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Complementary Therapies as a Strategy to Reduce Stress and Stimulate the Immunity of Women With Breast Cancer

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Abstract

The stress associated with cancer development leads to disturbances in the hypothalamic-pituitary-adrenal axis and suppresses important facets of the immune response. The use of complementary therapies in the treatment of women with breast cancer has demonstrated therapeutic benefits that entail improvements in the patients' quality of life. The objective of this article is to present evidence on the use of complementary therapies as a stress reduction strategy and on its stimulating effects on the immune system of women with breast cancer. This is a reflexive updating article that will support the health professionals' understanding on the use of complementary therapies in breast cancer care. The use of complementary therapies in the treatment of women with breast cancer has significantly improved these subjects' stress, depression, fatigue, anxiety, and consequently, their quality of life, as well as their immune response, which is mainly illustrated by the increased number and cytotoxic activity of natural killer cells. Clinicians, health professionals and patients need to be cautious about using complementary therapies and fully understand the real benefits and risks associated with each therapy. Little or no supporting evidence is available to clarify the effects on the immune system of women with breast cancer, and the consequent therapeutic benefits obtained through the use of these practices.

Keywords

breast cancer, complementary therapies, physiological stress, immune system

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Despite the increased survival rate of cancer patients, there is a continuing need for research to assess the effects of treatment and diagnosis on patient's quality of life (QoL).[1] The social stigma of the disease, widely related to QoL, has a negative impact on these patients' health condition.[1] Breast tumors, which are one of the most frequent types of cancer worldwide, are the tumors women fear the most, mainly because they affect the main symbol of femininity. They compromise not only patients' physical condition but also their mental health, as they can affect their self-perceived image.[2] The stress, anxiety, and sometimes depression experienced in the course of the disease and after treatment, can cause different behaviors in the patients and negatively affect their QoL. In addition, the physiological stress experienced as the disease evolves suppresses important facets of the immune response, such as the activity of natural killer (NK) cells and the proliferation of T cells,[3] which play an important role in the immune response against cancer, participating in the fight against tumor cells and in the monitoring of their disordered growth.[4] Because stress is considered an imminent risk factor for the occurrence of breast cancer,[5] it has become more important to analyze the trajectories of stress,

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depressive symptoms, and immunity in the cancer population, including survivors.[6]

In an attempt to alleviate some of the treatment-related symptoms, breast cancer patients take advantage of several nonpharmacological treatments, including complementary therapies.[3] Besides the significant improvement of stress, depression, fatigue, and anxiety, breast cancer patients in use of complementary therapies have also shown improvements of the immune response, as illustrated by the increased number and cytotoxic activity of NK cells.[3,7,8] Although complementary therapies have provided improvements in patient's QoL and immune system function, most of these therapies are supported by little, if any, scientific evidence. Certainly, this lack of evidence prevents us from bridging the gap between basic research and clinical practice, and at the same time, requires an extensive compilation and discussion on the evidence already published in order to unveil the possibilities of scientific and clinical exploration.[9,10]

The objective of this article is to present evidence on complementary therapies as a stress reduction strategy and on its immune response–stimulating effects in women with breast cancer. From the standpoint of translational research, this short communication is a concise, but reflective report representing a significant contribution to complementary therapies arena and integrative oncology. This article serves as a call for further research to help clinicians, patients and health care professionals in making informed decisions that achieve meaningful clinical results. We aimed to provide support for health professionals' reflections on the use of complementary therapies in the care of cancer patients, an attempt to contribute to their evidence-based use and to the demystification of these practices.

