 3 below). However, review of the reference lists of full-text research papers obtained during second screening, revealed 4 additional studies found eligible for review. Therefore, finally 26 papers were identified and included for review procedures. Of note in this sample of 26 papers, there were two pairs of manuscripts (2 RCTs[94,95] and 2 pretest-posttest studies[47,52]) that had reported results during different phases of the same larger intervention. These 2 pairs of papers were collapsed and considered to be single studies; which led to 24

original studies (reported in 26 manuscripts) obtained at the end of the search and selection process. For the review procedures, information was extracted from all 26 manuscripts.

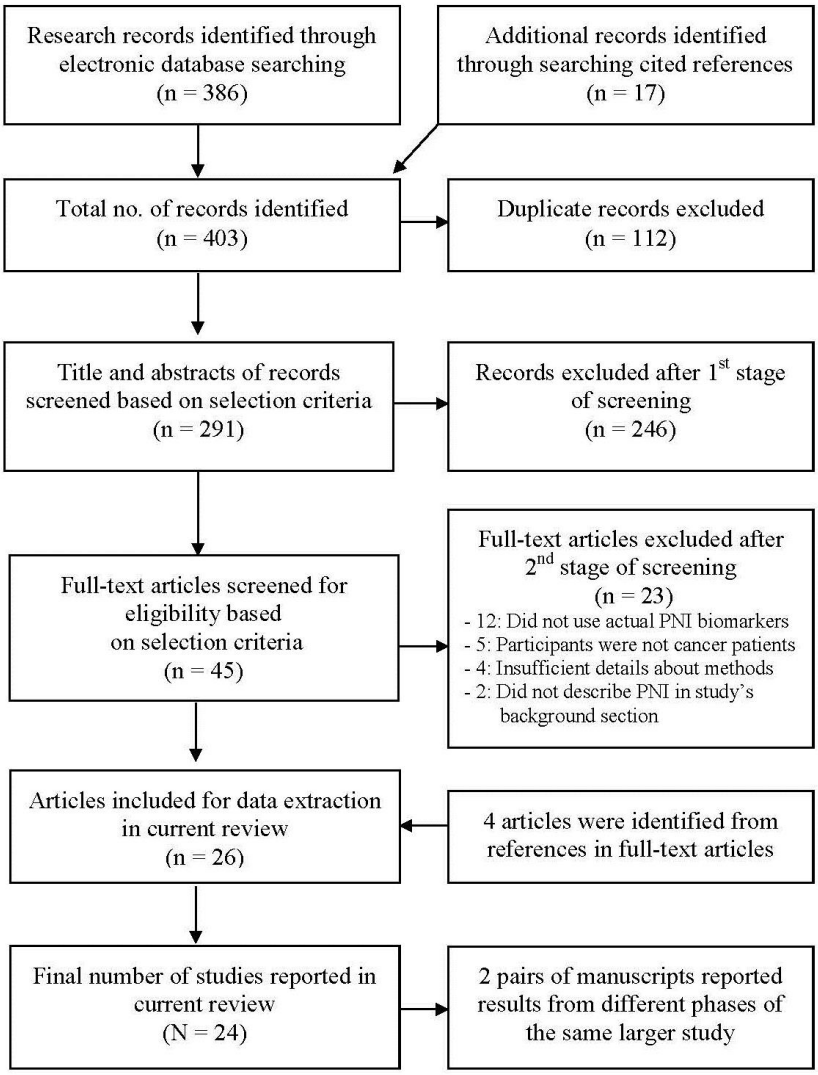



**Figure 3: Flowchart of literature review**

### d) Data Extraction Procedures

The reviewers prepared a detailed data extraction manual. This manual was applied to the sample of 26 papers. Data were extracted and entered into an Excel spreadsheet. Studies were categorized based on the strength of their study design as suggested by the evidence-based approach for therapeutic interventions previously suggested by some health scientists[96,97]. This

categorization involved placing RCTs first, followed by NRCTs and finally pretest-posttest studies (Table 1). One RCT that reported results from only their intervention group participants was included in the pretest-posttest study group for review procedures[98]. Data from the manuscripts of the 2 RCTs[94,95] and 2 pretest-posttest studies [47,52] which reported findings from the same intervention, were pooled and reported collectively in their respective study groups.

The following data were obtained from the research papers: a) first author, year of publication; b) stage and type of cancer; c) number of participants in the intervention group; d) the type of control condition and number of participants in control group; e) the type and duration of intervention and length of each session, f) psychosocial measure(s) used, g) neuroendocrine measure(s) used and h) immunological measure(s) used. Other noteworthy points (e.g. adequacy of sample size, analysis of mediators) were included as i) additional remarks. Since this review aimed to appraise studies with regards to the specific research questions (stated above), methodological quality scores were not assigned to the studies.

**Review Results**

This literature review included results from 19 RCTs, 1 NRCT and 4 pretest-posttest studies of PNI-based psychosocial interventions conducted in the cancer population. Table 1 gives an outline of the type and duration of the interventions and their effects on the respective psychosocial, neuroendocrine and immunological measures used. Specific findings related to the research questions posed by this review are presented below.

**Q1) Cancer population.** Most studies consisted exclusively of women diagnosed with breast cancer (18/24, 75%). The studies of women with breast cancer consisted of 9 studies that had patients with early stage breast cancer (stage I or II),[99-107] and 7 studies that included patients with stage III breast cancer[94,98,108-112]. Only 1 study included patients with metastatic breast

cancer (stage IV)[113] and 2 studies included breast cancer survivors[114,115]. The next most common type of cancer population was patients with prostate cancer (4/24, 16.7%). In terms of prostate cancer staging, 3 studies included patients with early-stage localized prostate cancer patients[99,100,116], while 1 study had prostate cancer survivors[116,117]. In the aforementioned studies, 2 studies used a mixed population of patients with early-stage breast and prostate cancer[99,100]. Only 8.3% (2/24) of PNI-based psychosocial therapies included persons with cancers other than breast and or prostate cancer. These studies consisted of one study of cervical cancer survivors[118]; and another study involving mixed cancer populations including persons with lung and colorectal cancers, as well as person with prostate and breast cancers in the entire range of cancer stages, including cancer survivors[119].

**Q2) Types of psychosocial interventions.** The two major types of interventions identified were i) cognitive-behavioral therapies (15/24, 62.5%) and ii) complementary medical therapies (9/24, 37.5%). Each study was assessed for the types of therapeutic activities employed in the psychosocial intervention.

***Q2. A) What activities did the interventions employ?*** All studies used more than one therapeutic activity during the delivery of their intervention. Table 2 presents a complete list of activities employed in each study. The two most common activities, used by more than half of all psychosocial therapies reviewed, were relaxation training and education (Table 2). Descriptions of the kinds of activities used by psychosocial interventions for cancer patients elucidated by the IOM[3] and National Institutes of Health (NIH)[92,120] were reviewed to guide categorization of interventions. Studies were either classified as a cognitive-behavioral therapy or a complementary medical therapy based on the activities involved in the intervention.

i) Cognitive-behavioral therapies consisted of interventions that emphasized cognitive

and behavioral activities and approaches such as cognitive restructuring, psycho-education and coping skills training (Table 2). Some studies delivered highly structured cognitive-behavioral programs, such as CBSM, that were specifically designed to meet the psychosocial needs of breast cancer patients[104,108,113]. Few studies used supportive care activities such as individual supportive care, home care and group social-support (Table 2). Several studies also included progressive muscle relaxations, meditation, abdominal breathing, and guided imagery (Table 2). There were 3 cognitive-behavioral studies that particularly emphasized visualizations. Of these, 2 studies asked patients to mentally visualize personal and metaphorical images of their immune systems effectively removing cancer cells from their bodies[103,107], while the third study employed hypnosis to guide visualizations[107]. Another intervention included cognitive-behavioral activities specifically tailored for insomnia and sleep management, e.g., stimulus control[121]. One study utilized an expressive writing intervention that asked patients to write about their experience with prostate cancer and its treatment and other traumatic and upsetting experiences in their lives[117]. Finally, a cognitive-behavioral study also included counseling for relationship and sexual problems faced by their participants[118].

ii) Complementary medical therapies involved activities such as yoga, meditation, qigong, mindfulness-based stress reduction (MBSR) and massage (Table 2). In this group of therapies, 5 studies emphasized stress-management through meditation. One yoga study combined activities including breathing exercises, meditations, a set of yoga postures (*asanas*), along with relaxation and mental imagery[109]. Another study delivered an integrated yoga program at the bedside before and after a surgical operation and provided patients with audiotapes of instruction for yoga exercises to be practiced at home[111]. The other 3 studies delivered a structured MBSR program[99-101,122] previously developed by another researcher[123].

MBSR consisted of teaching participants to achieve mindfulness, defined as a "non-elaborative, non-judgmental present-centered awareness"[124(p232)] and help participants enhance the acceptance of their life experiences[123]. Participants learned MBSR through the use of breath awareness, sitting and walking meditations and yoga techniques and were also provided with educational materials and workbooks to help them with cognitive reappraisals and in practicing mindfulness in daily life.

There were 3 complementary therapies that encouraged stress-reduction through either active behavioral practices, such as body movements, or passive behavioral techniques such as massage. One yoga intervention consisted exclusively of performing poses from the "Iyengar yoga" tradition, that were executed slowly with the help of props to maintain proper orientation and posture[114]. One study of medical qigong consisted of body movements during specific standing postures along with meditation training, visualization and a range of breathing exercises including chest and abdominal breathing[119]. One massage intervention employed a protocol that consisted of a combination of massage and acupressure techniques that promoted relaxation[106]. Finally, one study emphasized a body-mind-spirit connection and combined yoga and massage techniques with psychosocial approaches such as forgiveness therapy[115].

***Q2. B) What were the method(s) of delivery?*** Studies delivered their respective psychosocial therapies to participants either within a group-setting (15/24, 62.5%) or on an individual basis (9/24. 37.5%). On average 7 participants were included in the group-based therapies, but group-size ranged between 3 and 15 participants. Most studies involved in-person interactive (21/24, 87.5%) sessions with participants. There were 3 studies that did not involve any personal interactions with participants (3/24, 12.5%). Of these, 2 studies delivered their intervention exclusively through phone-conversations[105,118] and one study delivered an

expressive writing therapy through oral and written instructions given to the patients and followed-up with patients through a phone call[46]. The interventions delivered entirely through phone conversations consisted of one study that used a telephone conference call to deliver group-therapy[105], and another study that conducted individual telephone-counseling sessions with participants[118]. It was noteworthy that two studies provided therapy sessions on the morning of scheduled surgery to mentally prepare patients for surgical procedures[111,116], and one supportive therapy intervention was provided to participants on a residential basis[102].

Who delivered the therapies? Half the psychosocial therapies were delivered by clinical psychologists, while 3 therapies were delivered by nurses, and 2 therapies involved physicians (Table 1). Supportive care services were delivered by a variety of health professionals including group therapists, social workers, art therapists and visualization specialists[102,105]. The complementary medical therapies, also employed a variety of allied health professionals, such as clinical massage therapists and instructors trained in yoga and qigong techniques[102,106,109,114].

***Q2. C) What were the durations of the interventions?*** The average duration of interventions using PNI-based psychosocial therapies (taken over all 24 studies) was roughly a total of 10 hours (600 minutes). The 10 hours of psychosocial intervention were delivered over an average period of 8 weeks consisting of approximately 8 therapy sessions, with each session lasting for about 70-75 minutes. However, the duration of interventions, including the time required for each session varied considerably among the studies. The briefest intervention was expressive writing, which lasted for a total of 1.3 hours (80 minutes) over a single week, with 4 sessions taking 20 minutes per session over 4 consecutive days[117]. In contrast, the lengthiest intervention was 20 times greater in duration, and consisted of a cognitive-behavioral therapy intervention of 27 hours (1620 minutes) over 18 consecutive weeks, with 18 therapy sessions

that lasted about 90 minutes per session[108].

**Q3) PsychoNeuroImmunologic (PNI) outcome measures.** Only a third of studies (8/24) in this review collected outcome measures for all three PNI subsystems. All studies, except one (23/24) used at least one psychosocial measure. With regards to PNI biomarkers, less than half (11/24) the studies, employed biomarkers of the neuroendocrine system, as opposed to the majority (22/24) of studies that used some type of immune biomarker.

***Psychosocial measures (P).*** All studies used self-report scales to measure participants' psychosocial profiles, except 1 study that did not report measures of any psychosocial construct[98]. The most commonly employed measure of psychosocial outcomes was the profile of mood states, POMS (11/24, 45.8%) scale. Most studies measured negative psychological states such as depression, negative mood, distress and anxiety[102,104,105,108,109,114]. Even though most interventions aimed to reduce stress in patients, only three studies actually used psychometric measures of stress[103,109,112]. Studies also assessed psychosocial well-being and function by measuring of quality of life and functional assessments related to cancer treatments and living with cancer[100,105,119]. Some studies were interested in the psychological coping response of participants and measured constructs such as benefit finding[104] (i.e., perceived benefits arising from the experience of being diagnosed and treated for breast cancer), and coping with illness[101,117]. Finally, 3 studies used measures that were closely related to the constructs emphasized in the therapies; for example, the cognitive-behavioral intervention aimed at improving sleep behavior measured the severity of insomnia[121], one CBSM intervention measured the specific psychosocial skills that were targeted by the CBSM program[95] and one MBSR study measured mindfulness attention and awareness[101].

***Neuroendocrine measures (N).*** The glucocorticoid stress hormone, cortisol, was the

most common neuroendocrine measure, used in all 11/24 research studies that had neuroendocrine parameters (45.8%). Studies measured cortisol levels in the participants' blood using radioimmunoassay techniques[95,101] or in saliva using enzyme linked immunosorbent assay (ELISA) techniques[99,109,114,122]. Other neuroendocrine parameters measured included a) catecholamine stress hormones, including epinephrine, norepinephrine in urine[106]; b) neurotransmitters, including urinary dopamine and serotonin[106] and salivary melatonin[122]; and c) serum levels of the corticosteroid hormone, dehydroepiandrosterone-sulphate (DHEA-S) [122].

***Immunological measures (I).*** The 22/24 studies that reported immunological measures (91.7%) obtained blood samples for immune analysis. The most commonly measured immune outcome was the cytotoxic function of natural killer cells (9/24, 37.5%). Most studies typically evaluated both types of immune measures[89], including enumeration of immune cells, e.g. T lymphocyte counts, and functional measures of the immune system[89], e.g. cytokine levels (15/24, 62.55%). However, 6 studies exclusively used functional immune measures (6/24, 25%) and 1 study measured only certain immune cell counts (4.2%),%), namely $CD4^+$ and $CD8^+$ T lymphocytes and NK cells[105]. Only a couple of studies did not use any type of immune outcome measure (2/24, 8.3%). We noted that only one study measured the inflammatory biomarker, C-reactive protein (CRP)[119] and another study measured serum immunoglobulin (Ig) levels (IgG, IgM and IgA) [111].

**Efficacy of Psychosocial Therapies for Patients with Cancer**

Due to the wide diversity of interventions and PNI measures reported, statistical comparisons required for a meta-analysis were not possible. Hence, limited comment could be made about the statistical evidence for the efficacy of psychosocial interventions on PNI-based outcome measures in the cancer population. However, we do deliberate over studies that reported

significant changes in PNI outcome measures. Firstly, with respect to psychosocial measures, 20 studies that included 13 RCTs, one NRCT and 3 pretest-posttest studies reported significant effects on at least one psychosocial measure (Table 1). Secondly, in terms of neuroendocrine outcomes, 6 studies reported significant results for changes in at least one neuroendocrine measure, including 4 RCTs, one NRCT and one pretest-posttest study (Table 1). Finally, regarding immune measures, 16 studies reported effects on at least one immune measure, which included 11 RCTs, one NRCT and 4 pretest-posttest studies (Table 1).

Effectiveness with respect to types of interventions indicated that more than half the studies using cognitive-behavioral therapies (10/15, including 8 RCTs) reported significant findings for at least one neuroendocrine or immune outcome measure. One cognitive-behavioral intervention reported a significant effect on an immune outcome up to twelve months after initiating the intervention[110]. Some cognitive-behavioral therapies statistically modeled the variables in the PNI framework and demonstrated that psychosocial constructs had an influence on immune outcomes. For example, one study reported that benefit finding was correlated with an increase in the T lymphocyte proliferative response to anti-CD3,[104] and another study showed that anxiety and depression mediated the increase in blood levels of the cytokine, interferon-$\gamma$[121]. Thus, several studies of cognitive-behavioral therapies reported significant effects on neuroendocrine-immune function through PNI interactions in patients with cancer.

**Table1.** Summary of psychosocial interventions for cancer patients using psychoneuroimmunology (PNI) - based outcome measures

| No | First author, year [citation] | Stage & type of cancer | Intervention (n) Control condition (n) | Type of therapy [b] and duration of intervention | Psychosocial measure(s) [ab] | Neuroendocrine measure(s) ab | Immunological measure(s) ab |
|---|---|---|---|---|---|---|---|
| | | | | RANDOMIZED CONTROLLED TRIALS (RCTs) | | | |
| 1 | Rosenberg[c], 2002[117] | Prostate cancer survivors | Intervention (n=15) Assessment only control (n=15) | Individual expressive writing intervention. 20 minutes of continuous writing over four consecutive days. | (↓) BPI<br>(X) MOS-SF-36<br>(X) SCL-90-R<br>(X) POMS<br>(X) Rumination[d]<br>(X) WOC-CA<br>(X) FACT-P | | (X) TNFα<br>(X) IL-4<br>(X) IL-10<br>(X) $CD4^+$ T cells<br>(X) $CD8^+$ T cells |
| 2 | Heiney, 2003[105] | Stage I or II breast cancer. | Intervention (n=33) Standard of care control (n=33) | Therapeutic group intervention through a telephone conference call. 6 weekly sessions lasting 90 minutes each. | (↑) POMS total<br>POMS *subscale*<br>(↑) *tension*<br>(↑) *anger*<br>(X) QOL-BCV | | (X) $CD4^+$ T cells<br>(X) $CD8^+$ T cells<br>(X) NK cells |
| 3 | Andersen, 2004[108] | Stage II or III breast cancer. | Intervention (n=114) Assessment only control (n=113) | CBT sessions with trained psychologists in small patient groups.18 weekly sessions lasting 90 minutes each. | (↑) PSS-Family<br>(↓) POMS total<br>POMS *subscale*<br>(↓) *anxiety*<br>(X) IES | | No (↓) LPR to PHA<br>(↑) LPR to Con A<br>(X) T lymphocytes<br>(X) NK Cell count<br>(X) NK Cell lysis |
| 4 | McGregor, 2004[104] | Stage I or II breast cancer. | Intervention (n = 18) 1 day seminar control (n = 11) | Group-based CBSM program. 10 weekly meetings lasting 120 minutes each. | (↑) BFS<br>(X) Distress[e] | | (↑) LPR to anti CD3<br>(X) Lymphocytes |
| 5 | Hernandez-Reif, 2004[106] | Stage I or II breast cancer. | Intervention (n = 18) Wait list control (n = 16) | Individual massage sessions. 3 massages a week for 5 weeks with every massage session | (↓) POMS<br>STAI *subscale*<br>(↓) *Anxiety* | (↑) Dopamine<br>(↑) Serotonin<br>No (↑) in Nor- | (↑) NK Cells<br>(X) NKCC<br>(X) Lymphocytes |

[a] (↑) Significantly higher in: intervention group compared to control group in RCTs; & post-intervention compared to pre-intervention in pretest-posttest studies
(↓) Significantly lower: in intervention group compared to control group in RCTs; & post-intervention compared to pre-intervention in pretest-posttest studies
(X) No differences between: intervention and control groups in RCTs; & post-intervention compared to pre-intervention in pretest-posttest studies

[b] Note: Full forms of all abbreviations used in Table 1 are provided in Annexure for Table 1

[c] Only a smaller subset of the sample completed immune measures

[d] Rumination measured using 10 items from a study assessing moderating effects of goal beliefs that influence rumination, depression and physical complaints

[e] A distress index was developed using descriptive adjectives from scales developed in a previous research published by Carver et al.

| No | First author, year [citation] | Stage & type of cancer | Intervention (n) Control condition (n) | Type of therapy b and duration of intervention | Psychosocial measure(s) [ab] | Neuroendocrine measure(s) ab | Immunological measure(s) ab |
|---|---|---|---|---|---|---|---|
| | | | | lasting 30 minutes each. | SCL-90-R *subscale*<br>(↓) *Depression*<br>(↓) *Hostility* | epinephrine<br>(X) Epinephrine<br>(X) Cortisol | |
| 6 | Savard, 2005[121] | Chronic insomnia secondary to breast cancer | Intervention (n = 27)<br>Wait list control (n = 30) | Group-based CBT for insomnia management. 8 weekly sessions with psychologists lasting 90 minutes each. | (X) POMS<br>(X) ISI[f]<br>(X) MFI<br>(X) HADS[g] | | (↑) IFNγ<br>(↓) Lymphocytes<br>(X) WBC<br>(X) Monocytes<br>(X) $CD3^+$ T cells<br>(X) $CD4^+$ T cells<br>(X) $CD8^+$ T cells<br>(X) NK Cells<br>(X) IL-1β<br>(X) NK cell activity |
| 7 | Savard, 2006[113] | Metastatic breast cancer patients with depression | Intervention (n=25)<br>Wait list control (n=20) | Individually-based CT intervention. 8 weekly sessions with psychologists lasting 60 to 90 minutes each. | (↓) HDRS<br>(X) BDI<br>(X) HADS<br>(X) MFI<br>(X) ISI<br>(X) EORTC-QLQ-C33 | | (X) $CD3^+$ T cells<br>(X) $CD4^+$ T cells<br>(X) $CD8^+$ T cells<br>(X) $CD16^+$ T cells<br>(X) Lymphocytes<br>(X) WBC<br>(X) Monocytes<br>(X) IFNγ<br>(X) IL-1β<br>(X) NK cell activity |
| 8 | Andersen, 2007[110] | Stage II or III breast cancer. | Intervention (n=114)<br>Assessment only control (n=113) | 8-month maintenance phase group CBT intervention which followed-up patients from the Andersen, 2004 study.[108]<br>8 monthly CBT sessions with trained clinical psychologists lasting 90 minutes each. | (↓) POMS<br>(X) IES | | No (↓) LPR to PHA<br>(X) LPR to Con A |

[f] (↓) ISI mediated : (↑) IFNγ, (↑) WBC and (↑) Lymphocytes
[g] (↓) HADS mediated : (↑) IFNγ, (↑) WBC and (↑) Lymphocytes

| No | First author, year [citation] | Stage & type of cancer | Intervention (n) Control condition (n) | Type of therapy b and duration of intervention | Psychosocial measure(s) [ab] | Neuroendocrine measure(s) ab | Immunological measure(s) ab |
|---|---|---|---|---|---|---|---|
| 9 | Nunes, 2007[103] | Stage I or II breast cancer | Intervention (n=20)<br>Assessment only control (n=14) | Relaxation and visualization in groups with psychologists. 30 minute sessions delivered daily over 24 consecutive days | (↓) ISSL<br>(↓) STAI<br>(↓) BAI<br>(↓) BDI | (X) Cortisol | (X) LPR to PHA<br>(X) LPR to DEX<br>(X) LPR to CORT |
| 10 | Nelson, 2008[118] | Cervical cancer survivors | Intervention (n=17)<br>Standard of care control (n=19) | Psychosocial telephone counseling therapy. 6 sessions with psychologists lasting 45-50 min each. | (↑) FACT-Cx | (X) Cortisol<br>(X) DHEA | (↓) IL-10<br>(X) PBMC<br>(X) IFN- γ<br>(X) IL-5 |
| 11 | Lindemalm, 2008[102] | Early stage breast cancer patients undergoing radio/chemo-therapy. | Intervention (n= 21)<br>Assessment only control (n=20) | Support group consisting of oncologists, art therapists, masseuses and person trained in qigong and mental imagery was offered on a residential basis. Week long program with a 4 day follow-up 2 months later. No information about duration of sessions. | (X) HADS<br>(X) NFQ | | (X) NK cells<br>(X) NKCC<br>(X) Lymphocytes<br>(X) IFN-γ<br>(X) IL-2<br>(X) IL-4 |
| 12 | Phillips, 2008[95] & Antoni, 2009[94] | Stage I, II and III breast cancer | Intervention (n=63)<br>1-day education seminar control (n=65) | Group-based CBSM program. 10 weekly meetings with psychologists lasting 2 hours each. | MOCS *subscale*<br>(↑) *Relaxation*[h]<br>IES *subscale*<br>(↓) *Intrusion*<br>(↓) HAM-Anxiety<br>(X) ABS | (↓) Cortisol | (↑) IL-2<br>(↑) IFN-γ<br>(↑) IL2:IL4 ratio<br>(X) IL-4<br>(X) IFN-γ: IL4 ratio<br>(X) $CD4^+$ T Cells<br>(X) $CD8^+$ T Cells<br>(X) $CD56^+$ T Cells |
| 13 | Rao, 2008[111] | Stage II and III breast cancer | Intervention (n=45)<br>Supportive therapy control (n=53) | Integrated yoga program. 4 individual sessions with yoga instructor at bedside lasting 60 minutes. | (↓) STAI<br>(↓) BDI<br>(↑) FLIC | | (↑) $CD56^+$ T Cells<br>(↓) IgA<br>(X) $CD4^+$ T Cells<br>(X) $CD8^+$ T Cells<br>(X) IgG<br>(X) IgM |

[h] (↑) Relaxation did not mediate (↓) Cortisol

| No | First author, year [citation] | Stage & type of cancer | Intervention (n) Control condition (n) | Type of therapy b and duration of intervention | Psychosocial measure(s) [ab] | Neuroendocrine measure(s) ab | Immunological measure(s) ab |
|---|---|---|---|---|---|---|---|
| 14 | Raghaven-dra, 2009[109] | Stage II and III breast cancer | Intervention (n = 44)<br>Supportive therapy control (n = 44) | Yoga education and training program. 6 weeks program with 3 sessions per week (total 18 sessions) lasting 1 hour each. | (↓) HADS<br>(↓) PSS | (↓) Cortisol | |
| 15 | Oh, 2010[119] | Range of cancers (and stages) including breast, lung, prostate cancers | Intervention (n=79)<br>Assessment only control (n=83) | Medical Qigong (MQ) group therapy. 10 week MQ program with Qigong instructor consisting of two sessions per week lasting 90 minutes each. | (↑) FACT-G<br>(↑) FACT-F<br>(↓) POMS | | (↓) CRP |
| 16 | Cohen, 2011[116] | Prostate cancer | Intervention (n=38)<br>Standard of care control (n=44) | Individual sessions consisting of CBT with a clinical psychologist and stress management information. Two sessions lasting 60 to 90 minutes each. | (X) POMS | | (↑) NKCC<br>(↑) IL-1β<br>(X) IL-12p70<br>(X) TNF-α<br>(X) IFN-γ<br>(X) IL-6<br>(X) IL-8<br>(X) IL-10 |
| 17 | Banasik, 2011[114] | Breast cancer survivors | Intervention (n=9)[i]<br>Wait list control (n = 9) | Iyengar yoga practice consisting of different poses. Group yoga practice sessions twice a week for 8 weeks lasting 90 minutes each. | FACT-B *subscale*<br>(↓) *Fatigue*<br>(X) FACT-B Total | (X) Cortisol | |
| 18 | Hsiao, 2012[115] | Breast cancer survivors | Intervention (n=26)<br>1-session education-seminar control (n=22) | Body-mind-spirit (BMS) group therapy. Weekly sessions over 8 weeks lasting 2 hours each. | MLQ *subscale*<br>(↑) *Search*<br>(X) BDI-ii | (↓) Cortisol | |

[i] Considerably underpowered study

| No | First author, year [citation] | Stage & type of cancer | Intervention (n) Control condition (n) | Type of therapy [b] and duration of intervention | Psychosocial measure(s) [ab] | Neuroendocrine measure(s) [ab] | Immunological measure(s) [ab] |
|---|---|---|---|---|---|---|---|
| 19 | Baker, 2012[112] | Stage I, II & III breast cancer | Intervention (n=6)[i] Standard of care control (n=6) | Integrated support program consisting of 2 day support workshop with a maximum 12 hours consultation with therapist. Exact duration of intervention not described. | (↑) SOSI<br>MFI *subscale*<br>(↓) *mental fatigue*<br>(X) FACT-G total<br>FACT-G *subscale*<br>(↓) *endocrine-specific symptoms*<br>(X) POMS | (X) Cortisol | No (↓) NKCA<br>No (↓) PBMC-Arginase<br>(X) $CD4^+$ T Cells<br>(X) $CD8^+$ T Cells<br>(X) NK Cells |
| | | | | NON-RANDOMIZED CONTROLLED TRIAL (NRCT)[j] | | | |
| 20 | Witek-Janusek, 2008[101] | Early stage breast cancer. | Intervention (n=38) Assessment only control (n=28) | Group-based MBSR training. 8-weekly (2.5 hours/week) sessions plus one full day session held after the 5th week | (↑) QOL- CVIII<br>JCS *subscales*<br>(↑) *Supportant &*<br>(↑) *Optimistic effectiveness*<br>(X) MAAS | (↓) Cortisol | (↑) NKCA<br>(↑) IFNγ<br>(↓) IL-4<br>(↓) IL-6<br>(↓) IL-10 |
| | | | | PRETEST-POSTEST STUDY DESIGNS | | | |
| 21 | Bakke, 2002[107] | Stage I and II breast cancer | Total N= 25<br>No control | Individual hypnotic-guided imagery delivered by medical doctor. 8 weekly sessions lasting 60 minutes each | POMS *subscale*<br>(↓) *Depression*<br>(X) WCC | | (↑) NK Cells<br>(X) NKCC |
| 22 | Carlson, 2003[32] & Carlson, 2004[122] | Early stage breast and prostate cancer | Total N=42<br>No control | Group-based MBSR delivered by psychologists. 8 weekly sessions lasting 90 minutes each and a 3 hour silent retreat between weeks 6 and 7. | (↓) SOSI<br>EORTC-QLQ-C30 *subscales*<br>(↑) *Global QOL*<br>(↑) *Appetite*<br>(X) POMS | (X) Cortisol<br>(X) Melatonin<br>(X) DHEAS<br>(X) Cortisol/ DHEAS Ratio | (↑) IFNγ<br>(↑) IL-4T<br>(↑) Eosinophils<br>(↓) Monocytes<br>(X) NK Cells |

[j] Participants self-selected either treatment or control group

[b] Note: Full forms of all abbreviations used in Table 1 are provided below in the Annexure for Table 1.

| No | First author, year [citation] | Stage & type of cancer | Intervention (n) Control condition (n) | Type of therapy b and duration of intervention | Psychosocial measure(s) [ab] | Neuroendocrine measure(s) ab | Immunological measure(s) ab |
|---|---|---|---|---|---|---|---|
| 23 | Carlson, 2007[99] | Early stage breast and prostate cancer | Total N=51<br>No control | Group-based MBSR delivered by psychologists. 8 weekly sessions lasting 90 minutes each and a 3 hour silent retreat between weeks 6 and 7. | (↓) SOSI<br>(X) POMS<br>(X) EORTC-QLQ-C30 | (↓) Cortisol | (↑) Eosinophils<br>(↓) Monocytes<br>(↓) IFNγ T cell production |
| 24 | Kang, 2011[98] | Stage I, II and III breast cancer | Intervention (N=49)<br>Data from control group not presented | Group-based CBSM intervention. 8 weekly sessions lasting 90 minutes each | | | (↑) NKCC<br>(↑) LPR to PHA<br>(↑) IL-4<br>(↑) IL-10<br>(X) IL-2<br>(X) IL-6<br>(X) IFN-γ |

**Annexure for Table 1:** Abbreviations = Full Form

| | |
|---|---|
| Interventions | CBSM = Cognitive Behavioral Stress Management, CBT = Cognitive Behavioral Therapy, CT = Cognitive Therapy, RVT = Relaxation and Visualization Therapy, BMS = Body-Mind-Spirit, MBSR = Mindfulness Based Stress Reduction. |
| Psychosocial Measures | BFS = Benefit Finding Scale, POMS = Profile of Mood States, DES-IV = Differential Emotions Scale-IV, CES-D = Center for Epidemiological Studies Depression Scale, IES = Impact of Events Scale, LOT = Life Orientation Test, MOS-SF36 = Medical Outcomes Study—Short Form—36, SCL-90-R = Symptom Checklist—90 Revised, BPI = Brief Pain Inventory, WOC-CA = Ways of Coping Inventory – Cancer Version, FACT-P = Functional Assessment of Cancer Therapy – Prostate, QOL = Quality of Life, BCV = Breast Cancer Version, ISSL = Inventory of Stress Symptoms Lipp (for adults), PSS-Family = Perceived Social Support from Family, BAI = Beck Anxiety Inventory, STAI = State-Trait Anxiety Inventory, ISI = Insomnia Severity Index, MFI = Multidimensional Fatigue Inventory, HADS = Hospital Anxiety and Depression Scale, HDRS = Hamilton Depression Rating Scale, HAM-anxiety = Hamilton Rating Scale for Anxiety, ABS = Affects Balance Scale, BDI = Beck Depression Inventory, FLIC = Functional Living Index of Cancer, MLQ = Meaning in Life Questionnaire, EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, NFQ = Norwegian Fatigue Questionnaire, MOCS = Measure of Current Status, PSS = Perceived Stress Scale, FACT-B = Functional Assessment of Cancer Therapy – Breast, QOL-CVIII = Quality of Life Index –Cancer Version III, MAAS = Mindfulness Attention Awareness Scale, JCS = Jaloweic Coping Scale, WCC = Ways of Coping Checklist, SOSI = Symptoms of Stress Inventory. |
| Neuroendocrine Measures | DHEAS = Dehydroepiandrosterone-sulphate |
| Immunological Measures | NK = Natural Killer, IFN = Interferon, TNF = Tumor Necrosis Factor, IL = Interleukin, CD = Cluster of Differentiation, LPR = Lymphocyte Proliferative Response, NKCC = Natural Killer Cell Cytotoxicity, WBC = White Blood Cells, PHA = Phytohaemagglutinin, ConA = Concavalin A, DEX = Dexamethasone, CORT = Corticosterone. |

**Table 2: Activities involved in PNI-based psychosocial interventions**[k]

| Name of activity | **Study No.**[l] (Type of therapies) using specified activities | | % of studies[m] |
|---|---|---|---|
| | **Study No.** [l] (Cognitive-behavioral) | **Study No.** [l] (Complementary medical ) | |
| Relaxation training | **3, 4, 8, 9, 11, 12, 16, 19, 21, 24,** | **13, 14, 15, 17, 18, 20, 22, 23** | 75% (18/24) |
| - Breathing exercises/techniques (e.g. deep breathing) | **- 4, 8, 9, 12, 16, 19, 21, 24,** | **- 13, 14, 15, 17, 18, 20, 22, 23** | - 67% (16/24) |
| - Imagery/guided imagery and visualizations | **- 4, 8, 9, 12, 16, 21, 24,** | **- 14, 18, 20, 22, 23** | - 50% (12/24) |
| - Progressive muscle relaxation | **- 3, 4, 8, 9, 12, 16, 21, 24** | | - 33% (8/24) |
| Psycho-Education | **2, 3, 4, 6, 8, 9, 11, 12, 16, 19, 21, 24** | **15, 18, 20, 22, 23** | 71% (17/24) |
| Coping skills training (e.g. problem solving, setting goals) | **2, 3, 4, 7, 8, 10, 12, 16, 24,** | **13, 14, 18,** | 50% (12/24) |
| Cognitive restructuring | **4, 6, 7, 8, 12, 16, 24** | **20, 22, 23** | 42% (10/24) |
| Yoga training (e.g. *asanas*) | **19** | **13, 14, 15, 17, 20, 22, 23** | 33% (8/24) |
| Group social-support | **2, 3, 4, 8, 12, 24,** | **20, 22, 23** | 38% (9/24) |
| Personal stress awareness | **2, 3, 7, 12, 16** | **20, 22, 23,** | 33% (8/24) |
| Expressing emotions and feelings | **1, 2, 4, 8, 12, 24** | **18,** | 29% (7/24) |
| Meditation | **4, 8, 9, 12,** | **13, 14, 15,** | 29% (7/24) |
| Physical Exercise | **3, 11, 19, 24** | **17,** | 21% (5/24) |
| Emphasizing the mind-body connection | | **17, 18, 20, 22, 23,** | 21% (5/24) |
| Qigong training | **11, 19** | **15, 18,** | 8% (4/24) |
| Mindfulness meditation training | | **18, 20, 22, 23,** | 8% (4/24) |
| Conflict resolution and anger management | **12, 4, 8, 12** | | 8% (4/24) |
| Assertiveness training | **3, 4, 8, 12** | | 8% (4/24) |
| Individual supportive care | **16, 19** | | 8% (2/24) |
| Massage | | **5, 18** | 8% (2/24) |
| Diet/nutritional advice | **3, 19** | | 8% (2/24) |
| Art therapy | **11, 19** | | 8% (2/24) |
| Counseling for relationship and sexual problems | **10** | | 4%(1/24) |
| Forgiveness therapy | | **18** | 4% (1/24) |
| Stimulus control | **6** | | 4% (1/24) |
| Expressive writing | **1** | | 4% (1/24) |
| Insomnia management (Sleep restriction) | **6** | | 4% (1/24) |
| Hypnosis/hypnotherapy | **21** | | 4% (1/24) |
| Communication skills training | **3** | | 4% (1/24) |
| Specialized homecare and leisure activities | **11** | | 4% (1/24) |

[k] Activities listed in Table 2 are based on the types of psychosocial treatments identified in a previous meta-review of psychological interventions in cancer patients[41]

[l] Study no.'s are referenced in the first column of Table 1

[m] Numbers for percentages reported are rounded off to next integer

With regards to complementary medical therapies, two-thirds of the studies (6/9) showed significant effects on at least one neuroendocrine or immune outcome measure. Though therapies involving yoga, qigong, and massage were evaluated using RCT designs, only two RCTs that included the aforementioned therapeutic activities reported significant effects on functional immune measures[111,119]. MBSR was not evaluated using a RCT study design; however, all three studies that used MBSR, involving one NRCT[101] and 2 pretest-posttest studies, had significant impacts on PNI biomarkers[99,100]. This suggests that complementary medical therapies are emerging psychosocial therapies which require more investigation regarding their impact on PNI-based outcomes in patients with cancer. We found a few brief and inexpensive psychosocial interventions appealing for further investigation in this study.

**A Brief and Inexpensive Psychosocial Intervention for Cancer Patients**

A significant finding in our review regarding the implementation of psychosocial interventions was that most interventions were delivered over 60-90 minute sessions conducted by health professionals over a span of several weeks (commonly 6-8 weeks), thereby, making most psychosocial interventions expensive and resource intensive. One intervention that emerged in this review was the expressive writing (EW) intervention, which is a brief (total of 80 minutes over 4 days) and inexpensive (does not need trained health professionals) psychosocial intervention which can be technologically adapted (computer-based format using the internet) for greater access and appeal. EW interventions in cancer patients have demonstrated improvements in self-reported physical symptoms of cancer patients and other self-reported psychological outcomes such quality of life[125]. Only one study was identified that employed EW in CS and used PNI measures[117], which was found to be problematic, since only a smaller subset (N=20) of the sample completed actual PNI measures. Researchers have proposed that a proactive approach

to the psychosocial care of CS can help prevent or mitigate stress during re-entry as well as lead to positively adaptive survivorship[14]. Therefore, empirically testing the effect of EW on CS psychological state and neuro-hormonal indices will provide significant advancement in the science of psychosocial health services for the cancer population, specifically for CS. Previous research conducted in other populations has demonstrated that EW has an effect on PNI-based outcome measures.

**The Influence of EW on PNI Interactions**

Disclosing emotional and stressful experiences through writing has been studied as an intervention to improve health outcomes in healthy as well as clinical populations. Three meta-analyses published in 1998, 2004 and 2006 have concluded that expressive writing has a significant positive impact on a variety of health outcomes[126-128]. EW has shown to impact a variety of neuroendocrine and immunologic variables. Scientific studies of EW that have used neuroendocrine measures (i.e. cortisol) have shown that expressive writing decreases cortisol secretion[129]. In the landmark study conducted by Pennebaker, Kiecolt-Glaser and Glaser (1988)[130], EW improved the response of two mitogens—phytohemagglutinin (PHA) and concanavalin A (ConA)–which are proteins that increase the proliferation of T lymphocytes that are important components of the immune system. Anti-body production was increased by EW for individuals injected with Hepatitis B vaccine[131] as well as those having chronic Epstein Barr Virus (EBV)[132] infection. In HIV infected population, an EW intervention demonstrated a significant increase in levels of CD4+ T Cells[133]. EW has demonstrated an improvement in immune function for healthy individuals as well as certain clinical populations such as post-traumatic stress disorder [129], fibromyalgia [134] and HIV+ patients[133]. However, researchers are still working on a robust theory that can explain the psychological and physiological effects of EW.

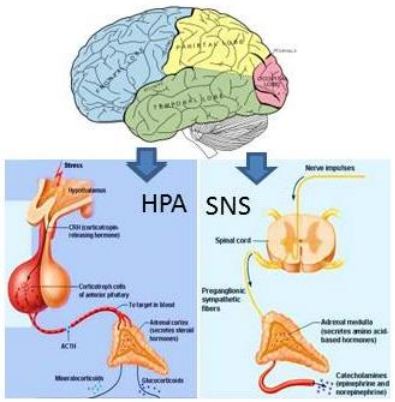
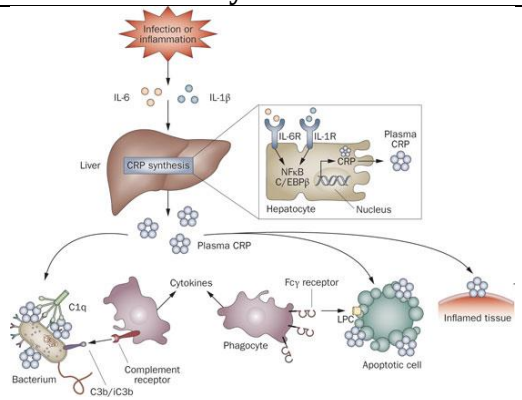
**How does EW regulate psychosocial stress and impact PNI outcomes?** Initially, EW was considered to work through the expression of inhibited thoughts and feelings (disinhibition theory) which are disclosed during the process of writing[135]. Subsequently, further studies of EW revealed the importance of cognitive processing, wherein EW was thought to help individuals make sense of or gain insight into stressful events that affected them, as well as organize and integrate their stressful experiences[135]. However, there is no consensus among researchers on a singular theory that adequately explains or predicts the diverse psychobiological effects of EW. In fact, the pioneer of EW, Dr. James Pennebaker, suggests that a single theory of EW is unlikely, since EW "affects people on multiple levels—cognitive, emotional, social, and biological."[136 (p.138)] Therefore, decisions on choosing a theory for EW intervention should be based on the outcomes (that are economically valuable to the population), and the issues faced by the population of interest[135,136]. The emotion-regulation of theory of EW[137] provides a sound framework for evaluating the effect of EW on psychosocial as well as PNI outcomes in CS.

**Expressive writing helps regulate stress through emotion-regulation.** Emotion-regulation theory suggests that emotional responses in individuals have three components. The first is the experiential, which involves positive (e.g. pleasure) or negative (e.g. pain) valence states, and includes the subjective cognitions and feelings of the individual. The second is the physiological component, which is involved with the regulation of stress hormone secretions (e.g. adrenaline and cortisol) through the HPA axis or the SNS. The third is the behavioral component, which include verbal and bodily responses[137]. Therefore, unresolved emotional responses (e.g. fear of cancer recurrence in CS) act as chronic stressors which deregulate stress hormone secretions and lead poor health behaviors (e.g. smoking). Psychosocial interventions such as EW help regulate these emotional responses and improve health outcomes.

Some evidence exists to support the emotion-regulation effects of EW on experiential (cognitive and affective) and physiological (PNI) outcomes, however, in general EW has had very low effects on behavioral outcomes[128]. The EW intervention allows individuals to see their stressful experiences at a distance and helps them give those experience structure and meaning[137,138]. This helps in generating positive coping responses to the stressors and cognitive reappraisal of negative emotional experiences[139] and a reduction in perceived psychological stress[140]. Also, the process of observing oneself expressing and controlling emotions during EW, gives the participant a newfound or greater sense of self-efficacy for regulating emotions[128] and coping with cancer. Emotional self-efficacy makes stressful experiences and emotions more controllable, and hence reduces negative affect. Regulation of psychological and emotional stressors reduces the chronic stress stimuli that are acting on the HPA axis and SNS, which regulate hormonal secretions, and in turn will help in bolstering immune function, as described in the PNI framework[77,141], see Table 3. However, no study of EW in the cancer population has empirically demonstrated the emotional regulation effects of EW and elicited the pattern of changes in secretion of neuro-endocrine hormone levels over time.

Cancer survivors are known to have changes in the rhythms of their neuro-hormonal secretions[39,142]. Therefore, it is essential to collect data over multiple time points, in order to empirically demonstrate how EW leads to reduced stress and improves PNI outcomes. The current study was designed to determine the psychoneuroimmunologic processes that occur over time, when CS write expressively about their stressful experiences related to cancer, by collecting repeated measures of neuroendocrine function and psychological status over a 6 week period. In order to provide increased accessibility and comfort to CS participating in EW, this study used technology to adapt the traditional pen-paper writing format to a computer-based one.

**Table 3: Theoretical framework of PNI for our expressive writing intervention**

| Psychosocial Intervention | Theoretical framework of Psychoneuroimmunology (PNI) | | |
|---|---|---|---|
| | **Psychosocial (P)** | **Neuroendocrine (N)** | **Immune (I)** |
| Expressive Writing → | Psychosocial Stress → | Neuroendocrine system → | Immune system |
| | **Respective Outcome Measures** | | |
| | i ) Percieved Stress<br>ii) Fear of cancer recurrence<br>iii) Self-efficacy for coping with cancer | Response from<br>i) Hypothalamo-pituitary adrenal (HPA) axis: Cortisol<br>ii) Sympathetic nervous system (SNS): α-Amylase | Inflammatory response of immune system:<br>i) C-Reactive Protein (CRP) |
| | **Possible Mechanisms of Action** | | |
| | **Emotion Regulation** | **Regulation of neuro-hormonal response from HPA and SNS axes** | **Regulation in secretion of inflammatory molecules of the immune system** |
| | **Habituation/ Desensitization**: Become less bothered by intrusive thoughts about the stress they are experiencing<br>**Insight**: Develop new insights about their self or the stressful experience<br>**Emotion Regulation:** Greater working memory |  |  |

## Chapter III. Specific Aims

For this study, a 20 minute EW intervention for cancer survivors (who have completed radiation treatment) was implemented over 4 consecutive days delivered using an online computer-based format. Neuro-hormonal response from the HPA axis as a result of EW was the primary outcome of interest and was measured by salivary cortisol levels. Secondary outcome measures of physiological (α-amylase and c-reactive protein; CRP) and psychological function (perceived psychological stress, negative emotion, and efficacy for coping with cancer) were also included. Using a two-arm (EW and control-writing) randomized-controlled trial (RCT) study design, the specific aims and hypotheses of this study were:

**Specific Aims and Hypotheses**

• **Aim 1**: Determine the efficacy of EW to impact the HPA axis in CS as measured by salivary cortisol levels, i.e. the primary outcome of interest.

