The Ecology of Breast Cancer

The promise of prevention and the hope for healing

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October 2013

Stress, social support, and breast cancer

Chapter summary

Stress depends on our surroundings, how we perceive them, and how we respond. The stress response is non-specific. It involves the brain, endocrine, reproductive, and immune systems. The nature of the response can be highly dependent on individual coping skills, personal history, age, health status, and socio-cultural circumstances. Recent studies of stress have made considerable progress in demonstrating mechanisms by which stress can influence health status as well as showing that reducing stress can improve health and modify the course of diseases in beneficial ways.

Although many people feel strongly that stress can cause or increase the risk of developing cancer, evidence is inconsistent. However, animal and human studies show that stress can promote tumor growth through a variety of mechanisms. Thus, at least in some instances, stress may advance the time at which a slowly-developing latent tumor becomes clinically apparent.

A variety of psychotherapeutic interventions can reduce stress and beneficially modify associated biologic markers. Techniques that have undergone fairly rigorous scrutiny in epidemiologic studies and clinical trials often involve variations on mind-body-spirit interventions. These include meditation, yoga, mindfulness exercises, guided imagery, music, and cognitive behavioral therapy, among others. But, in addition to psychotherapeutic interventions, establishing and taking advantage of existing social support networks can markedly reduce stress and improve outcomes through many pathways, including providing services and needed resources as well as a sense of being valued, loved, and cared for by others.

Improved quality of life

Rigorously conducted studies show that stress reduction can significantly improve quality of life in people with breast cancer. In general, group therapy, education, structured and unstructured counseling, and cognitive behavioral therapy help significantly to reduce anxiety, depression, and fatigue and generally improve functional ability and quality of life. For many people, guided imagery, music therapy, meditation, and relaxation training are highly beneficial. A number of these interventions also improve indicators of immune function.

Improved survival / delayed recurrence

Observational studies show the most significant associations of lower stress levels with improved outcomes in groups of women who do not have metastatic disease at the time of initial diagnosis and treatment. In groups of women with metastatic disease, reduced stress is not clearly associated with delayed recurrence and improved survival, but within those groups some individuals appear to benefit. Stress reduction is clearly associated with improved quality of life in women with all stages of the disease. It is increasingly clear that outcomes improve most when conventional therapy is combined with more comprehensive interventions that not only reduce stress but also improve diet, exercise, sleep, and social support.

Stress is a subjective, highly individualized experience. Within large groups of study participants there will always be individuals who will benefit more or less from a particular intervention. The results of the studies described here may serve as a guide for developing general policies and recommendations. But they should not be interpreted as being a definitive guide for all individuals and families making complex treatment-related decisions. Some individuals are likely to benefit from psychological interventions and practices more than others. This is a highly personal decision. However, considerable evidence supports a choice to pursue psychological practices in response to a diagnosis of breast cancer. For breast cancer prevention, the data are less clear. It is also important to keep in mind that stress reduction and the development and maintenance of social support have proven benefits for a variety of other diseases and disorders as well.

Many aspects of our social, political, physical, chemical, and biologic environments shape conditions that foster health and promote disease. How we perceive and ultimately experience what happens to us also plays a role. Stressors and our bio-psychosocial responses to them involve the brain, endocrine, reproductive, and immune systems, with behavioral and health consequences over the short- and long-term. This chapter reflects on a long his-

tory of evolving theories of stress. It summarizes findings of epidemiologic studies addressing the role of stress and stress reduction related to breast cancer. It makes no attempt to describe extensive studies in laboratory animals that add richer insight.

An immediate fight-or-flight stress reaction to an imminent danger can, of course, be life-saving. Learning to cope with ordinary stressors of daily life so that they are not too disruptive is also healthy. But, unusual or prolonged stress, particularly when combined with limited coping skills and resources needed to respond, can be detrimental to health. The consequences of stress are not only deeply related to what happens to us but also who we are, our interpretation of events, and where we live.

Long before current understanding of stress and stress-related diseases developed, theories related to the role of personality and psychological variables in the origins of disease were formulated. Michael Lerner reviews this history as it relates to cancer, including whether there may be a "cancer-prone personality," in *Choices in Healing: Integrating the best of conventional and complementary approaches to cancer.*[1]

Briefly, Galen (c.130–c.210 A.D.) subscribed to Hippocrates' bodily humors theory, which held that differences in human moods are a consequence of imbalances in one of four bodily fluids: blood, yellow bile, black bile, and phlegm. Galen saw breast cancer more often in melancholy (literally, "black bile") women. Outwardly, they were creative, kind, and considerate. Some saw more cancer in women who were anxious, depressed, or grieving.[2]

Much later LaShan, Bahnson, and others proposed a role for "psychophysiological complementarity"—or mind-body connections—in the origins and treatment of cancer.[3,4] Their experiences began to convince them that "malignant processes are related to certain psychosocial conditions and psychodynamic states," although the mechanisms explaining those relationships were unclear.

