THE EFFECTS OF MINDFULNESS BASED STRESS REDUCTION ON BREAST CANCER SURVIVORS

by

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ABSTRACT

Breast cancer is the most common type of cancer among women in the United States. Cancer diagnosis and treatment usually induce significant amount of psychological stress on patients, and breast cancer patients are especially susceptible to cancer-related distress. Chronic stress activates the hypothalamic-pituitary-adrenal (HPA) and the sympathetic-adrenomedullary (SAM) axis, whose prolonged activation initiates physiological events harmful to the immune system and negatively influence cancer progression and recurrence. Therefore, it is important to identify and introduce effective cancer-related stress management programs and incorporate them into the standard cancer care routine besides conventional therapy.

Mindfulness-based stress reduction (MBSR) is an 8-week stress reduction program that has deep roots in ancient Buddhist practice and is used widely in clinics around the world nowadays. Is has been demonstrated to be effective in relieving stress and promoting well-being in a variety of populations, both clinical and nonclinical. And now it has started to be adapted into a complementary breast cancer therapy. However, much of MBSR’s mechanism is still unknown,
and no definite proof exists to show its efficacy in improving the negative psychological and physiological side effects of breast cancer treatment. This thesis summarizes and evaluates the current evidence of MBSR’s effectiveness in relieving psychological and physiological stress symptoms among breast cancer patients and survivors.
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<th>Description</th>
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<tr>
<td>ACS</td>
<td>American Cancer Society</td>
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<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
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<td>ANS</td>
<td>autonomic nervous system</td>
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<td>ARC</td>
<td>awakening cortisol response</td>
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<tr>
<td>AVP</td>
<td>arginine vasopressin</td>
</tr>
<tr>
<td>ASD</td>
<td>acute stress disorder</td>
</tr>
<tr>
<td>CAM</td>
<td>complementary and alternative medicine</td>
</tr>
<tr>
<td>CRH</td>
<td>corticotrophin-releasing hormone</td>
</tr>
<tr>
<td>DCIS</td>
<td>ductal carcinoma in situ</td>
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<tr>
<td>DEHA</td>
<td>dehydroepiandrosterone</td>
</tr>
<tr>
<td>ER</td>
<td>estrogen receptor</td>
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<tr>
<td>HPA</td>
<td>hypothalamic-pituitary-adrenocortical axis</td>
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<td>IL-6</td>
<td>interleukin-6</td>
</tr>
<tr>
<td>LCIS</td>
<td>lobular carcinoma in situ</td>
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<tr>
<td>MBSR</td>
<td>Mindfulness-based stress reduction</td>
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<tr>
<td>NK cells</td>
<td>natural killer cells</td>
</tr>
<tr>
<td>PR</td>
<td>progesterone receptor</td>
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<tr>
<td>PPS</td>
<td>perceived stress scale</td>
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<tr>
<td>SAM</td>
<td>sympathetic-adrenomedullary axis</td>
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<tr>
<td>TA</td>
<td>telomerase activity</td>
</tr>
<tr>
<td>TL</td>
<td>telomere length</td>
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TNFα .......................................................tumor necrosis factor alpha
TNBC......................................................................triple negative breast cancer
VEGF .................................................................vascular endothelial growth factor
INTRODUCTION

Breast cancer is the second most common cancer among women in the United States. In 2015, an estimated 231,780 new cases of invasive breast cancer will be diagnosed in women (American Cancer Society (ACS), 2014). As a result of increased awareness, early detection through screening, and advances in medical treatment, deaths rates from breast cancer have been declining since 1989 and have led to increases in the number of breast cancer survivors. As of 2014, there are more than 2.8 million breast cancer survivors in the United States, including women under treatment and who have completed treatment. A cancer diagnosis is considered the most stressful and life-threatening diagnosis a person can receive and it creates immediate psychosocial distress for the patient (Carlson et al., 2004). Reviews on the prevalence of depression among cancer patients suggest that the rates of depression symptoms are the third highest for breast cancer patients, exceeded only by patients with pancreatic cancer or head and neck cancer (Golden-Kreutz et al., 2004). Half of all breast cancer patients suffer from psychological distress related to the disease itself or side effects from the treatment and met the criteria of acute stress disorder (ASD) (McGarvey, 1998). Such numbers necessitates the development for effective long-term stress-reduction coping strategies for breast cancer patients and survivors.

Mindfulness-based stress reduction (MBSR) is a mindfulness-based meditation program used widely in clinical and nonclinical settings. The practice
has its roots in the ancient Buddhist tradition in which practice of meditation aims to cultivate a state of mindfulness, defined as “a moment-to-moment non-judgmental awareness” in the practitioners (Kabat-Zinn, 1985). MBSR was first introduced into hospital by Jon Kabat-Zinn at the University of Massachusetts Medical Hospital, and uses a combination of mindfulness-meditation, body scanning and simple yoga postures to help people cope with stress, distress, pain, and illness difficult to treat by conventional approaches. It also aims at increasing degrees of equanimity, wisdom, compassion and mindfulness in people (Matchim et al., 2011). MBSR has been the subject of increasing research interest, and it has been shown to have beneficial effects for various groups of clinical population, including cancer patients (Dobkin, 2008). However there is no direct link between MBSR practice and reduced stress level in breast cancer survivors. The objective of this study is to 1) to assess the effect of stress in breast cancer development and recurrence; and 2) to assess the effect of MBSR in reducing stress in breast cancer survivors.
PUBLISHED STUDIES

Breast Cancer

The prevalence, incidence and lifetime risk of breast cancer indicates the importance of conducting studies in the area of breast cancer treatment and patient care. Breast cancer is the most commonly diagnosed cancer in women in the United States, accounting for approximately 30% of all incident cancers among this group. It is also the second leading cause of cancer death in women in the United States, exceeded only by lung cancer (ACS, 2014). In 2015, it is estimated that there will be 231,840 new cases of breast cancer and an estimated 40,290 people will die of the disease. Approximately 1 out of 8 women will be diagnosed with breast cancer at some point in their lifetime. In 2015, there are an estimate 2.8 million women in total living with breast cancer in the United States, including women currently being treated and who have finished treatment.

Risk Factors for Breast Cancer

Many risk factors for the development of breast cancer have been identified (Freedman et al., 2005). Many of the factors cannot be modified, including gender, age, ethnicity, family history, and genetics. Breast cancer incidence rises sharply with age and is most common with middle age and older women. The rate of increase in breast cancer incidence also increases with age,
but slows substantially after menopause, when the level of endogenous hormones declines. Although these factors cannot be changed, knowing their existence may help detect breast cancer earlier by regular self-examination and screening. Screening mammography has been shown to be effective in detecting breast cancer at early stages and decreasing mortality rate (Fracheboud et al., 2004).

Family history is recognized as a strong risk factor for the development of breast cancer, although the majority of the cases are sporadic and without any known family history. A woman’s risk of developing breast cancer doubles if her first-degree relative (mother, sister, or daughter) has been diagnosed with the disease (American Cancer Society, 2014). Familial breast cancers with known germline genetic mutations account for 5% to 10% of all breast cancer cases. Some high-penetrance genes include BRCA1, BRCA2, TP53, PTEN, STK11, and CDH11 (Campeau, 2008). Of these, mutations in the tumor suppressor genes BRCA1 and BRCA2 are the most prominent, accounting for 20% to 25% of familial breast cancer and 5% to 10% of all breast cancers (Narod, 2010). Both BRCA1 and BRCA2 mediate cellular response to DNA damage and mutations in either gene increases the lifetime risk for the development of breast cancer by 60% to 80% (Matsen et al., 2013). BRCA1 and BRCA2 are also associated with other cancer types, including ovarian cancer. BRCA1 is more strongly associated with ovarian cancer, while BRCA2 is more strongly associated with breast cancer in male and pancreatic cancer (Wickerham, 2010). Breast cancer arising from
germline mutations in BRCA1 and BRCA2 tends to develop at a younger age than their non-familial counterparts, and the majority of BRCA1-associated cases are triple-negative, both are independent indicators of a poor prognosis (Anders et al., 2008). The BRCA mutation carriers also have a significant higher 5-year and 10-year recurrence rate (11-20% and 25-27%, respectively) than individuals without a BRCA mutation (1-3% and 1-9%, respectively) (Trainer, 2010). Discovery of BRCA mutations enables genetic testing that can help target unaffected women at high risk for primary prevention and close surveillance. Genetic testing available at the time of diagnosis helps decide better tailored treatment for patients because the response of BRCA-associated cancers to treatment is related to the underlying genetic defect and can be different from other cancers with similar histological characteristics (Figure 1a).
Some risk factors are environmental and life style-related, including bodyweight, alcohol consumption, physical activity, pregnancy, use of birth control, exposure to diethylstilbestrol (DES) and hormonal therapy after menopause (Vijayvergia & Denlinger, 2015). These factors are modifiable and thus have important implications in planning breast cancer prevention strategies.