Stress and Immune Response: Notes on the Physiopathology of Cancer

The field of psychoneuroimmunology has reached a firm ground in the past 50 years of research to validate the link between the central nervous system and peripheral immune cells in lymphoid organs.[11] Studies have shown that stress is associated with different illnesses, playing an immunosuppressive effect.[3] Stress initiates a cascade of information-processing pathways in the central nervous system and in the periphery, which activates the autonomic nervous system or the hypothalamic-pituitary-adrenal (HPA) axis. Cognitive and emotional feedback from cortical and limbic areas of the brain modulate the activity of hypothalamic and brain stem structures directly controlling autonomic nervous system and HPA activity. Individual differences in the perception and evaluation of external events (appraisal and coping processes) create variability in autonomic nervous system and HPA activity levels. Autonomic nervous system responses to stress are mediated primarily by the activation of the sympathetic nervous system, and subsequent release of catecholamines (mainly norepinephrine and epinephrine) from sympathetic neurons and the adrenal medulla. HPA responses are mediated by the hypothalamic production of corticotrophin-releasing factor (CRF) and arginine vasopressin, which activates the secretion of pituitary hormones such as adrenocorticotrophic hormone (ACTH), encephalin, as well as endorphins. ACTH induces the downstream release of glucocorticoids such as cortisol from the adrenal cortex.[12,13] Glucocorticoids control growth, metabolism, and immune function, and have a pivotal role in regulating basal function and stress reactivity across a wide variety of organ systems.

Most physiologic systems are negatively affected by prolonged exposure to glucocorticoids and catecholamines. It is widely accepted that over time chronic, changes in stress hormones contribute to tumor initiation and development through modulation of the activity of multiple components of the tumor microenvironment, including DNA repair, oncogene expression by viruses and somatic cells, and production of growth factors and other regulators of cell growth. Once tumor development has begun, neuroendocrine factors can regulate the activity of proteases, angiogenic factors, chemokines, and adhesion molecules involved in invasion, metastasis, and other aspects of tumor progression.[12-14]

A substantial amount of research has shown that chronic activation of the stress response can lead to increased tumor growth mainly due to the disruption of the delicate balance between the central nervous system, endocrine, and immune systems.[14] Previous literature showed that stressful life events are associated with increased risk of lymph node involvement in breast cancer.[15] Relevant neuroendocrine and immune system interactions include direct synapse-like connections between sympathetic nerves and lymphocytes in lymphoid organs, neural and endocrine modulation of lymphocyte trafficking, and modulation of leukocyte function through glucocorticoid and other receptors.[12-14] Chronic stress has been shown to suppress many facets of immune function, including antigen presentation, T-cell proliferation, and humoral and cell-mediated immunity, enabling tumor cells to avoid elimination.

Stress hormones, specifically glucocorticoids (which take the form of cortisol in humans), influence the polarization of naive Th0 cells into Th1 and Th2 cells. These molecules act on lymphocytes to induce the production of Th2 cytokines and to decrease the production of Th1 cytokine precursors and consequently Th1 cytokines.[15,16] Glucocorticoids work by directly suppressing interleukin (IL)-12 production, preventing the production of the cytokines necessary to reducing the ability of IL-12 to stimulate the production of other Th1 cytokines such as interferon-γ (IFN-γ). In addition, glucocorticoids induce both IL-4 and IL-10 production.[15] Thus, in physiological concentrations, glucocorticoids may cause a shift from a Th1 immune response pattern to Th2 via alteration of cytokine production. Indeed, breast cancer patients who underwent surgery have shown lowered T cell-mediated secretion of Th1 in comparison with Th2 cytokines. Moreover, they have exhibited poorer T-cell responses to mitogen stimulation and reduced NK cell activity.[17] The relationship between glucocorticoids and Th1/Th2 cytokine production and differentiation adds an important layer to the relationship of psychological stress and cytokines.[16]