LeShan reported a statistically-significant relationship between cancer and 1) a lost relationship prior to the diagnosis; 2) an inability to express hostility in one's own defense; 3) feelings of unworthiness and self-dislike; and 4) tension in the relationship with one or both parents, when compared to a control group. Bahnson thought "the phenomenological experience of loss, despair, and strain is the significant variable, since individuals react quite differently to conditions of 'external' stress."

Much of this work was happening during a time of emerging interest in the physiology of stress. Hans Selye, an endocrinologist and pioneer of research in this field, developed a framework in many ways similar to Bahnson's.[5,6] Selye described what he called "the general-adaptation syndrome" as having three chronologic stages: 1) the alarm reaction; 2) the stage of resistance; and 3) the stage of exhaustion. He believed prolonged stress would even-

tually exhaust an individual's response capacity and result in "diseases of adaptation." He saw stress as the combination of external events and the way they are experienced, including resultant changes in various neuroendocrine pathways, including cortisol, frequently called the "stress hormone." For Selye, stress was both the stimulus and response.

Selye's study of stress took place within an evolving concept of homeostasis—an idea that can also be traced to antiquity, where harmony and balance were associated with health, while disharmony and imbalance led to disease. Selye's work was influenced by 19th- century experimental physiologist Claude Bernard, who spoke of the "*milieu interieur*", and later by Walter B. Cannon, both of whose work was rich with empirical measurements of physiologic responses to various stressors.

Homeostasis refers to maintenance of an internal physiologic balance. Feedback loops responding to changing conditions are fundamental to homeostatic processes. Physiologists used terms like *stresses* and *strains*, but they were generally referring to specific stressors and a specific adaptive response, rather than what Selye saw as a less specific stress-response paradigm that could be triggered and maintained by a number of different stressors.

Levels of hormones, neurotransmitters, and various markers of immune function normally fluctuate in a pattern over the short- or medium-term timeframe. Various events—an infection, imminent danger, acute hunger—perturb them in useful, adaptive ways. As events resolve, homeostatic equilibrium is re-established. But some events—e.g., loss of a loved one, prolonged hunger, financial hardship, job stress, chronic danger—along with the patterns of arousal or emotion that they evoke in an individual, result in long term changes in these same physiologic measures that can ultimately be mal-adaptive.[7]

It is now apparent that ongoing stress continues to alter a variety of neuroendocrine pathways, and this response can itself become damaging to health. Allostasis, a more recent concept that builds on a homeostatic framework, refers to maintaining relative stability through change.[8,9,10,11] Allostasis incorporates the realization that the response to predictable and unpredictable events often involves re-tuning of various physiologic processes because of the way these events are experienced. Over the long-term, the response may turn out to be mal-adaptive. Allostatic load refers to the cumulative cost of maintaining a semblance of stability in the context of multiple stressors. Chronically stressful conditions can result in long-term changes in stress hormones, neurotransmitters, markers of inflammation, and other variables. Excessive allostatic load can increase the risk of a variety of illnesses, including cardiovascular disorders, diabetes, asthma, and cancer.[12,13,14]

Stress and breast cancer

The relationship of psychosocial stress to breast cancer onset or prognosis covers a range of topics and is difficult to study. Personality, age, defense mechanisms, coping strategies, history of psychological stress, socioeconomic status, and cultural history create a baseline context. Within that diverse mix, stressful events happen—e.g., the loss of a partner, illnesses, job loss, or financial difficulty—that can alter lifestyle, behavior, and outlook, triggering changes in empirical measures of physiologic function in the brain, endocrine, and immune systems.

Physiologic changes associated with stress depend to some extent on one's capacity to cope. Without coping mechanisms, an individual may react with feelings of helplessness or hopelessness. But coping mechanisms themselves may be of low- or high-cost. Facing a challenge and fears, participation in problem-solving, and seeking social support can improve resilience and help restore health. In contrast, denial, avoidance of conflicts, suppression of emotions, and disengagement may provide short-term benefits but are often ultimately detrimental.[15] Within this context, individual differences in other known risk factors for breast cancer increase the complexity, making it extremely challenging to identify the contribution of stress to the onset or prognosis of the disease.