Types of Breast Cancer and Stages

Breast cancer is not a single disease, but a highly heterogeneous one. There are multiple subtypes of breast cancer that have different etiology and mechanism, respond to different types of treatments, and can be more or less invasive. Historically, breast cancer has been classified by a histological typing and grading system based on the site of origin of the tumor, spreading of tumor cells, and distinct morphological features of the abnormal cells and tissues.
Human breasts primarily consist of connective tissue supporting the mammary glands. The secretary unit of the gland is organized into 15 to 20 lobules, which in turn consist of smaller structures, lobes. Lobes are connected through a network of ducts, which eventually merge and exit skin through nipple. Human breasts are highly vascularized with an extensive network of blood vessels, lymphatic vessels and nodes, and nerves. The lymphatic drainage of the breast primarily goes into the axially lymph nodes, which is of special importance in the context of breast cancer because lymph nodes are prominently involved in cancer metastasis in advanced cases. Most breast cancer develops at the terminal ductal lobular unit, and the most common noninvasive breast cancers are ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Most breast cancer starts as DCIS and approximately 20% of them are confined to the ducts. If detected early, DCIS has a high likelihood of being cured (Vatovec et al., 2014). In very rare cases (1% to 4% of all breast cancer cases), cancer cells can spread to the dermis of the nipple in a condition called Paget’s disease, and it is considered benign if no other invasive tumor is present (Chen, 2006). If DCIS begin to spread to surrounding tissues or invade adjacent lobes, ducts or connect tissue it becomes invasive ductal carcinoma (IDC). There exist a large number of invasive breast cancer subtypes, of which IDC is the most common type and comprises approximately 80% of all invasive breast cancer cases (Matsen, 2013). In more advanced conditions, cancer cells may spread through lymph nodes and blood to distant parts of the body, most often the bones, lungs, liver,
or brains. The Nottingham histologic grading system of breast cancer grades a tumor based on three criteria—tubular formation, nuclear feature, and mitotic activity. The grade of a tumor is representative of its potential invasiveness, with low-grade tumors being less invasive and more likely to have better prognosis than high-grade tumors (Elston & Ellis, 1991). The grading system is augmented with a clinical staging system, the TNM system, which takes into consideration tumor size (T), lymph node involvement (N), and distant metastasis (M) to provide a more complete picture of tumor development. The systems work by assessing the T, N, M, categories of a tumor and combining the information in an aggregate scoring system that assigns a numerical stage number 0 to IV to a tumor (Table 1). While Stage 0 is the least advanced, in situ cancers that are confined to the layer of cells where the cancer develops (DCIS and LCIS), Stage IV is the most advanced tumor that has spread to distant tissues outside the breast. The staging system is a well-validated and important prognostic tool in clinical settings because it provides a more accurate prognosis for the disease and helps determine treatment options appropriate for the patient. When planning and conducting a clinical research study, it is important to know the tumor stage and the type of treatment a patient has received to reduce bias when selecting a cohort.
Table 1. 5-year Survival Rate by Stage.

<table>
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<tr>
<th>Stage of Cancer</th>
<th>5-year Relative Survival Rate*</th>
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<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>I</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
<td>93%</td>
</tr>
<tr>
<td>III</td>
<td>72%</td>
</tr>
<tr>
<td>IV</td>
<td>22%</td>
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*Data from American Cancer Society.

Breast Cancer Treatment

The treatment of breast cancer is multidisciplinary and can include local and systemic therapy. Local therapy aims to remove tumor cells without affecting the rest of the body, and common approaches of local therapy includes surgery and radiation. Systemic therapy aims to treat cancer cells that have spread outside the breasts and is usually used as adjuvant treatment following local therapy to reduce the risk of recurrence. Chemotherapy and hormone therapy are commonly used systemic therapy. Many factors, including hormone receptor status, tumor stage and histology, and genetic profile are taken into account when choosing the right type and sequence of therapies for a patient.

Clinically, breast cancer can be categorized into three basic therapeutic groups: the estrogen receptor (ER) positive group, the HER-2/neu gene amplified...
group, and the triple negative breast cancer (TNBC) group (Perou et al., 2000). The ER-positive breast cancers are the most prevalent. Expression of ER in breast cancer cell, whether or not with co-expression of progesterone receptor (PR), makes good candidates for hormonal anti-estrogen therapies, since these cancers need supplies of estrogen to grow. The most widely used drugs in this group of treatment are ER-blockage tamoxifen and aromatase inhibitors, the latter only used in postmenopausal women whose major source of estrogen is from the aromatase pathway. They stop the growth of cancer cells by either suppressing estrogen production or competing with estrogen for ER receptors on breast cancer cells. 5 years of anti-estrogen therapy with either tamoxifen or aromatase inhibitors has been shown to reduce breast cancer recurrence and mortality in early and advanced stage patients (Davies et al., 2013). Tamoxifen also proves beneficial to breast cancer prevention by lowering the risk of developing cancer in high-risk women with BRCA mutations (Gronwall et al., 2006).

The HER-2/neu amplified group has exceptionally high level of expressed in breast tissues. Amplification of HER-2/neu is associated with a poor prognosis, higher rates of recurrence and relative resistance to hormonal therapy (Tandon et al., 1989). Her-2 target therapy using monoclonal antibody against HER-2/neu, trastuzumab, improves outcomes in those patients (Paik et al., 2008). The last group of breast cancers TNBC is defined by the lack of ER and PR expression and the absence of HER2 /neu overexpression. It is one of the most aggressive
types of breast cancer, with a higher probability of metastasis, risk of recurrence and mortality from advanced disease compared with other breast cancer types (Tamao et al., 2015). TNBC confers resistance to hormonal therapy and is only treated with chemotherapy. Inhibitor of Poly (ADP-ribose) polymerase (PARP), an enzyme involved in repairing DNA double strand, is emerging as a potential treatment for both TNBC and BRAC-related cancers (Hastak et al., 2010).

**Trend in Epidemiology of Breast Cancer**

The incidence of breast cancer has increased for many decades since 1975 due to a combination of increased early detection through mammography screening and use of menopausal hormonal replacement therapy (Harding et al., 2015). The incidence rate dropped abruptly during early 2000 and has been stable over the past decade. Many factors contribution to the changes in incidence rate over time, including changes in environmental and behavioral patterns, improved screening methods and changes in screening behaviors. Mortality rates have declined during the past few decades, but have not changed significantly since 2002. However an overall steady improvement on 5-year survival rates has been achieved during the past few decades. Overall changes in incidence rates and 5-year survival rates suggest a growing number of breast cancer survivors, many of them are undergoing transition to post-treatment life.
Stress and Cancer

Defining Stress

Although stress is a common subject in our daily conversation, its meaning is somehow ambiguous. Stress is predominately used in the negative sense of ‘distress’, as being in a chronic state of physical or mental suffering, but also, in some cases, it might refer to a situation of challenge that induces a feeling of exhilaration and excitement. In 1936, Hans Selye first defined stress as the “non-specific response of the body to any demand for change” (Selye, 1975). This definition sees a stimulus, or a stressor, as a challenge to homeostasis, the
body’s maintenance of its important physical parameters within a certain range to sustain viability, and a body’s response to stress the reactions of the neurobiological systems that help preserve viability through change, or allostasis (McEwen & Seeman, 1999). A more integrated definition states that stress is a sequence of events, consisting of a stressor, perception of stress in the brain, and biological responses elicited in the body (Dhabhar, 2014). A stressor can be a physical one such as bacterial infection or toxin, or a psychological one such as depression, chronic sleep disruption, or traumatic life events. The brain is the master for the perception and interpretation of stress, and also a target of its effect (Gunnar & Quevedo, 2007). The outcome of the interpretation is communicated through a cascade of events which then triggers stress responses in the peripheral nervous system and across a variety of organ systems. To summarize, stress is a complex process involving environmental and psychological factors, and it initiates a cascade of physiological responses that have significant implications on human health.