**H1**: CS participating in EW (treatment arm) will have lower levels of salivary cortisol compared to CS participating in control-writing (control arm), 6 weeks post-intervention.

• **Aim 2**: Determine the efficacy of EW to impact the SNS in CS as measured by salivary α-amylase levels, i.e. a secondary physiological outcome of interest.

**H2**: CS participating in EW (treatment arm) will have lower levels of salivary α-amylase compared to CS participating in control-writing (control arm), 6 weeks post-intervention.

• **Aim 3**: Determine the efficacy of EW to impact the immune system in CS as measured by salivary CRP levels, i.e. a secondary physiological outcome of interest.

**H3**: CS participating in EW (treatment arm) will have lower levels of salivary CRP compared to CS participating in control-writing (control arm), 6 weeks post-intervention

• **Aim 4**: Determine the efficacy of EW to impact psychosocial functioning in CS as

measured by scores on self-report questionnaires: a) PSS (perceived psychological stress), b) FCRI-S (negative emotion), and c) CBI-B (efficacy for coping with cancer), i.e. secondary psychosocial outcomes of interest.

**H4**: CS participating in EW (treatment arm) will have lower scores on the PSS compared to CS participating in control-writing (control arm), 6 weeks post-intervention.

**H5**: CS participating in EW (treatment arm) will have lower scores on the FCRI-S compared to CS participating in control-writing (control arm), 6 weeks post-intervention.

**H6**: CS participating in EW (treatment arm) will have higher scores on the CBI-B compared to CS participating in control-writing (control arm), 6 weeks post-intervention

• **Aim 5**: Determine the effect of EW on the primary and secondary (physiological and psychosocial) outcomes of interest immediately after the intervention.

**H7**: CS participating in EW (treatment arm) will have higher levels of salivary cortisol, compared to CS participating in control-writing (control arm), 24 hours post-intervention.

**H8a**: CS participating in EW (treatment arm) will have higher levels of salivary α-amylase and CRP (secondary physiological outcomes), compared to CS participating in control-writing (control arm), 24 hours post-intervention.

**H8b**: CS participating in EW (treatment arm) will have higher scores on the PSS and FCRI-S and lower CBI-B scores (secondary psychosocial outcomes), compared to CS participating in control-writing (control arm), 24 hours post-intervention

## Chapter IV. Significance and Innovation

### Delivering the Expressive Writing Intervention in an Internet-Based Format

One of the most significant changes in individual lifestyles and societies in the modern world has been the use of computer technology and the internet. Recent statistics indicate that more than half the adults in the United States own a computer device that can access the internet, and 58% own a desktop computer, 61% have a laptop, and 18% own a tablet computer[143]. Smartphones are a recent technological innovation that offer a small computer interface and internet access, in addition to cellular phone use, and 45% of Americans own a smartphone, and the number goes up to 66% in age group 18-29[144]. In terms of access to the internet, recent data indicates that 82% of American adults can access the internet and 66% have a high-speed broadband connection at home[145]. In August of 2012, data reveals that 215 million Americans were active online and spent an average of 29 hours on the Internet that month[146].

The above data demonstrate the accessibility and popularity of computer-use and the internet amongst Americans and suggests it is a suitable medium for delivering psychosocial interventions such as EW. The computer-based format of EW also provides the participant to undertake their writing task at their own convenience, comfort and privacy, and the meta-analytic review of EW indicates that the settings in which EW is delivered moderates the outcome of EW[128]. Some studies have demonstrated an effective response for a computer-based and online EW intervention[147,148]. However, no study of EW has been done using an online computer-based format in cancer populations. A review of internet interventions in the oncology setting has suggested that cancer patients find internet based interventions to be highly acceptable and feasible, and psycho-oncology researchers have suggested that more psychosocial interventions should be delivered using the internet in the cancer population[149].

**Study Innovation**

The current EW study was a pioneering research effort designed to move the field of psychosocial interventions for cancer patients forward in terms of science, technology and service delivery. This was the first known study to collect repeated PNI based outcome measures for an EW intervention in CS. This research approach allows scientists to make inferences about the changes in neuroendocrine hormone secretions and immune parameters caused due to a psychosocial intervention (EW in this case) over time. Research shows that patterns of cortisol rhythms are indicators of survival rates in cancer patients[142]. Therefore, generating evidence to understand changes in the patterns of hormone secretion resulting from psychosocial interventions is crucial to our understanding of psycho-emotional effects on the biological function of CS. This knowledge will provide a significant contribution to the science of psychosocial health interventions for the CS population.

The NCI and IOM, in their 2008 report[3], *Cancer Care for the Whole Patient* have encouraged researchers and health practitioners to include psychosocial health of cancer patients and CS as part of routine cancer care. This study was the first to specifically target CS in the post-radiation re-entry phase of survivorship. This population (post-radiation CS) was deliberately chosen at a particular phase (re-entry) in the cancer-care trajectory, since research indicates an urgent need for psychosocial interventions for these individuals. Results from this study will contribute to the scientific understanding of patient outcomes from psychosocial interventions for re-entry phase CS that have completed radiation therapy. Lastly, this was the first study that takes the EW intervention to the medium of the internet and computers for the CS population. If online computer-based EW is shown to be effective in improving CS physical and psychosocial health (measured by PNI based outcomes), this health intervention has the potential

to reach millions of CS all over the US and the world over through the medium of computers and the internet. Therefore, this study also contributes to the knowledge base related to the technology and delivery of psychosocial health interventions for the cancer population.

## Chapter V. Methods

The ultimate aim of this study was to determine the efficacy of a brief and inexpensive psychosocial intervention (called expressive writing; EW) for the supportive care of CS after completion of radiation therapy. In view of this aim, a randomized controlled trial (RCT) provided an appropriate and rigorous study design that eliminates selection bias and group differences by way of random allocation of participants. Also, this study constituted an explanatory trial[150], since we aimed to contribute to the scientific understanding of PNI-based psychosocial interventions for CS. The research team for this study consisted of 1) the first author and chief research coordinator, Utkarsh B. Subnis (UBS), 2) study mentor and adviser Dr. Richard F. Brown (RFB), 3) study statistician, Dr. Maureen Wilson-Genderson (MWG), 4) nursing scientist and nurse practitioner, Dr. Angela R. Starkweather (ARS) and licensed clinical social worker (LCSW), Connie Macaluso-Dickerson (CMD).

### Randomized Controlled Trial (RCT) Study Design

A RCT study design is the gold standard design for determining therapeutic efficacy of a health intervention. The participants in this study were randomly allocated to either the treatment condition, or the control group through a randomization protocol to ensure that every participant had equal chance of getting either the treatment or the control condition. The unit of randomization in this study was the individual cancer patient.

**Randomization protocol.** Randomization of participants was performed through a computerized random numbers generator program. Two sets of random numbers were generated by the statistical software program SPSS for each group. The list of random numbers in each group was maintained in a secure location by UBS. These random numbers were then written on a piece of paper (5cm X 5cm) along with the group to which the random number belonged, for

example, “33 – Control group”. The random number also served as the participant ID number. These pieces of papers were folded twice and placed inside opaque envelopes. These opaque envelopes were then sealed and sequentially numbered. Each participant's name and email was entered on the front of the envelop (after study enrollment), and the research team was informed about the participant’s ID number, study group, name and email. The name and emails were de-identified from the participant ID number at the end of the study. There was no alteration in treatment allocation once random allocation procedures were completed. Measures to ensure adherence to protocol were taken, and are presented below.

**Intervention condition (EW group).** The intervention condition consisted of a prompt that encouraged patients to disclose their deepest possible emotions and feelings about their experience with cancer. Participants wrote about their stressful experiences over 4 consecutive days. The intervention protocol used in this study had been shown to be efficacious in improving stress related self-report and immune parameters as reported by previous meta-analyses[126-128]. Participants were instructed to, “Write your very deepest thoughts and feelings about your cancer experience.” Participants in the EW group were instructed to write continuously for between 20 - 30 minutes, and told to not worry about spelling, grammar or sentence structure. Please refer to Appendix N for the EW prompts.

**Control condition (Control group)**. This study had a control writing condition, equivalent to a placebo condition in RCTs for drug trials. The participants in the control condition also performed a writing task over four consecutive days. However, the control participants were asked to write about more mundane matters, i.e. how they spent their time, and were encouraged to approach the writing task in a more distanced and objective manner. The protocol used for the control writing had been developed and used in previous studies[151,152]. The

time allotted for writing the control condition was similar to the intervention condition, i.e. 20-30 minutes, over 4 consecutive days. Please refer to Appendix N for the control writing prompts.

**Delivery of intervention.** Participants in the treatment group and the control group received the writing prompt through an online link created using the web-based survey delivery software Qualtrics[153] and was delivered via email. Qualtrics is a HIPPA compliant survey delivery software, and participant's email addresses were entered in the program to directly deliver the surveys and writing prompts. Qualitrics generates a unique link for the survey which prevents spamming. By default, the anonymous survey link collects the user's IP address to help detect potential spam responses. However, the setting in Qualtrics was set to "anonymize responses" from participants; this prevented Qualtrics from obtaining any identifying information such as the IP address of participants.

**Manipulation check.** The intervention group was instructed to write about stressful and emotional experiences and the control group about mundane matters. However, it was important to determine if experimental manipulation of the intervention and control condition (by giving different directives for the two groups) was in fact successful. The EW literature suggests that data obtained from an EW writing intervention differ from data obtained from other writing tasks in language use. Therefore pronouns, cognitive terms, as well words denoting positive and negative affect are different. A software program that analyzes text for sentence and word use that is indicative of emotional expression, called the Linguistic Inquiry and Word Count (LIWC), has been developed by the pioneering EW researcher, James Pennebaker[154]. This LIWC software is able to detect and differentiate words and phrases routinely used when people write expressively as opposed to other writing tasks[155]. The LIWC software is updated on a regular basis and EW researchers have found it a reliable way of performing manipulation checks.

Therefore in order to check our manipulation, we submitted our participant's writing responses to a series of linguistic analyses performed through LIWC[154] to assess for use of positive and negative emotion words. The LIWC software application was available for download from the developer's website, http://www.liwc.net/index.php. All writing responses were deleted and destroyed after completing the text analysis procedures to maintain participant confidentiality.

**Trial Outcomes Measures**

The outcome measures for this study were chosen to help explain the psychosocial (P), neuro-endocrine (N) and immune (I) effects of EW. Each measure was carefully selected based on the scientific evidence regarding the reliability and validity of the measure, its role in the PNI interactions framework, and its relevance and importance for public health research, health care professionals and stakeholders, i.e. CS. The physiological measures were selected to provide information regarding activity of the HPA axis, SNS and immune system. The psychosocial measures were self-reported and were selected to provide information regarding the psychological processes influenced by EW and psychosocial functioning of the participant CS. To determine if EW was indeed helpful in managing stress for CS, we measured levels of perceived stress and severity of negative emotion. In addition, to determine if EW helped CS regulate emotions and improve their coping skills, we measured coping self-efficacy.

**Primary and secondary outcome measures.** Considering the specific aims and study design, it was appropriate to choose a "single main measure of clinical outcome," [156 p. 1075] that constituted the primary end point[157] of the RCT, referred to as the primary outcome measure henceforth. The primary outcome measure for this study was salivary cortisol levels (which described the activity of the HPA axis). A number of secondary outcomes that indicate both physiological and psychosocial functioning were also employed to help explain the multi-system

and PNI effects of psychosocial interventions. Salivary α-amylase levels (marker of SNS activity), and salivary levels of C- reactive protein—CRP (a parameter for the immune system), were used as secondary physiological outcome measures. In terms of secondary psychosocial outcome measures, reliable and valid self-reported psychometric scales were used which included the: a) Perceived Stress Scale (PSS) for levels of perceived psychological stress; b) Fear of Cancer Recurrence Inventory – Severity subscale (FCRI-S) for severity of negative emotion experienced by CS; and c) Cancer Behavior Inventory-Brief Version (CBI-B) for self-efficacy for coping with cancer.

All measures (primary and secondary) were obtained from each participant in the intervention and control groups at three time points, 1) 24 hours pre-intervention, i.e. baseline measure, 2) 24 hours post-intervention, i.e. immediate post-intervention measure and 3) 6 weeks post intervention, i.e. delayed post-intervention measure, see Table 4 below.

**Table 4. Outcome measures used and the timing of their collection**

| Outcome Measures | Pre Intervention | | Post Intervention | |
|---|---|---|---|---|
| | 24 hours (Baseline) | | 24 hours | 6 weeks |
| Primary Outcome (Salivary Specimen) | | | | |
| Cortisol | × | | × | × |
| Secondary Outcomes – Physiological (Salivary Specimens) | | | | |
| α-Amylase | × | | × | × |
| C-reactive protein – CRP | × | | × | × |
| Secondary Outcomes – Psychosocial (Self-reported questionnaires) | | | | |
| Perceived Stress Scale, PSS (14 items) | × | | × | × |
| Fear of Cancer Recurrence Inventory-Severity, FCRI-S (9 items) | × | | × | × |
| Cancer Behavior Inventory-Brief Version, CBI-B (12 items) | × | | × | × |

**Primary outcome: salivary cortisol.** Salivary cortisol was an appropriate primary outcome for this study, since levels of salivary cortisol have been demonstrated to be highly correlated with serum cortisol levels ($r$=0.91)[158]and is a reliable measure of HPA axis activity. Also, substantial evidence implicates a direct relationship between salivary cortisol levels and immune function[159,160]. These factors make cortisol levels a clinically relevant outcome measure for health researchers and professionals, and for our population, i.e. CS. Measuring levels of salivary cortisol has gained popularity in the social-behavioral sciences due the non-invasiveness of the procedure. However, it is important to take account the biological variations in cortisol secretion. Research indicates that there is a diurnal variation in cortisol level, which means there were considerable difference in a measure of cortisol level based on what time during the day the measure was collected[161]. Human beings experience a large spike in cortisol secretion 45-60 min after waking up from sleep, called the Cortisol Awakening Response (CAR)[162]. This initial spike during CAR reaches the peak cortisol release and is followed by a rapid decline and a gradual decrease and plateauing towards bedtime see Figure 4. CAR and the diurnal variation (from awakening to bedtime) of cortisol secretion have been associated with levels of psychosocial stress[162].

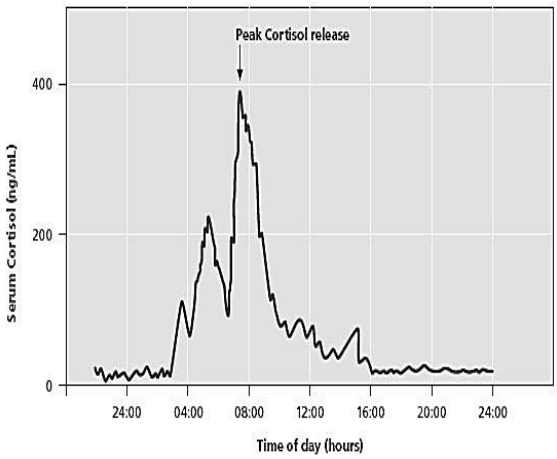



**Figure 4: Diurnal Cortisol Rhythm**

Therefore, in order to account for these patterns, bio-behavioral researchers recommend obtaining multiple measures of salivary cortisol during different times of the day[163]. Participants were asked to give their saliva samples by drooling into salivette tubes 3 times per day on every day of data collection, i.e. once at baseline (BOM), which is 24 hours before the intervention,

and twice after the intervention, specifically, 24 hours (POM1) and 6 weeks (POM2) post-intervention, see Table 4. Participants were requested to provide their saliva in their saliva containers at the following times: 1) immediately after waking up, for the waking response (W), 2) within 30 min after waking, for the peak response (P), and 3) immediately before going to sleep, for the bedtime response (B).

**Secondary physiological outcomes: salivary α-amylase and CRP.** Other elements of the PNI interactions such as the SNS/ANS and the immune system were assessed using two secondary physiological outcome measures. The procedures for collecting, storage and data analysis were identical to the salivary cortisol measures and are described below.

***1) Salivary α-Amylase.*** Biomarkers for the activity of the SNS/ANS in saliva have only recently investigated by researchers. Alpha (α) –amylase is an enzyme produced in the salivary glands that helps to degrade starch and aid digestion. Studies have shown that production of α-amylase in saliva increases in response to psychological stress (e.g., written examinations) and physical stress (e.g. exercise, heat and cold)[164]. Some research indicates that the secretion pattern of α-amylase does often correlate with cortisol levels during stress, suggesting a physiological stress response separate from the HPA axis[165,166]. A recent study found that α-Amylase was significantly correlated with blood levels of norepinephrine ($r$ = 0.33)[167]. α- Amylase is now considered a reliable correlate of sympathetic activity under conditions of stress[166]. Some research suggests a diurnal rhythm in α-amylase secretion, with pronounced decrease in the first hour after awakening and a steady increase during the rest of the day.

***2) C-Reactive Protein.*** C-reactive protein (CRP) was used as a secondary physiological outcome measure of the immune system since it provides information regarding the general level of inflammation in the body. CRP is a protein synthesized by the liver during inflammation and

the acute-phase response, and has been is widely used as a bio-marker of inflammation for a variety of conditions ranging from cardiovascular disease[88,168] (e.g. in myocardial infarction) to cancer[169,170]. CRP plays an important role in immune function and increases in levels during the body's response to physical stressors (e.g. infection, physical trauma, or malignancy). This involves a process of inflammation, which starts with recruitment of certain immune cells in the blood, i.e. white blood cells, WBCs, e.g. neutrophils. These WBCs secrete a number of signaling molecules called cytokines (e.g. Interleukins, IL) into the bloodstream. IL-6 induces increased production of CRP in the liver to assist with inflammatory processes[171]. CRP enhances the capacity of immune cells to produce more inflammatory cytokines[168,172] along with facilitating production of opsonin, that helps in destruction of pathogens and dead or dying cells[171,172].

CRP is also implicated in activation of other immune pathways (the classical complement pathway) and enhancing tumor-cell killing activity of immune cells (macrophages)[172]. Evidence also links psychosocial (chronic stress) and behavioral (exercise) factors with increased levels of CRP, which lends support to CRP's role in the PNI framework[173,174]. The ability to detect CRP levels in saliva has been a recent scientific development and data regarding correlation between blood and salivary levels is being established. However psychosocial interventions have found significant changes in CRP levels after improving participant's psychosocial functioning[174]. Hence, the saliva collected from CS was used to determine levels of CRP.

**Procedures for the collection and storage of saliva from participants.** Salivette tubes provided by the Center for Biobehavioral Clinical Research at the VCU School of Nursing were used for obtaining saliva samples from the participants in this study. This procedure needed a high level of adherence to protocols; therefore detailed training material was provided to potential participants to demonstrate how they would collect their saliva by drooling into the

salivette tube. An information booklet along with a link to a video demonstration of saliva collection was mailed to the participants prior to the study, see Appendix K. The study staff were also available to answer any questions participants had over the phone or voice/video chat as well. Salimetrics Inc.[175] Labs, which provide the assay kits for the analytes, recommend collecting a total volume of approximately 500 micro-liters (µl), when testing for three analytes. In their instruction and training booklet and video (please see Appendix K), participants were shown the marking on the salivette tube (Eppendorf tube) which would indicate that an adequate sample of saliva had been collected (i.e. at least 500 µl) for the purpose of this study.

Salimetrics reports their kits to be highly sensitive, reliable and valid ways to measure salivary cortisol, α-amylase and C - reactive protein, with a detection range of 0.012 – 3.0 µg/dl[176]. Also, past studies that have used these kits have reported that the intra-assay coefficient ranged from 3.35% to 3.65% and inter-assay coefficient ranged from 3.75% to 6.41%[177,178]. Participants were mailed the saliva collection kits (salivettes) for all three measures and for all three days of data collection at least one week before the intervention. The salivette tubes had a sticker pasted on the surface of the tube (see Appendix L), containing only the participant ID number along with a box to mark which type of sample it was based on the criteria for the timing of the sample described below.

**Timing of saliva collection on Day 2 (BOM), Day 7 (POM1) and Day 49 (POM 2).** Participants were asked to provide three samples at the following times on the day of outcome measures data collection:

1) Immediately after waking up, for the waking response (W),
2) Within 30 min after waking, for the peak response (P), and
3) Immediately before going to sleep, for the bedtime response (B).

Note: Saliva samples given at random times during the day (i.e. that do not meet with timing requirements of W, P or B) were also be marked as Other (O).

After giving their saliva sample, the participants were instructed to note the timing of their saliva sample by and checking a box on the labels on the salivette tubes and indicate whether the sample was W, P, B, or O, please see Table 5 below.

**Table 5: Timing of saliva samples and marking of samples**

| Sample number | What time during the day to collect your saliva sample? | Which box to check on saliva tube label? |
|---|---|---|
| **1.** | Please provide your first saliva sample **immediately after you wake up**. This is when you have opened your eyes and are ready to get up for the day.<br><br>(Note: You may keep the saliva collection tubes beside you the night before. This way you can collect your saliva before you get out of bed. You can also collect this sample immediately after getting out of bed.) | Please check box marked "**W**"<br>PID No. _____<br>**W☑** P☐ B☐ O☐ |
| **2.** | Please collect the second saliva sample at about **30 minutes after you have woken up** for the day. The timing of this sample is particularly important, so please make attempt to collect exactly 30 minutes after Sample 1. | Please check box marked "**P**"<br>PID No. _____<br>W☐ **P☑** B☐ O☐ |
| **3.** | Please collect the third and last saliva sample at bedtime. The timing for this sample is ideally **right before you get into bed**. | Please check box marked "**B**"<br>PID No. _____<br>W☐ P☐ **B☑** O☐ |
| **O** | In case you miss the timing for the samples or are unable to give a sample at any of the above 3 times, you can still provide your saliva sample at any time of the day. | Please check box marked "**O**"<br>PID No. _____<br>W ☐ P☐ B☐ **O☑** |

Participants were also provided with Ziploc freezer bags marked for each day of data collection, namely, Day 2, Day 7 and Day 49. Participants were instructed to store the saliva samples in the freezer compartment of their refrigerator. Researchers have indicated that saliva

samples for testing all three of our measures (cortisol, amylase and CRP) can be frozen for long-term storage (beyond 8 weeks), at negative (–) 20 degrees Celsius in whole, un-centrifuged salivettes, without loss of substances. Most home freezer compartments provide a temperature very close to the recommended freezing temperature. Therefore, I collected all samples from the participant after the entire study protocol was completed, i.e. six to seven weeks after the intervention. Samples were immediately transported, from the participant's location to the bio-behavioral clinical research laboratory at the School of Nursing at VCU, using temperature controlled kits. Once they arrived at the laboratory, the samples were centrifuged in order to remove mucous from the salivary specimens, and were subsequently stored and frozen at –70° F.

**Monitoring adherence to protocol of salivary data collection.** The following procedures were employed to ensure adherence to the study protocol:

1) Participants were educated about the timing for each of the three samples (W, P, B)
2) The salivette tubes had a sticker where participants were instructed to write down the time of the collection and check a box to identify whether the sample was W, P, B, or O.
3) It was emphasized to the participants that the Peak sample (P) must specifically be collected within 30 minutes of waking up. In case they give the sample beyond 30 minutes of waking up, they were asked to mark the sample as Other (O). Saliva samples given at random times during the day (i.e. that do not meet with timing requirements of W, P or B) were also requested to be marked as Other (O)
4) Participants were provided with an opportunity to enroll in an interactive reminder system. This involved participants listing their preferred method of communication (e.g. cell-phone number, email, instant-messaging-IM or landline) for being reminded on the days of data collection. Participants were also asked to provide the approximate time they wake-up, and

the time they would prefer a reminder message. On the day of day collection (i.e. baseline and 2 times post-intervention), participants were sent a text-message (or IM/e-mail) through a chat engine (e.g. GChat) reminding them about the timing for their salivary sample. Participants were sent a follow-up text-message asking them if they had given the sample at the required time point (i.e. W/P/ B/O). They were also sent a message inquiring if they had placed their samples in their freezer at the end of the day of data collection. Participants had the opportunity to respond as Yes or No, to this text-message (or IM) through their cell-phone (or other technological device). These responses were maintained as a record of participant's adherence to protocol. Participants were thanked for their participation at the end of each communication.

5) Participants were provided a detailed spreadsheet with dates and times for study activities such as when they would be filling out the online surveys, writing online.
6) Decision for excluding samples: As explained above, the O samples were to be included in our estimation of average cortisol secretion (Area Under the Curve), but excluded in our estimation of Cortisol Awakening Response and Diurnal Cortisol Secretion.
7) The survey program time stamped each writing entry (treatment and control) in order to monitor adherence to writing intervention protocol
8) Participants were informed that they could contact UBS or RFB at any time during the sample collection if there were any problems or clarifications.

**Secondary outcomes**: S**elf-reported psychometric measures**. This study also employed self-report survey items that were administered through an online survey link (Qualtrics) at the same time points as the biological measures, i.e. Day 2 (Baseline Outcome Measure), Day 7 (Post intervention outcome measure 1), and Day 49 (Post intervention outcome measure 2)

Previously validated measures were used to detect changes related to reduction in psychological and emotional stress and quality of life.

***1) Perceived Stress Scale (PSS).*** The levels of perceived psychological stress levels were assessed using the Perceived Stress Scale (PSS). The PSS is one of the most frequently used scales in stress research, and scores on the PSS have been correlated with physiological stress measures (salivary cortisol)[179]. The scores on the PSS provide information related to the amount of psychosocial stress as perceived by CS, which would help us determine if EW is indeed successful in reducing stress. The PSS is designed to detect the degree to which participants appraise stress in their daily life, and consists of dimensions such as unpredictability, loss of control, and overwhelm[180]. This psychometric instrument has 14 items (see Appendix N) that were answered by the participants on a 5-point Likert scale. This scale has a demonstrated good reliability in healthy and clinical populations, and has a Chronbach's alpha value of 0.86[180].

***2) Fear of cancer recurrence inventory– Severity subscale (FCRI-S).*** The fear of cancer recurrence is the most salient emotional stressor faced by CS during survivorship[24]. Therefore, the severity of fear of cancer recurrence (FCR) is a good indicator for the level of negative emotional stress experienced by CS. Interventions designed to regulate psycho-emotional stress in CS should be able to reduce FCR. Hence, in order to determine whether EW is actually able to help CS regulate their emotional stress, we used the 9 item severity subscale of the FCRI, the FCRI-S (see Appendix N). The FCRI is a 42 item multi-dimensional measure of FCR, which has been recently developed and validated and good reliability has been established[181]. The FCRI-S specifically describes the amount of emotional stress experienced by CS due to FCR and is a suitable instrument to detect the clinical response to psychosocial interventions such as EW[24]. FCRI-Severity-Subscale is strongly correlated with the total FCRI score (r = 0.84), and has high

internal consistency and adequate 1-month test–retest reliability[181,182].

***3) Cancer Behavior Inventory-Brief Version (CBI-B).*** The CBI-B, a 12 item self-reported instrument was used to measures the level of self-efficacy among CS for their capacity to cope with cancer[183]. The CBI-B has been shortened from its original 33 item long version, the CBI-L[184], to reduce patient burden. This psychometric measure assesses cancer patient's ability to cope effectively with cancer, and includes dimensions such (a) beliefs about maintaining independence and a positive attitude, (b) ability to participate in medical care, (c) coping and stress management skills, and (d) capacity to manage emotions/affect in stressful situations.

A major advantage of the CBI-B is that it is relevant to the specific psychosocial problems faced by patient with cancer. The CBI-B scores was chosen to help us determine if EW can improve coping and emotion regulation in CS. Since this measure was designed primarily for cancer patients undergoing treatment, we modified one item (i.e. item 7) to relate to cancer survivorship. All 12 items are rated on a 9-point likert scale that ranges from 1 ("not all confident") to 9 ("totally confident"). Reliability evidence for the CBI-B is strong and three large scale studies in oncology populations have provided a minimum internal consistency value of $\alpha = .84$[183]. The CBI-B is also highly correlated ($r$=0.95) with the CBI-L[183]. Table 6 summarizes the all information that was collected (i.e. cancer information and demographics) and the measures collected (primary and secondary) along with the timing of collecting those measures with respect to the intervention.

**Statistical Power and Estimation of Sample Size**

Since the study used a repeated measures RCT design the statistical test used to analyze study data needed to account for the correlation between repeated measures (e.g. Day 2 CRP correlates with Day 7 CRP and Day 49 CRP). Also, since this study used a balanced two-arm

RCT design, there was an equal number of participants randomized to the treatment or control condition. Thus, we used GPower statistical program to estimate sample size for our study for a multivariate analysis of variance (MANOVA) statistical test. The first step in the sample size calculations was to decide the on the parameters of statistical significance. This study's sample size calculation used 80% power ($\beta$=0.2) in order to estimate the number of subjects needed to show significant differences between the intervention and control groups with 95% confidence ($\alpha$=0.05). The next step in the power analysis was to determine the expected effect size for the intervention on the primary outcome measure.

An older meta-analysis of previous EW studies estimated a standardized effect size for the EW intervention in mixed populations[58] and reported a Cohen's d = 0.47. A more recent meta-analysis[60] reported a smaller standardized effect size, Cohen's d = 0.15. However, standardized effect sizes do not take into account variations in treatment effect based on the population and outcome measures. A standardized effect size for EW interventions within cancer population has not been estimated, although past studies have reported large effects, such as d = 0.896[56]. A meta-analysis of EW interventions in clinical populations[59] yielded a d = 0.21 for physical health outcomes, which included cortisol levels. Studies assessing the psychological determinants of the cortisol stress response[116, 117] suggest a standardized effect size of d = 0.3 for salivary cortisol. Therefore, the initial power analysis considered the primary outcome of interest (salivary cortisol) to detect a more conservative effect size (between *d* = .21 and .896) of *d* = .33

The a priori power analysis conducted by GPower statistical program based on the effect size for EW chosen (*d* = .33) indicated that a MANOVA could detect significant effects between two groups with 80% power in a total sample size of N=52 participants. However, oversampling was recommended due to the possibility of missing data which is common problem in

longitudinal RCT designs. Past studies and meta-analyses of EW indicate that an overall 20% of the study population has attrition and or missing data. This 20% of the population translated into 10 additional participants, which were added to the initial calculation of 52 participants. Thereby the total sample size estimated a priori for this study was N=62, participants, which translated to the recruitment and enrollment of 24 participants in each arm, i.e. n=31 in treatment arm (EW intervention) and n=31 in the control arm (control writing task). During the process of recruitment and enrollment, the study faced low accrual rates which is commonly encountered in psychosocial trials in the cancer population[185]. A preliminary report was conducted to determine the adequacy of participant completion of the study protocol. Finding that N=40 participants had completed the study protocol, it was decided to forego oversampling and continue with the analysis based on 20 participants in each arm.

**Table 6: Study protocol (activities, measures and data sources)**

| Prior to enrollment | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 49 |
|---|---|---|---|---|---|---|---|---|
| Provide study information + Screening + Informed consent | Confounds + Cancer-related information | Baseline outcome measures (BOM) | Writing | Writing | Writing | Writing | Post-intervention outcome measures (POM1) | Post-intervention outcome measures (POM2) |
| | | | Intervention → Expressive writing / Control writing | | | | | |
| 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes |

| | |
|---|---|
| Screening – 5 questions (*Telephone-based*) | • Cognitive dysfunction (Brief Screen for Cognitive Impairment: 3 items )<br>• Depression (Patient Health Questionnaire-2: 2 items) |
| Confounds – 28 questions (*Online survey*) | • Social support and Perceived social status<br>• Smoking, Alcohol consumption, Sleep, Oral health – gum disease<br>• Use of complementary and alternative medicine (CAM)<br>• Comfort with using computers and internet technology<br>• Demographics: Health insurance status; Employment status; Household income; Education level; Marital status; Age ; Gender ; Race/Ethnicity |
| Cancer-related information – 9 questions (*Online survey*) | • Cancer Diagnosis information (primary site, tumor stage)<br>• Cancer Treatment regimen information (date, toxicity, late and long term effects)<br>• Medication use |
| BOM, POM1 and POM2 (*Salivary Specimens*) | • Cortisol, α-Amylase and C-reactive protein – CRP |
| BOM, POM1 and POM2 – 33 questions (*Online survey*) | • Perceived Stress Scale<br>• Fear of Cancer Recurrence Inventory-Severity subscale<br>• Cancer Behavior Inventory-Brief version |

**Identification of Eligible Patients**

Potential participants were identified by using a defined set of inclusion criteria for patients with cancer at sites that were available for recruitment to this study. Participants identified through the inclusion criteria could have some characteristics that would be problematic with the study protocol. For example, participants with radiation treatment to the face region may be unable to produce adequate saliva (due to damaged salivary glands), and hence will not be able to complete the primary outcome measure. Therefore, exclusion criteria were used to help exclude certain participants that were initially eligible.

**Inclusion criteria.** Patients with cancer having the following characteristics were considered eligible to participate in our study; patients who: a) had completed their cancer radiation treatment (intent to cure), b) were cancer free, i.e. not having any diagnosis of primary/secondary cancer or any recurrence/relapse of cancer, c) were in the re-entry phase of cancer survivorship, i.e. 2-12 months post-treatment completion, d) had access to a computer and internet in a private setting, e.g. at home, e) were above the age of 21 years, f) were fluent in English, and g) were able to provide informed consent. The participants had received radiation as their final cancer treatment, and could have received other cancer treatments before radiation, such as surgery or chemotherapy. Participants were provided the option to discontinue their participation in the study due to any reason at any time during our intervention protocol. Participants had access to UBS and RFB for any assistance regarding contacting supportive care services provided to the patients.

**Exclusion criteria.** Eligible participants were excluded from the study if they met any one or more of the following criteria: a) scheduled to undergo any type of cancer treatment (intent to cure/palliative) in the future (e.g. surgery after completing radiation), b) on any kind of

corticosteroid medication (e.g. long-term prednisone therapy), c) having any condition that affects function of the adrenal glands (e.g. adrenal hyperplasia), d) limited ability to produce saliva, e.g. patients that received radiation (or surgery) on the face region or on salivary glands; or patient'ssuffering from dry mouth (e.g. Sjögren's syndrome), and e) suffering from inflammation of the oral cavity (e.g. gingivitis). Individuals on corticosteroid medication or those with diseases of the adrenal glands have irregularities in cortisol secretion that can interfere with data collection for the primary outcome measure, and hence were excluded from the study. Patients with limitations in salivary production would be unable to complete the primary outcome measure and were hence excluded. It was important to exclude patients with oral inflammation because their salivary measures may erroneously indicate increased inflammation, resulting from local inflammation in oral cavity, and not from systemic immune processes.

To take into account typing skills, potential participants were also asked if they would be comfortable typing on a computer for 20 -30 minutes over 4 consecutive days. Only patients that confirmed they were comfortable typing for that amount of time were included in the study. Patients were also screened for cognitive impairment and depressive symptoms (Brief Screen for Cognitive Impairment and Patient Health Questionnaire-2).

**Identification procedures.** The human subjects involved in this study were cancer patients who have finished their radiation treatment (intent to cure) and were in the re-entry phase of cancer survivorship (2-12 months post-radiation treatment completion). Eligible patients were identified based on the aforementioned set of inclusion and exclusion criteria. Medical records at the VCU Health system was accessed only for the purpose of identification of potential participants, no information from the medical records was used for research purposes. Once potential participants were identified, an initial letter regarding the study was mailed to the

patient that provided information about the study and contained the full contact information of the study mentor and UBS, see Appendix D. Subsequently, the potential participant was contacted by phone. If the potential participant's voicemail was reached during any phone interaction, no details about the study were mentioned. A voice message consisting of the name of the first author (Utkarsh B. Subnis, UBS) and affiliated institution (i.e. VCU), along with a call back number was left, see Appendix G. UBS was in communication with potential participants through email or their preferred method of communication (phone or mail) after the initial call.

**Recruitment Plan**

Firstly, we obtained permission from the Chair of the Dept. of Radiation Oncology at Massey Cancer Center (MCC), Dr. Mitch Anscher, to recruit patients from MCC. Support was also obtained from Clinical Research Nurses (CRN) at Virginia Cancer Institute (VCI), and Bon Secours Health System, Richmond, VA, to assist with recruitment. The research team identified potential participants, by working collaboratively with oncologists, nursing staff and CRNs at the Radiation Oncology Department at MCC and VCI and Bon Secours. Active and passive strategies (described in detail below) were used to recruit patients to this study.

**Active recruitment: Electronic health records.** Active recruitment was conducted by identifying eligible patients using the electronic records of the Virginia Commonwealth University Health System (VCUHS), which is a HIPPA compliant electronic medical information database as well as working with oncologists and research nurse personnel. The research team identified all potentially eligible cancer patients who had completed their primary radiation treatment through the VCUHS electronic health record database. The research team worked with the administrators at the VCUHS to organize access for to the relevant VCUHS

systems, Cerner and IDX. Access to these systems was obtained on a weekly basis to identify patients who were scheduled for follow up radiation therapy appointments, assess the time since last appointment and identify those patients whose last appointment was between 2 months and 12 months prior to the access date. This process involved creating patient lists of those who were discharged after radiation in the last 10 months. For example, if the VCUHS scheduling data base IDX was accessed on July 1, 2013, patients were identified whose last radiation therapy appointment was between June 1, 2013 and August 1, 2012, see Appendix C.

The radiation oncologist/nurse at the clinic from where the patients were discharged were contacted to inquire if the patients were eligible for the study. If patients were considered eligible by the oncologist, the patient's contact information, which included their name, phone number and mailing address was collected. Patient medical records were not accessed once eligibility was determined. An initial letter regarding the study was mailed to the patient containing the full contact information of UBS and RFB, see Appendix D. A "do not contact" return-addressed postage paid opt-out mail-card was sent along with the initial letter, see Appendix E. Two weeks after the recruitment letter was mailed, UBS attempted to reach the eligible participants by phone. In the first phone call, UBS asked the potential participant about the letter regarding the study. In case the participant mentioned that s/he did not receive the letter, UBS informed the potential participant that the letter would be mailed to them again, and that UBS would contact them again. If the potential participant acknowledged receiving the letter, UBS then explained the study in some more detail, conducted screening procedures (i.e. the BSCI and PHQ-2), answered any questions the participant may have, and requested for the participant's preferred email address.

Subsequently, UBS confirmed if the potential participant was interested in taking part in

the study on the phone and a hard copy of the informed consent document was mailed to the participant, see Appendix I. The participants were requested to mail the informed consent form back to UBS after signing it. An extra copy of the informed consent form was mailed along with the consent form. Also, a returned addressed postage-paid mail envelope was provided for participants to mail the consent form back, see Appendix I. Participants were enrolled once the signed consent forms were received. Potential study participants were in communication with UBS through email or the patient's preferred method of communication (phone or mail) after the initial call. UBS also offered a home visit or visit at a convenient location to the participants for explaining the study more in detail and having personal contact with the participant. UBS provided the participants with his full contact information, and the participants were able to contact UBS at any time for any doubts or reservations.

**Passive recruitment: Flyers.** A recruitment flyer containing some basic information about the study and with UBS's contact information was prepared. Also, UBS informed the nursing staff at MCC, VCI and Bon Secours about the details, inclusion and exclusion criteria for the study and provide the staff with the flyers, see Appendix A. The nurses handed out the recruitment flyers at the radiotherapy consultation departments to potential patients. UBS also visited and presented the study's flyer to community support groups for cancer patients in Richmond, VA, such as support groups at the VCU Massey Cancer Center; and bulletin boards of community health centers, such as the VCU community health education center. The information from the flyers was also posted on the VCU e-listserv for ongoing studies. CS interested in this study had the necessary information to contact UBS. If patient's contacted UBS regarding the study, UBS then explained the study in some more detail and conducted identical recruitment procedures (as described above), and answered any questions that potential

participants may have and request for contact details such as email and mailing address. UBS verbally ascertained interest in study participation on the phone and participants were mailed the informed consent form. Participants were kept informed about the study through their preferred mode of communication (i.e. email/phone/postal mail). UBS offered a home visit or visit at a convenient location to the participants for explaining the study more in detail and having personal contact with the participant. UBS also provided the participants with his contact information, and the participants were able to contact him for any doubts or reservations regarding the study.

**Recruitment at non-VCU sites.** Virginia Cancer Institute and Bon Secours Health System, both have radiation oncology units for treating patients in Richmond and surrounding counties. These Non-VCU centers were used only for passive recruitment of participants, and hence were considered not engaged. They only performed the following activities as described in OHRP's guidelines:

The Clinical Research Nurses and related health professionals at non-VCU sites:

a. informed prospective subjects about the availability of this research study;
b. provided prospective subjects with information about the research (which included a copy of IRB approved recruitment flyer) but did not obtain subjects' consent for the research or act as representatives of the investigators;
c. provided prospective subjects with information about contacting investigators for information or enrollment; and/or
d. sought or obtained the prospective subjects' permission for investigators to contact them.

UBS undertook liaising efforts with clinical research nurses and health professionals to identify patients based on inclusion and exclusion criteria. The identified potential participants

were handed flyers with information about the study. Those participants who were interested in the study contacted UBS. No medical records were accessed at Non-VCU institutions. The same precautions for the safety and protection of participants and their data (described above) were used for participants from Non-VCU institutions. Participants were informed that the study is primarily through VCU, being conducted by UBS.

**Screening patients before recruitment.** Potential participants were screened for cognitive dysfunction using the Brief Screen for Cognitive Impairment and depression using the Patient Health Questionnaire-2, before inviting patients to participate in the study. Screening for cognitive impairment and depression took place over the phone during the initial recruitment call. Potential participants having moderate to severe cognitive dysfunction were excluded from the study. Patients were also screened for depressive symptoms prior to consent using a validated depression screening questionnaire (Patient Health Questionnaire –PHQ –2). Using the PHQ-2 has been described in the literature as a suitable "first step" approach to screen for depressive symptoms and is not used for diagnosis and monitoring of depressive symptoms.

***Screening for cognitive dysfunction*.** Cognitive impairment can impact the ability of patients to provide informed consent, as well as this intervention requires a certain degree of cognitive effort and cognitive ability. Therefore excluded patients with cognitive dysfunction, and screened for cognitive impairment. Screening for cognitive dysfunction was performed before obtaining verbal assent from the eligible participants during the initial telephone conversation. The Brief Screen for Cognitive Impairment (BSCI), a previously validated (Hill et al., 2005) three item screening instrument for administration during a telephone conversation, was used for screening out cancer survivors with significant cognitive impairment. The time required to administer the BSCI is approximately 80 sec.

The first item on the BSCI consists of memory recall question is: 1) the participants were told three unrelated words (dog, apple, and house) after describing the purpose of the conversation to the participants. Then the participants were asked to repeat those three words after the details of the study were described to them. The responses from the participants were scored from a perfect score of 0 (no mistakes in recalling the three words correctly) to the worst score of 3 (none of the three words correctly recalled).

The other two items on BSCI included the following: 2) how frequently do you need help with planning trips for errands?; and 3) How frequently do you need help for remembering to take medications? Both these items were scored from 0 (never needs help) to 4 (frequently needs help). Finally, the scores were weighted and summed to arrive at the final BSCI score (scores from delayed recall and frequency of help with remembering to take medications was assigned a weight of 2.0 and the score from frequency of help with a trip for errands was assigned a weight of 1.0.). Patients with a score of >6 on the BSCI were considered to have significant cognitive impairment and were excluded from the study. The scores on BSCI have shown to be significantly correlated with scores for other tests of cognitive function such as the Mini Mental State Examination ($r = -0.83$) and the Alzheimer's Disease Assessment Scale ($r$=0.65).

***Screening for depression*.** Patients were also screened prior to enrollment for depressive symptoms using validated depression screening questionnaire (Patient Health Questionnaire – **PHQ –2**). The 2 items PHQ-2 depression scale is a very brief and extensively researched instrument for screening of depression. The PHQ 2 has 2 items and is rated from 0 – 6. The recommended cut off score for screening is ≥ 3. During the initial recruitment call, UBS scored potential participants on the PHQ-2 questionnaire in real-time on the phone after completing the

cognitive dysfunction questions. The actual questionnaire and scoring sheet is provided below in Table 7 and the psychometric properties of the PHQ-2 are described below in Table 8.

**Table 7: Patient Health Questionnaire -2 Telephone Screening tool for Depression**

| Over the past 2 weeks, how often have you been bothered by any of the following problems? | | | | |
|---|---|---|---|---|
| | Not at all | Several days | More than half the days | Nearly every day |
| Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| Feeling down, depressed or hopeless | 0 | 1 | 2 | 3 |

We did not expect to be contacting clinically depressed patients, or receiving responses from depressed patients. However the PHQ-2 enabled us to screen out patients who were in need of intensive mental health care.

**Table 8: Psychometric Properties of the Patient Health Questionnaire –PHQ –2[a]**

| Major Depressive Disorder (7% prevalence) | | | | Any Depressive Disorder (18% prevalence) | | | |
|---|---|---|---|---|---|---|---|
| PHQ-2 score | Sensitivity | Specificity | Positive Predictive Value (PPV*) | PHQ-2 score | Sensitivity | Specificity | Positive Predictive Value (PPV*) |
| 1 | 97.6 | 59.2 | 15.4 | 1 | 90.6 | 65.4 | 36.9 |
| 2 | 92.7 | 73.7 | 21.1 | 2 | 82. 1 | 80.4 | 48.3 |
| 3 | 82.9 | 90.0 | 38.4 | 3 | 62.3 | 95.4 | 75.0 |
| 4 | 73.2 | 93.3 | 45.5 | 4 | 50.9 | 97.9 | 81.2 |
| 5 | 53.7 | 96.8 | 56.4 | 5 | 31.1 | 98.7 | 84.6 |
| 6 | 26.8 | 99.4 | 78.6 | 6 | 12.3 | 99.8 | 92.9 |

* Because the PPV varies with the prevalence of depression, the PPV will be higher in settings with a higher prevalence of depression and lower in settings with a lower prevalence.

[a] Kroenke K, Spitzer RL, Williams LB. The Patient Health Questionnaire-2: Validity of a Two Item Depression Screener. *Medical Care.* 2003; (41) 1284-1294.

Patients that were found to have PHQ2 ≥ 3 were not included in this study. These participants were advised to not participate in the study at that time and were provided information about supportive care services. UBS also offered a referral plan for these patients (see below) and were asked if they would like to be contacted at a later time regarding their psychosocial needs.