Evidence indicates that circadian deregulation also influences the secretion of some stress-associated hormones, and this might explain the associations between stress and cancer.[18,19] Data from separate lines of investigation show that stress can disrupt circadian glucocorticoid rhythms[18,19] and favors tumor initiation and progression.[18,19] Nighttime shift work, a condition that is known to disrupt endocrine rhythms, is a risk factor for breast cancer.[20] Clinical studies have shown that the status of circadian cycles, such as cortisol or the 24-hour rest-activity cycle, can predict long-term cancer survival.[19,21] Stress-related disruption of circadian cycles might impair cancer-defense mechanisms through genetic and/or glucocorticoid and immune pathways. Animal studies have shown that behavioral factors such as imposed chronic jet-lag can alter the expression of the circadian gene *Per1* in the central nervous system,[22] which, together with other circadian genes, regulates tumor suppression, cellular response to DNA damage, and apoptosis.[23] Glucocorticoid rhythms that are driven by the central nervous system[20] are linked to functional immunity.[24] Sleep disruption can increase the release of cortisol as well as the expression of pro-inflammatory cytokines (eg, IL-6 and tumor necrosis factor-α) in cancer patients.[25] Pro-inflammatory cytokines might promote tumorigenesis by inducing DNA damage or inhibiting DNA repair through the generation of reactive oxygen species. Pro-inflammatory cytokines can also lead to the inactivation of tumor-suppressor genes, the promotion of autocrine or paracrine growth and survival of tumor cells, the stimulation of angiogenesis, or the subversion of the immune response (which leads to the activation of B cells rather than T cells in the tumor microenvironment).[26] Conversely, agents that are capable of reestablishing circadian regulation (eg, melatonin) might have antitumor effects. Indeed, melatonin has been shown to reversibly inhibit cell proliferation, increase *p53* expression, modulate the cell cycle, and reduce metastatic capacity in estrogen receptor–positive MCF-7 human breast cancer cells by increasing expression of cell-surface adhesion proteins.[27,28] Thus, circadian regulation may play an important role in the prevention and treatment of cancer.[12]

Considering the aforementioned information, it is plausible that successful management of stress might have a salubrious effect on the neuroendocrine regulation of oncogenesis, tumor growth, and metastasis. Stress-management interventions that dampen chronic stress–related physiological changes might facilitate immune system "recovery" and thereby increase immune surveillance during the active treatment of cancer.[29,30] In fact, psychosocial interventions in cancer patients have resulted in alterations in neuroendocrine regulation and immunological functions[30-32] that are relevant for monitoring neoplastic cell changes. For example, 2 recent randomized clinical trials reported increases in lymphocyte proliferation in patients with breast cancer following psychosocial interventions.[29,30] It is conceivable that stress management can not only reduce cancer progression but also improve the quality of life in cancer patients. Indeed, complementary therapies, as stress reduction modalities that potentially modulate autonomic nervous system and HPA hormonal activity,[30,33] have shown promising effects in oncology treatment.[3]

Complementary Therapies in Breast Cancer: Support for Health Care

Complementary therapies can be described as the health care techniques aimed at integrating physical, mental, and spiritual dimensions. The objective of complementary therapies differs from the allopathic care used in Western medicine, in which the cure of the disease is the result from direct interventions in injured organs.[34] Different classifications have been proposed for complementary therapies. The National Center for Complementary and Alternative Medicine (National Institutes of Health, USA) mainly categorizes them as: biologically based therapies; mind-body interventions; and manipulative and body-based methods.[35] We use this classification as a reference framework to present and discuss evidence from the literature that demonstrate the use of complementary therapies to minimize the stress and boost the immune system of women with breast cancer.

The science of complementary therapies has significantly grown in the past 50 years, especially in the integrative oncology context. The breakthroughs in the molecular-level research significantly helped increase the understanding of the biological events/pathways underlying complementary therapies use.[36-39] Nowadays, the tools and methods applied in molecular-level research are one of the most promissory aspects in progressing the field of complementary therapies.[6,40]

Women with breast cancer are increasingly adopting the use of complementary therapies in a regular basis as a strategy to reduce stress and stimulate the immunity.[3,40] Adoption of these practices offers different therapeutic benefits, which include symptom relief and reduction of the toxicity of conventional treatments, prevention of disease relapse and significant improvement of the immune system.[4]

Manipulative and Body-Based Methods

Among body-based practices, therapeutic massage is highlighted as the most commonly used (71%) complementary therapy modality.[41] The use of therapeutic massage has shown beneficial effects on the neuroendocrine and immune system of women with initial breast cancer, including the reduction of anxiety levels, depression, anger, and fear, as well as the increase of dopamine and serotonin levels, and of NK and lymphocyte counts.[12]

There is also evidence that massage therapy has a positive impact on stress levels, low back pain, muscle pain, sleep, blood pressure, heart rate, inflammatory markers, and mood improvement in several populations, including cancer patients[42,43] (Table 1).