**Physiology of stress response**

The stress response in humans is mainly mediated through two distinct but interrelated systems, the sympathetic-adrenomedullary (SAM) axis and the limbic hypothalamic-pituitary-adrenocortical (HPA) axis. Of importance is the release of stress hormones. The SAM axis is part of the sympathetic division of the autonomic nervous system (ANS), and upon activation it releases
catecholamines, principally adrenaline (epinephrine) and norepinephrine from sympathetic neurons and the adrenal medulla. The SAM axis is involved in acute stress response, and increased adrenaline level prepares the body for the fight-or-flight response. Circulating adrenaline and norepinephrine bind to adrenoreceptors in multiple targets, and some of the downstream effects include increase in heart rate and cardiac output, increase in respiratory rate, increase in gluconeogenesis in the liver, vasodilatation in muscles, and inhibition on digestive and reproduction system (Charmandari et al, 2005). In terms of evolution, acute stress response is considered a natural’s mechanism for survival, since it results in increased energy recourses for defensive response, and psychologically it increases vigilance, focused attention, and immediate arousal (Charmandari et al, 2005).

The HPA axis is mediated by production of corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) in the hypothalamus. CRH and AVP then activate secretion of pituitary hormones such as adrenocorticotropic hormone (ACTH). ACTH induces downstream production and release of steroid hormone glucocorticoid (cortisol in human) from the adrenal cortex. Cortisol is the major effector of HPA axis, and it regulates a broad range of effects including anti-inflammation responses and metabolism of carbohydrates, fats, and proteins (Glaser & Kiecolt-Glaser, 2005). The way it interacts with target cells is through binding to receptors inside the cells and initiating transcription of genes that have
glucocorticoid-responsive elements. Because it involves target gene expression, effects of cortisol take longer to produce and last longer.

Figure 3. Stress systems. Adapted from Antoni et al., 2006.

**Stress and the Immune System**

Stress has different effects on the human immune system depending on its duration. Short-term stress that lasts less than 2 hours may enhance some
aspects of immune functions, such as migration of leukocytes, most prominently natural killer cells (NK cells) and granulocytes, from lymphoid organs (spleen) to the peripheral blood and the skin (Dhabhar et al, 1995). The migration is mediated by stress-induced release of adrenaline and cortisol interacting with their receptors at the cell surface of lymphocytes, and it is hypothesized that such a redistribution of lymphocytes is beneficial because it significantly enhances skin immunity and wound healing (Dhabhar, 2014). In addition, short-term stress also enhances secondary immune response at the time of re-exposure to antigen by increasing the numbers of memory and effector helper T cells (Dhabhar & McEwen, 1997).

In contrast, chronic stress has been shown to suppress or dysregulate certain aspects of immune function through prolonged activation of SAM and HPA axis. Chronic stress induces a decrease in leukocyte mobilization from the blood to other body compartments, accompanied by a decrease in skin immunity. Chronic stress also suppress other immune parameters include antibody production, leukocyte proliferation, and number and activity of NK cells (Antoni, 2006). Of special interest are the NK cells because they are involved in tumor suppression. Low NK cell number is a prognostic factor for early breast cancer mortality and low NK cell cytotoxicity is predictive of a poor breast cancer outcome (Sephton et al, 2000). More specially, high levels of psychological stress are correlated with low NK cell cytotoxicity in ovarian cancer (Lutgendorf et
al, 2005), while positive social support is correlated with increased NK cell cytotoxicity in breast cancer (Levy, 1990)

Another mechanism through which chronic stress suppresses immune function is by inducing premature immune cell aging and senescence. Aging at the cellular level is usually measured as telomere length or telomerase activity. Telomeres are DNA-protein complexes at the ends of chromosomes that protect genome stability and shorten with each cell division cycle. Telomerase is an anti-aging enzyme that helps prevent telomere shortening by adding short nucleotide repeats to the telomere regions. The rate of telomere shortening is believed to reflect physical wellness and individuals with shorter telomeres are more susceptible to infection and mortality due to diseases like cardiovascular disease (Epel et al, 2006). Researches have shown links between stress and accelerated aging at cellular level. More specifically, women with high chronic stress levels have significantly shorter telomeres and lower telomerase activity in their blood lymphocytes compared to women with low chronic stress levels (Epel et al, 2004). In this way, chronic stress induced acceleration of immune cell aging can have deleterious effects on the human immune system and can increase the risk of developing age-related diseases.

Chronic stress also disrupts the body’s mechanism of regulating inflammation response and production of pro-inflammatory cytokines. Although acute inflammation is central to survival by providing the first line of defense against injury, chronic inflammation that goes on for days might be detrimental to
health. Increases in adrenaline and cortisol levels may increase the expression of pro-inflammatory cytokines such of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα). IL-6 has been linked to diseases including cardiovascular disease, arthritis, type 2 diabetes, and particularly, cancer (Harris et al, 1999). It is shown that IL-6 and TNF-α promote tumor initiation by inducing DNA damage and inhibiting DNA repair through the generation of oxidative species (Reuter et al, 2010). IL-6 and TNF-α also support tumor growth by preventing apoptosis in tumor cells and promoting angiogenesis (Balkwill & Mantovani, 2012).

**Psychological Stress**

Psychological stress response ensues when an event or environmental demand exceeds an individual’s perceived ability to cope. When making connections between psychological stress and disease risk, the psychological tradition focuses on individuals’ perceived stress level and their affective response. Perceived stress is a subjective evaluation of the degree to which life events are perceived as stressful. It is usually measured by self-report surveys in which participants are asked to rate their perceptions of stress on a scale by answering certain questions, or they may be questioned by researchers to assess the number and type of stressful life changes happened during a period of time. The most widely used instruments to assess perceived stress level are the Perceived Stress Scale (Cohen, 1983). The affective responses to psychological stress, which typically includes negative thoughts, emotion, are
usually assessed through changes in behavioral patterns including sleep
disturbance, and symptoms of general distress, anxiety, or depression. Measure
of perceived stress is augmented by measure of objective biomarkers of stress
including cortisol level and immune markers. These two factors combined show a
more accurate and comprehensive picture of how chronic stress influence
disease risk.

**Biomarkers of Stress**

Besides psychological testing on perceived stress, a set of physical
parameters is routinely used to measure objective stress level. These
parameters are categorized into two types: primary mediators of stress, and
secondary outcome measures, which are the consequences of action of primary
mediators.

The end products of SAM axis and HPA axis activation are easily
measurable in blood, saliva, and urine. Salivary cortisol level is the most
commonly used biomarker in stress studies due to its low-invasiveness and ease
of obtaining. The secretion pattern of cortisol has been well studied in normal and
pathological conditions (Kalpakjian et al., 2010). Under normal or unstressed
condition, secretion of cortisol shows distinct circadian rhythmicity, characterized
by a peak concentration in early morning hours, followed by a progressive
decline throughout the day, and ended with an abrupt elevation during the first
few hours of sleep. This diurnal secretion of cortisol is influenced by presence of
stress and is believed to reflect psychological and physical health (Ross, 2014). The peak in cortisol level immediately after waking is called the awakening cortisol response (ARC). ARC is known to be stable in each individual across days, but may be blunted or flattened due to high stress or poor health (Gunnar & Vazquez, 2001). It is shown that breast cancer patients who have a flattened daily cortisol secretion level have accelerated disease progression and early mortality (Touitou et al., 1996). Considerable attention has been given to account for inter-individual and intra-individual variances at different measuring times.