Mechanisms

Numerous independent and interconnected mechanisms can link stress to cancer initiation and progression. The hypothalamic-pituitary-adrenal axis (HPA axis), involving the hormones adrenalin (epinephrine), norepinephrine, and cortisol, among others, is deeply involved in stress resilience and vulnerability. Mental processing of various stressors influences systemic levels of hormones and neurotransmitters.[16] Independently and collectively, components of this interactive system can alter and impair functions of the brain, endocrine, reproductive, and immune systems, including antigen presentation, T cell proliferation, and antibody- and cell-mediated immunity.[17,18,19,20,21,22,23] Inasmuch as the immune system plays a vital role in ongoing surveillance and elimination of cancer cells, functional impairments may lead to increased risk of cancer or cancer progression. Stress-related hormones can increase blood vessel growth in tumors, enhancing their viability.[24] Stress can also increase the levels of inflammatory mediators in the blood, enriching the tumor microenvironment.[25]

Stress can promote DNA damage as well as reduce tumor-suppressing gene function.[26,27,28] One link is likely to be through cortisol. A study of 220 men and women 65-83 years old found a strong correlation between higher 24-hour urinary levels of cortisol and oxidative DNA damage.[29] Another recent report found that expression of the normal, non-mutated BRCA1 gene—which serves important breast tumor suppressor functions and when mutated, sharply increases breast cancer risk—is enhanced by connecting with the unoccupied

cortisol receptor. As cortisol levels rise, causing increased binding of cortisol receptors, BRCA1 activity is reduced.[30,31,32] Elevated cortisol levels may also influence breast cancer outcome. Cortisol levels normally vary diurnally, with higher levels in the morning and lower levels in the afternoon and evening. A study of 104 women with metastatic breast cancer showed that, compared to those whose cortisol levels dipped normally later in the day, women whose cortisol levels remained relatively constant were at risk of earlier death.[33]

Studies of stress as a risk factor for developing breast cancer

Many laboratory animal studies show stress-related changes in immune system function and various aspects of the tumor environment that are associated with increased tumor development and metastasis, as well as decreased response to chemotherapy and survival.[34] Studies of stress in humans find differing effects on markers of immune system function, depending on study design, age of participants, coping mechanisms, and the nature of the stress being investigated. Human studies generally distinguish between stress as a potential contributor to the onset of breast cancer or as an influence on breast cancer progression and prognosis.

Many people believe that stress can increase the risk of cancer generally and breast cancer specifically.[35] In epidemiologic studies, the hypotheses most commonly studied are that breast cancer risk increases with 1) major stressful life events (e.g. death of a loved one); 2) larger cumulative number of major life events; and 3) amount of self-perceived stress due to major life events. Many studies attempt to examine one or more of these connections, and their findings are inconsistent.

Several systematic reviews of the literature addressing stress as a causal contributor to the onset of breast cancer have been published.

- In 1999, Petticrew, et al. reviewed 29 studies of sufficient quality to meet a minimal set of criteria.[36] Fifteen were prospective studies, 14 of which were "limited prospective," meaning that stress exposure was assessed while participants were waiting for but did not yet know the results of a breast biopsy. Fourteen studies were case-control design. Combined analysis of twelve studies of bereavement as a source of stress found no association with breast cancer risk (Three of the studies identified a positive association, while nine did not.) Combined analysis of 15 studies examining other kinds of stress found that participants with breast cancer were more than twice as likely (OR 2.63; 95 percent CI 2.34-2.96) to report significant adverse life events. They included divorce or separation, job loss, financial problems, and interpersonal conflicts. When the analysis was limited just to studies of high quality, based on author criteria, no apparent relationship was found.

- A later meta-analysis used qualitative and quantitative data from 27 studies (10 retrospective case-control, 4 prospective case-control, 9 limited prospective cohort [participants waiting for biopsy results], and 4 prospective cohort studies).[37] The categories of stressful life events generally (OR 1.77, 95 percent CI 1.31–2.40), death of spouse (OR 1.37, 95 percent CI 1.10–1.71) and death of relative or friend (OR 1.35, 95 percent CI 1.09–1.68) were associated with a modestly increased risk of breast cancer. But after controlling for publication bias, death of a spouse was the only stressful event that remained significantly associated with increased risk.

At least some of the inconsistency in findings is likely to be due to differences in study design and variability in the measures of stress. For example, marital separation and divorce may be more stressful than bereavement after the death of a spouse.[38] Stress may have more marked effects on immune function when it is associated with depression.[39] Incorporating these and other more precise details into study design can be challenging.

Another limit of many studies follows from the latency period, perhaps as long as 15-20 years, between breast tumor initiation and when it becomes clinically apparent. Thus, studies that examine the influence of stressful events within the five years immediately before diagnosis are more likely measuring their impacts on tumor promotion than as an initial contributing cause.

Many studies also fail to consider the context in which major stressful events occur—an important component of the maladaptive stress model. For example, a limited prospective study of 514 women requiring follow up after a suspicious finding on mammography found no relationship between a major stressful event within the past two years and the likelihood of having breast cancer.[40] However, further analysis showed that a major stressful event in combination with lack of intimate emotional support was strongly associated with increased risk. Models that integrate stressful events with the capacity and resources to respond better accommodate the biology of stress than those addressing single variables independently.