**Referral plan after screening procedures**. Scores on the BSCI and PHQ-2 questionnaire were estimated by UBS in real time during the phone conversation. Based on standards provided for using the PHQ-2, patients with PHQ-2 scores above 3 are recommended to be further evaluated for a depressive disorder. Participants that had PHQ-2 scores ≥3 were advised to not participate in the study and were provided information about supportive care services. During the call, UBS offered to immediately conference call Connie Macaluso, for further evaluation. Connie Macaluso is a licensed clinical social worker (LCSW) and trained in dealing with mental health issues of cancer patients. In case the patient refused to be conference called to Connie Macaluso, UBS asked the participants if he could refer them to Ms. Macaluso for additional evaluation. The participant's response regarding this matter was honored and their right to refuse further assistance was respected. No further contact with the participant occurred. Since this was a student research project, limitations in resources precluded us from employing a trained neuropsychiatry health professional. Also, since UBS did not have training required for clinical management of mental health issues in patients, referring patients to a trained and licensed clinical social worker was considered an appropriate approach. For patients who were eligible after screening, UBS proceeded with assessing their interest in participating in the study.

**Assessing interest in study participation.** UBS again asked if there were any unanswered questions, as well as provided more details of the study as needed. Then UBS asked the patient if they would be interested in participating in the study. If the patient expressed interest in the study, UBS requested for their preferred email address (and other preferred modes of communication). The potential participant was then told that s/he would need to sign the informed consent form for this study before s/he could be enrolled in the study. After the initial call, UBS was in communication with potential participants who expressed interest in the study

through email or their preferred method of communication (phone or mail). Patients who declined participation were thanked for their time, and participants who wanted more time to think about the study, were contacted again at their convenience.

**Informed Consent Procedures**

A paper copy of the informed consent document was mailed to the participant along with additional copy of the consent document and a return addressed postage-paid envelope, see Appendices H and I. The participant then signed the consent document and mailed it back to UBS. Up to 3 reminders were sent to patients about their potential participation. The reminders informed patients that, a) UBS was following up about potential participation in this research study focusing on stress management or cancer survivors after radiation therapy using expressive writing, b) a consent form was mailed to the participant but UBS had not heard back from him or her yet, c) if the patient is interested in participating, they should please return the signed consent form in the reply envelope provided, and d) if the patient has any questions, please feel free to contact study staff. The contact information for UBS and RFB was provided on the consent document and UBS was available to further clarify any details of the study.

**Enrolment in study.** After receiving the signed informed consent document from the participant, the participant was enrolled in the study and mailed the salivette kits and study materials, see Appendix J and K. UBS offered home visits to the participants to personally deliver the salivary kits and go over the study procedures. Participants who provided written consent were enrolled in the study, and a Participant ID number was generated for them, using a random number generator computer program. The participants were requested to indicate 4 days in their upcoming time schedule for the writing intervention. Based on their preferred days, a schedule with specific dates and activities (including data collection) using the protocol (Table 6)

was prepared, see Appendix M. Participants were offered to enroll in the interactive reminder system. All data obtained from the participants was connected with the Participant ID number. The salivette kits and information booklets were subsequently mailed to the participant's home address. A web-link for the instructional video showing how to collect saliva in the salivette tubes was emailed to participants. The salivettes had the participant ID number printed on the labels; no identifying information was present on these salivette kits. The salivette kits were recovered from the participant's home at the end of the study.

**Data Sources**

The sources of data for this study were all from the participant's in the form of 1) self-report questionnaires, 2) responses from the writing prompts and 3) salivary specimens, see Table 9.

**Table 9: Data sources and research material**

| 1) Self-report questionnaires (administered online) |
|---|
| Health-related symptoms and behaviors: Social support, Perceived social status, Smoking, Alcohol consumption, Sleep, Oral health – gum disease, Use of complementary and alternative medicine (CAM), Comfort with using computers and internet technology<br>Demographics: Health insurance status; Employment status; Household income; Education level; Marital status; Age; Gender; Race/Ethnicity<br>Cancer-related information: Cancer Diagnosis information (primary site, tumor stage); Cancer Treatment regimen information (date, toxicity, late and long term effects); Medication use<br>Outcome Measures (BOM, POM1 and POM2): PSS, FCRI-S and CBI-B |
| 2) Responses from the writing prompts (administered online): |
| Responses to expressive writing prompt<br>Responses to control writing prompt |
| 3) Salivary specimens (provided at home, collected at the end of study) |
| Outcome Measures (BOM, POM1 and POM2): Cortisol, α-amylase and C-reactive protein – CRP |

**Compensation of Participants**

Since this was a student dissertation project, limited funds were available for this research. Participants were thanked in appreciation for their time and effort devoted to this study.

Participants also had an opportunity to indicate if they would be interested in periodic updates about the study results, progress and publication. Participants did not receive any monetary compensation for their participation. The participants had the opportunity to join a listserv that updates participants about the study results, publication and dissemination activities.

**Minimizing Potential Risks for Participants**

In the unlikely event that participants got distressed to the point of needing an intervention during their expressive writing activity, we ensured that adequate measures were taken to reduce risk for participants. The following measures were taken during the intervention process.

1. **Phone contact with participants during the intervention.** UBS contacted all participants on Day 2 and Day 7 to check if they were doing well during the intervention. If participants report requiring any additional support services, these were provided by actively referring these patients to Connie Macaluso, LCSW. UBS was available to the participants at any time, and UBS informed the participants that he would be available for phone contact or home visits at any point during the intervention. Patients with depression were not included in the study.
2. **Monitoring the participants writing responses for concerning depressive symptoms.** The participants writing responses were read as soon as they submitted them through the Qualtrics survey link. UBS was sent a notification whenever a participant submitted a response to their writing prompts. UBS then read the content for any statements that would be concerning, such as threat to harm themselves or others. Additionally, we also monitored the participants writing responses using the Linguistic Inquiry and Word Count (LIWC) software. The LIWC is composed of almost 4,500 words in different

categories. Below is an excerpt from the LIWC manual which gives details of the word categories of affective processes. The essays were monitored for negative emotion words. This helped us identify any concerning writing responses that may have been in the initial reading and monitoring. Participants with writing responses containing several negative emotion words identified by the LIWC were read again. Any participant with concerning symptoms was referred to the research clinical social worker, who is part of this study, to assess if they were in need of any psychosocial support services.

LIWC software word categories

| Process | Abbrev | Word examples | No. of words | Validity |
|---|---|---|---|---|
| Affective processes | affect | Happy, cried, abandon | 915 | |
| Positive emotion | posemo | Love, nice, sweet | 406 | .41 |
| Negative emotion | negemo | Hurt, ugly, nasty | 499 | .31 |
| Anxiety | anx | Worried, fearful, nervous | 91 | .38 |
| Anger | anger | Hate, kill, annoyed | 184 | .22 |
| Sadness | sad | Crying, grief, sad | 101 | .07 |

3. **Information about support services.** Participants were provided with information about supportive care services from the start of the intervention (provided on the consent form) as well as they had the contact information available on their computer screens while writing. The following information was available on the screen of the participants on the survey link while they were performing their writing tasks.

i) The screen of the writing task prompt had a hyperlink to the **National Cancer Institute's Support Services** Locator, **http://supportorgs.cancer.gov/** . The Toll-free phone number for NCI cancer support information was also be provided, **1-800-4-CANCER (1-800-422-6237).** The NCI provides this service in English and Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m. ET. The NCI provides a comprehensive list of psychosocial and other supportive care services to meet the supportive care needs of

patients with cancer.

ii) Additionally, the writing prompt screen also contained the toll-free phone number for the **Cancer Information and Counseling Line**, **1-800-525-3777**. The Cancer Information and Counseling Line (CICL) is a free nationally recognized telephone counseling service that provides a range of psychosocial supportive services to patients anywhere along the cancer continuum, Monday – Friday, 8:30 a.m - 5 p.m. MT. CICL services range from providing emotional support to resource referrals and medical information for patients and caregivers affected by cancer. CICL counselors are master's-level psychosocial professionals that offer brief, personalized and professional counseling over the phone. They can support and assist with managing feelings, resolving challenges related to having cancer and communicating with doctors and loved ones.

iii) In case participants needed information at odd hours, the **American Cancer Society (ACS) hotline** was also provided to them, **1-800-227-2345, http://www.cancer.org/ .** The ACS provides information and referral on various issues related to cancer treatment, services, literature, transportation, equipment, encouragement and support, 24 hours a day seven days a week at 1-800-227-2345.

**4. Referral plan in case of depressive symptoms.** Although steps were put in place to prevent contacting clinically depressed patients, or receiving responses from depressed patients, the PHQ-2 was used to screen out patients who were in need of intensive mental health. All phone calls to the participants were made during regular business hours. Referral to Connie Macaluso, LCSW occurred in case the following scenarios take place.

i) Participants at initial eligibility screening had scores ≥3 on the PHQ-2.

- UBS offered to immediately conference call Connie Macaluso, LCSW at support

services at Massey Cancer center. Ms. Macaluso is trained in managing psychosocial needs of cancer patients and survivors. Ms. Macaluso is also trained in connecting patients with appropriate mental health services. UBS also offered to conference call Ms. Macaluso or intake and referral the VCU psychiatric services, to patients at any time during the intervention or course of the study. Contact information for VCU Department of psychiatry was made available to the participants along contact information with other supportive care services. (The Dept. of Psychiatry at VCU School of Medicine is available at **(804) 828-2000 or (800) 232-0901** (Select option 2 for appointments or Option 3 for admissions; and has a system of Intake and Referral Service that expeditiously screen, evaluate and admit clinically appropriate patients to the various inpatient teams.

i) Participants who experienced depressive symptoms or needed any mental health services or support services during the intervention

- UBS contacted the participants on Day 2 and Day 7 of the intervention to inquire how participants were doing in the intervention. The referral plan in case patients need additional support services were identical to that described above, and involved follow-up by Connie Macaluso, LCSW. Participants were also informed about the possible support services they can use if they need assistance with any mental health problem. The participants were provided UBS's contact information if any assistance is needed for them for using any supportive care services.

A list of all support services provided by the NCI were given to the participants along with the informed consent forms, see Appendix I. Participants could make use of these services during as well as after the intervention. At the end of the intervention, i.e. at 6 weeks post-

intervention, participants were asked if they used any of the support services they were informed about. Finally, participants had the contact information of UBS at all times and could contact him at any point during the intervention. Participants were informed of their choice of withdrawing from the study at any point in time. Participants were assured that no contact would be made with their employer, insurance provider or health care provider. Hence, several measures were taken to minimize potential risks to the participants in this study. The research team used rigorous procedures for assuring subject anonymity as described above and in the training of research staff. The risks to subjects were minimal compared to the benefits of the research. Participants were free to withdraw at any time. The study protocol is scheduled as per participants' convenience. By using computers and the internet, the participants could complete the writing tasks and provide data at their own comfort and convenience.

**Protection of Patient Privacy**

The following steps were taken to ensure the privacy of participants.

1. UBS conducted all patient phone interactions, including recruitment and follow up calls, in a designated private office space. Participants were reminded that their privacy would be maintained at all times. If we reached the participant's voicemail during any phone interaction, no details about the study were mentioned. A voice message consisting of the name of RC and affiliated institution (i.e. VCU), along with a call back number was left.

2. Participants were informed that their writing responses and data were stored in secured HIPPA compliant servers at all time. Participants were also assured that no communication would occur with their employer, insurance provider, or health care professional. All participants were informed about their privacy and confidentiality and their right to discontinue the study at any time.

3. The surveys and writing responses were sent using Qualtrics. Qualtrics is web-based survey application that uses secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption which ensures security and confidentiality. Qualtrics has SAS 70 Certification and meets the rigorous privacy standards imposed on health care records by the Health Insurance Portability and Accountability Act (HIPAA). All Qualtrics accounts are hidden behind passwords and all data is protected with real-time data replication. Qualtrics service meets the standards for security required by CFR 45.46 (Federal Guidelines for Human Research) and by VITA (Virginia Information Technology Agency).

4. All salivette kits and mailing materials were affixed with the randomly generated participant ID number. This ensured that no salivary specimen could be linked back to the participant. Even the transportation containers for the salivary specimens had only the Participant ID numbers, and no other identifying information, in case of misplaced salivette tubes or containers.

5. All email communication was conducted through UBS's VCU email account that is secured by VCU Central Authentication Service, which is a centralized login system for Web applications at Virginia Commonwealth University. All data were stored in computers having firewalls and virus protection. The email communications were archived and downloaded and stored along with the study data. All these data will be destroyed within 3 years.

6. The temperature controlled transportation container for the salivette kits was labeled with Participant ID number, no other identifying information was present on the transportation container, in case it is misplaced or damaged due to any unforeseen circumstances.

7. A physical lock was placed on the Central Processing Unit (CPU) of the computers used for storing and accessing data, which secured the CPU to the physical location of the office,

and thus prevent loss due to theft or other circumstances. All stored data will be destroyed within 3 years of completing the study.

**Data Safety and Monitoring Plan**

The data and safety monitoring plan included: i) data security procedures, ii) identification of adverse effects, iii) quality assurance activities and iv) investigator-initiated procedures for data and safety monitoring.

Security Procedures for Transfer, Implementation and Storage of Data. All computers used to collect and send data during implementation of the study or to receive or store data at the central location were password protected. Patient surveys and expressive writing were web-based and stored within a secure, dedicated server with appropriate firewalls. Servers were routinely scanned for viruses and systems were in-place to detect attempts at unauthorized entry. All phone interactions and online surveys were conducted from a central location therefore data transfer were not be necessary.

Identification of Adverse Effects. The study staff monitored all adverse events identified during implementation of the trial. Adverse effects were monitored through 1) reading the writing prompts after participants complete their writing task online, and 2) phone interactions with the patient on Day 2 and Day 7 of the protocol. UBS documented any adverse effects reported to them by the patient. The research team also met weekly as a team to discuss any potential for an adverse event. In addition, patients were given UBS's direct telephone number so that any adverse events could be reported spontaneously by the subject. Participants were also provided with contact information for a variety of supportive care services, which included a telephone counseling service for cancer patients and survivors.

Quality Assurance Activities. UBS was available for questions on weekends and during

the evenings. If problems arose, the research team were instructed to call Utkarsh Subnis (UBS) or study mentor, Dr. Richard Brown (RFB). UBS was evaluated by the study mentor in areas such as the time management, inter-personal skills, participant recruitment procedures and how closely he adhered to set procedures such as checking call attempts. Booster training session were held as needed based on the quality assessment. Weekly meetings were held between the study mentor and UBS to address UBS's concerns and give project updates, as well as role-play different possible scenarios. UBS was given memos on any new procedures or protocols when necessary. Private one-to-one meetings were held with the research team as needed.

Investigator-Initiated Data and Safety Monitoring Plan. The research team for this study were responsible for oversight of the quality of the RCT. All violations of protocols were noted. If any adverse effects were reported or detected from the interventions, the study mentor was notified immediately. The study mentor and the study statistician determined if any portion of the protocol was violated and why and how such a violation may be related to the adverse event. A referral plan was is place in case of any inadvertent emotional harm due to study involvement was noted and the LCSW who was part of the research team had arranged to contact the study participant to determine safety of continuing in the study.

**Accrual to Study**

Study recruitment using both active and passive strategies was undertaken after receiving approval from the Institutional Review Board (IRB) of VCU. UBS and study mentor first contacted all the radiation oncologists at MCC by email. Most psychosocial interventions have been targeted towards surgical and chemotherapy patients, most commonly breast cancer. Therefore, we received acceptance and approval from all health professionals working in radiation therapy at MCC as anticipated. We identified N=372 patients in the cancer registries

through the VCUHS by mining data regarding cancer patients who have completed radiation treatments. We sent these 372 patients an initial contact letter and followed-up with them by phone. From these 372 patients, n=20 patients agreed to participate in our study, see figure 5. Reasons for the high refusal rates included 1) collection and provision of salivary data, 2) commitment of time since the study protocol involved four days of writing and three days of salivary data collection (three times a day), 3) mistrust with the government and collection of biological specimens, 4) disinterest in the study and 5) commitments to other research studies.

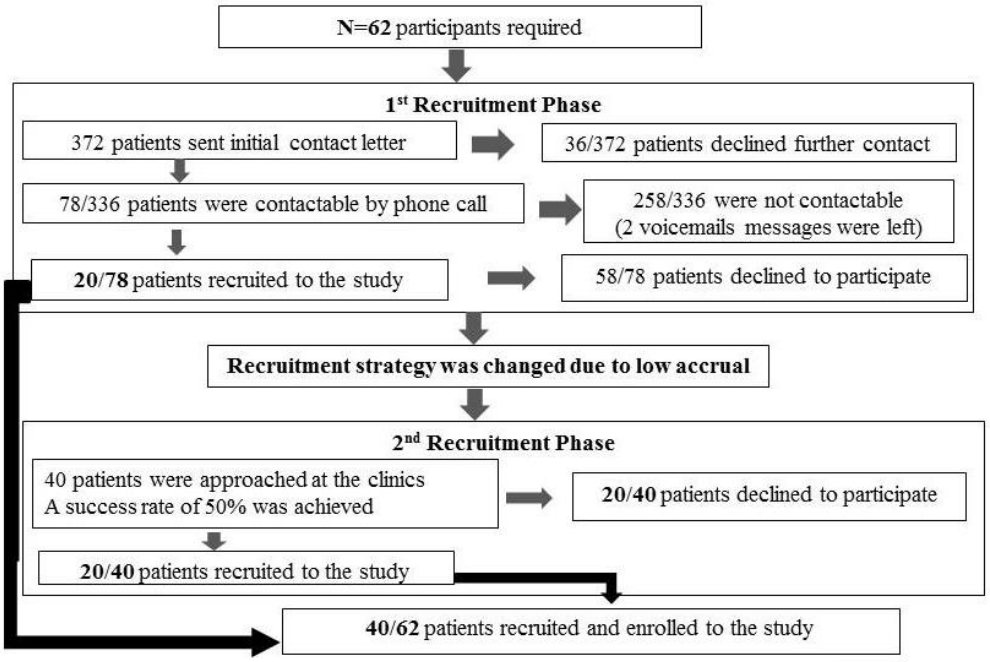



**Figure 5: Recruitment procedures**

After encountering low accrual from contacting participants by mail and following-up by phone, the research team decided to modify recruitment efforts. UBS liaised with multiple health professionals at the MCC, and VCI radiation oncology centers to advertise our study. UBS began following up with patients in the waiting rooms and follow-up consultations at MCC, downtown and Stony point cancer-care centers with patients who have completed their radiation treatments. This approach yielded another n=20 patients who agreed to participate in our study, see figure 5

of recruitment procedures. The EW meta-analysis described that 75% of EW studies reported less than 20% attrition rates[128]. Continued engagement with participants during and after the 4 day writing tasks was maintained to retain participants in this study. During the study, frequent contact was made with study participants to determine if they were encountering any problems with the study protocol, salivary data collection or had any general questions.

**Data Analysis Plan**

The unit of analysis in this study was the individual cancer survivor. Data were analyzed using the statistical software packages, SPSS[186] and JMP[187]. The first step for analyzing the study data was examining the distribution of the data for normality and for descriptive statistics, which included measures of central tendency and dispersion, e.g. mean, standard deviation, standard error, for each variable measured in this study. To assess if the randomization was successful, initial analyses were conducted to detect any significant differences in the EW and control groups based on the data obtained at baseline, i.e. demographics, confounds and primary and secondary outcome measures. This consisted of t-tests for continuous variables (e.g. treatment dosage) and $\chi^2$ analyses for categorical variables (e.g. sex). Any variable significantly different in the two groups would be used as a covariate for further analytic procedures.

Hypothesis testing was planned using the Multivariate Analysis of Variance (MANOVA), statistical test to determine differences between the EW and control writing groups based on the outcomes measures collected on Days 2, 7 and 49. Since this study design involves repeated measures, this type of data violates the analysis of variance's (ANOVA) assumption of independence of measures, due to the correlations that occur among subsequent repeated measures. Therefore, a multivariate repeated measures analysis of variance (MANOVA) can model each of the mean stress measures over time separately for each group, and was considered

an appropriate statistical approach.

**Intent to Treat Analysis.** Data related to recruitment, participation and drop-out rates were reported according to the guidelines given by the Consolidated Standards of Reporting Trials (CONSORT) statement[188]. All participants that entered our study were included in our analyses and were retained in the arm (treatment or control) to which they were originally randomly allocated. Participants were included in our analyses, regardless of their alignment with the inclusion criteria, the treatment they received, and if they withdrew from the intervention protocol (attrition) completely or deviated from the protocol (non-adherence). Therefore this study had an intent to treat (ITT) analysis design[188,189]. However, RCTs commonly have participants who were non-adherent to the protocol, which must be accounted for, since non-adherence interferes with the integrity of the design and determining the efficacy of the intervention.

Therefore this study also employed a modified intent-to-treat (MITT) approach, in which we included participants that received a minimum amount of the intervention and provided a minimum number of measures. The most recent meta-analysis of EW describes that participants who completed a minimum of two days of emotional disclosure were more likely to experience the effects of EW[128]. Also, previous studies of EW have excluded participant if they failed to give less than one post-intervention measure. Therefore, our MITT sample consisted of participants that completed at least two days of EW writing, and provided at least one post-intervention measure (i.e. either at 24 hours or six weeks, post-intervention). Statistical analyses from both, the ITT and MITT samples were presented and described in our results. A plan for handling missing data was also essential due to the repeated-measures design of this study.

**Management of missing data.** A meticulous record of all missing data was kept, and

reported in the results as per suggested guidelines. The CONSORT statement states that no universally accepted strategies exist for dealing with missing data[188]; however there are some suggested guidelines. We adopted the systematic approach to manage missing data in trials[190], which started with assessing the nature and mechanism of missingness. This involved determining if data were missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). Data were considered MCAR if data were missing for reasons that were not related to any inferences about intervention effects, e.g. saliva collection tube is lost for a measure, and is as likely to occur for every participant. MAR data is dependent on other variables in the study and the possibility of an association variable linking the probability of patient drop-out and the missing value, e.g. patients with a particular staging of cancer (e.g. Stage III) may not have responded well to EW and withdraw. The assumption for data considered MCAR and MAR is that missing cases were independent of the value of the unobserved (missing) data point.

Finally, data that were MNAR indicate a probabilistic relationship between the missing value and the time point at which it is missing, e.g. participants with lower levels of perceived stress (or negative emotion) at baseline may not experience the benefits of EW and not give the six month follow-up measure. Therefore, in data MNAR missing cases were dependent on the value of the unobserved (missing) data point, and cannot be ignored. To account for missing values, and approach called multiple imputations has gained considerable support from statisticians[191]. This approach allows for the uncertainty about the missing values by generating several different, plausible, imputed data sets (that replace the missing values with predicted or imputed values), and can appropriately combine results obtained from each data set[191]. In the systematic approach to managing missing data, all the investigators of this study first discussed

the possible mechanisms for missingness in the observed data set and rank their plausibility. Statistical models were generated based on the plausibility of missingness: 1) the most plausible missingness model, 2) similar missingness models and 3) least plausible missigness models. Statistical analyses were performed on data sets generated under the aforementioned categories and the investigators reconvened to discuss conclusions from the analyses and arrived at a valid interpretation of the data obtained for this study.

**Manipulation check.** In order to determine if our experimental manipulation of participants to the expressive writing and control writing conditions was successful, we analyzed participants writing responses for use of emotion words. The literature suggests that since EW encourages people to write their deepest thoughts and feelings, so EW participants typically use strong emotion words in their writing[128]. In this study, we expected to find that the EW group would use significantly more positive and negative emotion words in their writing tasks when compared to the control writing group. The Linguistic Inquiry and Word Count (LIWC) was used to analyze writing responses from both the EW group and control writing group on all 4 days of the writing tasks. The LIWC estimates the level to which people use different types of words in a given text. The text from the writing responses of all participants was analyzed using the LIWC to assess the use of positive and negative emotion words. We used one-way analysis of variance (ANOVA) tests to assess for differences with regards to usage of positive emotion words (POS_EMO) and negative emotion words (NEG_EMO) between the intervention and control groups for all fours days of the writing tasks (Days 3, 4, 5 and 6) during the intervention.

**Preparing salivary data for assay procedures.** The salivary data collection process yielded a total of 357 saliva samples, with the exception of one participant (from a total N=40) on one day of data collection, each participant providing a total of 9 samples over three days of

data collection (Days 2, 7 and 49). However, resource constraints allowed for the assay testing of all three salivary analytes, namely cortisol, α-amylase and CRP for 120 (out of 357) salivary samples. We decided to use our limited resources parsimoniously and chose to analyze specific sets of saliva samples from our data. The primary end outcome for our study was salivary cortisol levels at Day 49 ( six weeks post-intervention). Cortisol is known to have changes in secretion patterns based on time of the day. Research has shown that different biological mechanisms may determine the cortisol response within the first 30 minutes of awakening, referred to as the cortisol awakening response (CAR) as opposed to average cortisol secretion over the entire day, determined by calculating area under the curve (AUC)[162,192]. Thus, all three salivary samples (W, P, B, or O) obtained on Day 49 were essential for statistical modeling of CAR and AUC of salivary cortisol, and were selected for assay procedures, see Table 10 below.

**Table 10: Salivary samples selected for assay procedures**

| Assay | Day 2 samples | Day 7 samples | Day 49 samples |
|---|---|---|---|
| Cortisol | PID No. _____<br>W☐ P☐ B☐ O☐ | PID No. _____<br>W☐ P☐ B☐ O☐ | PID No. _____<br>**W☑ P☑ B☑** O☐ |
| a-Amylase | PID No. _____<br>**W☑** P☐ B☐ O☐ | PID No. _____<br>**W☑** P☐ B☐ O☐ | PID No. _____<br>**W☑** P☐ B☐ O☐ |
| C-Reactive Protein | PID No. _____<br>**W☑** P☐ B☐ O☐ | PID No. _____<br>**W☑** P☐ B☐ O☐ | PID No. _____<br>**W☑** P☐ B☐ O☐ |

Determining diurnal variations in secretion of salivary α-amylase and CRP were not critical to answer the study's primary aim. Also, there is some research evidence indicating that levels of salivary α-amylase and salivary cortisol are correlated[193,194]. Thus we assumed that values of salivary α-amylase estimated at baseline and immediately post-intervention could serve as surrogate values for salivary cortisol as well. Therefore, only one salivary sample each (W) was assayed for secondary physiological outcome measures (salivary α-amylase and CRP) on all three days of data collection (Days, 2, 7 and 49), see Table 10.

**Assay procedure.** All assay procedures were conducted in the Center for Biobehavioral Clinical Research laboratory in the VCU School of Nursing building located at 1100 East Leigh Street, Richmond, VA 23059-0567. The director of this laboratory, Dr. Jamie Sturgill had been informed about this study and supervised the assay procedures. The first step for the assay procedure involved thawing the frozen samples and centrifuging them at 2500 rpm for 15 minutes. The supernatant fluid available after thawing was used for assessment of cortisol and α-amylase levels. The levels were assessed using an enzyme linked immune sorbent assay (ELISA) method for cortisol, α-amylase and CRP. At the conclusion of the assay procedures, the assay kits were disposed of using protocols currently in place and utilized by the Center for Biobehavioral Clinical Research Laboratory. Data values from the assay procedures were provided in excel sheets for every participant and were entered into the statistical software programs JMP and SPSS for statistical modeling and analyses.

**Transforming Physiological Data for Statistical Analysis**

**Determining AUC.** Calculating AUC is a regularly used method in endocrinology research for data obtained from repeated measurement of a hormone during the same day[195]. It allows for making meaningful comparisons of data between groups, and collapses data for physiological measures by giving a single average value for each day of measurement. Therefore, AUC also limits the number of statistical comparisons that need to be done between groups. AUC allows researchers to determine the intensity or magnitude of the physiological response (i.e. distance from the ground) to a stimulus or intervention, and also assess the sensitivity of that response (i.e. called change over time). The formula employed commonly in PNI research were used, called area under the curve with respect to ground (AUCg). The AUCg values for both groups were estimated using the trapezoidal formula[195], see Figure 6. This is a

trapezoidal formulas that breaks down cortisol secretion as areas of triangles and rectangles in the area under the curve for the measures taken at W, P and B on Day 49. The $AUC_g$ accounts for all measures (W, P and B) i.e. the total area under the curve, and describes the magnitude of the average cortisol response over the entire day and was determined by summing all areas in the trapezoid (a1 + a2 + a3), see Figure 6. $AUC_g$ was calculated for Day 49 of data collection, and the AUCg values for the Day 49 measure were the primary end outcome measure for the analysis.

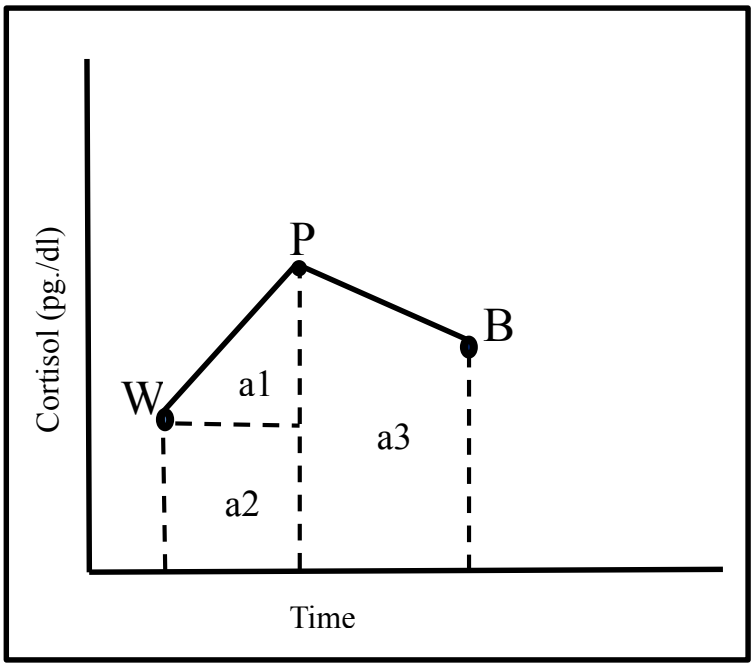



**Figure 6: Trapezoidal formula for determining AUCg and CAR of salivary cortisol**

**Modeling CAR and diurnal cortisol slope.** The CAR is the difference between the peak cortisol measure collected 30-45 min after waking up (P) and the measure collected immediately after waking up (W), i.e. P-W. Thus CAR is estimated in the similar way as AUC by estimating the triangle under the curve between the W and P measure (only a1), see Figure 6. CAR is considered to be mediated by different neurobiological mechanisms and is known to be relatively stable across time[196]. Next, the diurnal cortisol slope was determined which consisted of the rate of decline in cortisol levels across the day, i.e. wakeup to bedtime. Therefore slope for the simple regression equation that was anchored on the waking cortisol measure (W) and the end point is the bedtime measure (B) provided the diurnal cortisol slope (DCS) values for both groups. The CAR and diurnal cortisol slope for the 6 week measure (Day 49) were the end outcome. Next, all

three cortisol variables AUC, CAR and DCS were tested for normality of distribution.

**Hypothesis Testing**

We planned for using the multivariate analysis of variance (MANOVA) statistical test for testing all hypotheses since it accommodates the effects of repeated measurements. The MANOVA statistical formula used the variances of the groups (and not just the mean values, as in the case of t-tests) and provided F values within the degrees of freedom to determine if the hypotheses were significant, i.e. $p<.05$. Specific data analytic plan for each hypothesis is described below.

**Hypothesis one (H1)**. Neuro-hormonal response from the HPA axis to EW was the primary outcome of interest, and cortisol levels at 6 weeks post-intervention was the primary end outcome measure. Data included for testing the hypothesis were AUCg, CAR and DCS for cortisol at 6 weeks after the 4 day intervention. Since, baseline and immediate post-intervention data were not available for cortisol, analytic plan was modified to use independent sample t-test and one-way analysis of variance to test differences between the EW group and control writing group with respect to average values of AUCg, CAR and DCS on Day 49. Group differences for all cortisol values at Day 49 were planned to be reported with p-values.

**Hypothesis two (H2) and Hypothesis three (H3)**. Hypotheses 2 and 3 were regarding the values for secondary physiological outcomes (salivary α-amylase and CRP) at six weeks post-intervention. For H2 and H3, the MANOVA model had two predictor variables (intervention and control group) and three levels of the outcome variables (salivary α-amylase and CRP), namely 1) at baseline (Day 2), 2) immediate post-intervention outcomes (Day 7), and 3) delayed post-intervention outcomes (Day 49). The MANOVA estimated differences between factors (the EW group and control writing group) based on all three levels of the secondary

physiological outcome variables (baseline, Day 7 and Day 49), with a significance level of $\alpha < 0.05$ that were reported with the F-value within the degrees of freedom and respective p-values. The MANOVA model also tested for differences within factors for the repeated outcome measures at all three time points (baseline, Day 7 and Day 49) to determine changes over time for salivary α-amylase and CRP.

**Hypothesis four (H4), Hypothesis five (H5), and Hypothesis six (H6).** Hypotheses 4, 5 and 6 were pertaining to the values for secondary psychosocial outcome measures (scores on the PSS, FCRI-S and CBI-B) at six weeks post-intervention. For H4, H5 and H6, the MANOVA model had two predictor variables (intervention and control group) and three levels of the outcome variables (PSS, FCRI-S and CBI-B), namely scores at 1) baseline (Day 2), 2) immediate post-intervention outcomes (Day 7), and 3) delayed post-intervention outcomes (Day 49). The MANOVA estimated differences between factors (the EW group and control writing group) based on all three levels of the secondary psychosocial outcome variables (baseline, Day 7 and Day 49), with a significance level of $\alpha < 0.05$, that were reported with the F-value within the degrees of freedom and p-values. The MANOVA model also tested for differences within factors for the repeated outcome measures at all three time points (baseline, Day 7 and Day 49) to determine changes over time for PSS, FCRI-S and CBI-B scores.

**Hypothesis seven (H7).** Testing H7 was not possible due to unavailability of baseline cortisol data.

**Hypothesis eight (H8).** In the last hypothesis, H8, we wanted to assess the immediate post-intervention effects of expressive writing. The literature indicates that EW participants typically experience increased stress immediately after completing their writing tasks due to experiencing pent-up emotions[137]. Thus we expected to find increased stress in EW participants

immediately after the intervention (Day 7) with regards to their secondary physiological outcomes (salivary α-amylase and CRP; H8a) as well as their secondary psychosocial outcomes (PSS, FCRI-S and CBI-B scores; H8b). For H8, the MANOVA model had two predictor variables (intervention and control group) and two levels of the outcome variables (H8a: salivary α-amylase and CRP; H8b: PSS, FCRI-S and CBI-B scores), at 1) baseline (Day 2) and 2) immediate post-intervention outcomes (Day 7). The MANOVA estimated differences between factors (the EW group and control writing group) based on two levels of the secondary outcome variables (baseline and Day 7), with a significance level of $\alpha < 0.05$, that were reported with the F-value within the degrees of freedom and p-values. The MANOVA model also tested for differences within factors for the repeated outcome measures at two time points (baseline and Day 7) to determine changes over time for all the secondary outcome measures.

## Chapter VI. Results

Results of this study are reported under two major sections, namely descriptive analyses and hypothesis testing. The measured variables for this study are reported under four categories which include 1) sample characteristics, 2) disease and treatment characteristics, 3) health related symptoms and behaviors and 4) outcome variables (primary and secondary).

### Descriptive Analyses

**Sample characteristics.** The participants in this study had a mean age of 52.1 years (S.D., 14.74; range, 28 to 80 years) and were mostly white (29/40, 72.5%) women (25/40, 62.5%) that were married (22/40, 55%), see Table 11. Most participants were privately insured (25/40, 62.5%), employed full time (24/40, 60%) with a four year college education or post-graduate education (30/40, 75%) and were in the income range of $50,000 to $100,000 and above (20/40, 50%), see Table 11 for details of all sample characteristics.

**Table 11: Sample characteristics**

| **Variable Name** [Results of bivariate t-tests/ and chi-square test ($\chi^2$ ) between the EW and control groups] | Intervention Grp (n=20) Count (% of Total) | Control Grp (n=20) Count (% of Total) | Total (% of Total) |
|---|---|---|---|
| **Gender** [$\chi^2$ (1, N=40) = 0.107, p = .74] | | | |
| Male | 8 (20%) | 7 (17.5%) | 15 (37.5%) |
| Female | 12 (30%) | 13 (32.5%) | 25 (62.5%) |
| **Marital Status** [$\chi^2$ (3, N=40) = 5.82, p = .12] | | | |
| Single | 5 (12.5%) | 1 (2.5%) | 6 (15 %) |
| Divorced/separated | 1 (2.5%) | 5 (12.5%) | 6 (15 %) |
| Married | 11 (27.5%) | 11 (27.5%) | 22 (55%) |
| Living together with a partner | 3 (7.5%) | 3 (7.5%) | 6 (15%) |
| **Race** [$\chi^2$ (3, N=40) = 3.534, p = .2] | | | |
| White | 14 (35%) | 15 (37.5%) | 29 (72.5%) |
| Black or African American | 3 (7.5%) | 5 (12.5%) | 8 (20%) |
| Asian or Native Hawaiian or Pacific Islander | 2 (5%) | 0 | 2 (5%) |
| **Insurance type** [$\chi$2 (6, N=40) = 9.04, p = .06] | | | |
| Private Health Insurance | 12 (30%) | 13 (32.5%) | 25 (62.5%) |
| Medicare/Medicaid/ State-Sponsored Health Plan | 6 (15%) | 4 (10%) | 10 (25%) |
| No Coverage of Any Type | 2 (5%) | 0 (0%) | 2 (5%) |
| **Employment type** [$\chi^2$ (5, N=40) = 1.8, p = .9] | | | |
| Employed Full time | 13 (32.5%) | 11 (27.5%) | 24 (60%) |
| Employed Part time / Self-employed | 3 (7.5%) | 5 (12.5%) | 8 (20%) |
| Retired / Unable to work | 3 (7.5%) | 3 (7.5%) | 6 (15%) |
| **Income** [$\chi^2$ (4, N=40) = 6.75, p = .1] | | | |
| Up to $50,000 | 10 (25%) | 8 (20%) | 18 (45%) |
| $50,000 and above | 10 25(%) | 12 (30%) | 22 (55%) |
| **Education** [$\chi$2 (3, N=40) = 4.2, p = .24] | | | |
| Grade 12 or GED | 4 (10%) | 1 (2.5%) | 5 (12.5%) |
| College 1 year to 3 years | 2 (5%) | 3 (7.5%) | 5 (12.5%) |
| College 4 years or more | 14 (35%) | 16 (40%) | 30 (75%) |

**Disease and treatment characteristics**. With regards to cancer site, about half the participants were diagnosed with breast cancer (21/40, 52.5%), and other cancer diagnoses included, prostate, lung, brain and bone cancer, see Table 12. In terms of cancer stage, majority participants reported having a Stage II diagnosis (20/40, 50%), see Table 12, and had completed their last radiation treatment about 6-8 months (22/40, 55%) prior to study enrollment.

**Table 12: Cancer Site, Stage and Treatment**

| **Variable Name** [Results of bivariate chi-square tests ($\chi^2$ ) between EW and control groups] | Intervention Grp (n=20) Count (% of Total) | Control Grp (n=20) Count (% of Total) | Total (% of Total) |
|---|---|---|---|
| **Cancer Site** [$\chi$2 (3, N=40) = 3.83, p = .43] | | | |
| Breast | 12 (30%) | 9 (22.5%) | 21 (52.5%) |
| Prostate | 3 (7.5%) | 2 (5 %) | 5 (12.5%) |
| Lung | 2 (5%) | 1 (2.50%) | 3 (7.5%) |
| Brain | 1 (2.5%) | 5 (12.50%) | 6 (15%) |
| Other (Bone) | 2 (5 %) | 3 (7.50%) | 5 (12.5%) |
| **Cancer Stage** [$\chi$2 (3, N=40) = 2.67, p = .26] | | | |
| Stage I | 6 (15%) | 2 (5%) | 8 (20%) |
| Stage II | 10 (25%) | 14 (35%) | 24 (60%) |
| Stage III | 4 (10%) | 4 (10%) | 8 (20%) |
| **Cancer Treatments** | | | |
| **Radiation** [$\chi$2 (3, N=40) = 0] | 20 (100%) | 20 (100%) | 40 (100%) |
| **Chemotherapy** [$\chi$2 (3, N=40) = 0.17, p = .68] | 4 (10%) | 3 (7.5%) | |
| **Surgery** [$\chi$2 (3, N=40) = 0.5, p = .49 | 7 (17.5%) | 5 (12.5%) | |

**Health related symptoms and behaviors.** Participants reported having social support (e.g. someone to help with daily chores) available to them a little of the time (mean =2.07, S.D. = 0.75, scores ranging from 1 to 5). The average subjective social status (measured on a scale of 1-10) of participants in this study was 5. 23 (S.D. = 1.05). Participants were mainly non-smokers

(34/40, 85%) that reported consuming alcohol on a monthly basis or less (12/40, 52.5%). On average participants reported sleeping for 7.53 hours (SD=0.96) every day and having sleep related problems on some of the days (mean=2.04, SD=0.56). Participants reported being very comfortable using a computer (mean=1.18, 0.46), and on average used a computer almost weekly (mean=3.8, SD=1.56). Finally, participants reported using at least one type of CAM therapy once a month or less than once a month (mean=1.6, SD=0.6), please refer to Table 13.

**Table 13: Health-related symptoms and behaviors**

| **Variable Name** [Results of bivariate t-tests and chi-square tests ($\chi^2$ ) between the EW and control groups] | Intervention Grp (n=20) Mean (SD) or Count (% of Total) | Control Grp (n=20) Mean (SD) Count (% of Total) |
|---|---|---|
| **Cognitive Impairment (BSCI)** [t (38) = -0.35, p = .73] | 3.7 (1.34) | 3.55 (1.4) |
| **Depressive symptoms (PHQ2)** [t (32.6) = -0.82, p = .42] | 1.1 (0.45) | 0.95 (0.69) |
| **Social support (MOSS) [**t (37.8) = -1006, p = .0] | 2.2 (0.72) | 1.95 (0.78) |
| **Perceived social status** [t (38) = 1.056, p = .3] | 5.05 (1.05) | 5.4 (1.05) |
| **Smoking behaviors** | | |
| Smoking- frequency | | |
| Daily [$\chi$2 (1, N=40) = 1.03, p = .24] | 1 (4.47) | 0 |
| Weekly [$\chi$2 (1, N=40) = 1.03, p = .31] | 5 (22.36) | 0 |
| **Alcohol consumption** | | |
| Frequency [$\chi$2 (3, N=40) = 9.11, p = .105] | | |
| Monthly or less | 12 (20%) | 9 (22.5%) |
| ≥2 to 4 times a month | 5 (12.5%) | 9 (22.5%) |
| Prefer not to answer | 3 (7.5%) | 2 (5%) |
| **Sleep Related Behaviors** | | |
| Sleep Hours [t (30.7) = -2.65, p = .0125*] | 7.9 (0.64) | 7.15 (1.1) |
| Sleep Problems [t (38) = -0.66, p = .514] | 6.3 (1.72) | 5.95 (1.64) |
| **Oral health – gum disease** [$\chi$2 (3, N=40) = 3.8, p = .3] | | |
| Yes | 2 (5%) | 0 (0%) |
| No | 12 (30%) | 10 (25%) |
| Don't know/PNTA | 6 (15%) | 10 (25%) |
| **CAM Use** [t (37.4) = 1.24, p = .22] | 8.85 (3.22) | 10.2 (3.64) |
| **Comfort with using computers** [t (36.051) = - 0.45, p = .66] | 3.65 (1.14) | 3.45 (1.6) |

**Outcome variables (primary and secondary).** Baseline data for the primary outcome measure cortisol was not available. The means (and S.D.) of measurements for all secondary baseline outcome variables is reported in Table 14.

**Table 14: Means of outcome variables (Baseline: Day 2)**

| **Variable Name** [Results of t-tests between the EW and control groups] | Intervention grp (n=20) mean (SD) | Control grp (n= 20) mean (SD) |
|---|---|---|
| **Cortisol (pg/dl)** [Data N/A] | Data N/A | Data N/A |
| **a-Amylase (U/ml)** [t (38) = -1.58, p = .12] | 1.16 (0.73) | 0.793 (0.74) |
| **CRP (pg/dl)** [t (36) = 0.16 , p = .87] | 994.05 (455.12) | 1020.70 (581.84) |
| **PSS** [t (38) = -0.61, p = .55] | 31.95 (5.32) | 31.05 (3.89) |
| **FCRI-S** [t (38) = 0.33, p = .74] | 24.4 (3.62) | 24.7500 (3.06) |
| **CBI-B** [t (38) = 1.115, p = .27] | 75.45 (6.67) | 78.45 (10.013) |

**Distribution and tests of normality.** Study data pertaining to all variables in the study, sample characteristics, disease and treatment characteristics, health related symptoms and behaviors and outcome variables (primary and secondary) were analyzed for normality and outliers by using centered leverages and visual inspection of the data plotted on normal quantile plots. Outliers n=2 were found for CRP levels on Day 7 (z = 3.8) and Day 49 (z = 3.6) and were replaced with values 3 standard deviation above the mean. The Shapiro-Wilk test was used to assess if the data for all variables in the study were normally distributed. The Shapiro-Wilk goodness of fit test revealed that with the exception of cortisol, data for all variables in the study were normally distributed. All three variables related to salivary cortisol secretion on Day 49 did not follow a normal distribution, area under the curve (AUCg), W = 0.39, p<.0001, cortisol awakening response (CAR) W = 0.39, p<.0001 and Diurnal cortisol slope (DCS), W=0.81, p<.0001, please see figures of normal quantile plots in Appendix O. Since our study's primary aim was to determine EW's efficacy to reduce stress in CS as measured by salivary cortisol, we

expected to find that cortisol data on Day 49 would be skewed.

**Success of Randomization**

Of the n = 40 participants that were enrolled in the study, n = 20 were randomized to the EW group, and n = 20 were randomized to the control writing group. In order to assess if the randomization procedures were successful, we tested for group differences between the EW group and control group with regards to all four categories of variables, 1) sample characteristics, 2) disease and treatment characteristics, 3) health-related symptoms and behaviors and 4) baseline outcome variables. The first three categories of variables had variables measured as categorical as well as continuous, while baseline outcome measures were only continuous measures. Statistical comparisons between patients randomized to the expressive writing and control writing groups were made using t-tests for continuous measures and chi-square analyses for categorical measures. The null hypothesis ( $H_0$ ) for these tests stated that there would be no differences between groups with regards to all four categories of variables. Results showed that with the exception of one variable related to sleep behaviors, the null hypothesis was retained for all variables in the study and there were no significant differences between the EW group and control writing groups at baseline, please refer to Tables 11 – 14.