Another method to measure HPA axis activation is by the level of dehydroepiandrosterone (DHEA), which is also an adrenal hormone works by countering the actions of cortisol. Decline in DHEA is associated with stress-related symptoms since it leaves the action of cortisol less regulated. Other common biomarkers for HPA activation include components of the immune system such as the count and activity of NK cells, certain cytokines such as TNFα, IL-6, IL-1, and interferon gamma (IFNγ), and telomerase activity (McEwen, 2002).

Measurements of secondary physiological outcomes provide complimentary information to those of primary mediators like cortisol and inflammatory cytokines. Commonly measured outcomes include blood pressure and heart rate, which indicate changes in the cardiovascular system. Level of metabolism, cholesterol, and adipose tissue deposition are also assessed because they are thought to be influenced by increased cortisol activity.
Table 2: Biomarkers of chronic stress

<table>
<thead>
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<th>Some primary mediators and secondary outcomes*</th>
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<tbody>
<tr>
<td><strong>Primary mediators</strong></td>
</tr>
<tr>
<td>Elevated levels of inflammatory cytokines</td>
</tr>
<tr>
<td>Elevated and flattened diurnal cortisol rhythms</td>
</tr>
<tr>
<td>Elevated overnight urinary cortisol</td>
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<tr>
<td>Low DHEA: cortisol ratio</td>
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<td>Elevated levels of overnight urinary catecholamines</td>
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<td>Abnormal insulin levels (also assessed indirectly as abnormal glucose levels)</td>
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<th><strong>Secondary outcomes</strong></th>
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<td>Brain: atrophy of brain regions, cognitive impairment</td>
</tr>
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<td>Cardiovascular: atherosclerosis, left-ventricular hypertrophy, clotting actors, homocysteine, and oxidative stress markers</td>
</tr>
<tr>
<td>Immune system: impaired wound healing, retarded immunization response, suppressed delayed-type hypersensitivity, chronic pain and fatigue reflecting imbalance of immune system regulators in the CNS</td>
</tr>
<tr>
<td>Metabolic: glycosylated hemoglobin, HDL: LDL, cholesterol, abdominal fat deposition (as measured by the waist-hip ratio), bone mineral density</td>
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</tbody>
</table>

*Adapted from McEwen, 2002

**Effects of Stress-related Factors on Cancer Initiation and Progression**

Psychological factors have long been believed to influence the outcome of human diseases, including cancer. As early as AD 200, Glan observed that "melancholic women were more susceptible to ‘swellings’ of the breasts than were sanguine women" (Reiche, 2004). In the past 30 years, increasing clinical evidence suggest chronic stress contributes to cancer initiation, progression and metastasis.

Overall, studies linking stress and cancer incidence are mixed at best, possibly due to the difficulties in making accurate associations between stressor and disease onset across long year gaps. For example, a study in 2000 found
that women who have experienced extreme stress and are without positive social support have a nine-fold increase in risk of developing breast cancer (Price et al., 2001). A US cohort study found a similar relationship between maternal death in childhood and breast cancer in adulthood (Jacobs, 2000). These results are not strong indicators of a relationship between stress and cancer initiation.

It is generally acknowledged that stress plays more important a role in cancer progression and recurrence than initial onset of the disease. A study showed that women with breast cancer who had flattened ACR or abnormal diurnal changes in cortisol level had early mortality (Carlson, 2004). And in general, cancer patients who are under distress and tend to use negative coping styles have accelerated disease progression and higher recurrence rate (Reiche, 2004). By contrast, positive social support optimism predicts longer survival and better prognosis (Allison et al., 2003). Recent studies have started to understand the mechanism of action of stress. One theory proposes that activation of CNS and ANS by stress and the subsequent release of stress hormones change the tumor microenvironment in way that favors tumor-cell growth and migration (Antoni et al, 2006). Stress may also compromises DNA repair mechanism (Fischman et al., 1996), or enhance angiogenesis by promoting tumor production of vascular endothelial growth factor (VEGF) (Lutgendorf et al., 2002). Figure 4 illustrates the effects of stress factors on tumor microenvironments.
Figure 4. Stress and Cancer progression. Adapted from Antoni et al., 2006.
Stress in Breast Cancer Patients

A cancer diagnosis can be the most stressful and life-threatening event a person can experience, regardless of the prognosis, and the feeling of stress may in turn influence the disease trajectory. Based on gender, women are more susceptible to acute stress disorder (ASD) following diagnosis of cancer than men (McGarvey et al, 1998). It has also been shown that women undergoing a biopsy for breast cancer diagnosis have higher perceive stress and anxiety, accompanied by reduced NK cell activity and cytokine dysregulation (Witek-Janusek et al, 2007). Women who undergo breast cancer treatment experience greater emotional distress and mood disturbance, worry about prognosis and recurrence, and have decreased sense of well being (Boehmke & Dickerson, 2006). It is estimated that 50% of breast cancer patients meet the criteria for depression, 19% for post-traumatic stress disorder, and 33% for ASD (French-Rosas et al, 2011). The most common symptoms affecting breast cancer survivors are fatigue, insomnia, depression, cognitive dysfunction, and lymphedema (Pinto & Azambuja, 2011). Traumatic stress symptoms significantly impair patients’ quality of life and their ability to adjust to post-treatment life, and affect the disease outcome and recurrence rate.
Mindfulness-based stress reduction

Untreated cancer-related stress has huge negative impacts on all aspects of a patient’s life, decreases psychological and physical well being, lowers quality of life, and even impacts disease outcome and recurrence. Therefore management of stress in patients living with or beyond cancer is of significant importance. In addition to conventional cognitive behavioral interventions, the use of complementary and alternative (CAM) therapies among cancer patients has become popular. It is estimated that 64% to 86% of women with breast cancer used some form of CAM to cope with psychological distress (Lengacher, 2002). Some common forms of CAM, including acupuncture and music therapy, showed positive effects in reducing pain and vomiting in breast cancer patients (Alferi et al., 2001; Beck, 1991).

Over recent years, mindfulness-based therapies have become a more popular form of CAM used in conjunction with conventional treatment to reduce psychological and physical symptoms related to cancer or cancer treatment in women with breast cancer.

The idea of mindfulness originated in the ancient Buddhist Theravada tradition and it is viewed as the core of Buddhist teachings. Mindfulness is defined in the Buddhist context as ‘the clear and single-minded awareness of what actually happened to us and in us at the successive moments of perception’
(Bonadonna, 2003). The essence of mindfulness is a “moment-to-moment nonjudgmental awareness” (Kabat-Zinn, 1994). In this sense, mindfulness is a way of paying attention. Usually by concentrating attention to a sound, object, breath, visualization, or movement, the practitioner increases awareness of the deep interconnection of mind and body, and consciously brings awareness to the experience and observation at the present moment, without making judgments about it, and without thinking about the past and the future. The ability to direct attention in this way can be developed through the practice of meditation, and in order to build and maintain mindfulness, an individual needs to practice a certain set of meditation skills regularly with persistence (Matchim, 2007). The continued practice of mindfulness meditation is thought to elicit joy and end suffering in the Buddhist tradition. Also in this tradition, mindfulness meditation is not as much a specific technique for stress reduction but a way of being to be practiced regardless of the disease state. Promoting relaxation and spiritual growth are seen as some of the positive side effects for long-term practitioners.