Many studies highlight the relationship between massage therapy and biological effects through the investigation of IgA levels,[44,45] α-amylase,[44,45] salivary cortisol,[44,45] serum

Table 1. Summary of the Results and Statistical Significance of the Reviewed Biological Outcomes.

Type of Therapy	Authors (Year)	Patient-Reported Outcomes	Biological Outcomes
Manipulative and body-based methods			
– Therapeutic massage	McDonald et al (2005),[12] Listing et al (2010),[42] Listing et al (2009),[43] Fernandez-Lao et al (2012),[44] Cantarero-villanueva et al (2011),[45] Green et al (2010)[46]	Anxiety levels, depression, anger, fear,[12] stress levels, low back pain, muscle pain, sleep, blood pressure, heart rate, mood improvement[42,43]	Natural killer (NK) cells, lymphocyte counts, dopamine, serotonin levels,[12] IgA levels ($P = .655$),[44] ($P = .184$),[45] α-amylase ($P = .111$),[44] ($P = .046$),[45] salivary cortisol ($P = .363$),[44] ($P = .729$),[45] lymphocytes ($P = .05$), IL-1, IFN-γ ($P = .02$), IL-4 ($P = .02$), IL-10[46]
Mind-body interventions			
– Iyengar yoga	Banasik et al (2011),[49] Speed-Andrews et al (2010)[50]	Vitality, pain, emotional well-being ($P = .045$),[49] mental health ($P = .045$), vitality ($P = .033$), role-emotional ($P = .010$), and bodily pain ($P = .024$).[50]	Cortisol ($P = .006$)[49]
– Tai Chi Chuan	Janelsins et al (2011)[51]	Functional capacity, aerobic capacity, muscular strength and flexibility, self-esteem, bone health and quality of life[51]	IL-6, IL-2 (all $P \leq .05$), insulin ($P = .099$)[51]
– Psychological interventions (eg, hypnosis, guided imaging, and relaxation)	Chandawani et al (2012)[3]	Stress[3]	Neuroendocrine functioning, cortisol levels[3]
– Meditation and mindfulness	Witek-Janusek et al (2008),[52] Sarenmalm et al (2017)[53]	Coping strategies, quality of life,[52] physical symptoms ($P = .007$), psychological symptoms ($P = .008$), total symptom burden ($P = .004$)	NK cells and of IL-4 ($P = .039$), IL-6 ($P = .031$), IL-10 ($P = .035$), cortisol ($P = .024$),[52] NK-cell activity ($P = .015$), absolute number of CD19+9 ($P = .004$)[53]
– Cognitive behavioral stress management	Antoni et al (2016)[54]	None	CTRA gene expression ($P = .014$)[54]
Biologically based therapies			
– Acupuncture	Johnston et al (2011),[57] Mori et al (2013)[55]	Breathlessness, hot flashes and xerostomia,[55] pain, pulse rate[57]	NK cells ($P < .05$)[57]

Abbreviations: NK, natural killer; IgA, immunoglobulin A; IL, interleukin; IFN- γ, interferon-γ; CD19+9, B-lymphocyte antigen CD19+9; CTRA, conserved transcriptional response to adversity.

cortisol,[43] serotonin, lymphocytes,[46] Th1 molecules (IL-1, IFN-γ),[46] Th2 (IL-4, IL-10)[46] (Table 1).

Mind-Body Interventions

Mind-body based programs can also reduce stress and anxiety associated with the cancer experience. Data from breast cancer populations have suggested that mind-body based complementary therapies (eg, mindfulness, meditation, yoga, Tai Chi, Qigong, guided imagery, and affirmations) have the potential to influence the immune profile of breast cancer patients and survivors, along with decreasing stress levels by helping them in developing a greater sense of emotional balance and well-being.[47,48] Breast cancer survivors who undertook Iyengar yoga sessions for eight and twelve weeks, showed reduced morning and evening cortisol levels along with improved fatigue, emotional well-being,[49] vitality and reduced pain[50] (Table 1).