The only significant group difference at baseline was regarding sleep hours, see Table 13. Participants in the intervention group reported sleeping for an average of 7.9 hours (S.D. 0.641, SE 0.143, CI, 7.6, 8.2) and control group participants reported an average of 7.15 hours of sleep (S.D. 1.089, SE 0.243, CI 6.64, 7.66). Thus, intervention group participants reported sleeping approximately 0.75 hours (45 minutes) longer than the control writing group, $t(38) = -2.654$, $p < .05$. However, when participants were asked specific questions regarding sleep-related problems, such as difficulty falling asleep, difficulty staying asleep or problems waking up, no differences

emerged between the intervention and control groups. Therefore, the marginal difference in sleep hours between the two groups was not used as a covariate for further statistical analyses, and randomization was considered successful.

**Manipulation Check**

Experimental manipulation of participants to either the EW or control writing conditions was evaluated by assessing participants writing responses for use of positive and negative emotion words using the LIWC software. The average (mean and SD) use of positive emotion words for each group is described in Table 15, and the average (mean and SD) use of positive emotion words for each group is described in Table 16.

**Table 15: Means of LIWC Scores: Positive Emotion Words (POS_EMO)**

| Intervention Day | Intervention grp mean (SD) | Control grp mean (SD) |
|---|---|---|
| Day 3 | 4.69 (0.96) | 1.75 (0.41) |
| Day 4 | 3.48 (0.97) | 2.71 (1.13) |
| Day 5 | 3.47 (1.29) | 2.35 (1.09) |
| Day 6 | 4.34 (0.91) | 1.86 (0.67) |

**Table 16: Means of LIWC Scores: Negative Emotion Words (NEG_EMO)**

| Intervention Day | Intervention grp mean (SD) | Control grp mean (SD) |
|---|---|---|
| Day 3 | 3.8 (0.92) | 1.94 (0.52) |
| Day 4 | 3.44 (0.84) | 2.32 (1.3) |
| Day 5 | 3.41 (1.35) | 2.2 (0.98) |
| Day 6 | 4.91 (0.79) | 1.97 (0.86) |

Results of the ANOVAs conducted to test for group differences regarding LIWC scores showed that participants in the EW group used significantly more positive emotion words compared to the control writing group, on three days of writing Day 3 [F (1, 38) = 157.4, p

<.0001], Day 4 [F (1, 37) = 6.4, p <.05] and Day 6 [F (1, 24) = 18.24, p <.0001]. Results also revealed that the EW group used significantly more negative emotion words compared to the control writing group on Day 3, [F (1, 38) = 61.4, p <.0001], Day 4 [F (1, 37) = 11.93, p <.05] and Day 6. [F (1, 24) = 20.4, p <.0001], see Appendix P for mean difference plots for both groups with respect to LIWC scores. Only on one day, Day 5, there were no differences between the EW group and control writing group with regards to usage of either positive emotion words [F (1, 31) = 2.4, p =.13], or negative emotion words [F (1, 31) = 3.01, p <.1], see Appendix P for mean difference plots. Results of the differences in LIWC scores confirmed that the EW group overall used significantly more positive and negative emotions in their writing responses compared to the control writing group. Thus, we inferred that our experimental manipulation of participants was successful.

**Attrition Rates**

Overall participants in the study showed high rates of compliance with regards to completing the writing tasks as well as completing the outcome measures which included answering online survey questions and providing their saliva in Eppendorf tubes. All participants (n=40, 100%) provided information regarding demographics, disease and treatment information, health related symptoms and behaviors (Day 1) as well as baseline outcome measures (Day 2), see Figure 7. All participants completed their online post-intervention psychosocial outcome measures, i.e. immediate (Day 7) as well as the delayed 6 week post-intervention measure (Day 49). Specific rates of attrition regarding writing tasks and salivary outcomes measures are described below.

**Writing tasks.** With regards to their writing tasks all participants in both EW and control writing groups (N=40) completed the first day of writing. On the second day of writing only one

participant (n=1) in the control writing group did not complete their schedule writing task, all participants in the EW group completed their writing tasks. On the third day of the writing intervention, there were n=4 (10%) participants in the EW group and n=3 (7.5%) participants in the control writing who did not complete their writing tasks. Finally on the fourth and last day of writing, n=5 participants from the EW group and n=3 participants from the control writing group did not complete their writing tasks. Thus, almost all participants (n=39, 97.5%) completed at least two writing sessions, and majority of participants (n=33, 82.5%) completed at least three days of writing tasks. Thus participants demonstrated a satisfactory compliance with the writing interventions and both groups complete the minimum required two days of writing.

The average time (and SD) that participants in each group took for completing their respective writing assignments are described in the Table 17 below. To assess for differences in

**Table 17: Mean time taken for writing tasks by both groups**

| Day | n | Intervention grp min (SD) | n | Control grp min (SD) |
|---|---|---|---|---|
| Day 3 | 20 | 28.4 (5.92) | 20 | 29.34 (5.96) |
| Day 4 | 20 | 33.98 (6.05) | 19 | 31.77 (5.56) |
| Day 5 | 16 | 32.35 (5.81) | 17 | 29.91 (5.57) |
| Day 6 | 15 | 33.53 (4.49) | 11 | 31.75 (4.37) |

writing time between the EW group and control writing groups, we again used one-way analysis of variance (ANOVA) tests for all fours days of the writing tasks (Days 3, 4, 5 and 6) during the intervention. Results of the ANOVAs were unable to detect significant difference in the amount of time spent writing between participants in the EW group and participants in the control writing group on all four days of writing Day 3 [$F(1, 38) = 0.25$, $p = .64$], Day 4 [$F(1, 37) = 1.4$, $p = .24$], Day 5 [$F(1, 31) = 1.52$, $p = .23$], and Day 6 [$F(1, 24) = 1.03$, $p = .32$]. Thus participants in both groups of this study, the EW and control writing groups, contributed equal amount of

time for their writing tasks.

**Outcome measures: Salivary specimens.** With regards to salivary specimens, all participants (n=40, 100%) provided baseline (Day 2) and immediate post-intervention (Day 7) measures. For the delayed 6 week post-intervention measure (Day 49) only one participant (n=1, 2.5%) from the intervention group did not provide their salivary specimens. In terms of following the schedule for providing the three salivary specimens (waking, peak, bedtime and other), most participants (n=36, 90%) followed the instructions and provided samples marked at waking (W), peak (P) and bedtime (B). There were n=2 (5%) participants (n=1 from the EW group and n=1 from the control group) that provided samples marked as Other (O) for their Day 7 measure. Finally, n=1 participant from the EW group provided two samples marked as peak (P) on their Day 49 measure; one peak (P) sample was considered as Other (O) for data analysis. Overall, participants showed very low attrition with regards to completing the salivary outcome measures, see Figure 7.

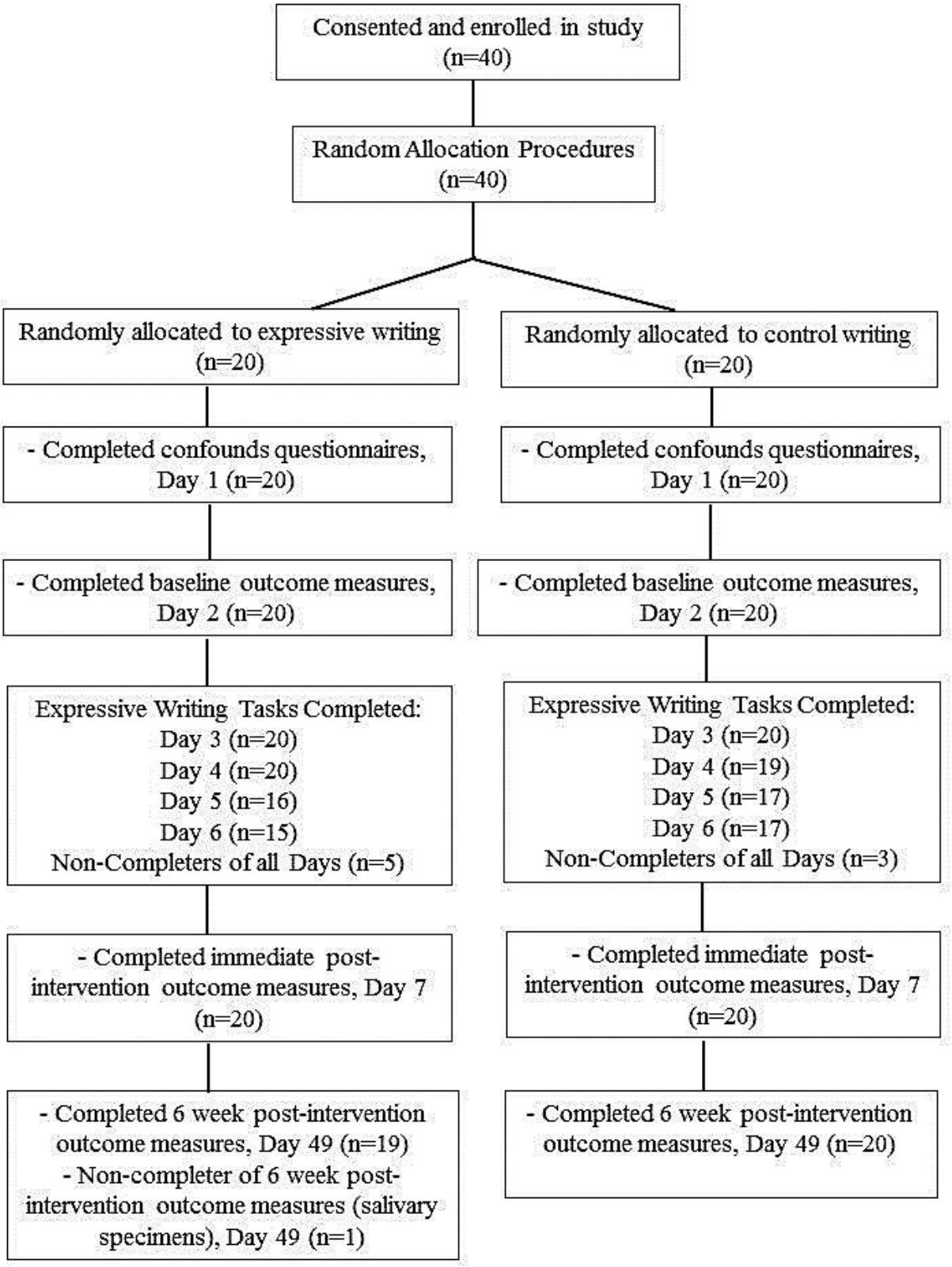



**Figure 7: Randomization flow chart of activities completed by participants**

**Statistical Tests**

Statistical tests on cortisol levels (AUCg, CAR and DCS) on Day 49 revealed that data were not normally distributed. Therefore, in order to compare the EW and control writing groups with data having a non-normal distribution, the nonparametric Mann-Whitney statistical test was chosen. The Mann-Whitney U test was used to compare mean ranks of AUCg, CAR and DCS between the EW and control writing groups and results for hypothesis one are reported under each respective cortisol variable. However t-tests were also conducted to compare results of both non-parametric (Mann-Whitney) and parametric (t-test) tests.

**Mann-Whitney (U) test.** The Mann-Whitney U test is employed when comparing differences between two independent groups when the outcome variable is measured as ordinal or continuous, but is not normally distributed. The Mann-Whitney U test ranks all the values in both groups from low to high, and then compares the mean ranks. Specifically, the Mann-Whitney U test assesses, what is the likelihood that a randomly selected value from the group with the higher mean rank will be greater than a randomly selected value from the other group. The null hypothesis ($H_0$) of the Mann-Whitney test posits that there will be no difference in the ranks of the two groups. A significant P value indicates that the null hypothesis is rejected and the mean rank of the one group is lower than the mean rank of the comparison group (here EW group vs control writing group).

However, there are three assumptions that have to be met when using the Mann-Whitney U test. The first assumption is that the outcome variable(s) must be measured at the continuous or ordinal level. This assumption is met by the study data, since cortisol concentration was measured as a continuous variable in units of pictograms/deciliter (pg/dl) in saliva. The second assumption is that the predictor variable must consist of two categorical, independent groups.

This assumption is also met by the study data, since this study is a randomized trial, the intervention and control groups are the categorical, independent groups operating as predictor variables. Finally, the last assumption requires the independence of observations, which means that there must be no relationship between the observations of the predictor variables or between the groups themselves. This means that the Mann-Whitney U test requires that there must be different participants in each group with no participant being in more than one group. Study data meet the last assumption as well, as randomization procedures ensured that participants had an equal chance of being assigned to either the intervention or control group at the start of the study.

**General Linear Model (GLM).** For hypothesis testing with respect to the secondary outcome variables, a General Linear Model accounting for repeated measures was selected. The study design for this research project consisted of two predictor variables (EW and control writing groups) and five outcome variables (amylase, CRP, PSS, FCRIS and CBIB) that were repeatedly measured at three time points (Days 2, 7 and 49). For this multivariate repeated measures design, the General Linear Model (GLM) test was selected to compare the two predictor variables, the intervention (EW) group and control (control writing) group, on each of the five outcome variables measured at baseline (Day 2), immediately after the writing tasks (Day 7) and a six weeks after the writing tasks (Day 49). The General Linear Model (GLM) test accounts for the variance that occurs in measures that are collected repeatedly over time as well as accounts for unequal n in predictor variables. The null hypothesis ($H_0$) of the GLM test posits that there will be no difference in the predictor variables with regards to the outcome variables of two groups. A significant P value in the GLM indicates that the null hypothesis is rejected and the mean of one group is lower than the mean of the comparison group (here EW group vs control writing group) with a respective effect size statistic (partial eta squared).

The GLM for this study assumed independence of observations data and normal distribution of data for all secondary outcome variables, physiological and psychosocial. Random allocation ensured that no participant completed both writing tasks and thus provided independent observations. The second assumption of the GLM was that the data for observations on the outcome variables had a multivariate normal distribution, which can decrease the chances of encountering Type I error. The multivariate normal distribution was assessed by reviewing the normal quantile plots for each variable, please see Appendix O. The graphs for all five outcome variables displayed an elliptical shape that is characteristic of normal distribution for each respective variable. Based on the results of these analyses, a multivariate normal distribution was assumed. The GLM also allows for groups to be unequal, since our final sample had unequal numbers of participants (Intervention (EW) group: n=19; Control (Control writing) group: n=20). The GLM allows for testing differences both within and between predictor groups. The GLM was used for primarily testing differences between the predictor variables (Intervention (EW) group, Control (Control writing) group) with respect to all secondary outcome variables involving hypotheses two through eight.

**Hypotheses Testing**

**Hypothesis one**. Hypothesis one was related to the primary outcome measure for this study which was cortisol. Research evidence indicates that salivary cortisol is a reliable measure of the HPA axis activity in human physiological stress response. In hypothesis one we expected that cancer survivors who participated in the expressive writing (EW group) stress-management intervention will have lower levels of salivary cortisol at 6 weeks post-intervention (Day 49) when compared with cancer survivors who participated in control-writing (control group). The first step in testing hypothesis one was to extrapolate the amount and rate of cortisol secretion

from the raw data cortisol data. This step involved determining the area under the curve (AUCg), cortisol awakening response (CAR) and diurnal cortisol slope (DCS) as described in the methods. The median values for AUCg, CAR and DCS for both groups is reported in Table 18.

**Table 18: Median values of cortisol variables on Day 49**

| Day | Intervention group (n=19) median (IQR) | Control group (n= 20) median (IQR) |
|---|---|---|
| AUCg | 0.32 (0.18, 0.91) | 0.98 (0.36, 4.58) |
| CAR | 0.013 (0.01, 0.03) | 0.04 (0.02, 0.2) |
| DCS | 0.001 (-0.004, 0.004) | -0.003 (-0.01, 0.005) |

Cortisol: Area Under the Curve (AUCg). The AUCg estimation described that the EW group had a median secretion of 0.32 (IQR= 0.18, 0.91) pg/dl of cortisol over the course of a 14 hour day (Day 49), while the control group secreted a median of 0.98 (IQR = 0.36, 4.58) pg/dl of cortisol over the course of a 14 hour day (Day 49). The Mann-Whitney mean ranks of AUCg values for both groups are reported in the Table 19 below.

**Table 19: Mann Whitney Ranks for AUCg (Day 49)**

| | Intervention group (n=19) | Control group (n=20) |
|---|---|---|
| Mean Rank | 14.95 | 24.80 |
| Expected Ranks | 380 | 400 |
| Sum of Ranks | 284 | 496 |

The results for the Mann-Whitney-Wilcoxon test for AUCg showed a statistically significant difference between AUCg values of the EW group and control writing groups for the 6 week post-intervention measure and the null hypothesis was rejected. On Day 49 the EW group participants had significantly lower AUCg values compared with the control group participants, U=94, p=0.006, r=0.432, see Figure 8. A t-test also confirmed that the mean AUCg values of the EW group participants were significantly lower than control group participants, t (37) = 2.2, p<.05 at Day 49.

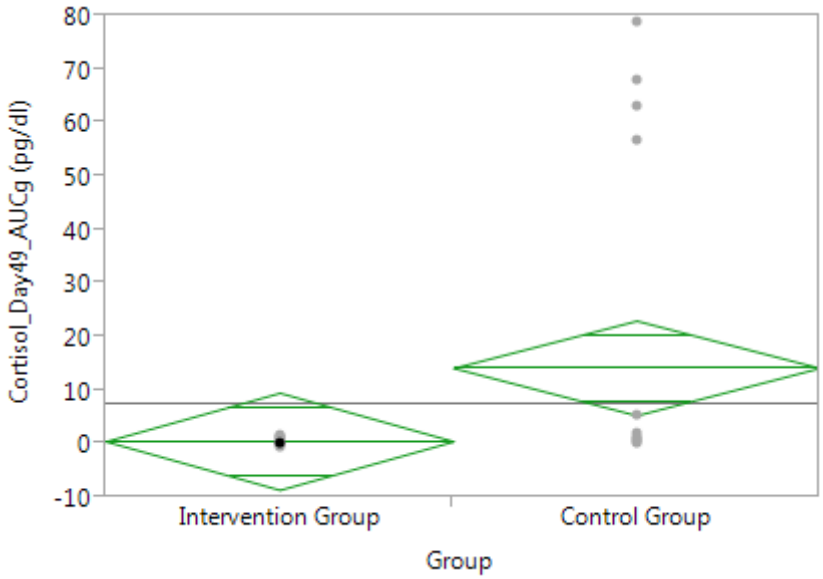



**Figure 8: Group differences for cortisol AUCg values at Day 49**

Cortisol: Cortisol Awakening Response (CAR). CAR evaluation described that over a period of half an hour (from waking to peak) on Day 49, the EW group secreted a median of 0.013 (IQR = 0.01, 0.03) pg/dl of cortisol and the control writing group had a median secretion 0.04 (IQR = 0.02, 0.2) pg/dl of cortisol. The Day 49 Mann Whitney mean ranks of CAR values for both groups are reported in Table 20 below.

**Table 20: Mann Whitney Ranks for CAR (Day 49)**

| | Intervention group (n=19) | Control group (n=20) |
|---|---|---|
| Mean Rank | 14.79 | 24.95 |
| Expected Ranks | 380 | 400 |
| Sum of Ranks | 281 | 499 |

Parallel to the results for AUCg, the Mann-Whitney U test for CAR on Day 49 also reported a statistically significant difference between the CAR of EW participants and control writing participants. On the 6 week post-intervention measure the intervention group participants had significantly lower CAR values compared with the control group participants, U=91, p=0.005,

r=0.45, see Figure 9 below. Similarly, a t-test confirmed that the mean CAR values of the EW group participants were significantly lower than control group participants, t (37) = 2.2, p<.05.

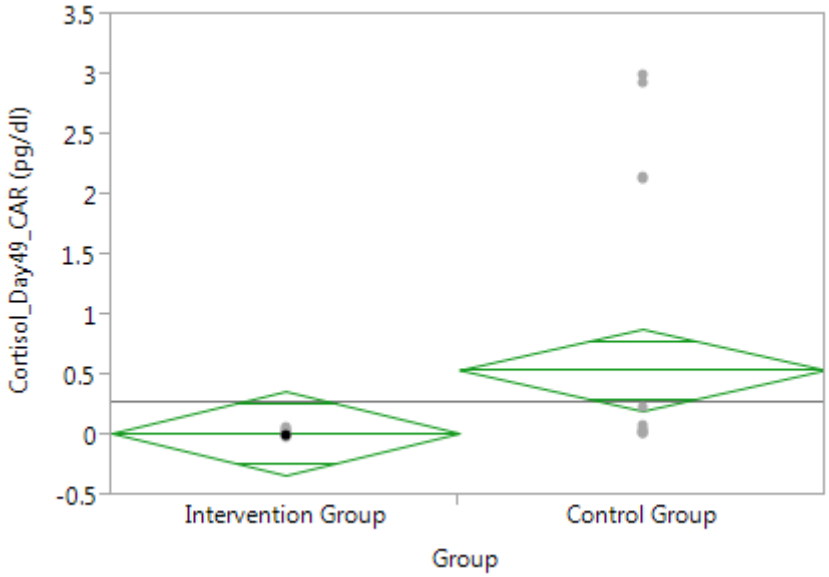



**Figure 9: Group differences for CAR values at Day 49**

Cortisol: Diurnal Cortisol Slope. The median DCS for the treatment arm was 0.001 (IQR = -0.004, 0.004) and the control arm median DCS was -0.003 (IQR = -0.01, 0.005). The Day 49 Mann-Whitney mean ranks of CAR values for both groups are reported in Table 21 below.

**Table 21: Mann Whitney Ranks for DCS (Day 49)**

| | Intervention group (n=19) | Control group (n=20) |
|---|---|---|
| Mean Rank | 21.74 | 18.35 |
| Expected Ranks | 380 | 400 |
| Sum of Ranks | 367 | 413 |

With regards to DCS the null hypothesis ($H_0$) for the Mann-Whitney U test for CAR on Day 49 was retained and no statistically significant differences were found between the DCS values of EW group participants and control group participants. On the 6 week post-intervention measure the EW group participants had similar DCS values compared with the control group participants,

U = 157, p=0.365, r=0.15, please see Figure 10 below. A t-test also confirmed that the mean DCS values of the EW group participants were similar to the DCS values of control group participants, t (37) = -.7, p=0.5.

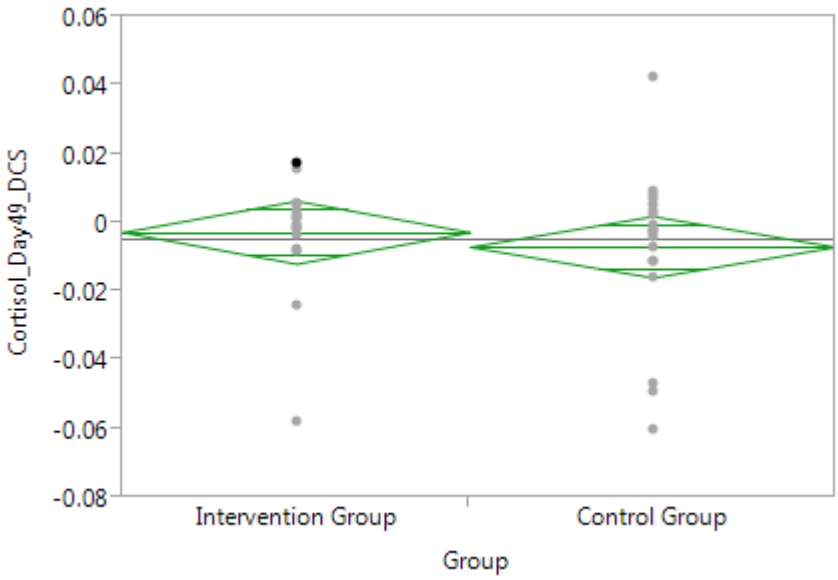



**Figure 10: Group differences for DCS values at Day 49**

The lack of baseline outcome measures and immediate post-intervention outcome measures for cortisol limits the inferences that can be made from the data for hypothesis one. For example, we could not estimate if control group participants had higher levels of cortisol than EW group participants at baseline before the intervention. Nevertheless, randomization was successful with all other variables in this study, including salivary α-amylase (sAA) and research indicates to a correlation between levels of cortisol and sAA in healthy subjects as well as clinical populations[193,194]. Thus we can assume that cortisol levels were not significantly different at the start of the study. A post-hoc power analysis using Gpower showed that we had 89% power (β) to detect differences between intervention and control groups (N=39, α=0.05) using the Mann-Whitney U test (effect size of r=0.43; *d*=0.96).

**Hypothesis two**. A novel aspect of this study was that in addition to measuring outcomes

of the HPA axis (salivary cortisol), we also measured the SNS (salivary α-amylase). The second hypothesis of this study stated that CS participating in EW (intervention arm) would have lower levels of salivary α-amylase (sAA) when compared to CS participating in control-writing (control arm) at 6 weeks post-intervention  The mean sAA levels for both groups on all three days of data collection are presented in the Table 22 below.

**Table 22: Mean salivary a-Amylase levels (Days 2, 7 and 49)**

| Day | n | Intervention group U/ml (SD) | n | Control group U/ml (SD) |
|---|---|---|---|---|
| Day 2 | 20 | 1.15965 (0.73) | 20 | 0.7928 (0.74) |
| Day 7 | 20 | 1.52910 (0.75) | 20 | 0.89695 (0.83) |
| Day 49 | 19 | 1.53242 (0.64) | 20 | 0.9388 (0.82) |

The GLM findings for hypothesis two did not support our anticipated results of lower sAA in EW group compared to the control group. Instead we found that the EW group had higher levels of sAA compared to the control group, $F(1, 37) = 8.117$, $p<0.05$, partial eta-squared ($\eta_p^2$) = .180, at six weeks post-intervention. However, it is important to note that baseline sAA was higher in the EW group compared to the control group. There was a significant effect of time on the sAA concentration, with an increase in AA on Day 7 and then a plateauing of sAA concentration by Day 49, $F(2, 36) = 4.145$, $p<0.05$, $\eta_p^2 = .178$, please see Figure 11.

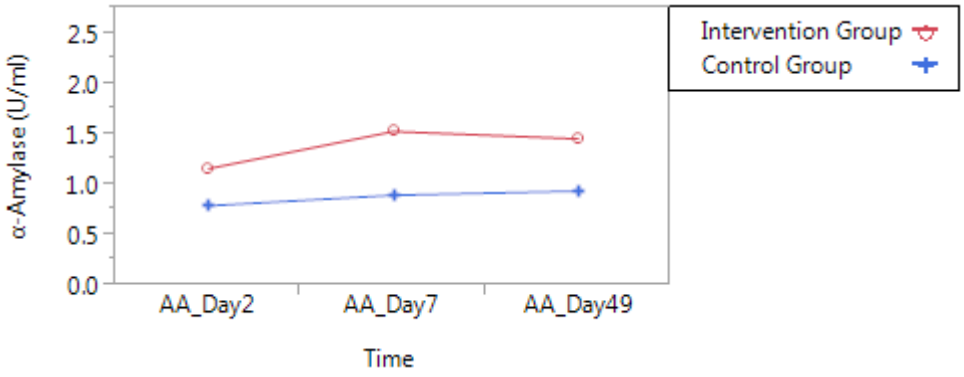



**Figure 11: Changes over time for salivary α-amylase (AA) in both groups over the six week intervention**

**Hypothesis three:** Another aim of this study was to investigate the effects of EW on immune function. CRP was the chosen outcome measure of immune function. The third hypothesis of this study stated that at 6 weeks post-intervention CS participating in EW (treatment arm) will have lower levels of salivary CRP when compared with CS participating in control-writing (control arm). The mean CRP levels for all three days of data collection (Day 2, 7 and 49 for both groups are presented in the Table 23 below.

**Table 23: Mean salivary CRP levels (Days 2, 7 and 49)**

| Day | n | Intervention group pg/dl (SD) | n | Control group pg/dl (SD) |
|---|---|---|---|---|
| Day 2 | 20 | 994.05 (455.12) | 20 | 1020.70 (581.84) |
| Day 7 | 20 | 1164.73 (571.38) | 20 | 1049.17 (575.99) |
| Day 49 | 19 | 986.73 (383.86) | 20 | 1012.59 (383.86) |

The GLM for hypothesis three revealed no significant differences in CRP levels between intervention and control group participants on Day 49 of the intervention, $F(1, 37) = 0.009$, $p = 0.927$, $\eta_p^2 = .0$, see Figure 12. The data also indicates that there was no impact of time on CRP levels for both groups, $F(2, 36) = 1.877$, $p=0.168$, $\eta_p^2 = .094$, see Figure 12.

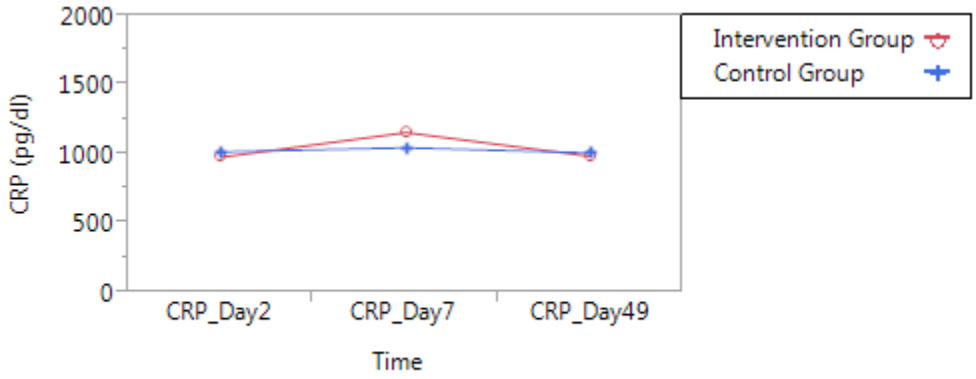



**Figure 12: Changes over time for salivary CRP in both groups over the six week intervention**

**Hypothesis four.** Hypothesis four was related to the psychosocial outcome measure of perceived stress as measured by the perceived stress scale (PSS). The mean PSS scores for both

groups on all three days of data collection are presented in the Table 24 below.

**Table 24: Mean PSS scores (Days 2, 7 and 49)**

| Day | Intervention group (n=20) mean (SD) | Control group (n= 20) mean (SD) |
|---|---|---|
| Day 2 | 31.95 (5.32) | 31.05 (3.89) |
| Day 7 | 36.1 (2.69) | 35.65 (2.6) |
| Day 49 | 23.9 (1.97) | 24.1 (1.99) |

Hypothesis four stated that CS in the EW group will have lower perceived stress indicated by lower scores on the PSS at 6 weeks post-intervention compared to CS in the control group. The results of the GLM for hypothesis four revealed no statistically significant results for group differences in PSS scores on Day 49 $F(1, 38) = 0.48$, $p=0.495$, $\eta_p^2 = .012$ , see Figure 13. However the data did reveal a significant effect of time for PSS scores in both groups, $F(2, 37) = 254.74$, $p<0.0001$, $\eta_p^2 = .932$. There was an increase in perceived stress immediately after the intervention (Day 7) and a significant decrease in perceived stress for both groups at 6 weeks post-intervention, please see Figure 13 below.

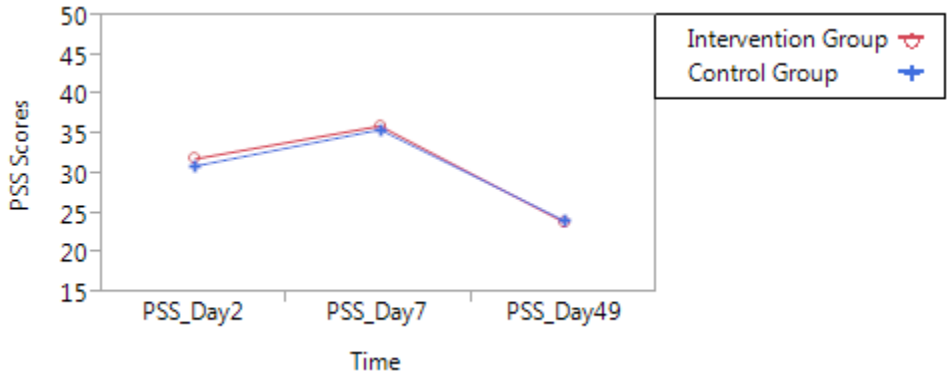



**Figure 13: Changes over time for PSS scores in both groups over the six week intervention**

**Hypothesis five.** One critical aim of this study was to test if EW is effective in emotion regulation by actually measuring levels of a relevant emotion for CS, which was fear of cancer

recurrence over time. The fear of cancer recurrence inventory – severity (FCRI-S) subscale was used to measure fear of cancer recurrence in the participants of this study. The mean FCRI-S scores for both groups on all three days of data collection are presented in the Table 25 below.

**Table 25: Mean FCRI-S scores (Days 2, 7 and 49)**

| Day | Intervention group (n=20) mean (SD) | Control group (n= 20) mean (SD) |
|---|---|---|
| Day 2 | 24.4 (3.62) | 24.7500 (3.06) |
| Day 7 | 31.35 (2.37) | 30.85 (3.2) |
| Day 49 | 18.2 (2.4) | 24.7 (5.2) |

Hypothesis five stated that on Day 49 (6 weeks post-intervention) CS participating in EW will have lower scores on the FCRI-S compared to CS participating in control-writing. The GLM test for hypothesis five demonstrated that fear of cancer recurrence was significantly reduced in the EW participants when compared to the control group participants, $F(1, 38) = 9.654$, $p=0.004$, $\eta_p^2 = .993$, at six weeks post-intervention (Day 49), see Figure 14 below. The data also showed that FCRI-S scores changes significantly with time for both groups, $F(2, 37) = 97.06$, $p<0.0001$, $\eta_p^2 = .84$, where both groups reported increases in FCRI-S scores immediately after the writing intervention (Day 7), followed by a significant decrease on Day 49, which was more pronounced for the EW group, please see Figure 14 below.

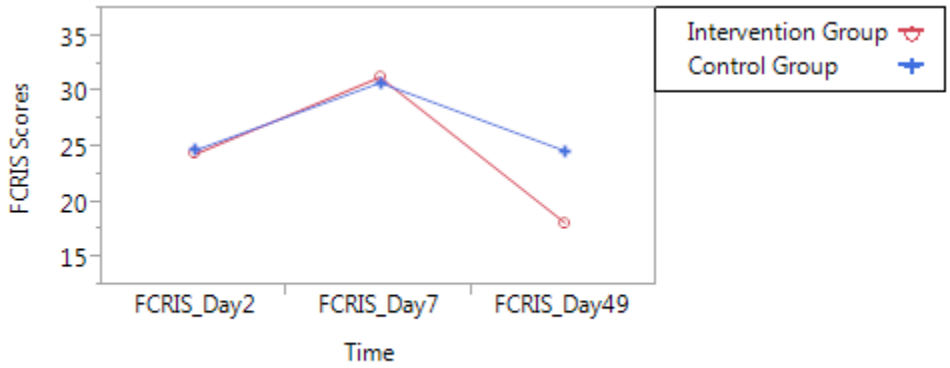



**Figure 14: Changes over time for FCRIS scores in both groups over the six week intervention**

**Hypothesis six.** An important way in which EW benefits participants is by boosting participants self-efficacy to cope with stressful experiences and stressful life events. Participants in this study completed a measure of their self-efficacy to cope with cancer called the cancer behavior inventory – brief version (CBI-B). The mean CBI-B scores for both groups on all three days of data collection are presented in the Table 26 below.

**Table 26: Mean CBIB scores (Days 2, 7 and 49)**

| Day | Intervention group (n=20) mean (SD) | Control group (n= 20) mean (SD) |
|---|---|---|
| Day 2 | 75.45 (6.67) | 78.45 (10.013) |
| Day 7 | 72.2 (3.43) | 71.05 (3.17) |
| Day 49 | 96.7 (6.26) | 89.4 (8.52) |

In hypothesis six we anticipated that CS who participated in EW will have greater self-efficacy to cope with cancer measured by higher scores on the CBI-B at 6 weeks post-intervention (Day 49) when compared to CS participating in control-writing. The GLM test for hypothesis six showed no significant overall group differences between the EW group and control group participants for CBI-B scores, $F(1, 38) = 2.765$, $p = 0.11$, $\eta_p^2 = .068$ on Day 49., see Figure 15. However, there was a significant effect of time on CBI-B scores for both groups, with a decrease in CBI-B scores immediately after the intervention (Day 7) and a significant increase in CBI-B scores on Day 49, $F(2, 37) = 118.115$, $p<0.0001$, $\eta_p^2 = .865$, see Figure 15.

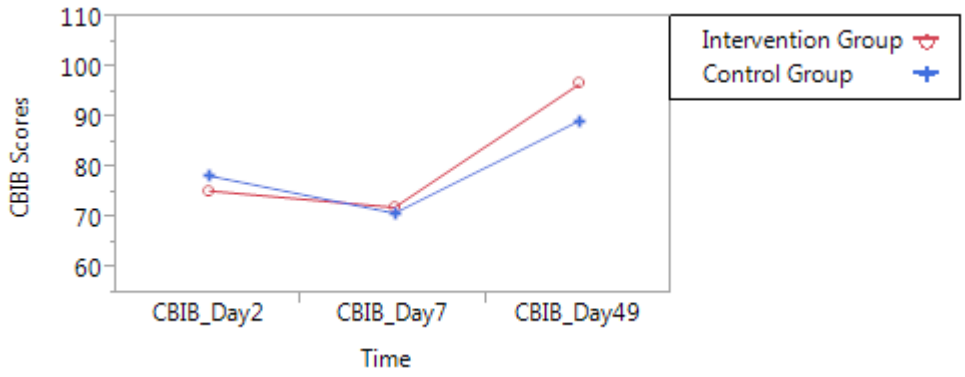



**Figure 15: Changes over time for CBIB scores in both groups over the six week intervention**

**Hypothesis seven.** Hypothesis seven was related to cortisol levels immediately after the intervention. Based on the literature, we expected an increase in stress immediately post-intervention (Day7). Hypothesis seven posited that CS participating in EW (treatment arm) would have higher levels of salivary cortisol, compared to CS participating in control-writing (control arm) at 24 hours post-intervention (Day 7). Hypothesis seven was not testable due to unavailability of data pertaining to cortisol for Baseline (Day 2) and immediately post-intervention (Day 7) due to resource constraints.

**Hypothesis eight.** An important aspect of this research study was that we wanted to establish the differential impact of EW on stress outcomes over time. The research literature related to EW suggests that there is an initial increase in stress since individuals to confronting pent-up emotions related to the stressful experiences and stressful life events. We wanted to demonstrate this by seeing how EW impacts stress outcomes immediately after the intervention. In hypothesis eight we expected an increase in stress immediately post-intervention (Day 7) as measured by physiological outcomes a-amylase, CRP (Hypothesis 8a) as well as by psychosocial outcomes PSS, FCRI-S, CBI-B (Hypothesis 8b)

Hypothesis 8a: α-amylase**.** In hypothesis 8a we anticipated that salivary α-amylase (sAA) levels measured at 24 hours post-intervention (Day 7) will be higher in the EW group

participants compared to CS participating in control-writing (control group). The mean sAA levels for both groups on days 2 and 7 of data collection are presented in Table 27 below.

**Table 27: Mean a-Amylase levels (Days 2 and 7)**

| Day | Intervention group (n=20) mean sAA U/ml (SD) | Control group (n=20) mean sAA U/ml (SD) |
|---|---|---|
| Day 2 | 1.15965 (0.73) | 0.7928 (0.74) |
| Day 7 | 1.52910 (0.75) | 0.89695 (0.83) |

Data indicated that baseline levels of sAA were higher in the EW group compared to the control group. The GLM for hypothesis 8a showed that α-amylase levels were higher in the EW group participants at Day 7 compared to the control writing group participants, F (1, 38) = 4.84, p=0.034, $\eta_p^2$ = .113, see Figure 16. However, this result could be attributed to preexisting higher levels of sAA in the EW group. A significant effect of time was also detected for α-amylase levels in both groups, and α-amylase secretion increased on 24 hours post-intervention (Day 7) as compared with their baseline (Day 2) levels, F (1,38)=8.145, p=0.007, $\eta_p^2$ = .177, refer to Figure 16.

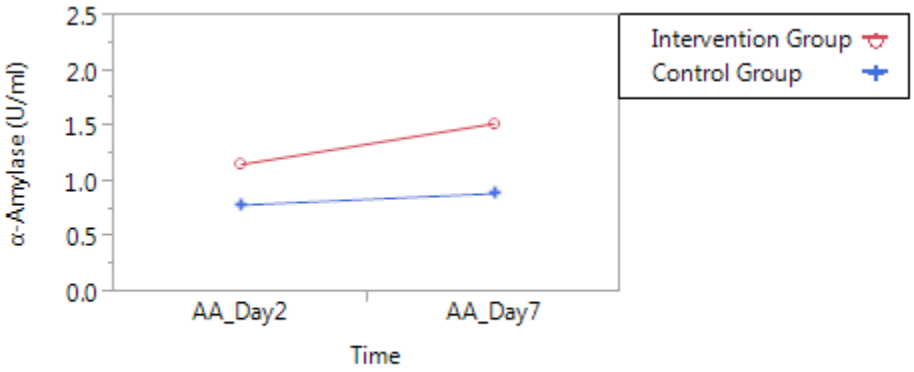



**Figure 16: Immediate post-intervention effects for salivary α-amylase (AA) levels**

Hypothesis 8a: CRP**.** In hypothesis 8a we also expected that increased stress immediately post-intervention would impact immune function by increasing inflammation in CS in the EW group and will result in higher levels of salivary CRP at 24 hours post-intervention (Day 7). The

mean CRP levels for both groups on days 2 and 7 of data collection are presented in Table 28.

**Table 28: Mean CRP levels (Days 2 and 7)**

| Day | Intervention group (n=20) mean CRP pg/dl (SD) | Intervention group (n=20) mean CRP pg/dl (SD) |
|---|---|---|
| Day 2 | 994.05 (455.12) | 1020.70 (581.84) |
| Day 7 | 1164.73 (571.38) | 1049.17 (575.99) |

Hypothesis 8a postulated that CRP levels at 24 hours post-intervention (Day 7) would be higher in EW group participants when compared with CS participating in control-writing (control group). The GLM for hypothesis 8a showed no significant difference in CRP levels between the EW and control group participants at 24 hours post-intervention Day 7, $F(1, 38) = 0.083$, $p=0.775$, $\eta_p^2 = .002$, see Figure 17. Results of the GLM also revealed that there was no impact of time on CRP levels for both groups at 24 hours post-intervention (Day 7), $F(1, 38) =1.561$, $p=0.22$, $\eta_p^2 = .039$, with both groups remaining close to their baseline CRP levels, see Figure 17.

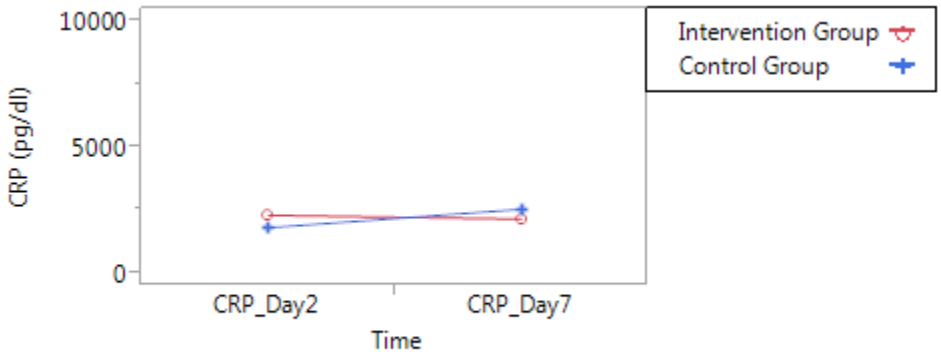



**Figure 17: Immediate post-intervention effects for salivary CRP levels**

Hypothesis 8b: PSS. The second aspect of hypothesis eight was related to the psychosocial outcome measures. The first of the psychosocial outcomes was perceived stress measured by the PSS. The mean PSS scores for both groups on days 2 and 7 of data collection are presented in the Table 29 below.

**Table 29: Mean PSS scores (Days 2 and 7)**

| Day | Intervention group (n=20) mean (SD) | Control group (n= 20) mean (SD) |
|---|---|---|
| Day 2 | 31.95 (5.32) | 31.05 (3.89) |
| Day 7 | 36.1 (2.69) | 35.65 (2.6) |

We anticipated an increase in perceived stress measured by the PSS in CS that participated in EW (EW group) compared to CS participating in control-writing (control group) at 24 hours post-intervention (Day 7). Results of the GLM test indicated no significant differences between the two groups with regards to PSS scores on Day 7, 24 hours post-intervention, $F(1, 38) = 0.64$, $p=0.43$, $\eta_p^2 = .017$, see Figure 18. However, the GLM did demonstrate that in both groups there was a significant increase in PSS scores from baseline (Day 2) to 24 hours post-intervention (Day 7), $F(1, 38) = 26.56$, $p<0.0001$, $\eta_p^2 = .411$, please see Figure 18.

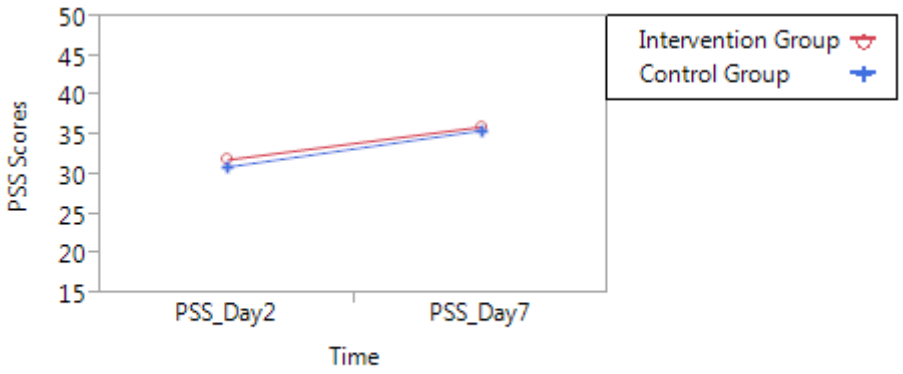



**Figure 18: Immediate post-intervention effects for PSS scores**

Hypothesis 8b: FCRI-S. The second psychosocial outcome measure in hypothesis eight was fear of cancer recurrence. The mean FCRI-S scores for both groups on days 2 and 7 of data collection are presented in the Table 30 below. In hypothesis 8b we expected an increase in fear of cancer recurrence (measured by FCRI-S) immediately after the expressive writing intervention (Day 7). Hypothesis 8b also postulated that FCRI-S scores at 24 hours post-

intervention (Day 7) would be higher in EW group participants compared to CS participating in control-writing (control group).