In contrast to the tradition of cognitive behavioral therapy, mindfulness meditation is not goal-oriented and does not encourage practitioners to challenge their thoughts or alter their way of thinking. And unlike traditional meditation forms, mindfulness meditation does not require practitioners to free their mind of all thoughts and maintain a state of mind that is no-self. The core of mindfulness meditation is to experience, observe, and accept any event happened around and thought or sensation that naturally come into consciousness at a particular
moment, and at the same time to maintain a neutral, non-interpretive and nonjudgmental perspective. Practitioners usually sit in a comfortable position in silence, and are taught to focus their attention on a particular object or a process, like a sound, a breathing rhythm, a visualization, or movement. Using this object or process of focus as an anchor, practitioners scan their thoughts in an open mental field while staying consciously aware of what is happening inside and outside their body. When sensations and emotions arise, they are taught to experience and describe them nonjudgmentally. When practitioners notice that the mind has wandered into memories and fantasies, or starts engaging in the process of rumination or analysis, they note the contents of their thoughts briefly and then redirect their attention to the object or process of focus (Ott et al., 2006). In this way, practitioners also learn effective ways of handling emotions by bringing awareness to their experience, as apposed to being caught up in an ‘automatic pilot’ state in which they just react automatically to environmental stimuli when they are feeling stressed (Zainal et al, 2013).

Mindfulness meditation was first incorporated into clinical intervention by Dr. Jon Kabat-Zinn at the University of Massachusetts Medical Center in 1979. Initially developed as a psychoeducational training program for chronic pain patients and stress-related conditions (Kabat-Zinn, 1994), mindfulness-based stress reduction (MBSR) is a highly structured group program usually conducted as an 8- to 10-week course for as many as 30 participants who meet weekly for mindfulness meditation techniques, yoga exercises, and group discussions of
stress and coping. The major goal of the intervention program is to train participants to monitor and self-regulate their mood disturbances and reduce perceived stress when confronted with stressful events. Participants take part in weekly sessions that typically last for 1 to 1.5 hours plus one silent retreat session. During class, participants are taught the fundamentals of mindfulness meditation, information about the psychophysiology of stress response, and experiential mindfulness practice. Participants also get plenty of supportive interaction between group members including group discussions about progresses of their at home practices, challenges and barriers they experience, and application of mindfulness in daily situation. During the first class, participants also receive educational materials like CDs or DVDs to be used to support their home practice sessions. Each participant is expected to practice 45 minutes at home on a daily basis to be considered compliant with the intervention routine.

The mindfulness meditation techniques taught in MBSR include sitting meditation, body scan, Hatha yoga, and walking meditation (Kabat-Zinn, 1985). These practices are introduced gradually in intensity and strength, and are hypothesized to lead to a gradual transformation on the practitioner’s level of mindfulness. Sitting meditation involves bringing awareness to bodily sensations, initially with a focus on the physical sensation of breathing. Once the practitioner learn how to pay attention to the breathing process and continue to do it, they will be able to breath more fully and easily, which is thought to alleviate stress.
response and elicit relaxation response in the body. After learning to focus on
breath awareness, they may proceed to focus on physical sensation of pain in
order to cultivate a realization that pains are not constant but change from
moment to moment, and they will learn to separate the physical sensation of
pains apart from its negative connotation such as cancer progression. The body
scan is another mindfulness meditation technique consisting of gradually shifting
one’s focus through various regions of the body from head to toe. This practice
aims to develop a deeper appreciation for the subtle changes happening inside
the body from time to time, and to foster deeper mind-body awareness. Hatha
yoga, or mindfulness movement, involves various postures and gentle stretches
to increase awareness of body in motion, and promote balance of mind and
strength in musculoskeletal system. The last technique, walking meditation,
which is similar to Hatha Yoga, aims to increases awareness of body in motion,
especially in walking activities. Learning and practicing these mindfulness
meditation techniques are instilled in the 8-week course along with homework
assignments and support group activities.

MBSR has been shown to be beneficial to both non-clinical and clinical
populations (Khoury et al., 2015; Gotink et al., 2015). It is most notable for its
efficiency for problems like chronic pain (Kabat-Zinn, 1982), anxiety disorder
(Miller et al., 1995), and hypertension (Schneider et al., 1995). Given that
emotional distress after cancer diagnosis is common, and cancer patients have a
strong desire to be active and take initiative in personal care, it is logical to study
the benefits of MBSR on cancer populations. Carlson et al conducted a prospective study with a sample of 59 patients with early stage breast and prostate cancer in 2003 and reported significant improvements in pre- to post-treatment in sleep quality and stress symptoms following MBSR intervention. Additionally they evaluated immune outcomes including lymphocytes counts and cytokine production. While they didn’t observe significant changes in numbers of any of the lymphocyte subtypes (NK, T, or B cells), there were statistically significant changes in some of the cytokines assessed, IL-4 and IL-10. They concluded that the overall pattern of immune changes is suggestive of a shift away from pro-inflammatory to anti-inflammatory environment (Carlson et al, 2003). A continuing study in 2004 reported additional results of the neuroendocrine outcomes of salivary cortisol, serum DHEAS, and salivary melatonin from the same sample of breast and prostate cancer patients. This study confirmed previous findings of improvement in stress symptoms, health behaviors, and overall quality of life, but observed no associated changes in stress hormones level. Although the overall cortisol, DHEAS, and melatonin levels did not change significantly pre-to post-intervention, diurnal cortisol secretion patterns demonstrated attenuation of more extreme values, indicating a shift towards a possibly healthier HPA axis functioning. DHEAS level also demonstrated gender-specific changes consistent with healthier patterns (Carlson et al, 2004). These studies are among the first to demonstrate the potential effects of MBSR as a cancer intervention therapy and they showed its
potential benefits on immune and neuroendocrine profile. But the results are not
generalizable due to their same sample size and lack of control groups. To study
effects of MBSR on breast cancer, it is important to study a homogenous groups
of female breast cancer patients stratified by cancer stage and treatment types,
since some stress responses are gender-based and patients may show
differential responses to the same treatment depending on the point at which
they are in the disease trajectory.

**Effects of MBSR on reducing stress in Breast Cancer Survivors**

**Psychological outcome**

Most of the studies on the effects of MBSR in reducing stress symptoms in
breast cancer patients have focused on psychological outcomes, including
perceived stress level, depression, anxiety, cognitive function, quality of life, and
fear of recurrence. However researchers have used different measuring scales,
study designs, and even different forms of MBSR practice, making it difficult to
compare and interpret their results.

In 2011, Matchim et al. preformed a meta-study summarizing the
outcomes from previous studies on MBSR practice and breast cancer women
(Matchim et al., 2011). Below is the chart showing the lists of studies he included and their results on psychological outcomes (Table 3).
Table 1. Studies of MBSR Among Breast and Other Cancer Survivors