Breast cancer patients who received Tai Chi Chuan training had significant improvements in functional capacity, aerobic capacity, muscular strength and flexibility, self-esteem, bone health, immune function, and QoL[51] (Table 1).

Also, psychological interventions like behavioral techniques, which include hypnosis, guided imaging and relaxation, have been used in breast cancer patients with positive results for stress reduction as well as immune response stimulation.[4] These results are associated with the reduction of cortisol levels and, consequently, with better neuroendocrine functioning.[3] The meditation mindfulness-based stress reduction (MBSR), practiced by women recently diagnosed with initial malignant breast tumors, reestablished the cytotoxic activity of NK cells and of IL-4, IL-6, and IL-10 levels. In addition, the women involved in the MBSR program showed lower cortisol levels, greater effectiveness of coping strategies and increased quality of life.[52]

A recent randomized controlled trial assigned 166 women with breast cancer to one of three groups: MBSR (8 weekly group sessions of MBSR), active controls (self-instructing MBSR) and non-MBSR. Blood samples were analyzed for NK-cell activity and lymphocyte phenotyping; concentrations of cytokines. Results show that mean baseline NK-cell activity increased significantly (mean = 19.1; SD = 8.2 to mean = 22.0 SD = 7.7; $P = .015$) within the MBSR group compared with the non-MBSR group[53] (Table 1).

Cognitive behavioral stress management (CBSM) is an empirically validated group-based psychosocial intervention, is a new modality of complementary therapies that has been recently tested in breast cancer patients. A study randomized 51 participants into 2 groups: 10-week group-based CBSM or a psychoeducation control group and followed up at 6 months, 12 months, and median 11 years. The study aimed to examine the relationships between CBSM, disease-free survival, and a potential biobehavioral pathway linking these variables through a gene expression composite representing the leukocyte conserved transcriptional response to adversity (CTRA). Patients randomized to CBSM showed attenuated 6- to 12-month change in CTRA gene expression, whereas patients randomized to control showed increased CTRA expression ($P = .014$).[54]

Biologically Based Therapies

A recent literature review reported evidence that acupuncture improves the immune function through the modulation of NK-cell activity.[55] A hypothetic model has been proposed to explain how acupuncture stimulates the immune response based on the stimulation of the acupoint ST36.[55,56] This point is known as the "immuno-enhancing acupoint" as it is capable of improving the functioning of the immune system. Its stimulation induces the release of nitric oxide, a neurotransmitter that stimulates, through sensory nerves, the lateral area of the hypothalamus, promoting the secretion of opioid peptides, such as β-endorphin.[55,56] This peptide, through the blood circulation, reaches the spleen and other body locations, binding to opioid receptors expressed on the surface of NK cells. On binding, β-endorphin stimulates NK cells to increase the expression of cytotoxic molecules, the production of IFN-γ, and consequently, the tumor-killing activity. IFN-γ, in turn, induces the expression of NK cell receptors and possibly the secretion of cytokines from other immune cells, orchestrating and expanding anticarcinogenic immune functions[57] (Table 1).

Conclusion

Considering that the stress experienced by breast cancer patients can negatively affect the immune response, potentially interfering in the development and progress of the disease, the use of complementary therapies might be an optimal approach to women with breast cancer in order to minimize stress. Indeed, most of the scientific literature has shown significant effects of different types of complementary therapies on stress-related aspects such as, fatigue, sleep disturbances, and QoL. However, bringing more scientific evidence through well-designed studies is still needed to regulate complementary therapies standards and to provide formal guidelines for making health care decisions.

Overall, the evidence provided so far lead us to conclude that complementary therapies may help improve patient's QoL and the use of these therapies should be part of a further health care model established toward comprehensive care, offering therapeutic modalities that can strengthen the mind-body-spirit during cancer patients' treatment journey.

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Authors Contributions

CA, EB, and LCLJ designed the initial draft, wrote the manuscript and did the literature review. GSB designed the initial draft, revised and edited the final version.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

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