**Table 30: Mean FCRI-S scores (Days 2 and 7)**

| Day | Intervention group (n=20) mean (SD) | Control group (n= 20) mean (SD) |
|---|---|---|
| Day 2 | 24.4 (3.62) | 24.7500 (3.06) |
| Day 7 | 31.35 (2.37) | 30.85 (3.2) |

The GLM for FCRI-S scores at 24 hours post-intervention (Day 7) also reported that there were no significant differences between the two groups, $F(1, 38) = 0.011$, $p=0.92$, $\eta_p^2 = .92$, see Figure 19. Though, the GLM did describe that both the EW and control groups reported a significant increase in fear of cancer recurrence after the writing tasks, indicated by higher FCRI-S scores on Day 7 in comparison their baseline FCRI-S scores (Day 2) values, $F(1, 38) = 100.1$, $p<0.0001$, $\eta_p^2 = .725$, please see Figure 19 below.

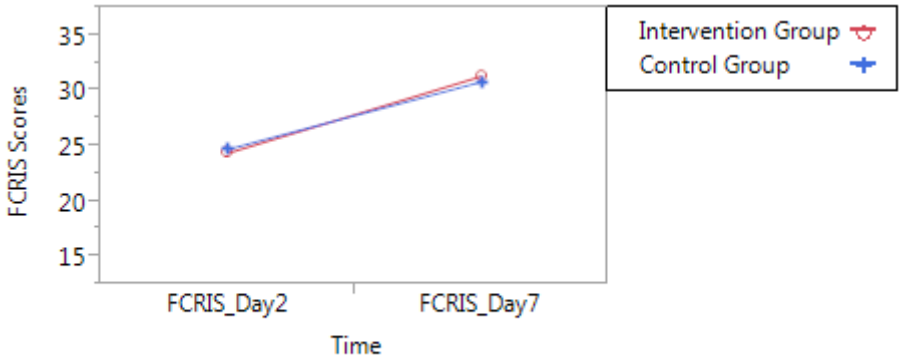



**Figure 19: Immediate post-intervention effects for FCRIS scores**

Hypothesis 8b: CBIB. Finally, the last psychosocial outcome was self-efficacy with coping with cancer measured by the CBI-B. In this hypothesis 8b, we expected to find a decrease in self-efficacy with coping immediately after the intervention due to the stress-induced from the EW. The mean scores for CBI-B for baseline (Day 2 ) and immediate post-intervention (Day 7) are reported in the Table 31 below.

**Table 31: Mean CBIB scores (Days 2 and 7)**

| Day | Intervention group (n=20) mean (SD) | Control group (n= 20) mean (SD) |
|---|---|---|
| Day 2 | 75.45 (6.67) | 78.45 (10.013) |
| Day 7 | 72.2 (3.43) | 71.05 (3.17) |

In hypothesis 8b we anticipated that EW participants (EW group) will have lower CBI-B scores compared to control-writing participants (control group) at 24 hours post-intervention (Day 7). The GLM test for this hypothesis also did not find any significant group differences with regards to CBI-B scores immediately after the intervention (Day 7), $F(1, 38) = 0.42$, $p=0.522$, $\eta_p^2 = 0.011$, see Figure 20. However, both groups showed a significant decrease in CBI-B over time, i.e. from baseline to immediately post-intervention, $F(1, 38) = 13.42$, $p=.001$, $\eta_p^2 = .261$, see Figure 20 below.

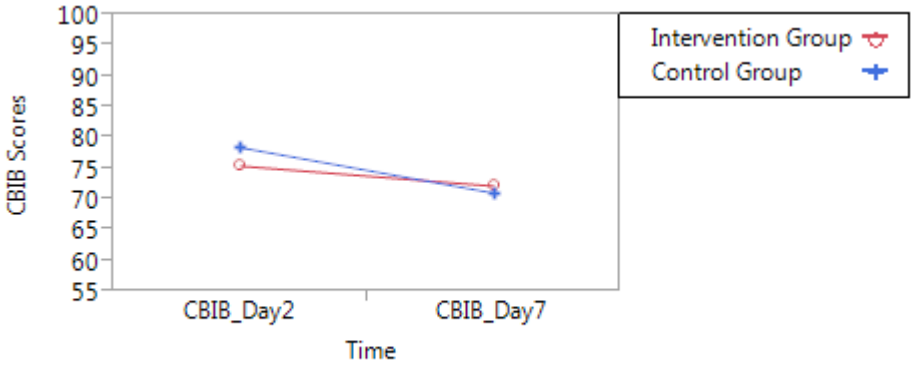



**Figure 20: Immediate post-intervention effects for CBIB scores**

## Chapter VII. Discussion

Chronic stress has been implicated in an array of negative impacts on the physical and mental health of individuals and is especially relevant to the cancer patients transitioning from completing their treatments to reassuming their roles in their family and work environments, defined as cancer survivors in this study. We conducted a two-arm randomized controlled trial (RCT) to determine the efficacy of expressive writing as a stress-management intervention for cancer survivors who were 2-12 months post-radiation treatment completion. The theoretical framework for this study was psychoneuroimmunology (PNI), which guided our choice of health outcome measures, that included salivary biomarkers of the neuroendocrine and immune systems as well as psychometric measures of psychosocial function. The results of this study revealed that expressive writing was effective in regulating stress over a period of six weeks in our samples of cancer survivors. Expressive writing (EW) is a very brief and inexpensive psychosocial intervention that can help manage stress in cancer survivors (CS). Results from this study have important implications for theory, practice and future research with regards to PNI-based psychosocial interventions such as EW in the growing population of CS worldwide.

### Aims and Hypotheses

This research study had five major aims and eight related hypotheses. The first three aims of this study were related to determining the delayed neuroendocrine and immune effects of EW for our sample of cancer survivors (CS) which were measured six weeks post-intervention (Day 49). The fourth aim was to determine the delayed impact of EW on the psychosocial outcomes of CS which were measured six weeks post-intervention (Day 49). The last aim of this study was to investigate the immediate post-intervention psychobiological effects of EW on CS which were measured immediately post-intervention (Day 7).

**Aim one: Hypothesis one**. The first aim of this study was to determine the effectiveness of EW to regulate stress in cancer survivors as measured by salivary cortisol levels which was the biomarker chosen to indicate HPA axis activity and the primary outcome for this study. In the first hypothesis we expected to find that CS that completed EW would have lower levels of salivary cortisol compared with CS that completed control writing when measured six weeks after completing the writing intervention. The EW literature indicates that EW's beneficial health impacts take effect after a period of approximately 6-8 weeks post-intervention[126]. During the 6-8 week period after completing their EW writing tasks, participants process the negative emotions and stressful experiences brought to their attention by EW as well as experience desensitization from repeated exposures to their emotions[128]. This emotion processing helps decrease arousal of the HPA axis and subsequent regulation of neuro-hormonal physiological stress responses of EW participants[137]. Results from our study demonstrated that EW successfully affected the HPA axis of CS in our sample as shown by significantly lower levels of salivary average cortisol secretion (area under the curve, AUC) and cortisol awakening response (CAR) in the EW group CS compared to CS in the control writing group at six weeks post-intervention.

Furthermore, results from this study report medium to large effect sizes (ES) for our online EW intervention with regards to our primary outcome variable, salivary cortisol (r=0.43 for AUC; r=0.45 for CAR) in a sample of CS post-radiation. The ES obtained in this study are equal to and even greater than those reported in the three key meta-analyses of EW interventions that we used for our sample size and power calculation (r=0.21 in healthy samples[126], r=0.1 in clinical samples[127] and r=0.075 based on wide ranging group of EW studies[128]. Salivary cortisol is an objective biomarker of stress and has been extensively studied by researchers[163]. This study

is an important contribution to the literature which demonstrates that EW is a brief and low-cost intervention that successfully reduced stress in CS which was objectively measured in saliva and which can be made readily accessible to a wide range of cancer patients and survivors through the internet. This study also lends support for the evidence-base with regards to the neuroendocrine effects of EW's stress-regulation mechanism of action[41]. In our literature review we noted that several studies of psychosocial interventions, including EW interventions, only mentioned the PNI framework as a mechanism of action without actually measuring corresponding PNI biomarkers[197]. This study will fill an important gap in the literature since this is one of the first studies of an online EW intervention in the cancer survivor population to report significant effects for neuroendocrine outcomes.

However, the results for our primary outcome should be viewed with restraint since we did not have the measures for baseline and immediate post-intervention for salivary cortisol. Thus, data for the six week post-intervention outcome measures does not reflect the correlations for repeated measures. Also, with respect to salivary cortisol, only AUC and CAR were significantly lower in the EW group compared to the control writing, however cortisol diurnal slope (DCS) was not significantly different for both groups. Previous studies have suggested that patients with comorbid psychological problems such as depression can have flatter and less responsive DCS profiles[198]. Further research is needed to investigate the DCS profile of the CS population and relationships between salivary AUC, CAR and DCS for CS post-radiation. Finally, though the delayed stress-regulating effects of EW are well-documented in the literature[128], however we still do not know how long these effects last. Future EW studies should incorporate more delayed post-intervention measures, e.g. 3 and 6 months post-intervention.

**Aim two: Hypothesis two**. In the second aim of this study we wanted to determine the effectiveness of EW to regulate stress in CS as measured by salivary α-amylase levels which was the biomarker chosen to indicate SNS activity. In the second hypothesis we anticipated that EW participants would have lower levels of salivary α-amylase (sAA) compared with participants that completed control writing measured at six weeks post- intervention. The rationale for hypothesis two was that we expected EW to have a delayed stress- regulating impact on the SNS similar to EW's effect on the HPA axis (hypothesis one) However, results for hypothesis two were opposite to what we had anticipated, and CS in the EW group had significantly higher levels of sAA compared to control writing participants at 6 weeks post-intervention. However, the data indicated that baseline levels of sAA were higher in the EW group compared to the control group. Therefore, the difference in sAA between the groups at Day 49 could be attributed to higher baseline levels of sAA, which plateaued after the expected increase in stress immediately after the EW intervention (Day 7).

Also, the SNS is a more rapid stress-response pathway responsive to acute stressors in contrast to the HPA axis which is involved in a more gradual and delayed stress response[166]. Therefore the SNS is more susceptible to be influenced by a range of stressors in the immediate physical and social environment of participants such as temperature or daily stress of commuting to and from work. Additionally, SNS reactivity is known to have individual variation in individuals with respect to acute and chronic responses. Thus, the higher sAA levels of the CS in the EW group at six weeks post-intervention may not be reflective of a response to the writing intervention. Also, sAA data with regards to average sAA secretion was not available for all three days that salivary data was collected. Future research is needed with regards to the impact of stress-regulation interventions on sAA and SNS activity. Researchers also need to examine

differential relationships between responsiveness of HPA axis biomarkers and SNS biomarkers to acute stress and chronic stress stimuli.

**Aim three: Hypothesis three.** In the third aim of this study, we wanted to determine the impact of EW on the immune system of CS as measured by salivary C - reactive protein (CRP) levels. CRP is an acute-phase response protein that is a biomarker of inflammation in the immune system. We expected to find lower CRP levels in CS that participated in EW compared to those participating in control writing at six weeks post-intervention. The rationale for hypothesis three was similar to the first and second hypothesis, where we expected EW to influence delayed neuroendocrine regulation in CS over six weeks, would in turn decrease inflammation in the immune system as measured by lower salivary CRP. The study results indicated that there was no impact of EW on CRP levels of CS, and participants in both groups, EW and control writing, had similar levels of CRP at six weeks post-intervention. CRP levels are also affected by a range of other conditions such as cardiovascular disorders, infections and inflammation and shares a complex relationship to glucocorticoids such as cortisol[199]. Moreover, the immune profiles of cancer patients and CS are affected in very complex ways due to treatments and the cancer itself.

The absence of an effect of EW on salivary CRP levels of CS in our sample could be due to 1) the CRP levels in the CS were sustained due to post-radiation inflammation, or 2) EW may exert a selective impact on the HPA axis activity, which may not have a mediating or moderating influence on inflammation in the immune system. This was one of the first EW studies to incorporate CRP as an outcome measure in the cancer population. A recent study of a psychosocial intervention in a population of youth in foster care showed a significant decrease in salivary CRP after the intervention[200]. Also, research indicates that cortisol exerts a

downregulating influence on CRP levels in populations faced with pneumonia and respiratory disorders[201]. Our study found no impact of EW on salivary CRP levels of CS post-radiation over six weeks. Thus more psychosocial interventions in the cancer population need to measure salivary CRP to assess CRP's responsiveness as well as determine the correlation of salivary CRP levels with levels of CRP in blood and other measures of the immune system that include functional immune measures such as cytokines and immune cell counts such as T lymphocyte counts. Future observational studies should also investigate the association between levels of glucocorticoids such as cortisol on levels of CRP in cancer patients, as well as in healthy individuals.

**Aim four: Hypothesis four**. The fourth aim of this study was to determine the efficacy of EW to impact psychosocial functioning in CS as measured by scores on self-report questionnaires: a) PSS (perceived psychological stress), b) FCRI-S (negative emotion), and c) CBI-B (efficacy for coping with cancer). Data for aim four was tested in three hypotheses, for each self-report outcome measure, i.e. PSS, FCRI-S, CBI-B. In hypothesis four, we expected to find lower PSS scores for the EW group compared to the control group on Day 49. Results were contrary to what we predicted, and in hypothesis four we found no significant differences between the EW and control writing groups with regards to scores on the perceived stress scale (PSS). However, the data showed that that in both groups, there was a significant effect of time and PSS scores increased immediately after the intervention followed by a significant decrease at six weeks post-intervention. This impact of time on perceived stress in CS could be attribute to the PSS scale and the natural impact that time has on stress and coping.

The PSS is an extensively used measure of stress which assesses the degree to which the participants regard their life circumstances to be stressful[180]. In this study, the PSS assessed more

global factors leading to stress such as how unpredictable, or overloaded the CS found their lives to be. Research indicates that CS gain coping skills and strategies as they transition through survivorship and these are incremental gains across the survivorship phase. Previous studies of EW have also demonstrated that EW initially increases perceived stress in participants immediately after the intervention which is followed by a delayed decrease (over a period of 6-8 weeks) in perceived stress[128,202]. Thus, decrease in PSS scores for both groups at the end of the intervention could be attributed to the natural coping strategies that CS adopt over time to cope with life stressors while reassuming their roles in their family and workplace. Also, the EW literature suggests that EW's mechanism of action is backed by research evidence with regards to only specific dimensions of psychosocial functioning, such as emotion regulation and cognitive restructuring, while excluding others such as stress perception and coping[137,203]. Future studies of EW should employing more precise measures of stress as they relate to EW's mechanism of action.

**Aim four: Hypothesis five.** The fifth hypothesis of this study was related to determining the efficacy of EW to regulate negative emotions, specifically the fear of cancer recurrence in CS. In the fifth hypothesis we aimed to generate evidence for EW's emotion regulation mechanism of action by demonstrating a decrease in the severity of a relevant and specific emotion for our sample of CS, which was fear of cancer recurrence (measured by the FCRI-S). As anticipated by our study, the EW group reported significantly lowered fear of cancer recurrence (FCR) compared to the control writing group at six weeks post-intervention. Results for hypothesis five is an important finding as this was one of the first studies of EW in the cancer population to measure the severity of a relevant negative emotion, i.e. FCR which particularly affects CS, and demonstrate that EW was effective in reducing the severity of that negative

emotion. This study will be a significant contribution to the EW and psycho-oncology literature since very few psychosocial intervention studies in the cancer survivor population have been conducted that have evaluated and assessed severity of FCR.

The fear of cancer recurrence is one of the most frequently reported problems in CS[181]. The research literature indicates that FCR is currently an important area of unmet psychosocial needs for CS[1]. The American Cancer Society website reports that CS commonly express concerns with regards to FCR, especially immediately after completion of treatments[204]. For example, the stress and tension induced by FCR is illustrated in the following story of a CS,

> I feel like if I knew my exact chances of the cancer coming back, I could deal with it. But when I ask my doctor, he gives me a range of statistics over a number of years. I can't live like this. I need more specifics[205].

In previous research conducted by the first author, a CS expressed her fear of cancer recurrence metaphorically such as, "Because parathyroid cancer has such a high recurrence, it's like having a Rottweiler on a short leash. Right now, I'm fine, but wary, always wary[206 (p.62)]." Both these narratives from CS describe a constant sense of uncertainty and fear with regards to cancer returning, but what both CS truly wished to know was that their cancer would never come back.

With a growing CS population in the United States and the world over, FCR is an important psychosocial stressor that needs to be extensively researched. Further research is needed with regards to the dimensions of FCR as well as the management of FCR throughout survivorship . Future studies should incorporate measures of FCR and include specific activities in psychosocial interventions e.g. FCR management in cognitive behavioral therapies (CBT) and coping strategies for CS to manage FCR immediately post-treatment as well as over the rest of their lifespan. This study provides evidence for the use of EW, a simple and inexpensive

psychosocial intervention, for reducing FCR in the CS population. Another approach for managing FCR could be providing CS with regularly updated information with regards to cancer survival rates. Finally, epidemiological studies are also needed to provide information with regards to the prevalence, severity and impact of FCR in the cancer survivor population.

**Aim four: Hypothesis six.** The sixth hypothesis was pertaining to the impact of EW on CS self-efficacy for coping with cancer. The EW research literature suggests that writing about ones deepest thoughts and emotions over four days gives EW participants repeated exposure to stressful stimuli[137]. During the practice of writing ones thoughts and feelings, participants gain a psychological distance from where they can process their thoughts and emotions as well as confidence for managing their emotions when they resurface[207]. Thus, we posited that EW would enhance CS self-efficacy for coping with cancer (measured using the CBI-B) over the period of six weeks post-intervention. The results from the analyses revealed that there were no significant differences between the EW group and control-writing groups with regards to CBI-B scores at six weeks post-intervention. However, there was a significant effect of time for CBI-B scores in both groups and the data indicated that there was a significant decrease in CBIB-B for both groups immediately after the intervention (Day 7) followed by a significant increase in CBI-B scores immediately after the intervention. The results for hypothesis six for CS self-efficacy for coping with cancer (CBI-B) followed a similar pattern to the results for hypothesis four (PSS).

Increases in CBI-B scores for both groups at the end of six weeks could be attributed to similar mechanisms that resulted in lower PSS scores for both groups at the end of six weeks. Majority of participants in both groups (EW and control writing) were CS who had completed their final radiation treatment six to eight months prior to being enrolled in this study. This phase has been referred to as the re-entry phase of cancer survivorship, since CS must reenter their

previously disrupted family and work lives[12,15]. During this transition phase, cancer survivors are known to experience stress with regards to reassuming their life roles and dealing with daily stressors[1]. During this transition period CS must also adopt coping skills and strategies over time to handle their daily responsibilities and life roles. The data for this study indicated that both, the EW and control writing groups, reported a significant increase in self-efficacy for coping with cancer (and significant decrease in perceived stress) six weeks after completing their intervention. Therefore, CS in both groups could have acquired coping strategies over the six weeks following their writing tasks and experienced increased self-efficacy for coping with cancer (CBI-B scores) and lower perceived stress (PSS scores) at the end of the six week period. Another possible reason for both groups to have experienced an increase in self-efficacy for coping with cancer (and lower perceived stress) could be that the control writing intervention inadvertently provided CS with coping skills. The control writing condition asked CS to write how they spent their time on four days, this writing task could have provided CS with practice with regards to listing their daily chores, activities and stressors. Thus CS in the control writing group could unintendedly have learned coping skills during their control writing tasks. Future longitudinal studies are required in the CS populations which can determine the specific coping strategies and psychosocial approaches that CS adopt over time across the survivorship phase.

**Aim five: Hypothesis seven.** The fifth aim of this study was related to eliciting the effects of EW on CS stress levels immediately after the intervention. The EW research literature consistently indicates that EW increases stress in participants immediately after the writing tasks[128,208]. In hypothesis seven we expected to see higher levels of salivary cortisol in the EW group compared to the control-writing group. However, hypothesis seven was not testable due to the unavailability of data for baseline and immediate post-intervention salivary cortisol due to

resource constraints, and was the only study hypothesis that was not tested.

**Aim five: Hypothesis eight.** In the final hypothesis of this study we wanted to determine the effect of EW on the secondary physiological outcomes (α-Amylase and CRP; hypothesis 8a) and the secondary psychosocial outcomes (PSS, FCRI-S and CBI-B; hypothesis 8b) of interest immediately after the intervention (Day 7). The literature consistently reports that EW increases stress during the intervention period[128]. In the course of completing the EW writing tasks, participants re-experience their past stressful events and bring back to attention the negative emotions associated with those stressful experiences. Therefore, EW participants are expected to have increased psychosocial stress immediately after the EW intervention. This increase in psychosocial stress in turn stimulates the HPA axis leading to secretion of stress hormones as well as autonomic arousal and increased SNS activity[209]. Previous meta-analyses of EW have reported small to medium effect sizes with regards to its post-intervention impacts on physical and psychological outcomes[126-128]. In this study, we expected that on Day 7, the EW group will have higher salivary α-Amylase and CRP levels (physiological outcomes) and higher PSS and FCRI-S scores and lower CBI-B scores (psychosocial outcomes) in comparison to the control writing group.

The results for the physiological outcomes for hypothesis eight showed that α-Amylase was found to be significantly higher in the EW group compared to the control group immediately after the intervention (Day 7). However, the data showed that α-Amylase was higher in the EW group at baseline. Hence the difference in α-Amylase levels between the EW group and control groups at Day 7 could be due to the preexisting higher levels of α-Amylase in the EW group. Salivary α-amylase is a reflection of the immediate SNS response to stressful stimuli in human beings and is correlated with other acute stress hormones such as adrenaline. The bio-behavioral

research literature indicates that short-term stressors typically increase salivary α-amylase levels in healthy as well as clinical populations[164,166]. Although, α-Amylase levels rose on Day 7 in the EW group compared to the control group, no conclusive statement could be made regarding the SNS reactivity of our sample to the EW intervention. Additional data regarding changes to α-amylase levels during the day (e.g. diurnal variation) would have provided a clearer picture of the SNS reactivity of the CS in our sample to EW. Future studies of EW should further investigate EW's impact on SNS reactivity by employing measures similar to salivary α-amylase, e.g. adrenaline.

The second physiological outcome in hypothesis eight was salivary CRP. We assumed that EW would increase CRP levels in CS immediately after the intervention based on the fact that CRP is an acute phase response protein which increases within a couple of hours after the onset of inflammation[210]. The results indicated there was almost no change in CRP levels for both groups after completing their intervention. These results indicate that CRP may not be responsive to short-term increases in stress. It is noteworthy that both salivary α-amylase and CRP are new biomarkers in PNI research and more data are needed with regards to mediators and moderators of their salivary secretion patterns. Also, further data are needed with regards to the sensitivity and specificity of salivary α-amylase and CRP and their correlation with other biomarkers of stress and inflammation. Future research is needed with regards to EW's influence on CRP levels in healthy and clinical populations, e.g. cardiovascular disorders.

The results for the psychosocial outcomes for hypothesis 8 showed that both groups, EW and control writing, experienced a significant increase in perceived stress (higher PSS scores) and fear of cancer recurrence (higher FCRI-S scores) immediately after the intervention (Day 7). Results also described that both groups, EW and control writing, reported a significant decrease

in self-efficacy for coping with cancer (lower CBI-B scores) immediately after the intervention (Day 7). We had expected to find the changes in the psychosocial outcomes for CS in the EW group only. A possible explanation for increases in perceived stress and fear of cancer recurrence (FCR) in both groups could be that the questions in the surveys may have sensitized CS to experience stress and negative emotions. For examples the FCRI-S asked questions such as, "how often do you think about the possibility of cancer recurrence?" Answering questions pertaining to stressful experiences and emotions can trigger those negative emotions in the minds of participants. Since both participants answered the surveys at baseline (Day 2) and immediately after the writing intervention (Day 7), participants in both groups could have been sensitized to increased stress and FCR. Having increased in stress and FCR could also explain the inverse decrease in self-efficacy for coping with cancer found in both groups on Day 7. Further research is needed with regards to EW's differential impact on specific psychosocial outcomes immediately after the intervention. We recommend future EW studies to include psychosocial outcomes that are closely aligned with aims of the intervention, for example in our study we measured of severity of emotions (FCR) that were relevant to our study sample (CS).

Overall, the results from the aims and hypothesis provided partial support for our theoretical model which posited that EW would have a stress-regulating impact for CS as measured by their PNI outcomes. The results of this study cannot be interpreted as confirming or disconfirming EW's stress-regulating capacity, but instead as offering evidence for particular assumptions while raising questions about others. Specifically, we found evidence for EW's ability to impact cortisol secretion in saliva (HPA axis) and reduce fear of cancer recurrence in CS during a six week period after the intervention. We support existing consensus in the literature with regards to EW's initial stress-inducing impact on participants immediately after

the writing tasks, which is followed by a delayed stress-regulating influence over a six week period[128,211]. Almost three decades of research have provided consistent evidence for EW as a short-duration and low-cost intervention that can be easily administered to a variety of clinical populations[128]. EW seems even more attractive with the advent of the internet and EW's adaptability to technology. However, more research evidence is required in the literature with regards to the theoretical aspects of EW's mechanisms of action. This study lends support for the emotion-regulation theory for explaining EW's stress-regulating effects.

**Expressive Writing and Psychoneuroimmunology: Implications for Theory**

A critical aspect of this study was that we wanted to understand the stress-regulating effects of EW from the theoretical perspective of PNI. This study is one of the first studies that employed outcome measures for all three parts of the PNI framework, which were the psychosocial (P), neuroendocrine (N) and the immune (I) systems. The results of this study partially supported the tripartite PNI theoretical model, see Table 32. In the first part, we anticipated that through the process of emotion regulation, EW would help CS regulate negative emotions (FCR). In the second part, we posited that emotion regulation impact CS neuroendocrine response (from the HPA axis and SNS). In the third part, we expected that neuroendocrine regulation would decrease inflammation in the immune system. We discuss finding from our study with respect to each part of the PNI theoretical framework.

**EW and psychosocial function: Emotion-regulation.** The disclosure literature as well as other clinical studies describe that EW facilitates emotion regulation through two main processes, namely emotional habituation and cognitive reappraisal of emotions[137]. Emotional habituation refers to the concept that during EW, participants repeatedly confront their negative emotions regarding stressful experiences, thereby the physiological and possibly the perceived

intensity of those negative emotions decreases over time[137]. Empirical studies of EW in the patients having post-traumatic stress disorder (PTSD) indicate that in effective habituation, participants initially experience strong negative emotions, with decreases in negative emotion within and across writing sessions[212-214]. Results for this study lend evidence for the emotion habituation component of EW's emotion-regulation mechanism of action. Participants in this study reported a significant increase in FCR immediately after their four day writing tasks, and then a significant decrease in FCR across 6 weeks. Thus, CS showed habituation by first experiencing high FCR after their writing and subsequently having significantly decreased FCR after 6 weeks. This is one of the first studies of EW to measure the intensity of a negative emotion (FCRI-S) that is specific to a cancer population (CS). We suggest future EW studies to adopt population specific measures of the intensity of negative emotions and demonstrate habituation by collecting longitudinal data.

The second component of emotion-regulation theory involves the cognitive reappraisal of emotions. The cognitive reappraisal of emotions describes that during EW, participants must actively face and process negative emotions which could strengthen their self-efficacy for managing those negative emotions[137,215]. Also, EW provides participants with psychological distance to view their stressful experiences and a lens from which they can observe themselves better understand, validate and accept their emotional reactions and to those stressful experiences[137]. Previous research of supportive-expressive group therapy for cancer patients has reported that disclosing emotions related to their cancer and fears of dying during group therapy sessions improved cancer patients self-efficacy to manage those emotions[216]. In this study we found that inconclusive results with regards to EW's ability to improve cancer patients self-efficacy for coping with cancer (measured using the CBI-B). However, the data did indicate a

significant effect of time on self-efficacy for coping with cancer. CS who participated in EW had lower CBI-B scores immediately after the intervention and significantly higher CBI-B scores six weeks after completing EW. This study lends limited support to the cognitive reappraisal component of EW's emotion regulation mechanism of action. Future studies of EW should incorporate measures of self-efficacy for managing emotions and test the duration to which EW helps participants improve self-efficacy for coping with cancer.

**EW and neuroendocrine function: HPA axis and SNS.** The psychophysiological effects of EW have been well documented in an extensive body of research[128]. EW has been shown to have wide-ranging effects on the nervous system and related hormones and neuropeptides as well as associated effects on the cardiovascular system[217]. Research evidence demonstrates that EW affects cortisol and epinephrine secretion, heart rate, blood pressure and heart rate variability[127]. The most extensively studied stress-response pathway in PNI research has been the HPA axis[218]. In this study we employed salivary cortisol as our primary outcome measure indicating HPA axis activity. Based on findings in previous research, we expected that EW would manifest its stress-regulating effects in CS over a period of six weeks. The results from this study showed that EW was successful in regulating the stress-response from the HPA axis in CS demonstrated by significantly lower salivary cortisol levels in EW group CS compared with control writing group CS. This study provides support to the growing evidence-base for EW's neuroendocrine effects.

The impact of EW on the HPA axis can be explained as a resulting effect of the emotional habituation described above. The evolution of the HPA axis is specifically related to fear and the fight or flight response[219]. Human beings evolved the fight or flight response to deal with stimuli that threatened our survival during early evolution, such as wild animals. This

neurobiological fight or flight response is activated by fear emotions leading to chronic stress which keeps the HPA axis activated. This leads to higher levels of blood cortisol which has negative impacts on multiple systems in body including the immune system. During EW participants repeatedly confront and re-experience their negative emotions which leads to desensitization and habituation. Also, EW helps participants gain more self-efficacy to manage their emotions. This study demonstrated that EW significantly lowered the negative emotion of FCR as well as lowered cortisol in CS over a period of six weeks, see Table 32. This study is an important contribution to the literature which demonstrates in the same study that EW was effective in regulating negative emotions (FCR) as well as HPA axis activity which will further our understanding of EW's mechanism of action. Future studies should investigate dose-response effects of EW intervention on the HPA axis.

Evaluating dose-response effects of EW on the HPA axis. Studies of other psychosocial interventions involving emotional disclosure such as supportive expressive-group therapy and cognitive behavioral stress management (CBSM) have shown that emotional expression has been successful with reducing serum cortisol levels in cancer patients[95,220]. Moreover, participants that had greater involvement in emotional expression (e.g. lower repressive defensiveness and greater expression of negative emotions) during group therapy had steeper cortisol slopes among metastatic breast cancer patients[78,221,222]. Meta-analyses of EW have also indicated to a dose-response association between EW and health outcomes[127,128]. This study supports previous research indicating that the HPA axis is most responsive to psychosocial interventions[208,223]. An average dose-effect of EW was not estimated in this study since limited measures were employed to reduce patient burden. Moving forward, quantitative evidence is needed with regards to dose-response associations between a) type of EW intervention, b) extent of involvement in EW, c)

duration of EW intervention and d) PNI outcomes, that can help guide clinical decisions regarding implementing EW in the therapeutic setting. Therefore, future studies should employ data collection procedures to assess dose-response effects of EW interventions in persons with cancer.

An innovative aspect of this study was that we also measured the impact of EW on the SNS by assessing salivary α-Amylase in CS. However, data revealed no significant stress-regulating effects of EW on salivary α-Amylase in CS. As described above, this may have been because the SNS is a pathway that is more responsive to acute stress and not as responsive to chronic stress stimuli. This finding suggest that perhaps EW's habituation and cognitive restructuring may be psychological mechanisms that are successful in reducing burden from chronic stress stimuli such as FCR and not acute stress stimuli. However, EW studies in healthy participants have demonstrated that the cardiovascular system, which is innervated by the SNS, is response to EW[224]. The negative results with regards to sAA in our study may also be attributed to the fact that sAA is a relatively new biomarker in bio-behavioral clinical research and data regarding its sensitivity and specificity needs further investigation. Further research is needed with regards to EW and SNS activity and we encourage researchers to use biomarkers of both HPA and SNS axes to provide a comprehensive picture of EW and stress reactivity.

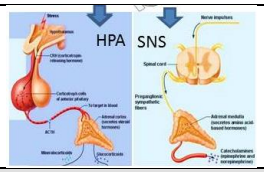
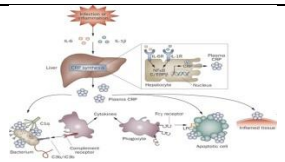
**EW and immune function: Inflammatory response.** Studies of EW have shown to impact all aspects of the immune system. Major advances in immunology research over the past decades have allowed researchers to measure various components of the immune system. At the broadest level, the immune system in humans consists of a) innate immunity, which includes cells (e.g. natural killer cells) inherently present to provide an immediate, but non-specific response against toxins or microorganisms, and b) adaptive immunity, which adapts its response

to the specific toxins or microorganism to improve detection and has two components, namely humoral immunity (mediated by antibodies generated by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes). The earliest research evidence with regards EW's impact on the immune system comes from the landmark EW study in college students that demonstrated that EW increased the mitogen-induced T-lymphocyte responses (adaptive immunity: cell-mediated)[130]. Similarly, other studies of EW in college undergraduates have found immune impacts of EW on antibodies against Epstein-Barr virus (EBV) and hepatitis B antigens, as well as in HIV positive patients EW demonstrated an increase in $CD^{4+}$ T lymphocytes (adaptive immunity: humoral)[131-133]. With regards to EW's impact on innate immunity, research has found that an EW intervention in patients with depression and anxiety patients decreased natural killer (NK) cell activity (innate immunity: NK cells)[225].

However, due to the complex nature of the immune system it is difficult to establish whether EW can actually enhance or boost immune function but rather that EW has the ability to influence immune behaviors in varied ways. Additionally, due to the heterogeneous immune profiles of EW study populations makes inferences regarding EW's impact on immune function problematic. For example, cancer patients and CS have different immune profiles than HIV+ patients and healthy individuals and the results of EW's influence on different immune profiles may not comparable. Results from this study indicate that EW was unsuccessful in affecting the immune system of CS which was measured by salivary CRP. Although CRP has been regularly used as an measure of inflammation, testing CRP levels in saliva is a relatively new biomarker of the immune system. CRP is an acute phase reactant and is considered to be a link between innate and adaptive immune systems. Further research is needed with regards to EW's influence on the immune pathways of cancer patients and CS. Past research indicates that participants that had

greater involvement in the EW disclosure process had a greater immune response. Future studies need to specifically explore the extent to which participants involve themselves into the EW process as well as individual differences in immune profiles of participants.

**Table 32: Expressive writing and the theoretical framework of PNI**

| **Psychosocial Intervention** | **Theoretical framework of Psychoneuroimmunology (PNI)** | | |
|---|---|---|---|
| | **Psychosocial (P)** | **Neuroendocrine (N)** | **Immune (I)** |
| Expressive Writing | Psychosocial Stress | Neuroendocrine system | Immune system |
| **BOM (Day 2)** | **Respective Outcome Measures** | | |
| **Writing (Day 3)**<br>**Writing (Day 4)**<br>**Writing (Day 5)**<br>**Writing (Day 6)** | PSS<br>FCRI-S<br>CBI-B | Cortisol<br>α-Amylase | C-Reactive Protein (CRP) |
| | **Possible Mechanisms of Action** | | |
| **POM1 (Day 7)** | **Emotion Regulation** | **Regulation of neuro-hormonal response from HPA and SNS axes** | **Regulation in secretion of inflammatory molecules of the immune system** |
| | **Habituation/ Desensitization** / **Insight** |  |  |
| **POM2 (Day 49)** | **Results after the intervention[14]** | | |
| | **Psychosocial**<br>**(X) PSS**<br>**(↓) FCRIS**<br>**(X) CBIB** | **HPA Axis**<br>**(↓) Cortisol** | **SNS Axis**<br>**(X) Amylase** | **Immune system**<br>**(X) CRP** |

[14] (↑) Significantly higher or (↓) significantly lower in intervention group compared to control group
(X) No significant differences between intervention and control groups

**Recommendations for validating the PNI causal framework.** This study provided partial support for the theoretical framework of PNI to explain the effects of the psychosocial intervention, EW in our sample of CS, see Table 32. In order to advance the science and theory of psychosocial interventions such as EW it is critical for researchers to understand the mechanisms of action of psychosocial interventions by using PNI as a causal theoretical framework. In general, we encourage researchers in this field to pay greater attention to methodological and implementation aspects of PNI-based psychosocial interventions for cancer patients and survivors. We suggest that future studies of EW and other psychosocial interventions can improve validity of evidence for the PNI causal theoretical framework by 1) employing outcome measures related to PNI processes, 2) defining the direction of change in PNI outcomes, 3) demonstrating statistical interactions between PNI subsystems, 4) accounting for missing data for PNI biomarkers, 5) collecting data regarding integrity of biomarkers collection procedures, 6) preventing publication bias: reporting negative results.

1. Employing outcome measures related to PNI processes. In the literature review for this study we noted that very few studies of psychosocial interventions specifically used outcome measures that were the focus of their intervention, such as the insomnia management cognitive-behavioral intervention.[121] In studies of PNI-based psychosocial therapies, different types of psychosocial factors may trigger differential PNI responses and several other external factors can influence the findings of a particular study[69]. An innovative aspect of this study was that we employed relevant outcome measures for all three parts of the PNI framework and measured the impact of EW on both the HPA axis and SNS. We recommend future studies also employ PNI measures associated with the specific aims of the study and measure all three aspects of the PNI framework. This will provide research evidence for PNI as a causal theoretical framework for the

stress-regulating effects of psychosocial interventions such as EW. Testing all three parts of the PNI framework will also assist future reviewers who can collectively appraise findings across studies that use PNI process related outcomes and provide a comprehensive understanding of the PNI effects of psychosocial intervention across cancer populations including cancer survivors.

2. Defining the direction of change in PNI outcomes. In our literature review we noted that some studies did not clearly report the direction in which they expected their PNI outcome measures to change. Postulating a trend in PNI outcomes is difficult in the cancer population, because factors such as stage of disease and treatment variations (e.g. chemotherapy vs. radiation) can affect PNI measures, particularly immune outcomes.[90,226] In this study we defined the direction of change for each PNI outcome measure and conducted one-tailed hypothesis testing. However, as explained above the neuroendocrine-immune systems are very complex to interpret and future intervention studies using PNI outcomes should clearly define the expected direction of change with regards to neuro-immune outcomes. Also, large scale epidemiological evidence for the normal average levels of PNI measures across specific populations is needed to enable researchers to make decisions about the expected direction of change in PNI outcomes.

3. Demonstrating statistical interactions between PNI subsystems. In this study we conducted statistical analyses to determine average differences in PNI outcome measures between the EW group and control groups. Due to limitations with regards to study design, we did not conduct statistical analyses to test for interactions among the three subsystems of the PNI framework. Recent advances in statistical modeling (e.g., structural equation modeling and hierarchical linear modeling) can help researchers make better inferences with regards to interactions among multiple variables and components of PNI framework. We recommend future researchers identify mediators and moderators of the PNI outcomes of psychosocial interventions

to understand their mechanisms of action.[207,227] Forthcoming studies of psychosocial interventions should attempt to demonstrate changes in psychosocial outcomes measures to predict changes (or show associations) in neuroendocrine-immune biomarkers over time to provide evidence for their mechanism of action. Studies should also attempt to measure the strength of association between level of participation in psychosocial interventions (e.g. extent of involvement in disclosure interventions) and PNI outcomes.

4. Accounting for missing data for PNI biomarkers. In this study we did not encounter any significant missing data with regards to completing the saliva measures for testing PNI biomarkers. However, we did encounter problems with maintaining our original sample size, which has also been reported in other studies of PNI-based psychosocial interventions, where studies were able to collect PNI biomarkers from only a smaller subset of their original sample. Having a smaller sample size to report certain outcomes, such as PNI biomarkers, can decrease the power of the statistical tests used to report results of those outcomes.[89] However, since PNI biomarkers need to be collected over multiple time points, sometimes blood draws, studies of PNI-based psychosocial therapies are faced with the likelihood of having missing data. Hence, future interventions should account for attrition and missing data during their power analysis (e.g., by oversampling) stage and establish a plan for handling missing data.

5. Collecting data regarding integrity of biomarkers collection procedures. In this study we also encountered a high degree of compliance with the collection procedures for saliva. However, since the data were reported by participants, there was no other way of verifying the validity of the participant's responses. Other psychosocial interventions have used similar ways of checking adherence to the PNI-measurement protocol; for example, one study gave participants wrist watches with preset alarms and asked participants to record the time when they

provided saliva samples on measurement tracking forms.[114] Researchers should be aware of more sophisticated ways of collecting protocol adherence data, such as the use of MEMS™ IV tracking caps on the saliva collection containers which have microcircuits that record times and dates.[118] Research shows that considerable methodological variation exists in relation to timing of collection PNI biomarkers, for example diurnal variations in cortisol production.[161] Therefore forthcoming research should employ more rigorous ways of collecting data with regards to assessing the integrity of measurement protocols regarding time-sensitive PNI-based outcomes.

6. Preventing publication bias: Reporting negative results. It is important for researchers to note that there continues to be discordance in the literature with regards to interpreting results related to the neuroendocrine-immune effects of psychosocial interventions for cancer patients. A systematic review of PNI-based psychosocial interventions for breast cancer patients published in 2009 concluded that there is evidence to suggest that cognitive-behavioral therapies impact neuroendocrine and immune measures.[64] However, other researchers that reviewed the same literature published a critical review in 2010 reporting that the evidence for psychological interventions having clinically significant impacts on the immune function of cancer patients is still "limited and unconvincing."[228(p21)] Therefore, it is important that researchers report negative findings with regards to the PNI effects of psychosocial interventions to avoid publication bias for positive results and the resulting file drawer effect[229].

**Study Limitations**

This study does have some limitations that need to be acknowledged. The first area of limitations is related to the outcome measures for this study. The primary outcome of this study was salivary cortisol and due to limitations in financial resources, we could not estimate the baseline and immediate post-intervention values for salivary cortisol. Although, we found that

salivary cortisol was significantly lower in EW group compared to the control group, the inferences that can be made from the results regarding our primary outcome are limited due to the absence of baseline and Day 7 measures. Furthermore, although the use of salivary measures provides a non-invasive approach, it also comes with methodological and practical problems. For example, even a subclinical oral infection can affect levels of salivary biomarkers, especially CRP[161,230]. We tried to eliminate this limitation by educating participants with specific details about oral hygiene prior to collecting saliva, see Appendix K. Also, measures of cancer participants' health behaviors, e.g. food habits, exercise, that could be potential moderators of PNI outcome measures, were not obtained in this study.

The second area of limitations in this study is related to the sample characteristics of this study. We chose a very specific and narrow cancer population for this study, which was CS that were disease-free and in the re-entry phase of survivorship (2-12 months post-radiation). These restrictive sampling criteria for this study limit the generalizability of the findings to wider clinical populations. Also, due to lower than expected recruitment rates, the sample size for this study was small. A larger sample size would have also possibly increased the diversity of our sample with regards to variables such as age, gender, race, type of cancer. Furthermore, due to the technology component of the EW intervention we may have excluded participants who were unable to use computers and the internet and would have benefited from EW using a paper-and-pencil format. However, data regarding access to the internet and computers has shown a consistent upward trend towards internet usage and device ownership across all segments of the population, regardless of race, income and age. Also, initiatives such as the "PC PLEDGE 100" from public-private institutions such as the Federal Communications Commission (FCC)[231] has called for corporations to recycle and divert computers to help low-income families get online.

Therefore, we expect internet-based interventions such as the one used in this study will soon be widely available to marginalized and underserved individuals and populations as well.

**"Lost in Transition:" Cancer Survivorship and Coping with Cancer**

The numbers of cancer survivors in the United States and the world over have been consistently increasing due to advances in early detection and treatments. Patients with cancer are now progressively more likely to survive and participate in their normal work and family lives, with almost 70% of patients with cancer surviving five years beyond their initial cancer diagnosis. Every year there will be a million new cancer patients that join the existing population of 13.7 million cancer survivors who are alive today[2]. These cancer survivors are faced with several physical as well as psychological and social (psychosocial) problems and limitations during their transition from after completing treatments to reassuming their roles in work and family. Health organizations such as the American Cancer Society (ACS), CDC and IOM have repeatedly advocated that researchers, health practitioners and policy makers in the oncology setting need to raise awareness of and attend to the unmet psychosocial needs of cancer survivors[1]. In this study we attempted to advance the IOM's recommendations with regards to taking steps to improve the science and delivery of psychosocial interventions and identifying ways to link cancer patients and providers with appropriate psychosocial interventions.

**What are the psychosocial health needs of cancer survivors?** Cancer has a unique psychosocial impact on patients different than other chronic illnesses and challenges individuals on their mental, emotional and social levels as well raises spiritual and existential questions in afflicted individuals. Every phase of the cancer care trajectory, from diagnosis and treatment to survivorship or palliative care, poses exceptional tribulations with regards to the psychosocial health of cancer patients. Patients transitioning from completing their treatments to long-term

follow-up, referred to as cancer survivors in this study, are at high risk for experiencing stress and were the focus of this study. Cancer survivors are faced with the early, late and long-term impacts of cancer diagnosis and treatments on their physical and psychosocial well-being through the rest of their lifespan. Psychosocial health issues in cancer survivors include stress, angry rumination, depression, loneliness, fear of cancer recurrence as well as sleep related problems such as insomnia or hypersomnia[1].

The incredible complexities of the psychosocial health needs of cancer survivors can grasped to a certain degree by studying cancer survivors experiences, such as the following quote of from a cancer survivor who had just finished her last radiation treatment,

> After my very last radiation treatment for breast cancer, I lay on a cold steel table hairless, half-dressed, and astonished by the tears streaming down my face. I thought I would feel happy about finally reaching the end of treatment, but instead, I was sobbing. At the time, I wasn't sure what emotions I was feeling. Looking back, I think I cried because this body had so bravely made it through 18 months of surgery, chemotherapy, and radiation. Ironically, I also cried because I would not be coming back to that familiar table where I had been comforted and encouraged. Instead of joyous, I felt lonely, abandoned, and terrified. This was the rocky beginning of cancer survivorship for me[232(p479)].

Other stressors for cancer survivors include follow-up clinical appointments and medical tests which often have wait times ranging from several days to weeks for laboratory confirmation. In previous research conducted by the first author, these wait times have been metaphorically described by cancer survivors as “torture” and being on a “roller coaster”[206]. Thus, cancer survivors have several psychosocial health needs with regards to reducing stress and negative

emotions and managing uncertainty. We urge patient advocates, health researchers and professionals to recognize that cancer survivors have unique psychosocial health needs during the survivorship phase. Therefore, we support the ACS and IOM's recommendations with regards to defining cancer survivorship as a separate phase of cancer care and taking measures to address the specific psychosocial needs of cancer survivors[1].

**How do we address the psychosocial health needs of cancer survivors?** An important first step in addressing the psychosocial health needs of cancer survivors is raising awareness about psychosocial health needs of cancer survivors amongst oncology care providers. The medical management of cancer is very complex and demanding for oncology care providers who primarily consider clinical outcomes such as the cancer cell morphology, possible metastases, grading and staging the cancer and monitoring the response to specific doses of the cancer treatments. However, health outcomes that are important to patients may include quality of life and subjective well-being[233]. The oncology-care literature indicates that while from the physicians' perspective the end goal is the cancer free patient, what the patient is experiencing during and after treatments seems insignificant and is often ignored by care providers[3]. Thus, there is a discrepancy between the health outcomes that oncology care providers are concerned about and the outcomes valuable to patients. We recommend care providers to consider patient-centered outcomes in addition to clinical outcomes during cancer treatments and most importantly during cancer survivorship. In the current team-based model of oncology care, we recommend oncology care providers to include staff trained in dealing with psychosocial issues such as psychologists or social workers. Also, psychosocial interventions that can bridge the gap between the world-view of the oncology-care providers and perspective of the cancer survivors are needed.