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
<th>Measure and Effect Size</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobkin, 2008</td>
<td>13 Canadian women with breast cancer who had completed medical treatment</td>
<td>Mixed method using quantitative and qualitative approaches</td>
<td>CES-D (0.655), Medical Symptom Checklist (0.904), Perceived Stress Scale (1.1), Sense of Coherence (0.44), Mindful Attention Awareness Scale (0.562), and Coping With Health Injuries and Problems (0.27)</td>
<td>Significantly improved in the use of palliative coping and mindfulness and decreased in perceived stress and medical symptoms. Qualitative themes were reported as acceptance, regaining and sustaining mindful control, taking responsibility for what could change, and spirit of openness and connectedness.</td>
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<td>Hebert et al., 2001</td>
<td>157 U.S. women with stage I or II breast cancer</td>
<td>A randomized, controlled trial concerning a nutrition education program (n = 50), an MBSR clinic program (n = 51), and usual care (n = 56). Follow-up measurement was conducted at 12 months.</td>
<td>Total energy, total fat, complex carbohydrates, fiber, body mass, Beck Depression Inventory, self-esteem scale, general symptom checklist, and seven-day diet recall&lt;sup&gt;6&lt;/sup&gt;</td>
<td>The nutrition education program group experienced a large reduction in fat consumption at 4 months, and much of this reduction was preserved at 12 months, whereas no change was found in either the stress reduction or usual care groups. A 1.3 kg reduction in body mass was evident at 4 months in the nutrition education group, whereas no change was observed in the stress reduction and usual care groups. The stress reduction group did not receive information about selecting and preparing food. Psychological outcomes were measured, but results were not discussed or reported.</td>
</tr>
<tr>
<td>Lengacher et al., 2009</td>
<td>84 U.S. women with stage 0–III breast cancer</td>
<td>A randomized, controlled trial focusing on MBSR (n = 41) and usual care (n = 43) groups</td>
<td>STAI, Concerns About Recurrence Scale, CES-D, Life Orientation Test, Perceived Stress Scale, General Health, and Medical Outcomes Social Support Survey on Spirituality&lt;sup&gt;7&lt;/sup&gt;</td>
<td>The MBSR group had significantly lower adjusted mean levels of depression, anxiety, and fear of recurrence; along with higher energy, physical functioning, and social role functioning. More compliance with MBSR was associated with improvements in energy and physical functioning.</td>
</tr>
<tr>
<td>Shapiro et al., 2003</td>
<td>63 U.S. women with stage II breast cancer</td>
<td>Randomized, controlled trial of MBSR (n = 31) and usual care (n = 32) groups</td>
<td>POMS, Beck Depression Inventory, Penn State Worry Questionnaire, STAI, FACIT—Breast, Shapin Control Inventory, Sense of Coherence, and a sleep diary&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Significant improvement on daily diary sleep quality was found in both MBSR and free choice; neither improved on sleep efficiency. Greater mindfulness practice was associated with higher sleep quality.</td>
</tr>
<tr>
<td>Tacon et al., 2004</td>
<td>27 U.S. women with breast cancer</td>
<td>One-group pre- and post-test design</td>
<td>Self-rated stress (1.657), STAI (1.408), Mental Adjustment to Cancer Scale (0.328), and Multidimensional Health Locus of Control Scale (0.467)</td>
<td>Significant decreases were observed on stress and state anxiety as well as significant improvement for mental adjustment to cancer and health locus of control.</td>
</tr>
<tr>
<td>Tacon et al., 2005</td>
<td>30 U.S. women with breast cancer</td>
<td>One-group pre- and post-test design</td>
<td>STAI (1.36), Problem-Focused Styles of Coping (0.422), and Mental Adjustment to Cancer (0.13)</td>
<td>Significant decreases were observed on anxiety, reactive and suppressive coping styles, as well as two scales of mental adjustment: helpless hopelessness and anxious preoccupation.</td>
</tr>
</tbody>
</table>

* No data for calculating effect size
* Effect sizes are post-MBSR and at 6 months, respectively.
* Effect sizes are post-MBSR, at 6 months, and at 12 months, respectively.
* Effect sizes are post-MBSR and at 12 months, respectively.

CES-D—Center for Epidemiologic Studies—Depression; EORTC QLQ—European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire; FACIT—Functional Assessment of Chronic Illness Therapy; MBSR—mindfulness-based stress reduction; POMS—Profile of Mood States Scale; PTGIR—Post-Traumatic Growth Inventory—Revised; SSSI—Symptoms of Stress Inventory; STAI—State-Trait Anxiety Inventory; VAS—visual analog scale.
Individual symptoms of psychological disturbance in breast cancer patients are not isolated phenomena, but are interrelated and may stem from the same sources or mediators. Fear of recurrence (FOR) is an established source of emotional distress among breast cancer patients and survivors. FOR is triggered by antecedent of physical symptoms like pain and rumination on those perceived risk result in psychological distress, decreased quality of lie, functional impairments and fatigue (Lengacher et al., 2014). Considering how FOR arises in patients, an MBSR program that focuses on paying attention to body sensations without thinking about its negative implications may help reduce intrusive thoughts, reduce FOR, and thereby reduce other FOR-related symptoms of psychological disturbance. Lengacher et al. studied FOR as a mediator of stress symptoms and how it is affected by MBSR practice. 84 early stage breast cancer patients were randomized into an MBSR practice group and a usual care group and were followed for 8 weeks from entry into the study to 2 weeks after the completion of MBSR. Outcome measures included perceived stress, depression, anxiety, quality of life, physical functioning, and FOR assessed by the Concerns about Recurrence Scale. As hypothesized, they found participants in the MBSR group were more likely to experience favorable reductions in FOR, improved psychological state and physical functioning compared to those in the usual care group. In the graph below, Lengacher et al hypothesized a biobehavioral logical model that postulates FOR might be the mediator of MBSR program to positive changes in psychological and physical symptoms.
The prevalence of sleep disturbance is high among cancer patients, and symptoms may persist many years after the end of treatment. The prevalence of clinically diagnosed insomnia is especially high among breast cancer survivors, which is about 68% (Palesh et al., 2010). Sleep difficulties are usually associated with high levels of chronic stress, and may contribute to fatigue and poorer treatment outcome (Vargas et al., 2013). As part of a large randomized clinical trial (NCT01177124) on the effect of MBSR on psychological and physical symptoms in breast cancer survivors, Lengacher et al. reported the effects of MBSR on objective and subject sleep parameters in 79 breast cancer survivors.

Figure 5. Hypothesized biobehavioral model: FOR as a result of participating in the MBSR program and mediate a range of positives changes. Adapted from Lengacher et al., 2014.
with a previous stage 0-III cancer diagnoses. Participants were randomized into either a 6-week modified MBSR program group or a usual care group, and measures were taken at entry into the study and at follow up 12 weeks after completion of program. (Lengacher et al, 2015). They found significant improvements in the subject sleep parameters from 6 to 12 weeks in the MBSR group using actigraphy measures of sleep efficiency (percentage of time in bed spent sleeping) and number of waking bouts, with a moderate magnitude of differences between groups. Comparable improvements in objective sleep parameters using sleep diaries and participants’ recall of sleep pattern and behaviors were not observed during the 12-week follow-up, though results seem to be in the trend of improving after MBSR intervention. These trends were in consistent with past studies by Anderson et al which found significant short-term improvements in sleep disturbances post-MBSR intervention among breast cancer survivors (Anderson et al., 2013), similar to a study by Carlson et al that found the beneficial effects of MBSR on subjective sleep duration and efficiency among breast cancer and prostate cancer patients (Carlson et al., 2005). However, controversy exists with regard to whether the amount of mindfulness practiced would predict the extent of improvement. Shapiro et al. found that MBSR is indeed a promising intervention to improve sleep quality in breast cancer survivors whose sleep complaints are due to stress, but also found that it needs to be practiced to have an effect. That is to say, the amount of mindfulness practice, as measure in weekly minutes, is associated with
improvement in sleep quality measures, and the effects are relatively transient (Shapiro et al., 2003). However, the Lengacher study made no much observation, possibly due to a relatively short follow-up period or the low average rates of mindfulness practice overall. At this moment, a consensus has not been reached, but it certainly has important implications for the implementation of MBSR treatment in the real world. If motivation is a major predictive factor for the outcome of MBSR treatment, the treatment might not be effective if a patient is not willing to or have the motivation to commit time to practice mindfulness. This condition is generally not covered in a clinical trial since patients were randomly assigned into a treatment condition and only results from those considered compliant with the intervention routine are included. But in the real world, it might suggest a new aspect to consider when screening potential participants for MBSR treatment (Lengacher et al., 2011).