**Psychosocial interventions for cancer survivors: Expressive writing.** In our literature review we identified two major categories of psychosocial interventions for cancer patients, a) cognitive-behavioral and b) complementary medical. We chose expressive writing (EW) as a psychosocial intervention (from the cognitive-behavioral interventions group) for reducing stress in cancer survivors transitioning of their final radiation treatment. Several aspects of the expressive writing intervention are discussed below which make it an appropriate psychosocial intervention for cancer survivors during survivorship care.

EW: Brief and inexpensive. A very convenient feature of EW is that it requires limited resources with respect to time and administration. Typically EW interventions require a total of 1.3-2 hours over four days (20-30 min per day) without any need for booster sessions. This short duration is appealing for cancer survivors who may not have large blocks of time to spare for stress-management interventions. Moreover, EW can be administered in almost any setting, from home to classrooms as well as in-patient and out-patient clinical settings. This makes EW very adaptable to relevant environmental constraints. In this study we administered EW online, so CS did not spend time travelling to the place of intervention. Also, since EW involves participants responding to written instructions, EW requires minimal training and input from trained health professionals making it a low-cost intervention. In this study we did not require any trained health professionals for administering EW to cancer survivors, although we had a licensed clinical social worker on our team to address any possible adverse situations. Our literature review found that one study consisting of only three hours of therapeutic interaction with a single psychologist[116] demonstrated significant changes in immune outcomes. Further research is needed to investigate other brief and inexpensive psychosocial interventions involving

expressive disclosure for cancer survivors as well as future studies need to define EW's minimum and maximum dose response effect for impacting physical and psychosocial outcomes.

EW: Coping with cancer. Due to rapid advances in cancer prevention, early detection and management, cancer is now considered to be more of a chronic disease rather than an acute life-threatening condition[234]. Thus coping with cancer on a long-term basis is an essential aspect of living as cancer survivor. After patients with cancer learn to cope with stress of diagnosis and treatment, as cancer survivors they must now learn to cope with loneliness and fears of cancer recurrence. Studies of coping strategies in cancer survivors have shown that survivors use strategies such as a "fighting spirit" attitude, social support, religious faith and spirituality to cope with cancer during survivorship[235]. Expressive writing, as a medium, can help patients cope with cancer through problem-focused coping as well as emotion focused coping. The research literature suggests that interventions which allow patients to read clinical experiences of other patients form a basis for making informed decisions about treatments and follow-up care[236]. Also, studies show that reading about cancer survivorship stories about individuals who were diagnosed with cancer and who are now successfully cured and living normal lives can decrease cancer survivors anxiety and improve coping[237,238]. Thus EW interventions that can connect communities of cancer survivors will help provide CS with health information (problem-focused coping) as well as provide a sense of social support (emotion-focused coping). Previous research indicates that cancer survivors describe benefits of expressing their emotions during the writing process, for example, at the conclusion of completing their writing a CS wrote "I realize this story was disjointed and rambled on, but it felt good to get off my chest" [206(p.85)]. Results from this study found that cancer survivors that participated in EW had a significant decrease in their

fear of cancer recurrence and further research is needed with regards to EW's coping function in CS.

EW: Health benefits. The positive health benefits of EW have a growing evidence-base in the research literature. EW has shown effects on all types of health outcomes, ranging from self-reported symptoms and psychosocial outcomes such as depression to neuroendocrine and immune outcomes such as $CD^{4+}$ T cells[127,239]. Also, beneficial health effects of EW are consistent across study populations that include healthy individuals as well as diverse clinical populations such as, HIV+ patients, cancer patients and survivors, and patients with asthma, autoimmune and cardiovascular disorders[127,128]. The results from this study adds to the research evidence for EW's health benefits specifically for the cancer survivor population. CS are particularly at risk for experiencing stress during their transition phase which is approximately 2-18 months after completing all treatments[223]. We found that expressive writing was successful as a stress-management intervention during this transition phase and CS who participated in EW had significantly lower levels of cortisol (regulation of HPA axis response) and reported lower fear of cancer recurrence (FCR) in the six weeks after completing their EW intervention. Further efforts from researchers and practitioners are needed to study the health benefits of EW specifically for CS and deliver EW interventions as part of cancer survivorship care.

EW: Building relationships between care-providers and cancer survivors. Currently the health care system is failing to understand cancer survivors' experiences and psychosocial needs by not including expressive disclosure interventions such as EW in oncology care. Several institutional and pragmatic limitations prevent oncology care providers from understanding the psychosocial needs cancer survivors and identifying health outcomes important for cancer survivors. Expressing emotions and experiences related to cancer is a time-consuming and

demanding task that care providers may not prioritize in their schedules. Expressive writing is a very practical tool that can enable oncology researchers and care providers to better understand the psychosocial needs of cancer survivors. Cancer survivors can write about their stressful experiences at their own convenience and time, and then present them to their oncology care providers for their perusal. The oncology care providers can learn valuable information with regards to the patient experience of survivorship including stressors and issues that concern cancer survivors and identify specific health outcomes important for cancer survivors during survivorship. These expressive writing narratives can also provide a lens through which researchers and oncology-care providers can vicariously experience the world of cancer survivors. Future research should also measure the benefits of incorporating EW interventions for the oncology care providers in addition to benefits for cancer survivors.

EW service delivery: Adaptable to technology and the internet**.** One of the most dramatic revolutions in modern times with regards to individual lifestyles and societies at large has been the advent of computers and the internet. In a less than three decades since the internet was first offered to the public by internet service providers (ISPs), the world has transformed into a global village allowing for human interaction to occur in cyberspace, which include psychosocial interventions. Researchers and professionals have been increasingly using the internet to deliver psychosocial interventions for patients with cancer and have encouraged other researchers to view the internet as an accessible and increasingly popular medium for reaching diverse cancer populations[149]. Patients with cancer have reported that internet-based interventions are acceptable and feasible. However, in our literature review we found only two studies used communication technology to deliver their interventions to cancer patients which were through telephone conversations[105,118]. An innovative aspect of this study was that we adapted the paper-

pencil format of EW to an online format which was delivered using the survey software Qualtrics.

There are several advantages to using the online format of EW for cancer survivors. After completion of treatments, CS generally have follow-up appointments that range from three to six months post-treatment. During this time most CS experience fears and uncertainty and do not have ready access to their health care team. In this transition phase, internet-based EW interventions can easily be made accessibly to CS which can help them express their thoughts and emotions. This will help ease pent-up anxiety and stress in CS as well as reconnect them to their health-care team. The EW essays will inform the survivorship-care team with regards to symptoms and concerns of CS. Thus, internet-based EW is a very simple and accessible way for the health-care team to deliver follow-up care to CS during survivorship. Our internet-based EW study was successful in reducing stress measured by lowered salivary cortisol and fear of cancer recurrence in cancer survivors 2-12 months post- radiation. However it is important to note that our study sample was predominantly well educated and higher income cancer survivors who had access to a computer and the internet. The ability and willingness to disclose experience in written format online could be attributed to the higher educational and socio-economic level of our sample. Future studies should also include oral expressive disclosure prompts to participants from diverse educational and socio-economic strata through the internet or by phone.

Important areas of concern with regards to internet-based EW interventions are audience responsiveness to the EW essays and data privacy. Research has shown that patients may alter the content of the EW essays based on the audience that is going to read their narratives. EW studies for CS should clearly inform participants as to which personnel will read their essays. Another are of concern is with regards to data privacy. The conversation with regards to internet

privacy continues to concern data providers as well as lawmakers and intelligence agencies. The revelations by whistleblower Edward Snowden with regards to the National Security Agency (NSA) surveillance[240] occurred during the recruitment phase of this study. One potential participant for this study expressed concerns with regards to data privacy issues and reported a mistrust with the government and associated agencies. We urge researchers to pursue defining specific guidelines to ensure confidentiality and privacy of data when adapting psychosocial interventions to the internet. Thus, several challenges remain for introducing EW into survivorship care and making psychosocial interventions part of the standard of cancer care.[3,241]

**Psychosocial Interventions in Cancer-Care: Preparing the Health Care System**

A comprehensive and well-organized approach towards post-treatment survivorship care is essential. The IOM has described that introducing psychosocial interventions for CS in the standard of cancer-care is faced with some major challenges. These challenges include 1) deficiency of health care professionals that specialize in care for CS, 2) immense diversity in the in psychosocial interventions and insufficient evidence-based guidelines for designing and delivering care for CS and 3) inadequate reimbursement for clinical and therapeutic services. In this section we discuss some steps to address these challenges in the immediate future.

**Education and training for health professionals.** This study concurs with the IOM's concern with regards to the lack of standardization in education and training materials for the wide variety of health professionals involved in psychosocial health interventions and services for cancer patients[3]. Psychosocial health professionals range from oncologists and physicians to nurses, social workers, psychologists and counselors. It is difficult to estimate the demand for psychosocial health services due to the lack of available data. Presently, comprehensive cancer-care centers have instituted guidelines and standards for health-care professionals to address

psychosocial issues in CS and providing CS with survivorship care plans[242]. However, these standards are ambiguous and do not define the specifics with regards to how these educational standards will be translated into credit hours, methods, or the delivery of survivorship care[242,243]. A first step towards addressing the gap in psychosocial care for CS is to raise awareness about CS unmet psychosocial needs amongst oncology care providers and primary health providers. We also recommend comprehensive cancer centers to design specific training modules for health professionals interested in specializing in psychosocial oncology care and service delivery for CS. Finally, we suggest that knowledge and skills required for the management of psychosocial problems of CS during survivorship care be introduced immediately within the current standards for educational accreditation and licensure by way of additional curricula and continuing medical education credits.

**Defining evidence-based guidelines for intervention studies.** An important deficiency in the psycho-oncology literature is the absence of evidence-based guidelines for developing psychosocial interventions for diverse cancer populations. Defining guidelines for the psychosocial management of cancer is more complex and difficult than it is for well-defined discrete chronic diseases such as asthma, diabetes, or heart disease. For example breast cancer has a considerably different psychosocial impact on patients than prostate or lung cancer. Furthermore, the particular psychosocial health care needs may vary for cancer survivors with regards to specific cancer sites (breast versus bone), stage of survivorship (re-entry versus long-term survivorship) and type of cancer treatments (chemotherapy versus radiation). Provided that there exist more than a hundred different types of cancer, defining generalized guidelines for particular psychosocial interventions is problematic since their efficacy can differ based on cancer site, stage and treatments. In this study we chose a cancer survivors 2-12 months post-

radiation since they were at risk for post-treatment stress and were an understudied cancer population. Our literature review uncovered a wide range of psychosocial interventions that could be beneficial to cancer patients. The results of this study found promising but incomplete evidence for EW as psychosocial intervention for reducing stress in cancer survivors.

We recommend that future studies of psychosocial interventions in cancer survivors, that employ PNI outcomes, should consider: a) clearly defining activities and therapies involved in the intervention; b) specifying duration of the interventions and time estimated for each session, including time for booster session(s); c) considering the timing of the intervention delivery with regards to treatment regimens (i.e. chemotherapy/ surgery); d) monitoring adherence to the intervention protocol; and e) evaluating sustainability of the intervention in routine clinical practice. We also urge researchers and policy makers to take action on the IOM's recommendation for developing "standard outcome measures"[3(p15)] for evaluating the efficacy of psychosocial therapies and services for cancer patients. Collaborative interdisciplinary efforts are needed to use similar approaches with regards to descriptions of the cancer populations, psychosocial interventions (including components and activities involved), psychometric instruments for psychosocial functions, and biomarkers for bio-behavioral outcomes (e.g. neuroendocrine-immune). Such efforts will contribute towards building a convincing empirical evidence-base for the effectiveness of PNI-based psychosocial therapies for cancer survivors.

**Policies for reimbursing psychosocial services**. As described above there are a wide variety of services and health professionals that provide psychosocial services for CS. Reimbursements for these psychosocial services are difficult due to the regulations that restrict insurance payments to health professionals. These restrictions make it difficult for psychosocial health service providers to be in same physical location as clinical and surgical oncology

professionals. The IOM also states that due to the low quality of health care, simply improving reimbursement will not improve health care services, and additional initiatives are needed such as quality measurement and improvement activities[3]. We urge policy makers to include provisions for psychosocial health care services and interventions for cancer patients and survivors. Recent changes in health policies are encouraging for increasing the availability and reach of psychosocial health services in the cancer survivor population.

The Patient Protection and Affordable Care Act (PPACA) has the potential to deliver one of the greatest expansions of coverage for psychosocial health services in a generation by requiring that most health insurance plans on the Health Insurance Marketplaces (HIM) to cover mental health services[244]. There are new requirements in the law (in the Mental Health Parity and Addiction Equity) that provide benefits for mental health services and expand protections for behavioral health to 62 million Americans. Starting in 2014 most health insurance plans will not be able to deny coverage because of a pre-existing mental illness. Also, the PPACA aims to reduce cancer-care disparities by expanding coverage for Medicaid and eliminating previous barriers to health coverage[244]. Also, the PPACA mandates that health coverage must now include preventive mental health services like depression screening for adults. In future steps, we recommend policy makers outline protections for specific health services, such as survivorship care for defined patient populations, for example CS. We also support policies that will provide guidelines for reimbursement with regards to health professionals, service providers and insurers involved in survivorship care and for delivering comprehensive survivorship care plans for CS.

## Chapter VIII. Conclusion

In this study we found that a simple and inexpensive online expressive writing (EW) intervention was successful in reducing stress in cancer survivors post-radiation. This study provides evidence for the potential efficacy of delivering online EW online to cancer survivors during survivorship care to aid in stress-management. This study supports to the movement towards integrative models of cancer care which seeks to synthesize evidence-based therapies that concurrently address the physical as well as psychosocial-spiritual needs of cancer patients.[245,246] We also support the IOM's appeal for designing a framework to develop and provide cancer care for the whole patient.

### Bio-psychosocial Model of Health: Providing "Cancer Care for the Whole Patient"

Several historic social-cultural factors in the science and research community favor investments for research and development for therapies impacting "hard" therapeutic outcomes such as tumor growth as opposed to "soft" psychosocial outcomes such as quality of life[247]. This bias towards investing primarily in technology driven inventions is demonstrated is by the breakthrough innovations in cancer detection and cancer treatments such as targeted chemotherapy and robotic surgery, as opposed to only marginal advances in the science and delivery of psychosocial interventions[3]. However, the turn of the 21st Century has given way to a considerable transformation in the understanding of disease and health care, particularly in the oncology setting. In 2001, a National Research Council (NRC) Committee on Health and Behavior overwhelmingly supported the bio-psychosocial model of health by concluding that "health and disease are determined by dynamic interactions among biological, psychological, behavioral, and social factors,"[248(p16)] and discussed implications of the science of stress and psychoneuroimmunology for patients with cancer. In less than a decade after that report, in 2008,

the IOM recommended psychosocial health interventions and services should be a part of the standard of cancer care and emphasized the unmet psychosocial needs of cancer survivors[3].

Furthermore, in the past decade health organizations such as the IOM, NCI and ACS have made significant efforts to raise awareness with regards to cancer patients psychosocial needs and have highlighted the need to include patient-centered outcomes in health decision-making. The PPACA helped institute the patient-centered outcomes research institute (PCORI) which aims to conduct research guided by patients, family members and caregivers, and the wider healthcare community to improve health decision-making, delivery and outcomes[249]. The PNI framework and the bio-psychosocial model of health have the potential to provide a bridge between clinically relevant outcomes and patient-centered outcomes. Furthermore, the bio-psychosocial model of health can also serve as a framework for interdisciplinary collaborations between stakeholders, social scientists, health professionals and policy makers. We will use the results from this study to inform health practitioners, researchers and policy makers interested in evaluating the use of psychosocial interventions such as expressive writing in the standard of cancer care. It is critical that we encourage conversations with regards to including patient-centered outcomes in cancer survivorship research and encourage lawmakers to provide better protections for patients during survivorship care.

**Dissemination Plan**

The results from the literature review conducted in preparation for this study have been published in the peer-reviewed international journal, Integrative Cancer Therapies[197]. The diffusion of findings from the results of this study research will be reported to cancer survivors, health practitioners, policy makers and the scientific community at large. We will present the findings from this study in the format of seminars and presentations for community oncologists

and mental-health professionals including the oncology-care staff and researchers at VCU Massey Cancer Center (MCC). We will also conduct awareness workshops to educate community health professionals with regards to stress-management interventions for cancer survivors and encourage researchers at MCC to introduce psychosocial interventions to reduce stress in their oncology practice. The findings of our study will be reported in a manuscript and submitted to a peer reviewed medical journal. We will also notify the science media about our study by contacting popular media outlets (e.g. Psychology Today) and freelance science journalists and reporters. The protocol for expressive writing will be provided to the science media, who can provide the writing prompt to readers in their article or give an online link the study protocol.

Findings from our study will be reported to the office of survivorship at the NCI. We will inform the American Cancer Society's cancer survivor network (CSN) with regards to our study and educate them about the possibility of conducting online expressive writing groups for cancer survivors during their survivorship care. We will also inform site administrators of online cancer survivors support groups such as a) Circle of Sharing (https://circleofsharing.cancer.org/default.aspx), b) I Can Cope (http://www.cancer.org/icancope/) and c) What Next (https://www.whatnext.com/acs/ ), with regards to the feasibility of delivering online expressive writing interventions for cancer survivors. Finally, to assist with national dissemination of this study, we will seek to get the citations for this study onto NCI/CDC best practices page. We will provide the NCI/CDC with all materials with regards to this intervention's delivery and protocol, and will contain relevant information with respect to our expressive writing intervention and other psychosocial interventions for cancer survivors. This will ensure that cancer survivors worldwide as well as the general public will have access to the EW intervention and the results from our study.

**Concluding Thoughts**

In conclusion, this study demonstrated that expressive writing can help cancer survivors (CS) regulate their stress and negative emotions. This study provided the first author an opportunity to interact with individuals who were faced with enormously stressful life events during their survivorship. Participants stressors ranged from job loss to family relationships and fears of death. However, what was touching was the CS willingness to help others despite their own stressors. In one email, a prospective participant wrote, "Let me know if I can help out...I don't want my experience to go to waste...," demonstrating that cancer survivors are often concerned with how their experience can help others. It is critical that the science and research community to take consistent steps towards raising awareness about psychosocial stress in cancer survivors and encourage applied public health interventions for helping cancer survivors, family members and caregivers and communities deal with an increasing complex, globalized and stressful world. It must be the endeavor of the science and research community to ensure that the millions of cancer survivors in the world today are able to lead healthy and productive lives.

Although this study lends evidence for using expressive writing as a stress-management intervention for cancer survivors, it is possible that EW may not be appreciated by all cancer survivors. This is an important consideration for researchers and practitioners involved in delivering survivorship care. Personalized approaches for managing psychosocial health are needed for cancer survivors that will provide CS access to the quality of life they deserve. This study has given the first author experience in conducting original research that will hopefully inform patient-centered decision-making in addition to clinical decision-making in oncology care. Greater commitments are needed from researchers and health practitioners to institute compassion and empathy in the delivery of survivorship care. This dissertation is a baby step

towards future research which will aim to create more meaningful and deeper relationships between cancer survivors and oncology care providers.

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**Appendix A.**

**Recruitment flyer**

Virginia Commonwealth University School of Medicine
Dept. of Social and Behavioral Health

## STRESS MANAGEMENT FOR CANCER SURVIVORS AFTER RADIATION THERAPY: A RANDOMIZED TRIAL OF EXPRESSIVE WRITING



- ***What it is:*** A study to learn about the effectiveness of a stress management therapy called expressive writing for patients with cancer who are cancer free after completing their last radiation treatment.
- ***Who can participate:*** If you are over 21 years old and have completed your cancer radiation treatment (more than 2 months ago, but less than a year), we would like to talk to you!
- ***What is involved:*** Writing on a computer for 20-30 minutes over 4 consecutive days. We will assess your stress levels before and after the writing assignments. To measure your stress, you will be asked to 1) fill out survey questions online regarding your stress levels and 2) provide your saliva samples to measure biological indicators of stress.
- ***Why it is important:*** Expressive writing may help you make sense of your stressful experiences with cancer and help to manage your emotional stress. Stress management is important since stress can have negative effects on physical and mental health. Results from this study will contribute to the science of stress-management therapies for cancer survivors.



*Participation is voluntary & confidential!*

*If you are interested in being interviewed for this study, please contact:*

**Richard Brown**
**(Principal Investigator)**
**804-628-3340**
**rbrown39@vcu.edu**

**Utkarsh Subnis**
**(Research Coordinator)**
**804-628-1454**
**subnisub@vcu.edu**

**Recruitment Flyer**
**Version: 5/1/2013**

## Appendix B.

## Study protocol description (for recruitment staff at oncology clinics)

VCU IRB# HM14971: Stress management for cancer survivors after radiation therapy: A randomized trial of expressive writing

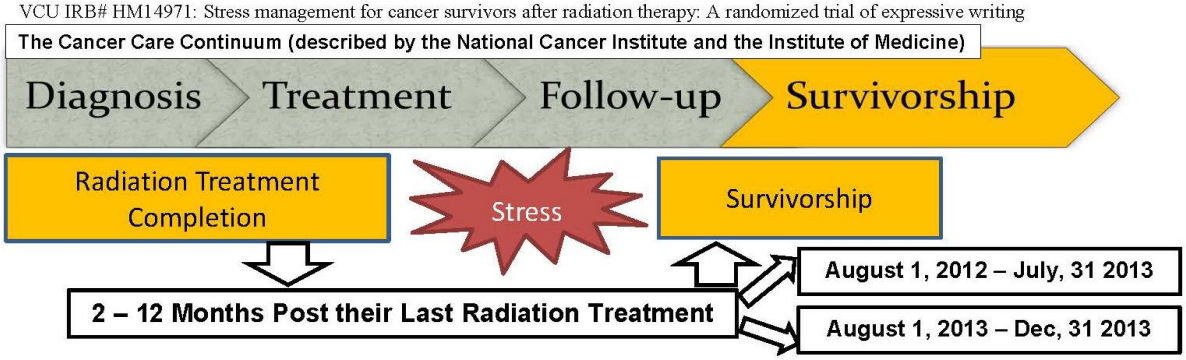
Study protocol (activities, measures and data sources)

| Prior to enrollment | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 49 |
|---|---|---|---|---|---|---|---|---|
| Provide study information + Screening + Informed consent | Confounds + Cancer-related information | Baseline outcome measures (BOM) | Writing | Writing | Writing | Writing | Post-intervention outcome measures (POM1) | Post-intervention outcome measures (POM2) |
| | | | Intervention → Expressive writing / Control writing | | | | | |
| 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes |
| Screening – 5 questions (*Telephone-based*) | • Cognitive dysfunction (Brief Screen for Cognitive Impairment: 3 items )<br>• Depression (Patient Health Questionnaire-2: 2 items) | | | | | | | |
| Confounds – 28 questions (*Online survey*) | • Social support and Perceived social status<br>• Smoking, Alcohol consumption, Sleep, Oral health – gum disease<br>• Use of complementary and alternative medicine (CAM)<br>• Comfort with using computers and internet technology<br>• Demographics: Health insurance status; Employment status; Household income; Education level; Marital status; Age ; Gender ; Race/Ethnicity | | | | | | | |
| Cancer-related information – 9 questions (*Online survey*) | • Cancer Diagnosis information (primary site, tumor stage)<br>• Cancer Treatment regimen information (date, toxicity, late and long term effects)<br>• Medication use | | | | | | | |
| BOM, POM1 and POM2 (*Salivary Specimens*) | • Cortisol, α-Amylase and C-reactive protein – CRP | | | | | | | |
| BOM, POM1 and POM2 – 33 questions (*Online survey*) | • Perceived Stress Scale<br>• Fear of Cancer Recurrence Inventory-Severity subscale<br>• Cancer Behavior Inventory-Brief version | | | | | | | |

## Appendix C.

## Study population description (for recruitment staff at oncology clinics)

VCU IRB# HM14971: Stress management for cancer survivors after radiation therapy: A randomized trial of expressive writing




### Study Population

| Patient characteristics for recruitment to study HM14971 |
|---|
| **Inclusion Criteria** |
| 1) Completed their final cancer radiation treatment (intent to cure),<br>2) Cancer-free (no current diagnosis of primary/secondary cancer), i.e. in remission/watchful waiting<br>3) 2-12 months post-radiation treatment completion (re-entry phase of cancer survivorship)<br>4) Have access to a computer and internet in a private setting, e.g. at home.<br>5) Above 21 years of age<br>6) Fluent in English<br>7) Able to provide informed consent |
| **Exclusion criteria** |
| 1) Scheduled to undergo any type of cancer treatment in the future (e.g. surgery after completing radiation),<br>2) Received radiation to large areas on the face/neck region (limits ability to produce saliva)<br>3) Known to be suffering from inflammation of the oral cavity (e.g. gingivitis).<br>4) Known to be on corticosteroid medication (e.g. long-term prednisone therapy)<br>5) Known to have any condition that affects function of the adrenal glands (e.g. adrenal hyperplasia) |

**Study contact**: Utkarsh Subnis, MBBS, MA, Dept. of Social and Behavioral Health, VCU School of Medicine
Phone: **804-628-1454**, email: subnisub@vcu.edu

## Appendix D.

## Patient initial contact letter

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Richard Brown PhD
Assistant Professor
Department of Social and Behavioral Health,
School of Medicine,
Chair, Massey Cancer Center, PRMS
Cancer Prevention and Control Subcommittee
Virginia Commonwealth University
One Capitol Square, 9th Floor,
830 East Main Street, P.O Box 980149
Richmond, Virginia, VA 23298
804 628 3340 (Office), 804 828 5440 (Fax)

Dear [Pt. Name],

My name is Dr. Richard Brown and I work in the Department of Social and Behavioral Health in the Virginia Commonwealth University Medical School. My research team is collaborating with Massey Cancer Center and your physician, Dr. [Name] on a research study about stress management for cancer survivors after radiation therapy. We are contacting you because you have completed your cancer treatments and are eligible for our study.

Our research team has developed a computer-based stress management intervention called expressive writing. This expressive writing intervention involves logging in to an online survey and writing in the survey about your thoughts and feelings about your cancer and how it has made a difference in your life. Research shows that cancer survivors may experience stress after finishing treatment. Stress can have negative effects on physical and mental health. We want to see if expressive writing can help reduce stress in cancer survivors.

This type of study is known as a "randomized controlled trial." People who join this study will be placed in to one of two groups. Half of the participants will participate in expressive writing and the other half will write about their everyday experiences. In a randomized controlled trial people are put in groups by chance or at random, like pulling names out of a hat. You have an equal chance of being in either group. Results from this study will improve the science of stress-management therapies for cancer survivors. If you decide to participate, we will need to measure your stress levels by asking you to answer survey questions online and provide your saliva samples before and after your writing assignments.

The Research Coordinator for this study, Mr. Subnis will be contacting you by phone to ask about your willingness to participate in this study. Mr. Subnis will provide you more details about the study and ask if you are interested in participating in this study. You will need to give written informed consent for participating in the study before you are enrolled in the study.

Everything you tell us will be kept completely confidential, and no information about you will ever be linked to your name. If you are interested or have questions about our study, please feel free to contact me or my research coordinator at the number or email address provided below.

APPROVED
BH /IR /5.10.13

OFFICE OF RESEARCH
MAY - 1 2013
SUBJECT PROTECTION

Sincerely,

Richard Brown, Ph.D.
Principal Investigator
Assistant Professor
Department of Social and Behavioral Health
Virginia Commonwealth University School of Medicine
Phone (804) 628-3340
Email: rbrown39@vcu.edu

Utkarsh Subnis, M.A., M.B.B.S.,
Research Coordinator
Graduate Assistant
Department of Social and Behavioral Health,
Virginia Commonwealth University School of Medicine
Phone: 804-628-1454; Fax: 804-828-5440
E-mail: subnisub@vcu.edu



Patient Letter: IRB # HM 14971 Version: 5/1/2013

**Appendix E.**

**Patient opt-out mail card**

If you would prefer not to be contacted, please indicate so below by checking the box, printing your name and address and returning this self-addressed stamped postcard. Thank you for your consideration.

❑ I do not want to be contacted.

Name: _____

Address: _____

_____

Tel. #: _____

I am not ready to be contacted right now, however you may contact me in

CIRCLE ONE: 1 month 2 months 3 months

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 1978 RICHMOND, VIRGINIA

POSTAGE WILL BE PAID BY ADDRESSEE

VIRGINIA COMMONWEALTH UNIVERSITY
DEPARTMENT OF SOCIAL & BEHAVIORAL HEALTH
ATTN: UTKARSH SUBNIS
P O BOX 980149
RICHMOND VA 23286-0440

## Appendix F.

## Recruitment script for phone contact

Instructions to RC: Once you contact the prospective participant by phone, be positive in your initial contact. Always keep in mind that participation in this study is completely voluntary. Be respectful of the prospective participant's time and inquire if they want to hear more about the study. Also, convey to the patient that their participation is voluntary and they can choose to discontinue the conversation at any point. However, do not be apologetic; patients may be interested and willing to participate in this study. During this conversation, do not allow much "silent time" to occur. Fill in silence with appropriate information about the study.

Follow guidelines for your conversation as a Research Coordinator (RC) with a prospective participant (PP):

RC: Hello, may I speak with Mr. /Mrs. _____?

PP: Speaking.

RA: Mr. /Mrs. _____, my name is _____. I am a research coordinator at Virginia Commonwealth University. I sent you a letter a few weeks ago about a study we're conducting about stress management intervention for cancer survivors after radiation therapy. Did you receive the letter?

PP: Yes. (If PP: No, then inform them you will resend the letter and continue conversation at a later time.)

RA: I am calling to give you more information about the research study and ask if you will be willing to participate. We are conducting a research study about using expressive writing for managing stress in cancer survivors. May I have a few minutes of your time to explain the study?

PP: Yes (If PP: No, then thank them for their time and ask for a better time to call)

RA: Before I start, I just want to let you know that your participation is voluntary and you can end this conversation at any point. Research shows that cancer survivors may experience stress after finishing radiation treatment. Stress can have negative effects on physical and mental health. We want to see if an online stress-management therapy called expressive writing can help reduce stress in cancer survivors. This expressive writing therapy involves logging in to an on-line survey and writing in the survey about your thoughts and feelings about your cancer and how it has made a difference in your life, Expressive writing requires 20-30 minutes of typing on a computer a day for 4 consecutive days.

RC: Do you have any questions at this point before I proceed further?

PP: No (If Yes, then provide clarification to PP's questions then proceed with rest of information)

RC: "Are you comfortable typing on a computer for between 20 – 30 minutes?"

PP: Yes (If No, then thank them for their time and conclude the conversation politely)

RC: So before, I describe the study any further, I would like to ask you a few questions regarding your health. These questions are to see if expressive writing is an appropriate stress-management therapy for you at this point. I have 3 questions about your mind function and 2 questions about depressive symptoms. They will take about 5-7 minutes to answer. Would you feel comfortable to answer these questions now?

PP: Yes (If No, then ask when would be a better time to call and thank them for their time and conclude the conversation politely)

RC: Ask BSCI and PHQ-2 questions and provide appropriate referral if needed (See Protocol: Section I)

RC: Your responses to the questions tell us that you are eligible for our study. So I would like to describe the study some more in detail. Do you have any questions at this point before I proceed further?

PP: No (If Yes, then provide clarification to PP's questions then proceed with rest of information)

RC: Ok I will continue then... So, this type of study is known as a "randomized controlled trial." People who join this study will be placed in to one of two groups. Half of the participants will participate in expressive writing and the other half will write about their everyday experiences. In a randomized controlled trial people are put in groups by chance or at random, like pulling names out of a hat. You have an equal chance of being in either group. No one decides which group you will join. If you decide to participate, you will be asked to fill out survey questions online and provide your saliva samples before and after your writing assignments. This is to measure your stress levels before and after the intervention. We will need to collect these measures 24 hours before the writing and 24 hours after and 6 weeks after the writing is completed. A schedule with dates for all activities involved in the study will be provided to you. Results from this study will improve the science of stress-management therapies for cancer survivors. Will you be interested in taking part in this study?

PP: Yes. (If PP: No, then thank them for their time and conclude the conversation politely)

RC: Mr. /Mrs. _____, thank you for your interest in participating in this study. Before we can enroll you in this study, you will need to provide us your consent. I will mail you the informed consent form for this study. You will need to sign this consent form and send it back to us. A postage paid return addressed envelope will be sent to you along with an additional copy of the form for your records. Do you have any further questions?

PP: _____

RC: (Give them more details about the study if they ask). Mr. /Mrs. _____, we appreciate you taking the time to participate in the study. Do you have any further questions for me?

---

## Appendix G.

## Script for voice messages

Instructions to RC: If you contact the prospective participant by phone and receive their voice mail, be polite and DO NOT leave any information about the research study. You do not need to sound apologetic. Read the following script:

RC: Hello Mr. /Mrs. _____. My name is _____ I am calling from Virginia Commonwealth University. My contact no. is _____. I would appreciate a call back. I have left this message on ___ (date) at ____ (time). Thank you.

## Appendix H.

## Patient follow-up letter for consent form

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Utkarsh Subnis, M.A., M.B.B.S.,
Research Coordinator
Department of Social and Behavioral Health,
Virginia Commonwealth University School of Medicine
Phone: 804-628-1454; Fax: 804-828-5440
E-mail: subnisub@vcu.edu

Dear [Pt. name],

Thank you very much for your interest in the research study regarding stress management for cancer survivors after radiation therapy. You will find inside this packet two copies of the consent form for this study. One page 5 of the consent form there is a place to print your name and signature. Please sign one copy of the consent form and mail it back to me in the postage paid return addressed envelope sent to you in the priority mail packet.

As soon as we receive your signed consent form, we will enroll you in the study. You will receive an additional packet containing the tubes for the saliva measures and detailed instructions in the mail. We will email you the survey links for the study as per your convenience and time schedule.

If you have any questions about the study, please feel free to contact me at the number or email address provided below.

Sincerely,

Utkarsh Subnis, M.A., M.B.B.S.,
Research Coordinator
Graduate Assistant
Department of Social and Behavioral Health,
Virginia Commonwealth University School of Medicine
Phone: 804-497-9890, 804-628-1454; Fax: 804-828-5440
E-mail: subnisub@vcu.edu

# Appendix I.

## Research subject information and consent form





**RESEARCH SUBJECT INFORMATION AND CONSENT FORM**

**TITLE:** Stress management for cancer survivors after radiation therapy using a technologically adapted psychosocial intervention: A randomized trial determining the effect of expressive writing on psychoneuroimmunology based outcomes



**VCU IRB NO.:** HM14971

**PRINCIPAL INVESTIGATOR:** Richard Brown, PhD
Dept. of Social and Behavioral Health
School of Medicine,
Virginia Commonwealth University, P.O. Box 980149
Richmond, VA 23298-0149
Telephone: 804-628-3340; Fax: 804-828-5440;
Email: rbrown39@vcu.edu

**RESEARCH COORDINATOR:** Utkarsh Subnis, M.A., M.B.B.S.,
Dept. of Social and Behavioral Health,
School of Medicine,
Virginia Commonwealth University, P.O. Box 980149
Richmond, VA 23298-0149
Telephone: 804-628-1454; Fax: 804-828-5440
E-mail: subnisub@vcu.edu

Please read this form carefully. It tells you about the research study. This form describes what you will be asked to do if you agree to participate. Please be sure to ask any questions that you may have about the study. You can contact Utkarsh Subnis (Research Coordinator) at any time to understand your potential involvement in this study. This form will help you think about this study. Feel free to discuss with family or friends before making your final decision to participate in this study.

**PURPOSE OF THE STUDY**

Cancer survivors may experience stress after radiation treatment. Stress can have negative effects on physical and mental health. This study aims to evaluate a computer-based stress-management therapy called expressive writing. This expressive writing therapy involves logging in to an online survey and writing in the survey about your thoughts and feelings about your cancer and how it has made a difference in your life. Expressive writing requires 20-30 minutes of writing a day for 4 consecutive days. We want to see if expressive writing can help reduce stress in cancer patients. Results from this study will improve the science of stress-management therapies for cancer survivors.

**DESCRIPTION OF THE STUDY AND YOUR INVOLVEMENT**

This type of study is known as a "randomized controlled trial." People who join this study will be placed in to one of two groups. Half of the participants will participate in expressive writing and the other half will write about their everyday experiences. In a randomized controlled trial people are put in groups by chance or at random, like pulling names out of a hat. You have an equal chance of being in either group. No one decides which group you will join.

This study involves the use of a computer. You will be directed to an online survey which contains a place for you to either type in your thoughts and feelings about your cancer (Group 1) or to type in your everyday

experiences (Group 2). People in both groups will be asked to go to the online survey and type continuously for about 20-30 minutes at one time on each of the 4 consecutive days.

If you agree to participate in the study, you will receive instructions on the topic to write about. Significant new findings can emerge during the course of this study. These finding may affect your willingness to continue participating in this study. These findings will be provided to you at the earliest time possible.

**Study Activities**

Please see Table 1 below for the study activities and estimated time required to complete them.

**Table 1: Study activities and estimated time required**

| Day No. | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 49 |
|---|---|---|---|---|---|---|---|---|
| Study Activity (s) | Answer online surveys | Answer online surveys + Provide saliva samples | Writing task | Writing task | Writing task | Writing task | Answer online surveys + Provide saliva samples | Answer online surveys + Provide saliva samples |
| Time required | 20 - 30 minutes | 20 - 30 minutes | 20-30 minutes | 20-30 minutes | 20-30 minutes | 20-30 minutes | 20 - 30 minutes | 20 - 30 minutes |

A detailed schedule based on your available dates will be prepared. Details of the activities are described below.

*What kind of surveys will be you answering*? On Day 1 you will be asked to fill out online survey questions regarding 1) general information such as your age and gender, and 2) information about your cancer such as symptoms of cancer treatments. On Day 2, Day 7 and Day 49 you will be asked to fill out online survey questions that inquire about your stress levels and how you feel about your cancer. For example, one question asks you, "How confident do you feel about expressing feelings about cancer?" In addition to the online surveys, you will also be asked to provide your saliva samples.

*Why we are obtaining your saliva?* We are collecting your saliva to test for biological indicators of stress such as 1) the hormone cortisol, 2) the enzyme α-amylase and 3) the immune marker C - reactive protein.

*What is the timing of saliva collection?* On Day 2, Day 7 and Day 49 you will be asked to provide your saliva samples. On these days, you will collect your saliva by yourself at three times of the day, 1) immediately after waking up, 2) 30 minutes after waking up and 3) before bedtime.

*How will you collect your saliva?* We will give you tubes to collect your saliva in. We have an instructional video that shows you how to collect your saliva in the tubes. This video will be available to you to watch online and a web-link for the video will be provided to you.

*Where will you store the saliva tubes?* After collecting your saliva samples, you will need to store the saliva tubes in your refrigerator. The research coordinator for this study will pick up the saliva tubes from your house at the end of the study.

If you decide to be in this research study, you will need to confirm that you have read and understood your involvement in this study. You will also confirm that you have had all of your questions answered and understand your participation in this study. You can contact Utkarsh Subnis (Research Coordinator) at any time

for any clarifications regarding your participation at **804-628-1454** or subnisub@vcu.edu. After reading this entire consent form, you will need to sign the consent section of this form on Page 5.

**RISKS AND DISCOMFORTS**
The expressive writing and some questions on the survey may bring back unpleasant memories of your experiences with cancer. You do not have to write about anything you don't feel comfortable about. You do not have to respond to any questions you do not want to think about. You may stop participating in the study at any time without penalty.

In case you experience any distress during or after completing the writing tasks, please consider using the **cancer supportive care services** listed at the end of this informed consent form (on page 6). You may contact the following members of our research team at any point during the study, and at any time of the day or night.

| Name of team member | Role in this study | Phone contact | Email contact |
|---|---|---|---|
| Utkarsh Subnis | Research Coordinator | (804)-628-1454 | subnisub@vcu.edu |
| Connie Macaluso | Licensed Clinical Social Worker | (804)-628-2106 | cmmacaluso@vcu.edu |
| Angela Starkweather | Registered Nurse and Researcher | (804)-828-3986 | astarkweathe@vcu.edu |
| Richard Brown | Principal Investigator | (804)-628-3340 | rbrown39@vcu.edu |

Just to make sure you are doing well during and after the writing tasks, members of research team (Utkarsh Subnis or Richard Brown) will be contacting you by phone on Day 4 and Day 7.

Please note that no information provided to you in his study is intended to provide legal or medical advice. Always seek the advice of your physician, other qualified health provider, or legal professional with any question you may have regarding the content in this information sheet or any medical condition.

**BENEFITS TO YOU AND OTHERS**
You will not receive any money as compensation for your participation. Expressive writing may help you make sense of your stressful experiences with cancer and help to manage your emotional stress. You will also have the opportunity to subscribe to email updates about the progress and results of this study. Although you may not benefit directly from participating in this study, the information we learn from people in this study may be useful to other cancer survivors. Your participation will also contribute to scientific knowledge.

**COSTS**
There are no costs for participating in this study other than your time.

**ALTERNATIVES**
You may choose not to participate in this research study. Your medical care will not be affected by this decision.

**CONFIDENTIALITY**
All data is being collected only for research purposes. Your data and saliva samples will be known by ID numbers. These ID numbers are randomly generated and cannot be connected to you in any way. The data will be entered directly in a password protected database that is accessible only to study personnel.

Your writing responses will be analyzed by a software program to identify patterns of words. Your writing responses will be destroyed after the data analysis is complete. The only circumstance under which we would break confidentiality would be if you express an immediate threat to harm yourself or others, such as expressing

suicidal thoughts. We would then need to take appropriate measures to prevent this, which include reporting the threat to appropriate authorities.

Potentially identifiable information about you will consist of your name and email address so that we can track your information over time. All personal identifying information will be kept in password protected files. Also, all identifying information will be removed and destroyed at the end of the study. All data from questionnaires, writing responses and saliva samples will be permanently anonymous upon completion of the study. A data file without any identifiable information will be kept indefinitely. Access to all data will be limited to study personnel. To protect your privacy and confidentiality, a data and safety monitoring plan has been established.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. We will not tell anyone the answers and responses you give us. What we find from this study may be presented at meetings or published in papers, but your name will never be used in these presentations or papers.

**VOLUNTARY PARTICIPATION AND WITHDRAWAL**

You do not have to participate in this study. If you choose to participate, you may stop at any time without any penalty. You may also choose not to answer particular questions that are asked in the study. If you choose not to take part in this study, or if you withdraw after you have started, you will not be penalized in any way, nor will the quality of care you receive be affected.

Your participation in this study may be stopped at any time by the study staff or the sponsor without your consent. The reasons might include:

- the study staff thinks it necessary for your health or safety;
- you have not followed study instructions;
- administrative reasons require your withdrawal.

**QUESTIONS**

In the future, you may have questions about your participation in this study. If you have any questions, complaints, or concerns about the research, contact Richard Brown or Utkarsh Subnis:

**Richard Brown**, PhD
Principal Investigator
Dept. of Social and Behavioral Health
School of Medicine, Virginia Commonwealth University
Richmond, VA 23298-0149, P.O. Box 980149
Telephone: 804-628-3340; Fax: 804-828-5440
Email: rbrown39@vcu.edu

**Utkarsh Subnis**, M.A., M.B.B.S.
Research Coordinator
Dept. of Social and Behavioral Health,
School of Medicine, Virginia Commonwealth University
Richmond, VA 23298-0149, P.O. Box 980149
Telephone: 804-628-1454; Fax: 804-828-5440
E-mail: subnisub@vcu.edu

The researchers named above are the best persons to call for questions about your participation in this study. If you have general questions about your rights as a participant in this or any other research, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000,
P.O. Box 980568, Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number for general questions, concerns, or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about

participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.
Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

**PROVIDING INFORMED CONSENT TO PARTICIPATE IN THIS STUDY**
If you decide to participate in this study, you will need to provide your consent. A copy of this form will be provided to you. Please keep that copy of this consent form for your records.

**CONSENT**
I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits, to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____
Participant Name
(Printed)

_____ _____
Participant Signature Date

_____
Name of Person Conducting Informed Consent Discussion
(Printed)

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

_____ _____
Principal Investigator Signature Date

## CANCER SUPPORTIVE CARE SERVICES

A list of supportive care services has been provided to you along with your mail-in packet. Please consider using any of the following services as per your needs.

If you want to talk to a counseling professional, you can call the **Cancer Information and Counseling Line Toll Free** at **1-800-525-3777**. The Cancer Information and Counseling Line (CICL) is a free nationally recognized telephone counseling service that is available Monday – Friday, 8:30 a.m. – 5 p.m. MT. CICL services range from providing emotional support to resource referrals. CICL also provide medical information for patients and caregivers affected by cancer. CICL counselors are master's-level psychosocial professionals that offer brief, personalized and professional counseling over the phone. They can support and assist with managing feelings, resolving challenges related to having cancer and communicating with doctors and loved ones.

In case you need an information service that is 24 hours and 7 days a week, you can reach the **American Cancer Society (ACS) hotline** at **1-800-227-2345, http://www.cancer.org/** . The ACS provides information and referral on various issues related to cancer treatment, services, literature, transportation, equipment, encouragement and support.

The National Cancer Institute (NCI) provides a comprehensive list of supportive care services to meet the supportive care needs of patients with cancer. You can make use of the **National Cancer Institute's Support Services** Locator at **http://supportorgs.cancer.gov/** . You can also call their toll-free phone number which is **1-800-4-CANCER (1-800-422-6237).** The NCI provides this service in English and Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m. ET.

You can also reach the VCU Dept. of psychiatry if you want to schedule an appointment with a board certified mental health professional. The Dept. of Psychiatry at VCU School of Medicine is available at **(804) 828-2000 or (800) 232-0901** (Select option 2 for appointments or Option 3 for admissions). The VCU Dept. of psychiatry has a system of Intake and Referral Service that expeditiously screen, evaluate and admit clinically appropriate patients to the various inpatient teams.

Finally, remember you can always contact members of our research team at any point and at any time of the day or night.

| Name of team member | Role in this study | Phone contact | Email contact |
|---|---|---|---|
| Utkarsh Subnis | Research Coordinator | (804)-628-1454 | subnisub@vcu.edu |
| Connie Macaluso | Licensed Clinical Social Worker | (804)-628-2106 | cmmacaluso@vcu.edu |
| Angela Starkweather | Registered Nurse and Researcher | (804)-828-3986 | astarkweathe@vcu.edu |
| Richard Brown | Principal Investigator | (804)-628-3340 | rbrown39@vcu.edu |

## Appendix J.

## Patient follow-up letter about saliva collection instructions

VCU MASSEY CANCER CENTER
Virginia Commonwealth University

Utkarsh Subnis, M.A., M.B.B.S.,
Research Coordinator
Department of Social and Behavioral Health,
Virginia Commonwealth University School of Medicine
Phone: 804-628-1454; Fax: 804-828-5440
E-mail: subnisub@vcu.edu

Dear [Pt. Name],

Thank you again for agreeing to participate in the research study regarding stress management for cancer survivors after radiation therapy. You will find inside this bubble mailer packet, the following materials:

- Instruction Sheet for Saliva Collection: Days & Timing
- Instruction Sheet for Saliva Collection: Steps & Procedures
- 1 sheet with your individual study activities schedule
- 3 Ziploc Freezer Bags Marked Day 2, Day 7 and Day 49
- 9 labeled saliva collection tubes (3 saliva tubes in each Ziploc freezer bag)
- 1 small Ziploc bag containing 9 pieces of straw
- 1 blue ball-pen

Please read the instruction sheets for the saliva collection. You can also watch a video for the saliva collection procedures at the following weblink: **http://youtu.be/zkH2CnMMwNM**

I will be in touch with you to set up a schedule for the study activities as per your convenience and time schedule. If you have any questions about the collection procedures, please feel free to contact me at any time by phone: 804-497-9890, 804-628-1454, email: subnisub@vcu.edu or Fax: 804-828-5440.

Sincerely,

Utkarsh Subnis, M.A., M.B.B.S.,
Research Coordinator
Graduate Assistant
Department of Social and Behavioral Health,
Virginia Commonwealth University School of Medicine
Phone: 804-497-9890, 804-628-1454; Fax: 804-828-5440
E-mail: subnisub@vcu.edu

# Appendix K:

## Instructions for saliva collection

If you have any questions please contact: Utkarsh Subnis: 804-628-1454; subnisub@vcu.edu

You are scheduled to collect your saliva samples on 3 days of the study. You are requested to collect 3 saliva samples on each day, please see Table 1 below.

**Table 1: Days for providing saliva samples**

| Day No. | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 49 |
|---|---|---|---|---|---|---|---|---|
| Study Activity (s) | Answer online surveys | Answer online surveys + **Provide 3 saliva samples** | Writing task | Writing task | Writing task | Writing task | Answer online surveys + **Provide 3 saliva samples** | Answer online surveys + **Provide 3 saliva samples** |

**Timing of collection of saliva samples**

Research has shown that human beings have changes in stress hormones levels as per the time of the day. That is why we need to obtain your saliva samples at three specific times of the day. We also need to able to identify the timing of collection of each saliva sample for our analysis. Hence, the saliva tubes have labels (shown on the right) which will help us identify the timing of the sample. The label contains no personal identifying information and cannot be connected to you.

PID No. _____
W☐ P☐ B☐ O☐

The table below describes in detail what times during the day you are requested to provide your 3 saliva samples. The table also provides instructions for which box you should check for each type of sample.

**Table 2: Timing of saliva samples and marking of samples**

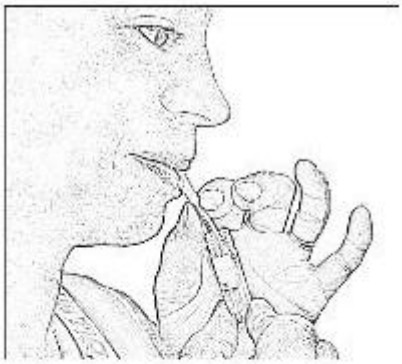
| Sample number | What time during the day to collect your saliva sample? | Which box to check on saliva tube label? |
|---|---|---|
| **1.** | Please provide your first saliva sample **immediately after you wake up**. This is when you have opened your eyes and are ready to get up for the day. (Note: You may keep the saliva collection tubes beside you the night before. This way you can collect your saliva before you get out of bed. You can also collect this sample immediately after getting out of bed.) | Please check box marked "**W**"<br>PID No. _____<br>**W☑** P☐ B☐ O☐ |
| **2.** | Please collect the second saliva sample at about **30 minutes after you have woken up** for the day. The timing of this sample is particularly important, so please make attempt to collect exactly 30 minutes after Sample 1. | Please check box marked "**P**"<br>PID No. _____<br>W☐ **P☑** B☐ O☐ |
| **3.** | Please collect the third and last saliva sample at bedtime. The timing for this sample is ideally **right before you get into bed**. | Please check box marked "**B**"<br>PID No. _____<br>W☐ P☐ **B☑** O☐ |
| **O** | In case you miss the timing for the samples or are unable to give a sample at any of the above 3 times, you can still provide your saliva sample at any time of the day. | Please check box marked "**O**"<br>PID No. _____<br>W☐ P☐ B☐ **O☑** |

If you have any questions please contact: Utkarsh Subnis: 804-628-1454; subnisub@vcu.edu

Please note: You are provided with 9 saliva collection tubes in 3 marked Ziploc bags, 9 straw pieces, and 1 pen.

**HOW TO GIVE A SALIVA SAMPLE***

1. First, please remove a straw piece from the Ziploc bag containing the 9 straw pieces.
2. Next, take one saliva collection tube and open the cap on the tube. Then place one end of the straw into the collection tube.
3. Then put the straw into your mouth, while holding the collection tube with the other hand. Please see the adjacent figure.
4. Close your mouth and imagine eating your favorite food. Tilt your head forward and drool your saliva down the straw into the collection tube. Continue until the saliva reaches the 0.5 mark line on the tube.
5. After collecting the saliva sample please discard the used straw.



6. Now please close the cap on the saliva tube. You will hear a gentle "click" sound when the tube is closed.
7. Please check the appropriate box on the saliva tube label, which is either "W" "P" "B" or "O", please see Instruction sheet for Saliva Collection: Days & Timing.
8. Place the saliva sample inside the marked Ziploc bag.
9. Repeat the same procedures for samples 2 and 3.

*Please note that a video describing these instructions for giving a saliva sample is available at the following weblink: **http://youtu.be/zkH2CnMMwNM**

10. Store the samples in the freezer compartment of your refrigerator.
Note: You may keep the collected samples in their Ziploc bags at room temperature for about 24 hours. However, please place them in your freezer compartment as soon as possible.

**HOW TO STORE YOUR SAMPLES**

11. After placing all 3 saliva samples into the Ziploc bag for the particular day, seal the Ziploc bag.
12. Place the Ziploc bag in the freezer compartment of your refrigerator.
13. Our study staff will contact you requesting for a convenient time to pick up your samples at the end of the study.

Please note BEFORE YOU GIVE A SAMPLE **AVOID:**

- Avoid consuming alcoholic beverages on the day you collect your samples.
- Avoid smoking or using tobacco or brushing your teeth 30 minutes before you collect a sample.
- Avoid eating anything between collecting sample #1 and #2.

## Appendix L.

## Saliva labels

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

PID No. _____
W□ P□ B□ O□

## Appendix M.

## Participant individual study activities schedule

**Your individual study activities schedule**

| Study Days | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 49 |
|---|---|---|---|---|---|---|---|---|
| Activities scheduled | Answer surveys online | Answer surveys online + Provide saliva samples | Writing online | Writing online | Writing online | Writing online | Answer surveys online + Provide saliva samples | Answer surveys online + Provide saliva samples |
| Time required | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes | 20 – 30 minutes |
| Dates | | | | | | | | |

**Study contact**: Utkarsh Subnis, MBBS, MA, Dept. of Social and Behavioral Health, VCU School of Medicine
Phone: **804-628-1454**, email: subnisub@vcu.edu

## Appendix N.

## Survey question on Day 1

- **Health-related symptoms and behaviors**

The following questions inquire about different areas of your general health and well-being. Please attempt to answer all questions. However, you may choose not to answer any question you do not feel comfortable with.

People sometimes look to others for companionship, assistance, or other types of support. ***How often is each of the following kinds of support available to you if you need it?*** If you are not sure about a question please rate it as best you can.

| | None of the time | A little of the time | Some of the time | Most of the time | All of the time | Don't know | Prefer not to answer |
|---|---|---|---|---|---|---|---|
| Someone to help with daily chores if you were sick | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Someone to turn to for suggestions about how to deal with a personal problem | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Someone to do something enjoyable with | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Someone to love and make you feel wanted | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

Think of this ladder as representing where people stand in the United States.


At the top of the ladder are the people who are best off—those who have the most money, most education and the best jobs. At the bottom are the people who are worst off—who have the least money. The higher up you are on this ladder, the closer you are to people at the very top and the lower you are, the closer you are to the bottom.


Where would you put yourself on this ladder?

Please place drag the bar on the red scale on the right to indicate as to where you think you stand right now in your life, relative to other people in the United State

Do you currently smoke cigarettes every day, on some days or not at all?

- ○ Every day
- ○ Some days
- ○ Not at all
- ○ Don't know
- ○ Prefer not to answer

The next couple of questions ask about the frequency of your smoking

| | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 | 50 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| How many cigarettes do you smoke on an average in a day? | | | | | | | | | | | |
| How many cigarettes do you smoke on an average in a week? | | | | | | | | | | | |

Have you smoked at least 100 cigarettes in your entire life?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Prefer not to answer

How often do you have a drink containing alcohol?

- ○ Never
- ○ Monthly or less
- ○ 2 to 4 times a month
- ○ 2 to 3 times a week
- ○ 4 or more times a week
- ○ Don't know
- ○ Prefer not to answer

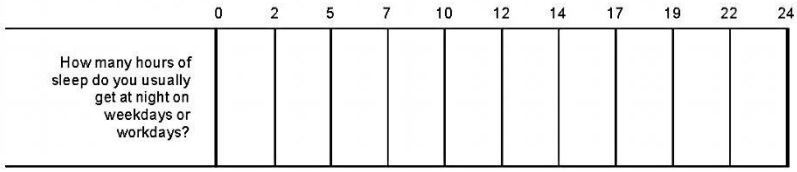
How often do you have 5 or more drinks on one occasion?

- ○ Never
- ○ Less than monthly
- ○ Monthly
- ○ Weekly
- ○ Daily or almost daily
- ○ Don't know
- ○ Prefer not to answer

Gum disease is a common problem with the mouth. People with gum disease might have swollen gums, receding gums, sore or infected gums or loose teeth. Do you think you might have gum disease?

- ○ Yes
- ○ Maybe
- ○ Don't know
- ○ Prefer not to answer

The following questions inquire about your sleep habits.




Have you ever been told by a doctor or other health professional that you have a sleep disorder?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Prefer not to answer

Over the last 2 weeks, how often have you been bothered by any of the following sleep related problems?

| | Not at all | Some of the days | More than half the days | Nearly every day | Don't know | Prefer not to answer |
|---|---|---|---|---|---|---|
| Difficulty Falling Asleep | ○ | ○ | ○ | ○ | ○ | ○ |
| Difficulty Staying Asleep | ○ | ○ | ○ | ○ | ○ | ○ |
| Problem Waking Up too Early | ○ | ○ | ○ | ○ | ○ | ○ |

Complementary and alternative medicine (CAM) consists of diverse medical and health care systems, practices, and products that patients report using for the purposes of stress-management and or improving general health and well-being. How often, if at all, have you used any of the following types of CAM in the past 12 months? Please check all that apply

| | Never | Less than Once a Month | Once a Month | 2-3 Times a Month | Once a Week | 2-3 Times a Week | Daily | Prefer not to answer |
|---|---|---|---|---|---|---|---|---|
| Mind/body practices, including hypnosis, meditation, yoga | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Positive psychology therapies - e.g. counseling, journaling, self-help seminars/audio-tapes | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Massage therapy, chiropractic manipulation, or other bodywork | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Naturopathy, acupuncture, or homeopathy | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Herbal products or dietary supplements | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| If Other, please specify | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

In the following questions please indicate how often you use computers during the week.

| | Seldom or Never use | 2 to 4 times a month | Once a Month | Weekly | Daily | Don't know | Prefer not to answer |
|---|---|---|---|---|---|---|---|
| How often do you use the computer at home? | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| How often do you use the computer at work? | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

How comfortable do you feel performing the following tasks?

| | Very comfortable | Somewhat comfortable | Not at all comfortable | Don't know | Prefer not to answer |
|---|---|---|---|---|---|
| Using a computer laptop/desktop to access the internet | ○ | ○ | ○ | ○ | ○ |
| Using email | ○ | ○ | ○ | ○ | ○ |
| Writing on your computer for 20 minutes continuously | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Survey questions on Day 1

- **Disease and treatment characteristics**

The following questions ask you about your cancer diagnosis and treatment. Please attempt to answer all questions. If you are not sure about any question please answer it as best you can. However, you may choose not to answer any question you do not feel comfortable with.

Have you personally been diagnosed with cancer?

- ○ Yes
- ○ No

Sorry, but we are currently conducting this study only for individuals who have been personally diagnosed and treated for cancer.

Where was the original site of your cancer (e.g. lung, breast)?

What was the stage of cancer at the time of diagnosis?

- ○ Stage I
- ○ Stage II
- ○ Stage III
- ○ Stage IV
- ○ Don't know/Not sure

What was the Date of Diagnosis (Month and Year) for the original cancer site?

| | Month | Year |
|---|---|---|
| Please Select: | ▼ | ▼ |

What type of treatment did you receive for the cancer?
(Please check all that apply)

- ☐ Chemotherapy
- ☐ Radiation
- ☐ Surgery
- ☐ Immunotherapy (For example, Interferon or Cancer Vaccines)
- ☐ Biological Therapy (For example, Gleevec, Iressa, Tarceva, Herceptin, Erbitux)
- ☐ Bone Marrow Transplant
- ☐ Peripheral Blood Stem Cell Transplant
- ☐ Hormonal Therapy
- ☐ Other

For how long did you receive radiation therapy for cancer?

- ○ Less than 3 months
- ○ 3 months
- ○ 6 months
- ○ 12 months
- ○ More than 12 months
- ○ Don't know/Not sure

What was the date of your last radiation treatment for cancer?

| | Month | Day | Year |
|---|---|---|---|
| Please Select: | ▼ | ▼ | ▼ |

## Appendix N.

## Survey questions on Day 1

- **Demographic characteristics**

What kind of health insurance or health care coverage do you have? (Please check all that apply)

- ☐ Private Health Insurance
- ☐ Medicare
- ☐ Medi-Gap
- ☐ Medicaid - Virginia Department of Medical Assistance Services (DMAS)
- ☐ Children's Health Insurance Program (CHIP)
- ☐ Military Health Care (TricareNa/Champ-Va)
- ☐ Indian Health Service
- ☐ State-Sponsored Health Plan
- ☐ Other Government Program
- ☐ Single Service Plan (e.g., Dental, Vision. Prescriptions)
- ☐ No Coverage of Any Type
- ☐ Don't know
- ☐ Prefer not to answer

How would you describe your current employment status? (Please check all that apply)

- ☐ Employed - Full time
- ☐ Employed - Part-time
- ☐ Self-employed
- ☐ Out of work for more than 1 year
- ☐ Out of work for less than 1 year
- ☐ A Homemaker
- ☐ A Student
- ☐ Retired
- ☐ Unable to work
- ☐ Don't know
- ☐ Prefer not to answer

What is the range of your annual family/household income?

- ○ Up to $25,000
- ○ $25,000 to $49,999
- ○ $50,000 to $74,999
- ○ $75,000 to $99,999
- ○ $100,000 and above
- ○ Don't know
- ○ Prefer not to answer

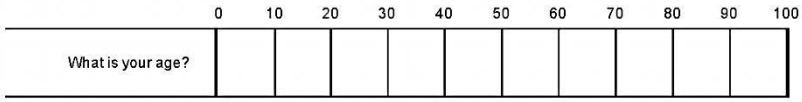
What is the highest grade or year of school you completed?

- ○ Never attended school or only attended kindergarten
- ○ Grades 1 through 8 (Elementary)
- ○ Grades 9 through 11 (Some high school)
- ○ Grade 12 or GED (High school graduate)
- ○ College 1 year to 3 years (Some college or technical school)
- ○ College 4 years or more (College graduate)
- ○ Masters/Doctorate (Post-graduate)
- ○ Don't know
- ○ Prefer not to answer

Are you currently ....?

- ○ Single
- ○ Divorced/separated
- ○ Married
- ○ Living together with a partner
- ○ Other
- ○ Don't know
- ○ Prefer not to answer

**What is your age? (*Please drag the slider below to point to your current age*)**




**What is your gender?**

- ○ Male
- ○ Female
- ○ Transgender
- ○ Other
- ○ Don't know
- ○ Prefer not to answer

Do you consider yourself as Hispanic/Latino?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Prefer not to answer

Which one or more of the following would you say is your race
[Please check all that apply]

- ☐ White
- ☐ Black or African American
- ☐ Asian or Native Hawaiian or Other Pacific Islander
- ☐ American Indian, Alaska Native
- ☐ Other [please specify]
- ☐ Don't know/Not sure
- ☐ Prefer not to answer

## Appendix N.

## Baseline outcome measures (Day 2)

- **Perceived stress scale (PSS)**

The following questionnaires inquire about your stress levels and your ability to deal with stress. Please click below a number to indicate your response. If you are not sure about a question, then please rate it as best you can. Please attempt to rate all questions. However, please remember that you may always choose not to answer any question that you do not feel comfortable with.

**The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Five possible responses to these questions are: 0 = Never, 1 = Almost Never, 2 = Sometimes, 3 = Fairly Often, 4 = Very Often.**

| | Never 0 | Almost never 1 | Sometimes 2 | Fairly often 3 | Very often 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| In the last month, how often have you been upset because of something that happened unexpectedly? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that you were unable to control the important things in your life? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt nervous and "stressed"? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt confident about your ability to handle your personal problems? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that things were going your way? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you found that you could not cope with all the things that you had to do? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you been able to control irritations in your life? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that you were on top of things? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you been angered because of things that were outside of your control? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? | ○ | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Baseline outcome measures (Day 2)

- **Fear of cancer recurrence – severity subscale (FCRI-S)**

**Research tells us that fear of cancer recurrence can be a stressor for some patients after completing cancer treatments. The following questions ask about how you feel about cancer recurrence. Please rate each question based on how you feel right now. Please remember that you may always choose not to answer any question that you do not feel comfortable with.**

| | Never 0 | 1 | 2 | 3 | All the Time 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| How long have you been thinking about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| How many times per day do you spend thinking about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| How often do you think about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| When I think about possibility of cancer recurrence, other unpleasant thoughts or images come to mind (e.g. suffering, consequences for my family)? | ○ | ○ | ○ | ○ | ○ | ○ |

**Please indicate your response to the following question and statements regarding cancer recurrence**

| | Not at all 0 | 1 | 2 | 3 | A great deal 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| In your opinion, what is your risk of having a cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| I am afraid of a cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |
| I am worried or anxious about the possibility of cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |
| I believe that I am cured and the cancer will not come back | ○ | ○ | ○ | ○ | ○ | ○ |
| I think it's normal to be anxious or worried about the possibility of cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Baseline outcome measures (Day 2)

- **Cancer behavior inventory – brief version (CBI-B)**

**The following questionnaire asks about your judgment of how confident you are to accomplish certain behaviors after completing cancer treatments. Please rate the following statements on how confident you are right now (or in the near future) that you can accomplish that behavior.**

| | Not at all confident 1 | 2 | 3 | 4 | Moderately Confident 5 | 6 | 7 | 8 | Totally Confident 9 | Prefer not to answer |
|---|---|---|---|---|---|---|---|---|---|---|
| Maintaining independence | O | O | O | O | O | O | O | O | O | O |
| Maintaining a positive attitude | O | O | O | O | O | O | O | O | O | O |
| Maintaining a sense of humor | O | O | O | O | O | O | O | O | O | O |
| Expressing feelings about cancer | O | O | O | O | O | O | O | O | O | O |
| Putting things out of my mind at times | O | O | O | O | O | O | O | O | O | O |
| Maintaining activities (work, home, hobbies, social) | O | O | O | O | O | O | O | O | O | O |
| Trying to be calm throughout survivorship and not allowing scary thoughts to upset me | O | O | O | O | O | O | O | O | O | O |
| Actively participating in treatment decisions | O | O | O | O | O | O | O | O | O | O |
| Asking physicians questions | O | O | O | O | O | O | O | O | O | O |
| Seeking social support | O | O | O | O | O | O | O | O | O | O |
| Sharing my worries or concerns with others | O | O | O | O | O | O | O | O | O | O |
| Managing nausea and vomiting (whether or not I have had these problems in the past) | O | O | O | O | O | O | O | O | O | O |
| Coping with physical challenges | O | O | O | O | O | O | O | O | O | O |
| Trying to be calm while waiting at least one hour for my doctor's appointment | O | O | O | O | O | O | O | O | O | O |

## Appendix N.

## Expressive Writing Prompts

- **Day 3**

For the next 4 days, I would like you to write your thoughts and feelings about your cancer experience. In your writing, I'd like you to really let go and explore your deepest emotions and thoughts about your cancer. You may tie your topic to your relationships with others, including parents, lovers, friends or relatives. You may write about the same general issues or experiences on all days of writing or about different topics each day. All of your writing will be completely confidential. Don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

If you feel the need to talk to a counseling professional, you can call the **Cancer Information and Counseling Line Toll Free** at **1-800-525-3777**. The Cancer Information and Counseling Line (CICL) is a free nationally recognized telephone counseling service that is available Monday – Friday, 8:30 a.m. - 5 p.m. MT.

In case you need an information service that is 24 hours and 7 days a week, you can reach the **American Cancer Society (ACS) hotline** at **1-800-227-2345,** http://www.cancer.org/

Also, the National Cancer Institute (NCI) provides a comprehensive list of supportive care services to meet the supportive care needs of patients with cancer. You can make use of the **National Cancer Institute's Support Services** Locator at http://supportorgs.cancer.gov/. You can also call the National Cancer Institute's toll-free phone number which is **1-800-4-CANCER (1-800-422-6237).** The NCI provides this service in English and Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m. ET.

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## Appendix N.

## Expressive Writing Prompts

- **Day 4**

Today is the second day of this expressive writing task. Again, I would like you to write your thoughts and feelings about your cancer experience. In your writing, I'd like you to really let go and explore your deepest emotions and thoughts about your cancer. You may tie your topic to your relationships with others, including parents, lovers, friends or relatives. You may write about the same general issues or experiences you wrote about yesterday. You may also write about different topics today. All of your writing will be completely confidential. Don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

If you feel the need to talk to a counseling professional, you can call the **Cancer Information and Counseling Line Toll Free** at **1-800-525-3777**. The Cancer Information and Counseling Line (CICL) is a free nationally recognized telephone counseling service that is available Monday – Friday, 8:30 a.m. - 5 p.m. MT.

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## Appendix N.

## Expressive Writing Prompts

- **Day 5**

Today is the third day of this expressive writing task. Again, I would like you to write your thoughts and feelings about your cancer experience. In your writing, I'd like you to really let go and explore your deepest emotions and thoughts about your cancer. You may tie your topic to your relationships with others, including parents, lovers, friends or relatives. You may write about the same general issues or experiences you wrote about yesterday. You may also write about different topics today. All of your writing will be completely confidential. Don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

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## Appendix N.

## Expressive Writing Prompts

- **Day 6**

Today is the fourth and final day of this expressive writing task Again, I would like you to write your thoughts and feelings about your cancer experience. In your writing, I'd like you to really let go and explore your deepest emotions and thoughts about your cancer. You may tie your topic to your relationships with others, including parents, lovers, friends or relatives. You may write about the same general issues or experiences you wrote about yesterday. You may also write about different topics today. All of your writing will be completely confidential. Don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

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## Appendix N.

## Control Writing Prompts

- **Day 3**

For the next 4 days, I would like you to write about how you use your time. Each session, you will get different writing tasks on the way you spend your time. In today's writing, your task is to describe what you did yesterday from the time you got up until the time you went to bed. For example, you might start when your alarm went off and you got out of bed. You could include the things you ate, where you went, which buildings or objects you passed by as you walked from place to place. In your writing, we'd like you to be as objective as possible, by concentrating on the facts and details of how you spend your time. We are not interested in your emotions or opinions; rather we want you to try to be completely objective. All of your writing will be completely confidential. Feel free to be as detailed as possible, but don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

If you feel the need to talk to a counseling professional, you can call the **Cancer Information and Counseling Line Toll Free** at **1-800-525-3777**. The Cancer Information and Counseling Line (CICL) is a free nationally recognized telephone counseling service that is available Monday – Friday, 8:30 a.m. - 5 p.m. MT.

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## Appendix N.

## Control Writing Prompts

- **Day 4**

Today is the second day of this writing task. Again, I would like you to write about how you use your time. In today's writing, your task is to describe what you have done today since you woke up. For example, you might begin when your alarm went off and write about your morning chores or activities. In your writing, we'd like you to be as objective as possible, by concentrating on the facts and details of how you spend your time. We are not interested in your emotions or opinions; rather we want you to try to be completely objective. All of your writing will be completely confidential. Feel free to be as detailed as possible, but don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

If you feel the need to talk to a counseling professional, you can call the **Cancer Information and Counseling Line Toll Free** at **1-800-525-3777**. The Cancer Information and Counseling Line (CICL) is a free nationally recognized telephone counseling service that is available Monday – Friday, 8:30 a.m. - 5 p.m. MT.

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## Appendix N.

## Control Writing Prompts

- **Day 5**

Today is the third day of this writing task. Again, I would like you to write about how you use your time. In today's writing, your task is to describe what you will do as soon as this writing session is over until you go to bed tonight. For example, you may say watch TV, and also list the TV shows you will watch. In your writing, we'd like you to be as objective as possible, by concentrating on the facts and details of how you spend your time. We are not interested in your emotions or opinions; rather we want you to try to be completely objective. All of your writing will be completely confidential. Feel free to be as detailed as possible, but don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

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## Appendix N.

## Control Writing Prompts

- **Day 6**

Today is the fourth and final day of this writing task. Again, I would like you to write about how you use your time. In today's writing, your task is to describe what you will be doing over the next week. For example, you could write down your tasks and "to-do" lists or activities for next week. In your writing, we'd like you to be as objective as possible, by concentrating on the facts and details of how you spend your time. We are not interested in your emotions or opinions; rather we want you to try to be completely objective. All of your writing will be completely confidential. Feel free to be as detailed as possible, but don't worry about spelling, grammar or sentence structure. The only rule is that once you begin writing, you should continue writing for 20 minutes, at most for 30 minutes. You can begin writing in the space provided below:

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## Appendix N.

## Immediate post-intervention outcome measures (Day 7)

- **Perceived stress scale (PSS)**

The following questionnaires inquire about your stress levels and your ability to deal with stress. Please click below a number to indicate your response. If you are not sure about a question, then please rate it as best you can. Please attempt to rate all questions. However, please remember that you may always choose not to answer any question that you do not feel comfortable with.

**The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Five possible responses to these questions are: 0 = Never, 1 = Almost Never, 2 = Sometimes, 3 = Fairly Often, 4 = Very Often.**

| | Never 0 | Almost never 1 | Sometimes 2 | Fairly often 3 | Very often 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| In the last month, how often have you been upset because of something that happened unexpectedly? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that you were unable to control the important things in your life? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt nervous and "stressed"? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt confident about your ability to handle your personal problems? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that things were going your way? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you found that you could not cope with all the things that you had to do? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you been able to control irritations in your life? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that you were on top of things? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you been angered because of things that were outside of your control? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? | ○ | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Immediate post-intervention outcome measures (Day 7)

- **Fear of cancer recurrence – severity subscale (FCRI-S)**

**Research tells us that fear of cancer recurrence can be a stressor for some patients after completing cancer treatments. The following questions ask about how you feel about cancer recurrence. Please rate each question based on how you feel right now. Please remember that you may always choose not to answer any question that you do not feel comfortable with.**

| | Never 0 | 1 | 2 | 3 | All the Time 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| How long have you been thinking about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| How many times per day do you spend thinking about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| How often do you think about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| When I think about possibility of cancer recurrence, other unpleasant thoughts or images come to mind (e.g. suffering, consequences for my family)? | ○ | ○ | ○ | ○ | ○ | ○ |

**Please indicate your response to the following question and statements regarding cancer recurrence**

| | Not at all 0 | 1 | 2 | 3 | A great deal 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| In your opinion, what is your risk of having a cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| I am afraid of a cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |
| I am worried or anxious about the possibility of cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |
| I believe that I am cured and the cancer will not come back | ○ | ○ | ○ | ○ | ○ | ○ |
| I think it's normal to be anxious or worried about the possibility of cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Immediate post-intervention outcome measures (Day 7)

- **Cancer behavior inventory – brief version (CBI-B)**

**The following questionnaire asks about your judgment of how confident you are to accomplish certain behaviors after completing cancer treatments. Please rate the following statements on how confident you are right now (or in the near future) that you can accomplish that behavior.**

| | Not at all confident 1 | 2 | 3 | 4 | Moderately Confident 5 | 6 | 7 | 8 | Totally Confident 9 | Prefer not to answer |
|---|---|---|---|---|---|---|---|---|---|---|
| Maintaining independence | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Maintaining a positive attitude | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Maintaining a sense of humor | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Expressing feelings about cancer | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Putting things out of my mind at times | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Maintaining activities (work, home, hobbies, social) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Trying to be calm throughout survivorship and not allowing scary thoughts to upset me | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Actively participating in treatment decisions | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Asking physicians questions | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Seeking social support | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Sharing my worries or concerns with others | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Managing nausea and vomiting (whether or not I have had these problems in the past) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Coping with physical challenges | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Trying to be calm while waiting at least one hour for my doctor's appointment | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Delayed post-intervention outcome measures (Day 49)

- **Perceived stress scale (PSS)**

The following questionnaires inquire about your stress levels and your ability to deal with stress. Please click below a number to indicate your response. If you are not sure about a question, then please rate it as best you can. Please attempt to rate all questions. However, please remember that you may always choose not to answer any question that you do not feel comfortable with.

**The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way. Five possible responses to these questions are: 0 = Never, 1 = Almost Never, 2 = Sometimes, 3 = Fairly Often, 4 = Very Often.**

| | Never 0 | Almost never 1 | Sometimes 2 | Fairly often 3 | Very often 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| In the last month, how often have you been upset because of something that happened unexpectedly? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that you were unable to control the important things in your life? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt nervous and "stressed"? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt confident about your ability to handle your personal problems? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that things were going your way? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you found that you could not cope with all the things that you had to do? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you been able to control irritations in your life? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt that you were on top of things? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you been angered because of things that were outside of your control? | ○ | ○ | ○ | ○ | ○ | ○ |
| In the last month, how often have you felt difficulties were piling up so high that you could not overcome them? | ○ | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Delayed post-intervention outcome measures (Day 49)

- **Fear of cancer recurrence – severity subscale (FCRI-S)**

**Research tells us that fear of cancer recurrence can be a stressor for some patients after completing cancer treatments. The following questions ask about how you feel about cancer recurrence. Please rate each question based on how you feel right now. Please remember that you may always choose not to answer any question that you do not feel comfortable with.**

| | Never 0 | 1 | 2 | 3 | All the Time 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| How long have you been thinking about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| How many times per day do you spend thinking about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| How often do you think about the possibility of cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| When I think about possibility of cancer recurrence, other unpleasant thoughts or images come to mind (e.g. suffering, consequences for my family)? | ○ | ○ | ○ | ○ | ○ | ○ |

**Please indicate your response to the following question and statements regarding cancer recurrence**

| | Not at all 0 | 1 | 2 | 3 | A great deal 4 | Prefer not to answer |
|---|---|---|---|---|---|---|
| In your opinion, what is your risk of having a cancer recurrence? | ○ | ○ | ○ | ○ | ○ | ○ |
| I am afraid of a cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |
| I am worried or anxious about the possibility of cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |
| I believe that I am cured and the cancer will not come back | ○ | ○ | ○ | ○ | ○ | ○ |
| I think it's normal to be anxious or worried about the possibility of cancer recurrence | ○ | ○ | ○ | ○ | ○ | ○ |

## Appendix N.

## Delayed post-intervention outcome measures (Day 49)

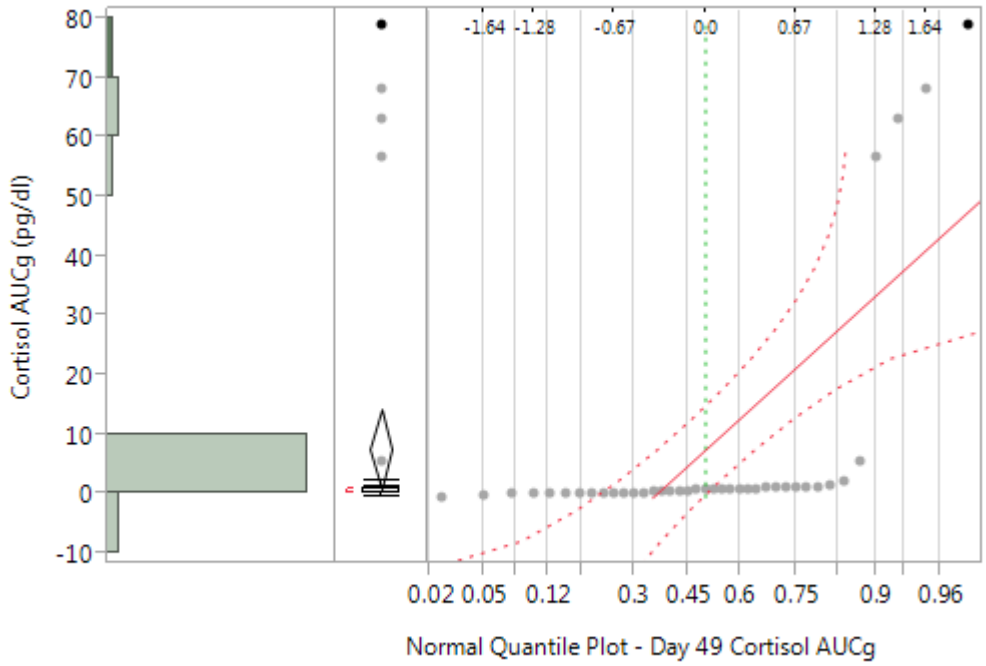
- **Cancer behavior inventory – brief version (CBI-B)**

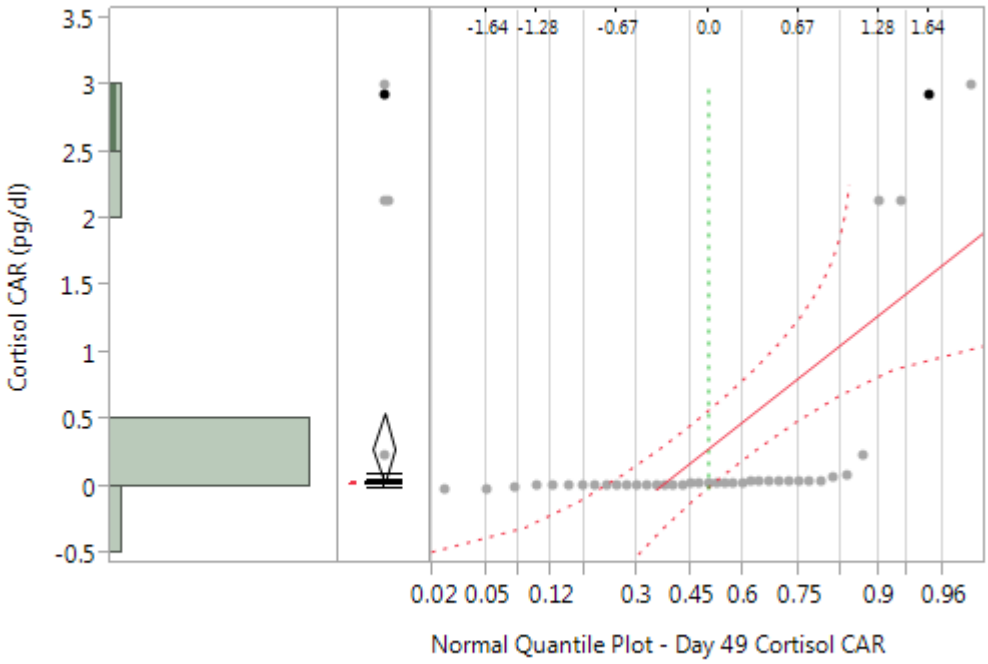
**The following questionnaire asks about your judgment of how confident you are to accomplish certain behaviors after completing cancer treatments. Please rate the following statements on how confident you are right now (or in the near future) that you can accomplish that behavior.**

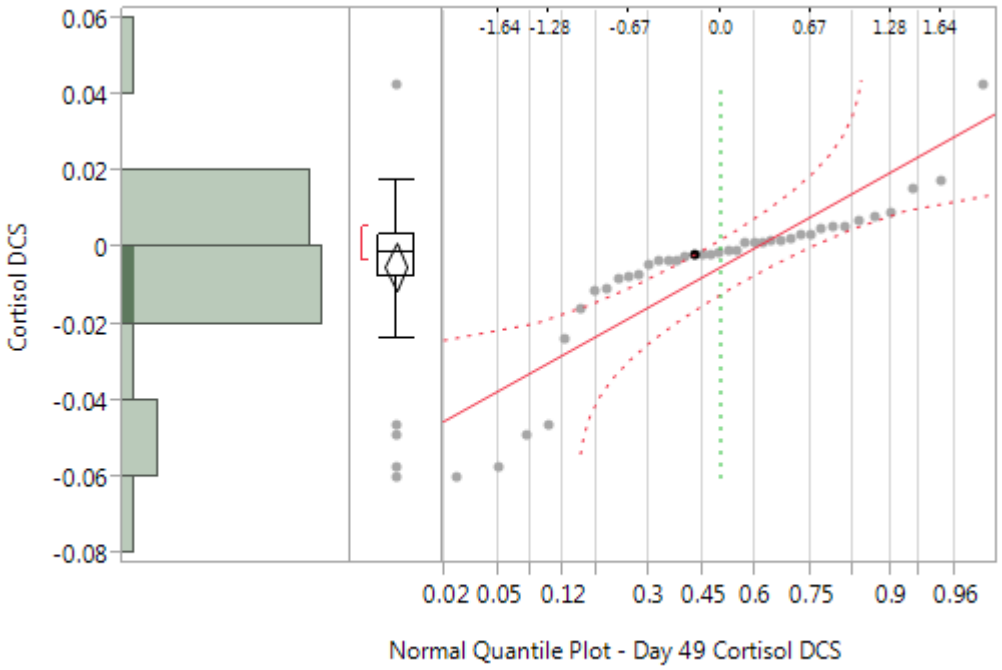
| | Not at all confident 1 | 2 | 3 | 4 | Moderately Confident 5 | 6 | 7 | 8 | Totally Confident 9 | Prefer not to answer |
|---|---|---|---|---|---|---|---|---|---|---|
| Maintaining independence | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Maintaining a positive attitude | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Maintaining a sense of humor | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Expressing feelings about cancer | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Putting things out of my mind at times | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Maintaining activities (work, home, hobbies, social) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Trying to be calm throughout survivorship and not allowing scary thoughts to upset me | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Actively participating in treatment decisions | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Asking physicians questions | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Seeking social support | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Sharing my worries or concerns with others | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Managing nausea and vomiting (whether or not I have had these problems in the past) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Coping with physical challenges | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Trying to be calm while waiting at least one hour for my doctor's appointment | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

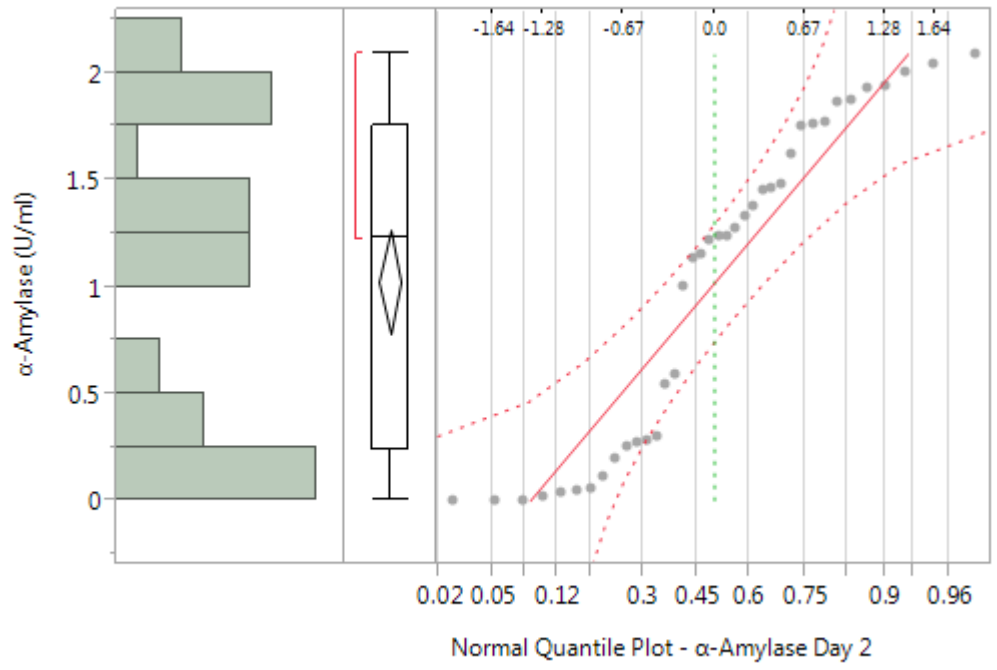
## Appendix O.