**Neuroendocrine function (stress hormone)**

Matousek et al. reviewed the literature related to cortisol changes following MBSR intervention and found significant reduction in daily cortisol levels in various populations during 12-month follow-up (Matousek et al., 2010). He found cortisol to be a reliable biological marker to assess the effectiveness of interventions intended to reduce stress, since it is directly linked to adrenocortical activity in response to stress and generally responsive to stress-reducing interventions. Later Matousek et al. evaluated changes in the cortisol awakening
response (CAR) in 33 early stage breast cancer patients who has completed medical treatment for cancer and took an 8-week MBSR program (Matousek et al., 2011). CAR, a distinct characteristic of HPA axis in response to the natural stressor of awakening in the morning, is highly stable in each individual and might be blunted following chronic stress (Chida & Steptoe, 2009). Results from the study showed that MBSR intervention was positively associated with CAR, with the cortisol level showing a significant and prolonged increase after awakening during the post-MBSR period. In participants with the higher CAR at the start of the intervention, increase in CAR was accompanied by significant reduction in depression level, perceived stress, and medical symptoms. These results suggest MBSR is associated with psychological and physiological improvements, but the small sample size and lack of a randomized control group without MBSR intervention prevents us from drawing solid conclusions. Plus, without a reliable baseline CAR level for reference, the meaning of the changes in CAR profile, pre- and post-intervention, cannot be explained without speculation. A more comprehensive assessment of other stress markers, including DHEAS and immune system markers may be needed to draw a solid conclusion about MBSR-related improvements on neuroendocrine functions.

**Telomere length and telomerase activity**

Current research has shown that cellular markers of aging, telomere length (TL) and telomerase activity (TA), are in part regulated by chronic
psychological stress, depression, and anxiety, although the mechanism remains unclear. Psychological and oxidative stress may lead to shortened telomere length and reduced telomerase, and shortened telomeres may further cause chromosome instability (Desmaz et al., 2003) and increased risk of developing cancer (Fordyce et al., 2005). However, previous studies have demonstrated that telomeres are dynamic structures that can be shortened or lengthened (Blackburn et al., 1989), and stress-reducing interventions may improve telomere length and telomerase activity (Daubenmier et al., 2011). Therefore it is logical to hypothesize that beneficial changes initiated by MBSR are partly due to restoration of telomere length and telomerase activity, and should there be changes in telomere length and telomerase activity, they may correlate with the established improvements in psychological outcomes.

Lengacher et al. reported findings from the first randomized clinical trial that examined the effects of MBSR on TL and TA in breast cancer survivors (Lengacher et al., 2014). During a 12-week participant follow-up including 6-weeks in the MBSR program, TA increased approximately 17% in the MBSR group compared to 3% in the usual care group.

The steady increase in TA over time and significant between-group difference suggest a positive post-treatment effect of MBSR on TA. However, no evidence showed that MBSR significantly improved TL in the 12 week post-treatment. Similarly, no association between higher TA and higher mindfulness or better psychological outcome was observed. The results with respect to TA
increase were promising, but inconclusive with regard to the association between MBSR and cellular aging. Especially because telomerase acts by adding nucleotide to ends of telomeres, elongation of telomeres is expected if telomerase activity increases. It might be due to a short follow-up of 12-weeks, since change in telomere length due to behavioral interventions may take at least 1 year to be evident (Ornish, 2008). It leads to the even more interesting question of what is the mechanism linking stress cognition, psychological well-being, and aging at the cellular level. One theory suggests that levels of stress hormones mediate the process. Epel suggests meditation decreases the levels of stress hormones and oxidative stress, and increases the levels of hormones beneficial to telomeres and telomerase (Epel et al., 2009). Further randomized clinical trials should examine the effect of MBSR on longer time frame in order to assess telomere length.

**Immune function**

One of the first studies to assess the effects of participation in MBSR on immune function was done by Carlson and colleagues in 2007 (Carlson et al., 2007), in which they assessed the cell counts of lymphocytes and productions of cytokines. Within the lymphocyte subtypes (NK cells, B cells and T cells) showed no significant change over the course of 1-year follow up. However, pro-inflammatory cytokines, including INF-gamma, TNF alpha, IL-4, and IL-10, decreased continuously over 1 year. Pro-inflammatory cytokines have been
linked with increased self-reported stress symptoms and mood disturbance (Audet et al., 2014), so the results were consistent with the hypothesis that MBSR reduces stress symptoms. However, this study lacked a control group and included a sample of mixed gender and heterogeneous types of cancer. The results should be analyzed and reported separately to draw a conclusion about MBSR and breast cancer recovery alone because these factors may predict a different response to the intervention.

Witek-Janusek et al. investigated the effects of MBSR on immune function in breast cancer patients alone (Witek-Janusek et al., 2008). Their investigation used a non-randomized study design where early stage breast cancer patients self-selected into an 8-week MBSR program or into a control group with assessment only. Outcomes, including immune function, quality of life, and cortisol level were assessed from at least 10 days after surgery to 4-weeks after MBSR completion. At the first assessment, the baseline assessments for both groups showed immune dysfunction characterized by a general reduction in NK cell activity and IFN-gamma production, and an increase in pro-inflammatory cytokines IL-4, IL-6 and IL-10 production. However over time, the MBSR group showed significant restoration of NK cell activity and IFN-gamma production, with a decrease in IL-4, IL-6, and IL-10 production. Women in non-MBSR group continued to show immune dysregulation. A similar restoration of cortisol was seen in MBSR group compared to non-MBSR group. However the conclusions from this study are limited because participants were not randomly assigned to
the MBSR or usual care group. Self-selection may reflect selection bias since participants who chose the MBSR group might have preconceptions or expectation for the MBSR program and that might influence their stress level, quality of life, and indirectly influence their objective stress parameters and immune function.

To study immune function after breast cancer treatment and MBSR with a most strictly controlled design, Lengacher et al. did a randomized clinical trial with 82 participants newly diagnosed with stage O-III breast cancer and randomly assign them into a 6-week MBSR intervention or a control group (Lengacher et al., 2013). Assessments were made at baseline, 6-weeks, at MBSR completion and 6-week follow up. They found that between the baseline and 6-week period, cell counts for lymphocytes increased by a similar extent in both groups, suggesting a natural history of lymphocyte recovery after completion of conventional breast cancer treatment, and the recovery appears to be independent of MBSR practice. However in the 6-week follow up, a significant increase in lymphocyte subset (PHA-induced T cell activation) and restoration of cytokines was seen in patients enrolled in MBSR program compared to usual care group. The conclusion is that MBSR confers positive effects on immune recovery following breast cancer treatment, but only at a time when patients are further removed from cancer treatment and immune depression. The mechanism of how MBSR facilitates immune recovery is still unclear. It was hypothesized that MBSR is likely to reduce the activation of stress-induced neuroendocrine
system and lower levels of stress hormones including glucocorticoids and
catecholamines, which are responsible for the dysregulation of cytokines. To
confirm that, further measurements on cortisol level along with immune recovery
are required.
DISCUSSION

Breast cancer is the most common type of cancer and second leading cause of cancer death among women in the United States. Approximately 231,840 of new cases will occur in 2015 and an estimate of 2.8 million women is living with breast cancer. In contrast with the increasing incidence and prevalence of breast cancer, due to early detection and advances in treatment, the 5-year survival rate for women diagnosed with breast cancer is increasing at a steady rate. This trend results in an increasing number of women living with or beyond treatment and at some point may be challenged to overcome the possible adverse effects resulting from cancer diagnosis or treatment on their daily life. Studies have shown that patients going through the continuum of cancer management, from the early diagnostic phase, to cancer treatment, and post-treatment survival, are all likely to exhibit symptoms of psychological and immunological disturbances of varying severity. The prevalence is exceptionally high in women with breast cancer even compared to patients with other cancer types, with approximately one in every three breast cancer patients experiencing psychological problems such as stress and related depression, anxiety, fatigue, and fear of recurrence. Untreated psychological disturbance may have huge negative impact on disease progression and recurrence, lower the survivor’s quality of life, hinder their transition to post-treatment life, and decrease their ability to cope with illness. Consequently it is of great importance to promote
approaches that can help patients reduce cancer-related stress and make them essential components of cancer care besides conventional therapy.