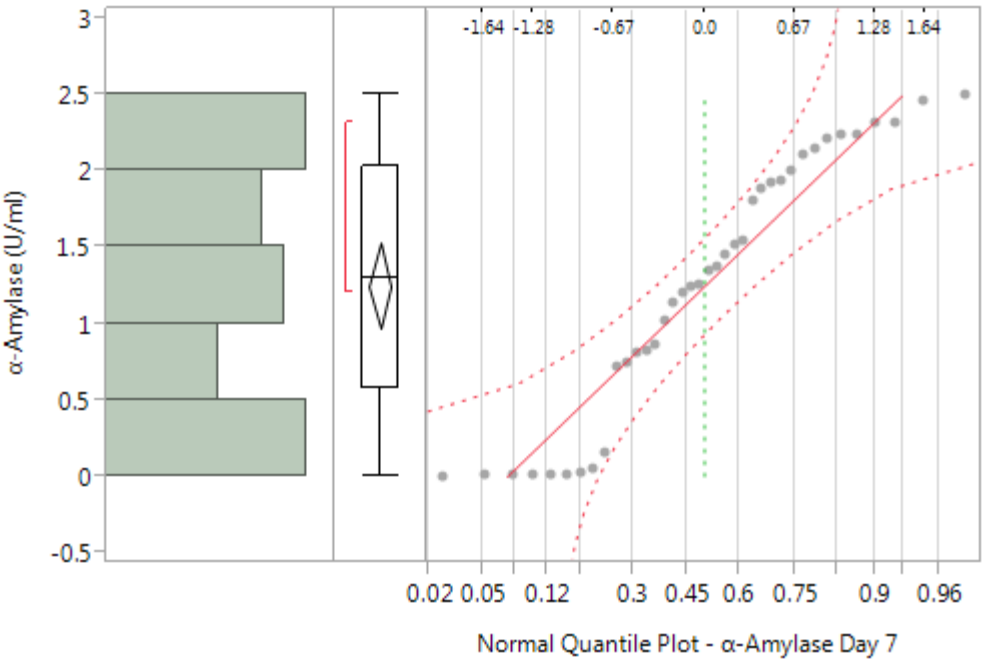
**Figures of normal quantile plots for distribution of all outcome variables in study**

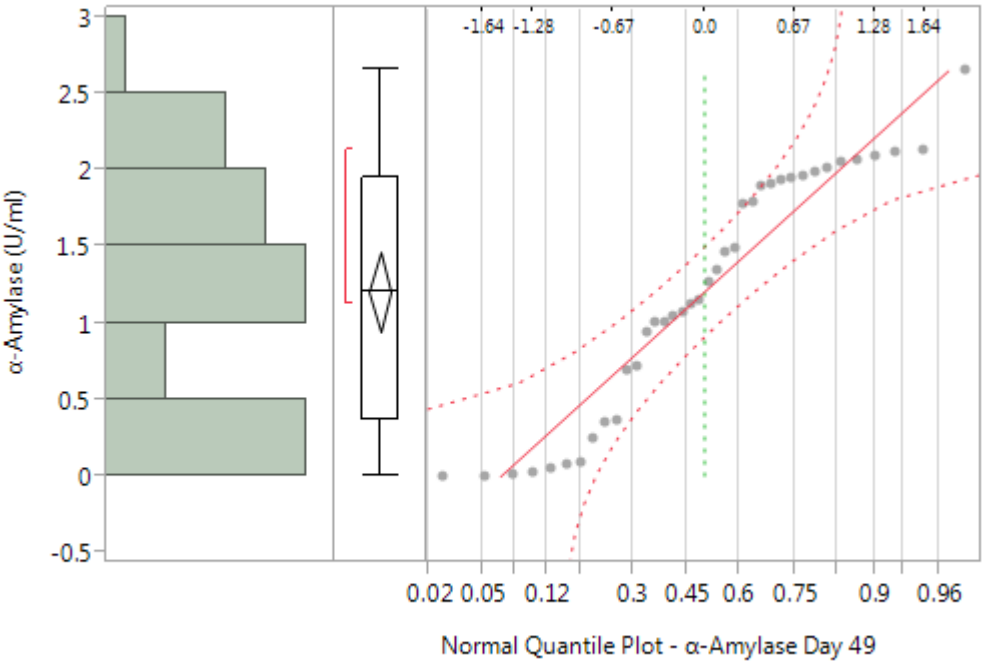


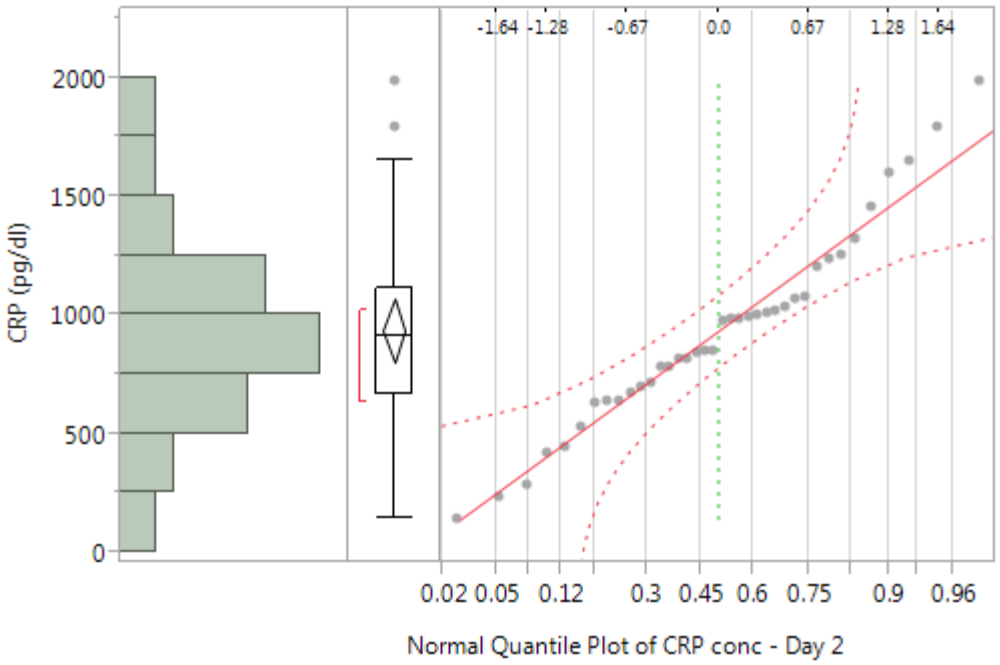





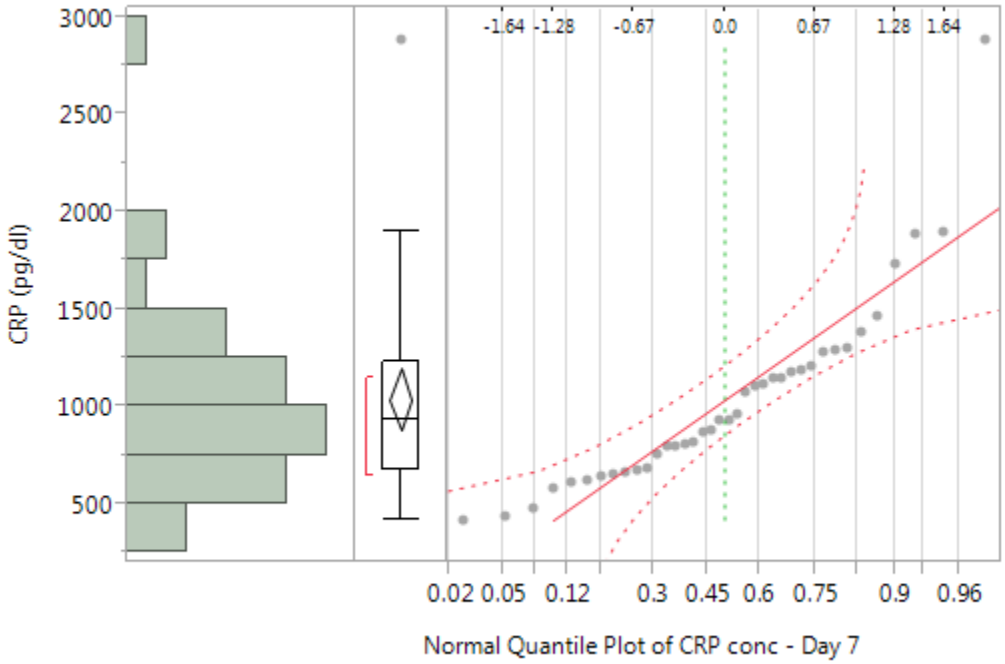





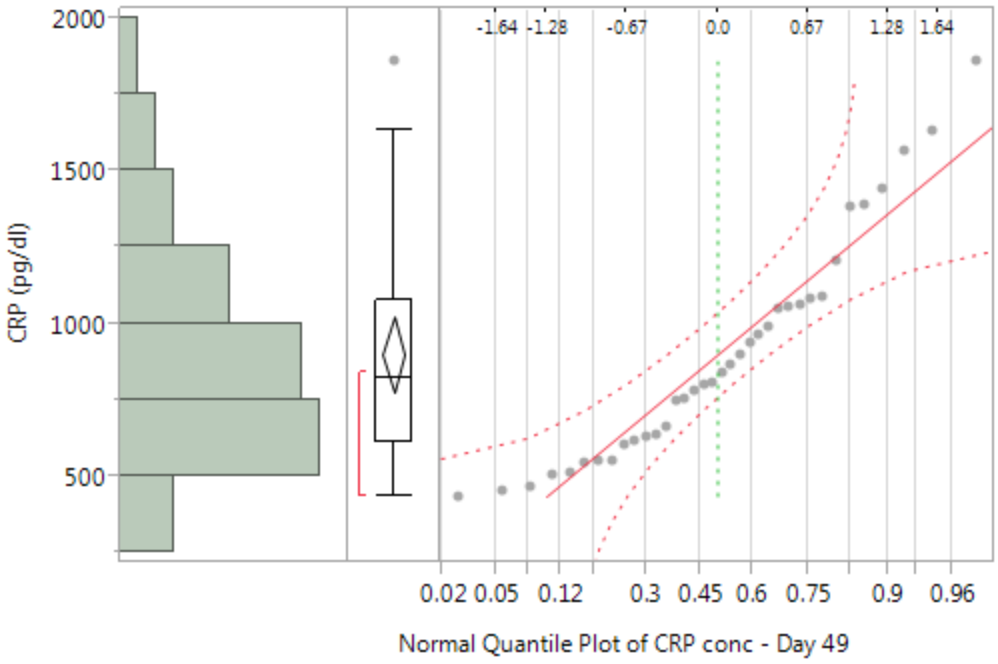






Normal Quantile Plot of CRP conc - Day 2




Normal Quantile Plot of CRP conc - Day 7

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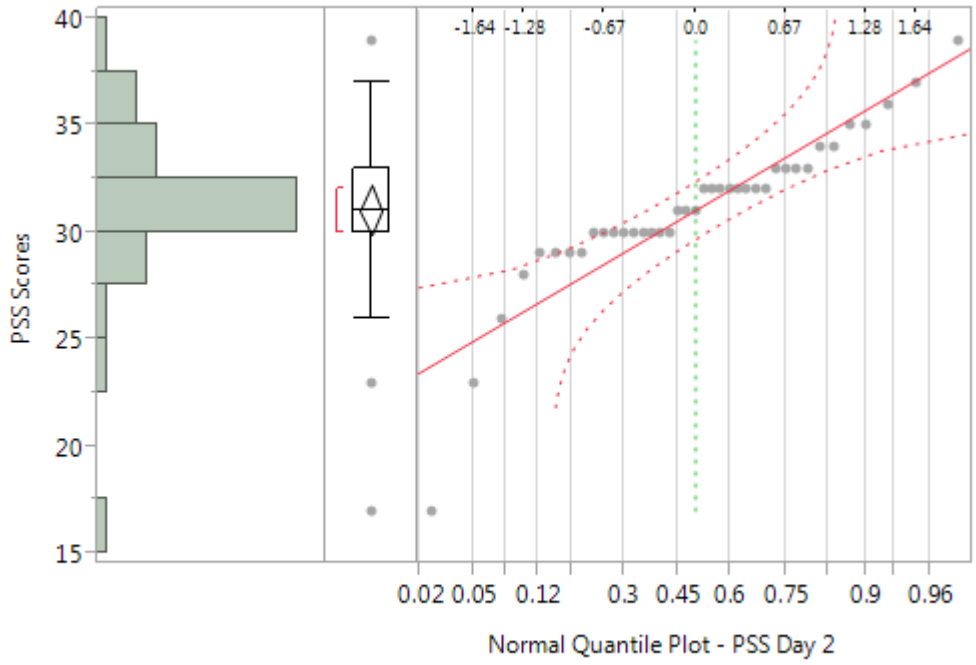
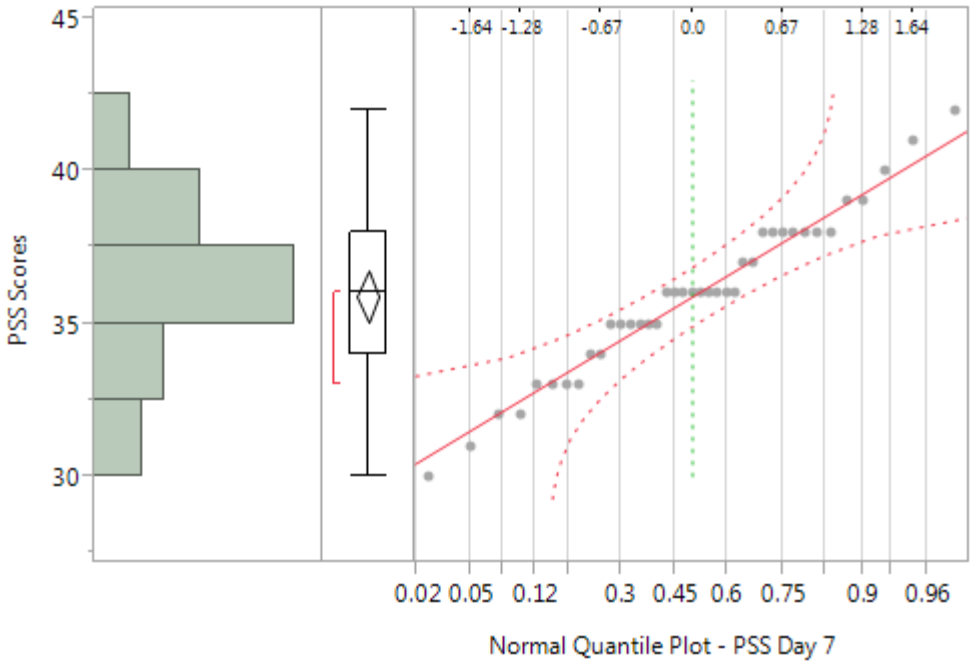
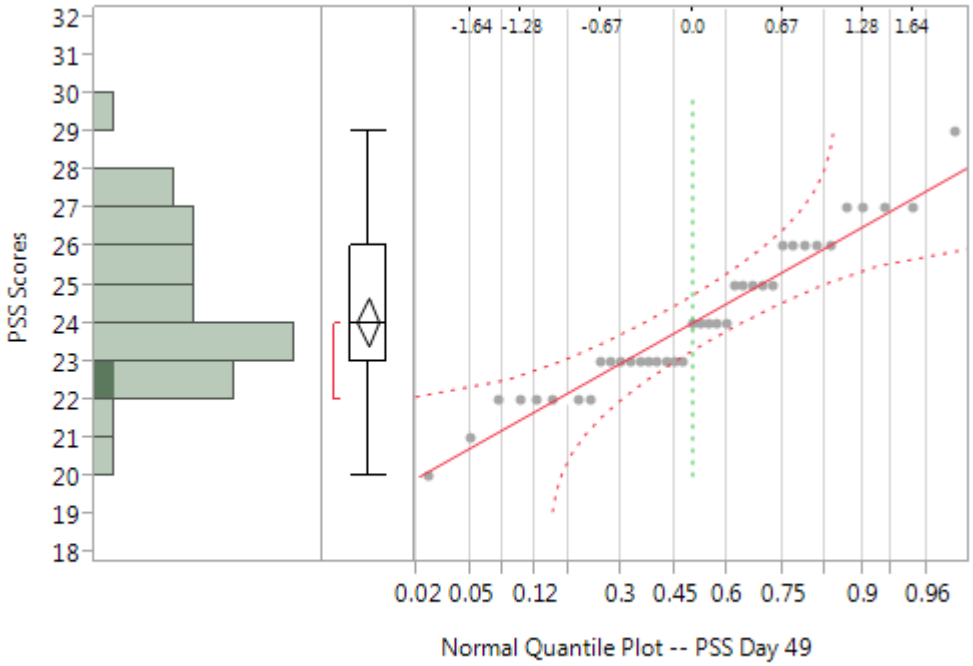
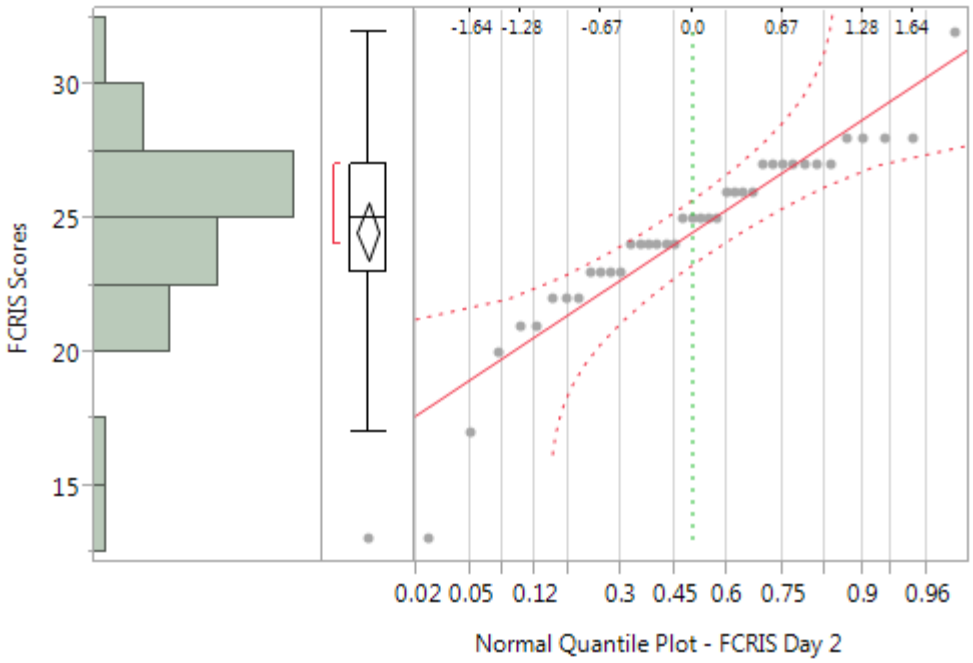
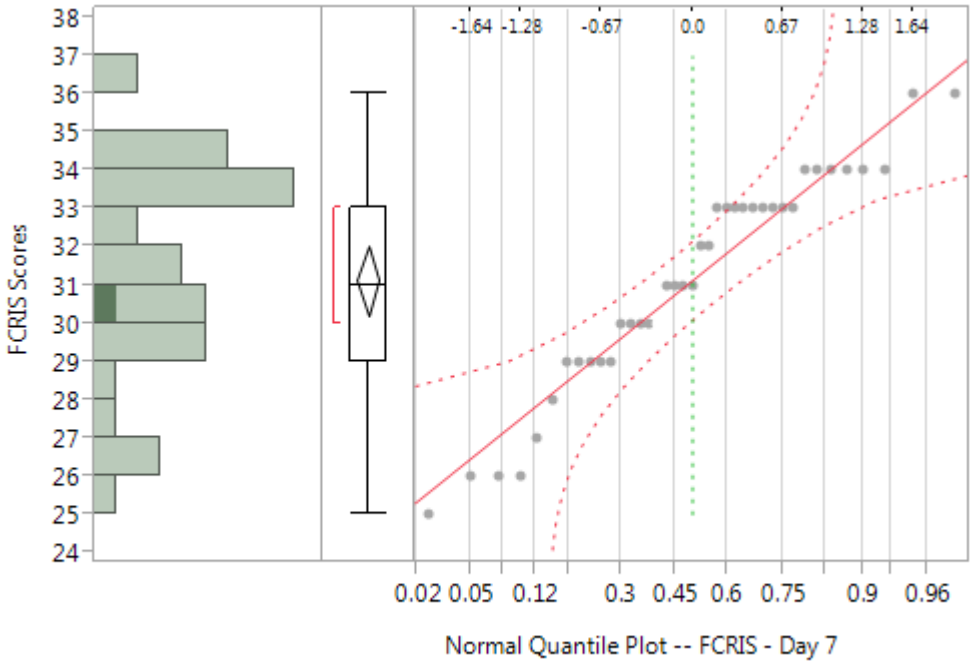
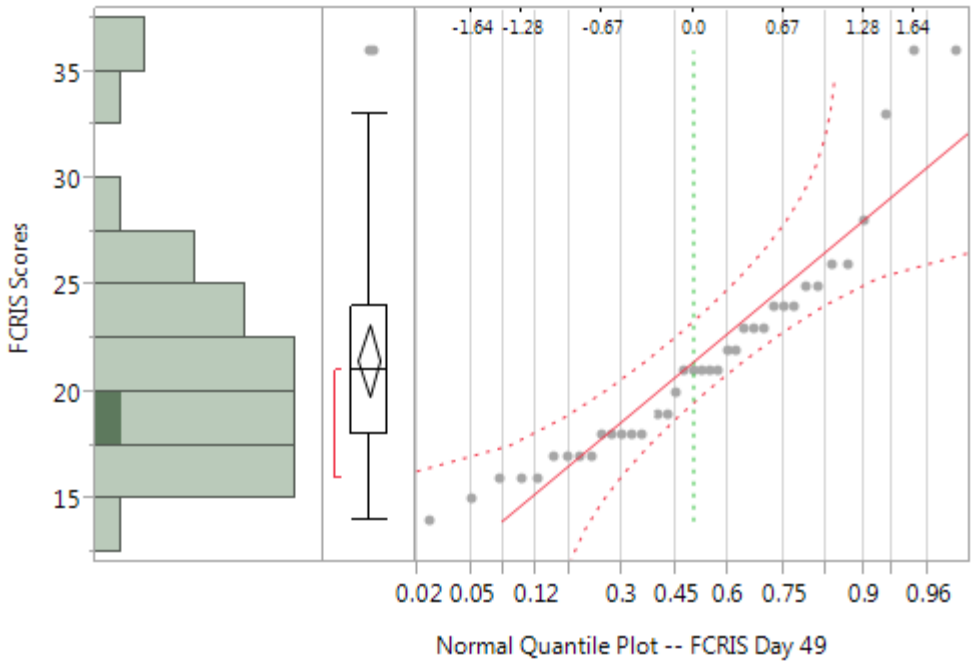


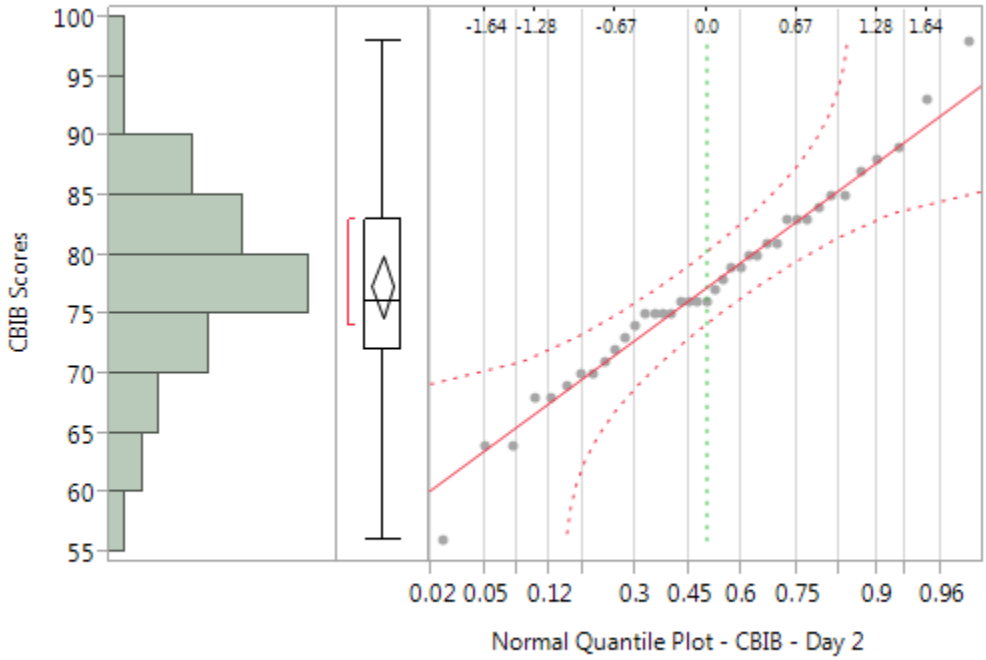


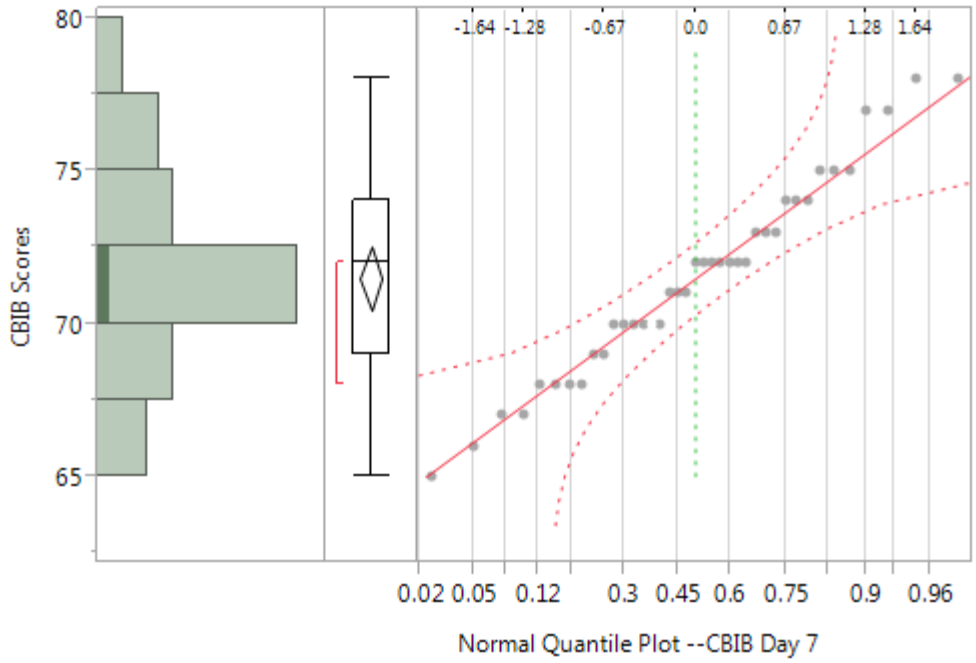



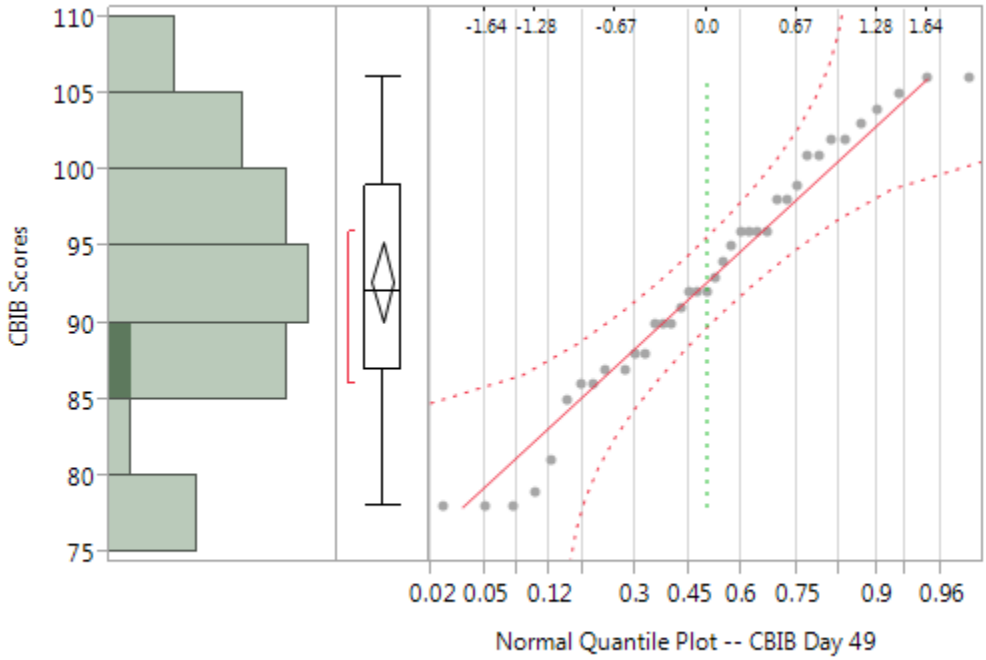






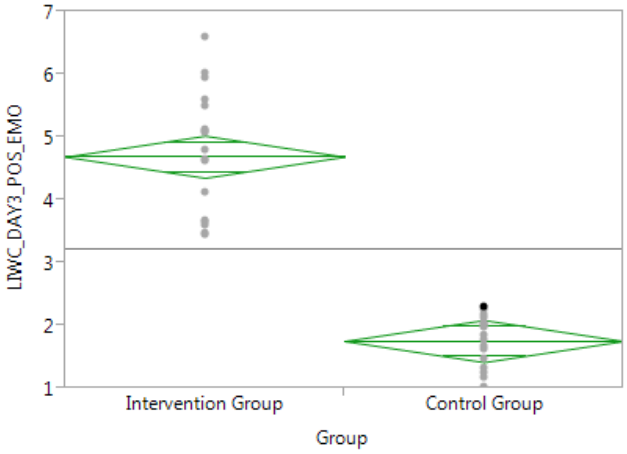
## Appendix P.

### Figures for group differences in LIWC word counts

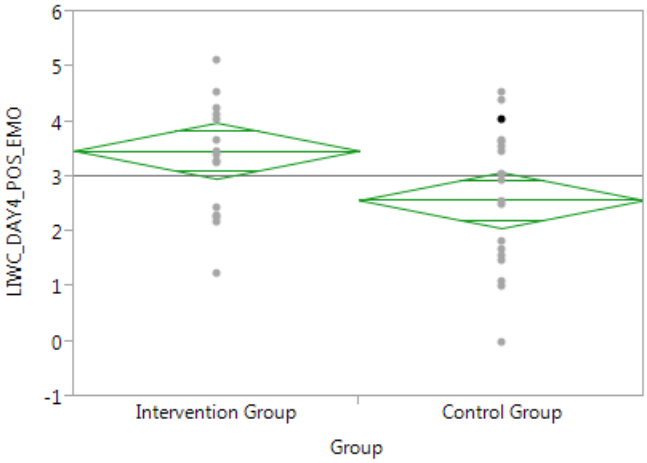
- **Positive emotion words (POS_EMO) used on days 3, 4, 5 and 6**
- **Negative emotion word (NEG_EMO) used on days 3, 4, 5 and 6**

Positive Emotion Words Used (POS_EMO)

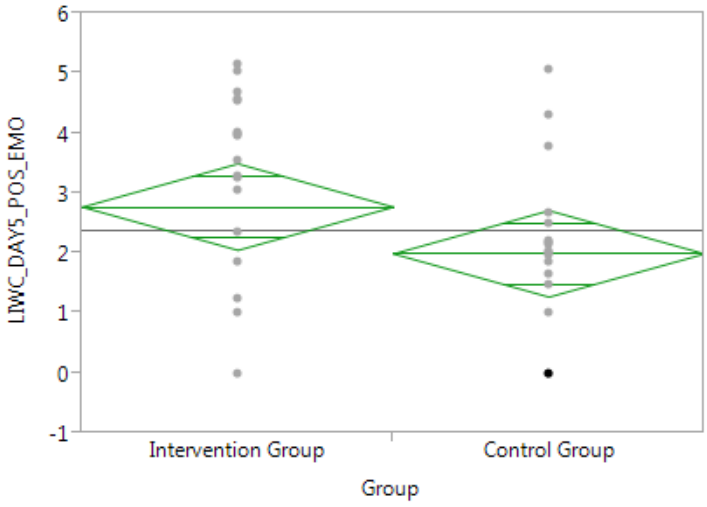
Day 3



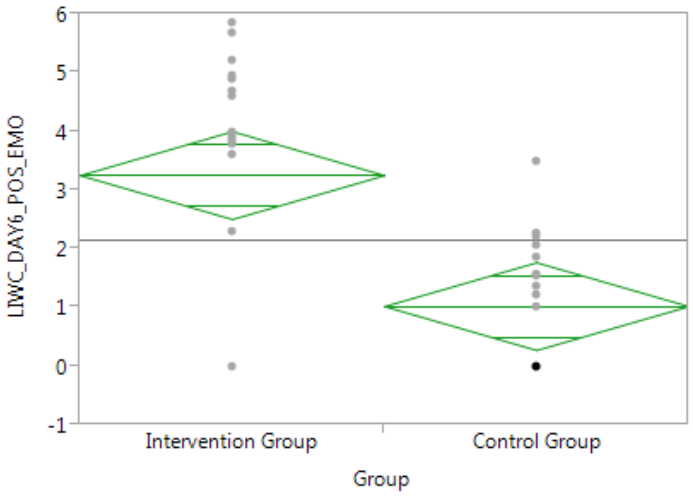

Day 4



Day 5

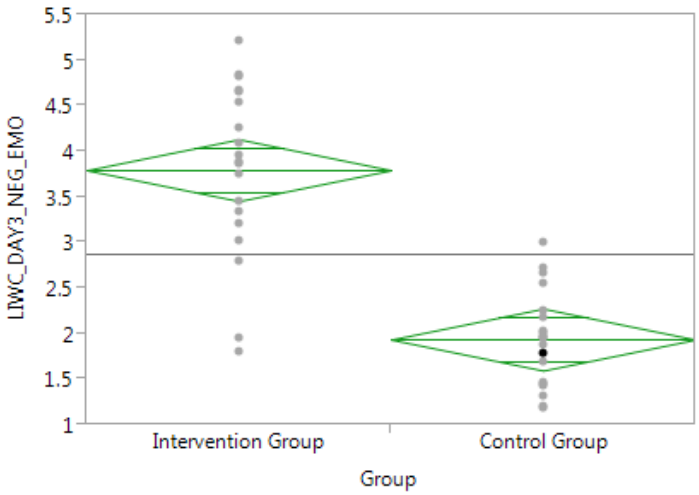



Day 6

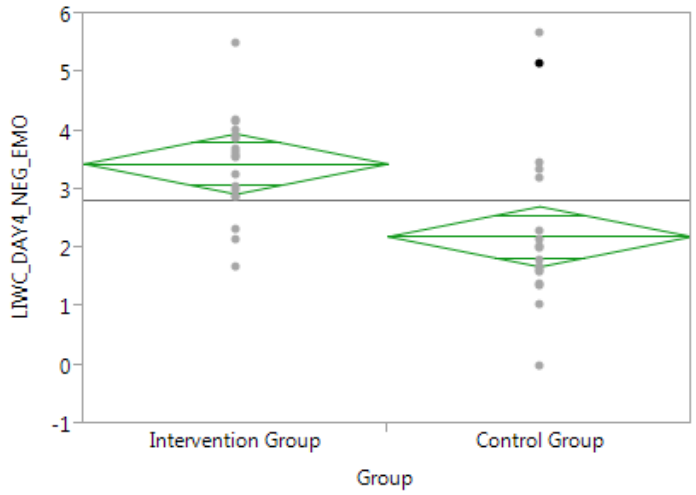


Negative Emotion Words Used (NEG_EMO)

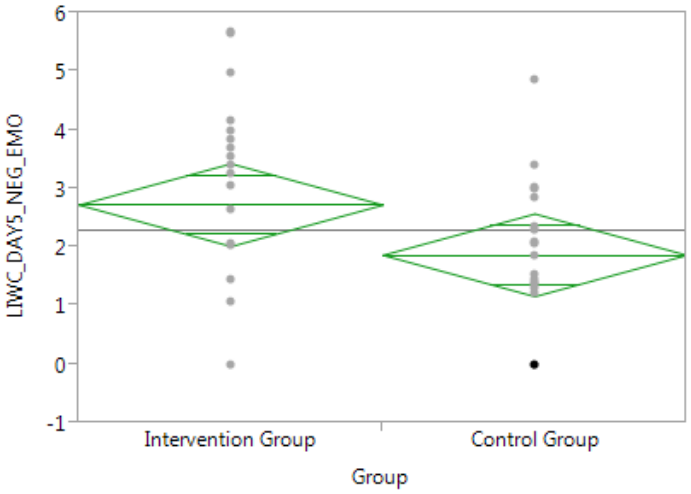
Day 3



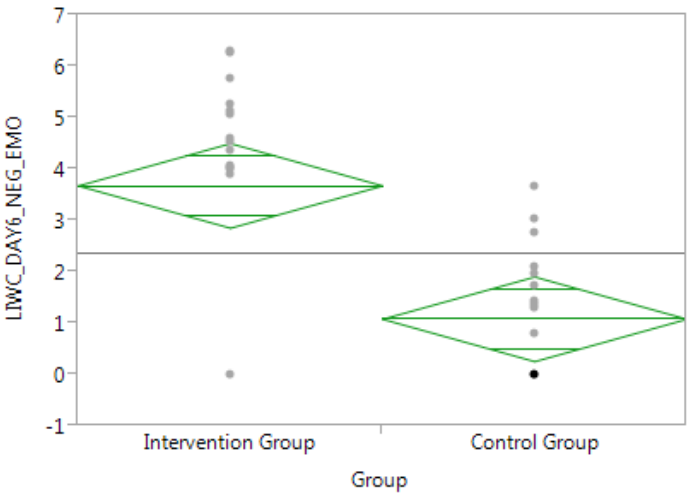

Day 4



Day 5




Day 6



## Vita

Utkarsh Bandunana Subnis was born on June 15, 1984, in Mumbai, India and is a citizen of the Republic of India. He graduated from Jai Hind High School in 2002. He completed his medical training and received his Bachelor of Medicine and Bachelor of Surgery Degree from Maharashtra University of Health Sciences, Nashik, Maharashtra, India in 2008. He then received his Master of Arts in Health Communication from Pennsylvania State University, University Park, PA, USA in 2011. He worked as graduate research assistant for Dr. Richard Brown in the Dept. of Social and Behavioral Health from 2010-2014. All details of education and employment are described below.

### Personal information

Name: Utkarsh B. Subnis

Contact: (Res) 42800 Hay Road, Ashburn VA 20147
Cell Phone: 804-497-9890; Electronic mail: subnisub@vcu.edu, us6684@gmail.com

### *Education*

| Degree | Field | Institute and Location | Year |
|---|---|---|---|
| Ph.D. | Social and Behavioral Health | Virginia Commonwealth University, School of Medicine, Richmond, Virginia, USA | 2014 |

Areas of study: Research Methods in Social and Behavioral Sciences, Internet-based Health Interventions, Integrative Medical Therapies, Psychoneuroimmunology, Psychobiology, Biomarkers of Stress, Psychometrics, Cancer Survivorship, Technology in Human Subjects Research, Medical Anthropology, Patient-Provider Communication, Evaluation of Health Programs/Policies, Philosophy of Science

*Dissertation: Stress management for cancer survivors using a technologically adapted psychosocial intervention: A randomized trial determining the effect of expressive writing on psychoneuroimmunology based outcomes* [Advisor: Dr. Richard Brown; Committee: Dr. Jennifer Elston-Lafata, Dr. Maureen Wilson-Genderson, Dr. Nancy McCain, Dr. Angela Starkweather, Dr. Wendy Kliewer]

| | | | |
|---|---|---|---|
| M.A. | Communication Arts and Sciences | Pennsylvania State University, College of the Liberal Arts, University Park, Pennsylvania, USA | 2011 |

Areas of study: Health Communication, Patient Narratives and Coping with Cancer, Patient Experience of Cancer, Qualitative Research Methods, Applied Linguistics in Health, Lifespan Communication, Social Influence, Communication Theory, Qualitative Research in Information Science and Technology

*Thesis: Triumph over adversity: A qualitative study of narrative, coping and experience in individuals diagnosed with cancer.*[Advisor: Dr. Roxanne Parrott, Co-Advisor: Dr. Michelle Miller-Day; Committee: Dr. Jon Nussbaum, Dr. Rachel Smith]

***Education***

| Degree | Field | Institute and Location | Year |
|---|---|---|---|
| M.B.B.S. | Bachelor of Medicine and Bachelor of Surgery | Maharashtra University of Health Sciences, Nashik, Maharashtra, India | 2008 |

Activities: Participated in initiatives for educating and counseling patients regarding health behaviors. Involved in outreach programs through public health department of medical school for increasing awareness about infectious diseases in underserved and disadvantaged communities.

***Research Experience***

| Designation | Institution | Dates |
|---|---|---|
| Graduate Research Assistant | Patient/Community Centered Outcomes Core (PC-COC), Dept. of Social and Behavioral Health; and Cancer Prevention and Control Subcommittee, Massey Cancer Center, School of Medicine, Virginia Commonwealth University | 8/2013 – present |

Role: Coordinating consultations with investigators to provide information about research methodology (including qualitative, quantitative and mixed methods) and identifying of patient centered outcomes in grant projects. Facilitating delivery of applied research services such as the incorporation of new computer/internet based technologies for measuring and analyzing patient centered outcomes data.

| | | |
|---|---|---|
| Graduate Research Assistant | Dept. of Social and Behavioral Health, School of Medicine, Virginia Commonwealth University | 8/2010 – 8/2013 |

Role: Conducting systematic literature reviews, grant writing for R-01, R-03, and R-21 National Institutes of Health grant funding mechanisms, using technology to manage and share bibliographic collections, and analyzing qualitative and quantitative data sets.

| | | |
|---|---|---|
| Research Assistant | Center for Health and Risk Communication, Dept. of Communication Arts and Sciences, the Pennsylvania State University | 8/2008 – 8/2009 |

Role: Coordinating meetings with participating faculty members; conducting comprehensive literature reviews for topics such as personalized medicine and communication about participation in clinical trials, and analyzing quantitative and qualitative data.

***Peer-reviewed Publications***

**Subnis, U. B.**, Starkweather, A. McCain, N.L. & Brown, R.B. (2014). Psychosocial therapies for patients with cancer: A current review of interventions using psychoneuroimmunology-based outcome measures. *Integrative Cancer Therapies 13* (2) 85 –104, doi: 10.1177/1534735413503548. URL: http://ict.sagepub.com/content/13/2/85

Subnis, U. B & Parrott R.L. "Triumph over adversity": A qualitative study about patient's coping with cancer through narratives. (Manuscript in preparation)

Subnis U. B., Miller-Day M & Parrott R.L. "Going strong": A narrative research study describing patients' experiences with cancer. (Manuscript in preparation)

### *Awards and Scholarships*

Received financial award to the amount of $1, 000 from the Massey Cancer Center's (MCC) Cancer Prevention and Control (CPC) Research Proposal Development Program, 2014. This is a highly competitive award given to PhD students completing their dissertation research.

Received "Top Student Research Presentation of Distinction Award" at DC Health Communication (DCHC) Conference, George Mason University, Fairfax, VA, 2013.

Received "Graduate Student Travel Grant Award" to the amount of $100 from the Graduate School, Virginia Commonwealth University, Richmond, VA, 2013.

Received "The Lotus Trust Scholarship" financial award to the amount of 50,000 INR (=$1,000 USD approx.) by the Lotus Trust, Mumbai, India. The Lotus Trust Scholarship is a highly competitive financial award given to students from India with an outstanding undergraduate academic record for pursuing higher education overseas.

Received financial award to the amount of 35,000 INR (=$700 USD) by the Manekji & Shrinibai Neterwalla Education Trust. This is a competitive financial award given to outstanding students for engage in higher education abroad.

### *Conference and Poster Presentations*

**Subnis, U.** (2013) *Narrative as a Medium for Health Communication Interventions for Coping with Cancer: A Qualitative Study in Patients Diagnosed with Cancer*. Research presentation given at the annual DC Health Communication (DCHC) Conference, George Mason University, Fairfax, VA.

**Subnis, U.** (2013). *Psychosocial therapies for patients with cancer: A current review of interventions using psychoneuroimmunology based outcome measures*." Research presentation given at the annual Forbes Day Graduate Student Colloquium, Virginia Commonwealth University (VCU), Richmond, VA.

**Subnis, U.** (2013). *Metaphors Used By Patients to Describe Their Experiences with Cancer*. Poster session presented at the Graduate Student Symposium, VCU, Richmond, VA.

Brown, R.F., **Subnis, U.**, Starkweather., A & McCain, N. (2012) *The effect of psychosocial interventions on psychoneuroimmunologic outcomes: A systematic review.* Research presentation given at the 14th World Congress of Psychooncology, Brisbane, Australia.

**Subnis, U.** (2011) *Triumph over adversity: A qualitative study of narrative, coping and experience in individuals diagnosed with cancer*. Poster session presented at the Annual Daniel T. Watts Medical Research Symposium, Virginia Commonwealth University, School of Medicine, Richmond, VA.

Soon, K., & **Subnis, U.** (2009) *The Influence of Source Credibility and Controversial Content on the Third-person Effect*. Research paper presented at Association for Journalism and Mass Communication Conference, Boston MA.

***Employment History and Professional Experience***

| Type of employment | Institute and Location | Dates |
|---|---|---|
| Graduate Research Assistant | Dept. of Social and Behavioral Health, School of Medicine, Virginia Commonwealth University, USA | 8/2010 – present |
| Teaching Assistant | Dept. of Communication Arts and Sciences, College of the Liberal Arts, Pennsylvania State University, USA | 8/2009 – 8/2010 |
| Research Assistant | Center for Health and Risk Communication, Pennsylvania State University, USA | 8/2008 – 8/2009 |
| Self-employed (as Consulting Primary-Care Physician) | Urban and rural community-based primary care private medical practice, Mumbai and Aurangabad, Maharashtra, India. (Maharashtra Medical Council Medical Practitioner Registration No: 2008/07/2818) | 5/2008 – 8/2008 |
| Medical Intern | i) Government Medical College, Miraj, Sangli (District), Maharashtra, India<br>ii) Topiwala National Medical College & BYL Nair Charitable Hospital, Mumbai, India<br>[Medical internship involved one year of intensive clinical rotations in the following medical disciplines: Community Medicine (Urban Health Centre - *2 months*; Rural Primary Health Care Centre - *1 month*), Internal Medicine (*1½ months*), Surgery (*1½ months*), Obstetrics & Gynecology (*1½ months*), Pediatrics and Neonatal Care (*1 month*), Orthopedics and Trauma (*15 days*), Emergency and Casualty Care (*15 days*), Elective Rotations: Ophthalmology (*15 days)*, Diagnostic Radiology (*15 days*)] | 2/2007 – 3/2008 |
| Screen writer and creative advisor | Richmond Bloom Company, Mumbai, India (Worked on project for a medical education DVD series, "Innovative Surgical Clinics") | 7/2006 – 8/2007 |
| Education and Training | Smart center, Mumbai, India | 9/2005 – |

| Type of employment | Institute and Location | Dates |
|---|---|---|
| Professional | (Trained students with English as a second language in software programs such Microsoft Word and Excel) | 5/2006 |

***Research Positions Held***

| Designation | Name of Project | Dates |
|---|---|---|
| Primary Research Coordinator | "Stress Management for Cancer Survivors Using a Technologically Adapted Psychosocial Intervention: A Randomized Trial Determining the Effect of Expressive Writing on Psychoneuroimmunology Based Outcomes" Dissertation Project (PI: Dr. Richard Brown) | 5/2013 – present |
| Principal Investigator (PI) | "Messages in Cancer Communication" study of cancer patient narratives (advised by Dr. Roxanne Parrott) | 6/2009 – 10/2010 |
| Co-investigator | "Health and Heritage Project," that aimed to understand family communication about genetics and genetically transmitted diseases (PI: Dr. Roxanne Parrott). | 10/2008 – 6/2009 |

***Teaching Experience***

| Teaching Role | Name of course | Institute | Level | Dates |
|---|---|---|---|---|
| Teaching Assistant* | SBHD 634, "Patient-Provider Communication" | VCU[a] | Graduate | 1/2013 – 5/2013 |
| Teaching Assistant* | SBHD 692, "Qualitative Research Methods" | VCU[a] | Graduate | 8/2012 – 12/2013 |
| Teaching Assistant* | CAS 202, "Introduction to Communication Theory" | PSU[b] | Undergraduate | 8/2010 – 12/2010 |
| Primary Instructor# | CAS100 A, "Effective Speech" | PSU[b] | Undergraduate | 8/2009 – 8/2010 |

*Role: Instructed laboratory sections, which involved designing activities for experiential learning of subject material and graded written work and class assignments.
#Role: Developed syllabus, designed class activities and assessments and assigned final grades.
[a]: Virginia Commonwealth University
[b]: Pennsylvania State University

***Expertise in Technology and Software Programs***

| Type of Software | Name of software program/application |
|---|---|
| Graphical User Interface (GUI) Operating Systems | Computer-terminal keyboard based**:** Windows 9x, XP, Vista, 7 and 8; Linux;<br>Mac OS Tiger and Mountain Lion 10x<br>Touch screen based (e.g. smartphones/tablets)**:** Android, iOS, Windows Phone |
| Cross-platform Cloud Data Storage Applications and Ecosystems | Dropbox, SugarSync, Box, Just cloud, SkyDrive, Google Drive, SpiderOak, iCloud, Amazon Cloud Drive |
| Word-processors and Text/Graphic Editors | Microsoft Office (v97-2003, v2007, v2010, v2013), Adobe Acrobat Professional (v8, v9, vX,) Google Docs, Open Office v3, Office Libre v3&4, Scrivener v1, v2 |
| Web-based Survey Delivery And Data Collection Suites | Qualtrics, REDCap, SurveyMonkey, LimeSurvey |
| Quantitative Data Analysis | Microsoft Excel (v97-2003, v2007, v2010, v2013), SPSS v21, JMP |
| Qualitative Data Analysis | Atlas.ti, NVivo |
| Bibliography and Reference Management | EndNote, RefWorks, Mendeley |
| Email services and clients | Gmail, Outlook, Yahoo, GMX-Mail, Mail.com |

***Community Service and Applied Work***

- President, Social and Behavioral Health Student Association (SBHSA), Virginia Commonwealth University School of Medicine, 2012 – present.
- Social activities chair for Social and Behavioral Health Student Association (SBHSA), Virginia Commonwealth University School of Medicine, 2011 – 2012.
- Provided education and counseling for patients with chronic diseases, in particular patients with hypertension, diabetes, chronic pain and sleep disorders at Government Medical College, Miraj, Sangli (District) India, and T.N. Medical College and B.Y.L. Nair Charitable hospital, 2007 – 2008.
- Participated in public health programs for educating middle-school children, in the age range of 10-16 years, about personal hygiene and nutrition in over 20 schools in rural Maharashtra, India, 2007.
- Developed a "doctor-patient sharing" initiative, which involved encouraging patients to communicate with medical students, interns and residents about their disease and treatment experiences, in the in-patient surgical wards of Grant Medical College and Sir J.J. Group of Hospitals, Mumbai, India, 2005 – 2006.

***Community Service and Applied Work… contd.***

- Participated as a student speaker in the annual medical college debate competitions that engaged the medical student community on issues pertaining to medical ethics and public health problems, 2006.
    - Awarded best speaker for debates concerning 1) medical eugenics and 2) public-health implications of prostitution and sex-work, 2006.
- Scripted and performed in a street play for an annual World AIDS day (Dec 1, 2004) public health initiative for rural and disadvantaged communities near Miraj City, (India) that was broadcasted on local and regional television networks. Street play was designed to raise awareness about HIV/AIDS, affect community member's perceptions to reduce stigma related to HIV/AIDS for afflicted individuals, 2004.

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***Contact Information for References***

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Phone: 804.628.4623 (O); 804.828.5440 (F); Email: kecarlyle@vcu.edu
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Richard F. Brown PhD
Assistant Professor
Department of Social and Behavioral Health, Virginia Commonwealth University School of Medicine
Chair, Massey Cancer Center, PRMS Cancer Prevention and Control Subcommittee
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