MBSR is a form of CAM therapy that has been used by some cancer patients for self-regulation of stress. Rooted in the ancient teachings of Buddhist tradition and adapted by Dr. Kabat-Zinn into an 8-week course, MBSR program’s goal is to teach patients to take an active role in stress management. It encourages patients to keenly observe and be more aware of their surroundings, monitor their inner emotions and changes in body sensations, and at the same time maintain an open, nonjudgmental, and non-interpretive perspective. In general, MBSR enhances attention and awareness, promotes self-regulation, and in this way leads to a relaxation state in the body. The 8-week MBSR program teaches patients various mindfulness meditation techniques combined with group activities and at home practices to achieve this goal.

The increasing popularity of MBSR as an alternative therapy to cancer calls for the necessity to conduct research in this field to determine whether it really helps reduce stress in cancer patients. The distinctive characteristics of women with breast cancer make them the ideal group of patients to start with because 1) breast cancer is a specific clinical condition and responses may different from patients with other oncology, and 2) women with breast cancer are particularly susceptible to cancer-related stress symptoms. Since 2000, there were several studies on the effects of MBSR on breast cancer patients. Most of them focused only on psychological outcomes. Using different measures
including Perceived Stress Scale, depression scales and others, they unanimously reported improvement in stress, depression, mood disturbance, fear of recurrence, and quality of life in breast cancer patients practicing MBSR (Dobkin, 2008; Lengacher et al., 2009; Shapiro et al., 2003; Tacon et al., 2005; Lengacher et al., 2014). Some studies reported improvement in subject and objective sleep pattern and quality as well (Lengacher et al., 2015; Shapiro et al., 2003). Only a few studies assess the effects of MBSR on biologic outcomes in breast cancer patients. Two studies reported MBSR has positive effects on the recovery of counts and activity of lymphocytes and cytokine production (Lengacher et al., 2013; Witek-Janusek et al., 2008). One study reported MBSR’s effect in lowering cortisol and normalizing CAR (Matousek et al., 2011). Another study reported MBSR restores telomerase activity even in a short follow-up period (Lengacher et al., 2014). These results are all consistent with a more balanced, healthy immune system and reduced activation of the stress response system, HAP and SAM axis.

But these results should be interpreted with caution, since the studies are all of limited study design. The Matousek study on cortisol level compares the pre- and post- MBSR outcomes without a control group, making the interpretation of results ambiguous. The Witek-Janusek study used a nonrandomized control group, which is subject to selection bias. The only studies that assess the effects of MBSR on homogenous breast cancer women only with a randomized control design are those by Lengacher et al. Their results show that the trend is in favor
of MBSR’s positive clinical effects on psychological and biological outcomes, although it needs to expand the follow up time window to see effects on telomere length, cortisol level and a few other biologic outcomes. As preliminary studies, they certainly yield results that warrant conducting further studies to validate.

From current results, there is controversy with regards to whether time in practice MBSR and class attendance is correlated with an increase in mindfulness and improvement in measured outcomes. The two studies by Carlson and Speca which include pre- and post-intervention assessment of the same sample of whom 43% were breast cancer female survivors found that more number of minutes in practice and the number of session attended is positively associated with a greater magnitude of improvement in mood disturbance and stress symptoms. Similarly, Shapiro et al. reported participants in the MBSR group who engaged in more mindfulness practice had greater improvements in sleep quality. In contrast, Lengacher et al. found no such association between total minutes of MBSR practice and positive changes in psychological outcomes and quality of life. Arguments could be made for both sides. From one perspective, mindfulness is a state of mind that, just as it came from the tradition of Buddhist monks who make it an everyday routine, needs continuous effort to maintain and sustain. Therefore the observation that time engaged in practice being associated with improvement in outcomes serves as direct evidence that MBSR is the main driving force for stress reduction. But from the other perspective, it could be that once the teachings and concepts of mindfulness,
including an attitude of non-judging and acceptance, is instilled through MBSR, its beneficial results are self-sustaining and do not need further formal practice to maintain. Another possibility is that a particular component of the MBSR program, mindfulness meditation, mindfulness yoga, or supportive group discussion, is the most effective in reducing stress. Further research is needed to determine which theory is correct.

Based on current studies, people have noticed the possibility of predicting the success of MBSR using baseline biomarkers obtained at the start of the study (Reich et al., 2014). Targeting which breast cancer patients would benefit more from the program has important implications for its application to a broader population, especially if MBSR needs continuous practice and motivation on patients' part to be effective. Targeting a certain group of people who are likely to respond to this treatment will lead to higher cost-effectiveness, greater success, and a reduction in time and energy wasted by patients. Lengacher et al. found that different baseline immune biomarkers were associated with improvement in different symptom clusters, including psychological stress symptoms, gastrointestinal-related symptoms, and cancer-related fatigue and sleep disturbance (Lengacher et al., 2011). It appears that women with an increased baseline immune activity experience greater improvements in all these symptoms compared to women with weaker baseline immune activity after MBSR program. However due to the small sample size, further studies are needed to validate the predictive value of these immune biomarkers on MBSR
outcome, and test if these biomarkers can be generalized to a broader population. If the results are validated, they will also have important implications on the optimal application time window of MBSR program for breast cancer patients and survivors.

MBSR are currently offered in healthcare settings around the world for patients with different backgrounds. Preliminary clinical studies show promising outcomes with regards to MBSR’s beneficial effects on reducing subjective perceived stress, depression and mood disturbances, and increasing quality of life and sleep pattern in breast cancer patients. Although the trend is in support of MBSR, more data from controlled randomized clinical studies are necessary in order to draw a reliable conclusion on its effectiveness in reducing stress through measurements of objective stress markers and immune functions. Since MBSR costs relatively less and shows some positive effects, it will not be harmful to implement MBSR more widely in breast cancer patients as a complementary therapy. However, to fully understand its value, concept, application and benefits, a more comprehensive understanding on its mechanism of action, including how MBSR initiates changes in the immune system and stress-triggered activation of neuroendocrine system, is of great importance.
REFERENCES


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Working Experience:

Assistant of Project Management Office at Bruker (Beijing) Scientific Technology Co., Ltd, Beijing, China
May-August 2013
Worked in a team to assess external client needs and design project approach, determined action plan to increase client engagement and expand client network, organized and assisted in conference and exhibitions.

Research Intern at Guangzhou Medical University, Guangzhou, China
February-April 2013
Performed literature reviews, conducted research on animal models, analyzed and interpreted data to produce research report.

Summer Research Intern at Bruker Daltonik GmbH, Leipzig, Germany
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Performed literature reviews, conducted research using MALDI-TOF Mass Spectrometry, analyzed and interpreted data to produce research report.

Research Assistant at DePauw University Department of Biology, Greencastle, IN, US
August 2011-May 2012
Performed literature reviews, conducted research on animal models, analyzed and interpreted data to produce research report, presented key findings at weekly lab meetings and poster sessions: identified Locarserin’s effect on suppressing nicotine-seeking behavior.
Intern at Guangzhou Institute of Respiratory Disease, Guangzhou, China
November 2010-January 2011
Performed literature reviews, processed and analyzed patients’ lung samples, helped produce patients care reports.

Teaching Assistant at New Oriental Education & Technology Group Inc., Beijing, China
June-August 2010
Teaching Assistant for high school and undergraduate level English class, hosted seminal discussions of 30 students, grades homework and exams, assisted with classroom support.

Associate, Editor, Web Design at Taiyue Cultural Communication Co., Ltd, Beijing, China
June-August 2010
Designed website, edited scripts for documentaries.

Other Experience

Volunteer at Dream Corps International, Beijing, China
May-June 2010
Organized service trip by facilitating meetings and providing administrative logistic support for day-to-day operations, provided briefs on meetings and forums, streamlined and performed information management to enhance recruitment and commitment-tracking efficiency, participated in volunteer support conversations.

Volunteer Putnam County Public Nursing House, Greencastle, IN, US
2009-2011
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Editor at D3TV, Greencastle, IN, US
August 2009- May 2010
Edited pictures and videos, coordinated with freelance staff to meet deadlines for weekly TV program.

Honors and Awards
DePauw University President’s Award for Excellence, 2009-2013
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