The timing and duration of stress also appear to be important. A prospective study of 1213 women, averaging 43 years old at baseline, followed up14-16 years later, found that maternal death in childhood or lifelong depression with periods of severe exacerbation were independently strongly associated with increased risk of breast cancer.[41] In this study, recent stressful events were not associated with increased risk.

Another limited prospective study in Finland found that women with breast cancer were somewhat more likely to have reported more severe losses and cumulative stresses in childhood and adolescence than women with benign breast disease.[42]

Stress reduction and quality of life in people with breast cancer

Many investigators have explored stress reduction as a way to help improve the lives and survival of people with breast cancer. Adding to pre-existing sources of stress, a diagnosis of cancer and various aspects of treatment are themselves, of course, highly stressful. Cancer patients' ability to carry out daily activities decreases, distress and depression may increase, which depletes energy, disrupts sleep, and adds to fatigue. Survivors face fear of recurrence, managing treatment-related physical and emotional effects, maintaining or resuming an intimate relationship with a partner, maintaining or establishing a social support network, and reconsidering life's meanings. Documented links among psychological factors and immune system function, inflammation, blood vessel growth, and tumor promotion have led many investigators to wonder if psychotherapeutic interventions might help to reduce symptoms, delay recurrence, and increase survival.

Early trials of group therapy, self-hypnosis, and education reported improvements in mood, pain, anxiety, self-perception, and adjustment in people dealing with cancer.[43,44,45] Since then, many additional studies of varying quality have attempted to assess the value of adding psychotherapeutic interventions to the care of people with cancer.

A 1995 critical review by Fawzy and colleagues assessed the published literature examining the value of education, behavioral training, individual psychotherapy, and group interventions in the care of people with cancer.[46] They concluded that a variety of psychological therapies can help cancer patients in a variety of ways, saying,

> "A short-term, structured, psycho-educational group intervention is the model that we propose to be used for newly diagnosed patients and/or patients with good prognoses. The focus is on learning how to live with cancer. We also encourage the development of ongoing weekly group support programs for patients with advanced metastatic disease, based on the studies of Spiegel et al., that focus on daily coping, pain management, and dealing with the existential issues related to death and dying. Psychiatric interventions should be used as an integral part of competent, comprehensive medical care and not as an independent treatment modality for cancer."

A 2002 systematic review of the benefits of various forms of psychotherapy in cancer therapy began by noting a strong existing view that psychotherapies may help in the care of people with cancer by increasing their knowledge about their disease and treatment, improving emotional adjustment, quality of life, coping skills, satisfaction with care, physical health and functional adjustment; by reducing treatment-related and disease-related symptoms;

by increasing patients' compliance with traditional treatments; by improving indicators of immune system function; and by increasing the length of survival or time to recurrence.[47]

The authors identified hundreds of studies and, based on rigorous pre-established quality criteria, narrowed the final assessment to 34 trials with psychosocial outcomes, 38 trials with side effect outcomes, and 10 trials with survival or immune system outcomes. Based on their analysis, the authors made tentative recommendations for routinely incorporating psychological therapies in treatment to improve cancer patients' outcomes. They concluded that:

- In general, group therapy, education, structured and unstructured counseling, and cognitive behavioral therapy offer the most promise for their medium- and long-term (up to five-six years) benefits for many psychosocial outcomes.
- For anxiety reduction, structured or unstructured counseling, including music therapy, provides long-term benefits. Individual therapy, cognitive behavioral therapy, communication skills training, guided imagery, and self-practice of chosen interventions hold promise and warrant further exploration.
- Of all the strategies investigated, relaxation training, and guided imagery appeared to be most beneficial for reducing treatment-related side effects.
- Interventions involving structured or unstructured counseling and guided imagery improve patients' general functional ability and quality of life.
- Group therapy improves patients' coping or control skills and interventions involving relaxation training, cognitive behavioral therapy, and communication skills training warrant further exploration.
- Group therapy and cognitive behavioral therapy are beneficial for fatigue reduction.
- Although no intervention strategies clearly improved patients' length of survival, a number of interventions improved indicators of immune system function.

A more recent Cochrane review of individual psychosocial interventions intended to improve quality of life and reduce general psychological distress in the first 12 months after cancer diagnosis found modest but significant benefits.[48] Cochrane reviews use strict evidentiary criteria, and studies not meeting those criteria are not considered. In this review, only randomized controlled trials of psychosocial interventions involving interpersonal dialogue between a "trained helper" and individual newly diagnosed cancer patients were selected. Only trials measuring quality of life and general psychological distress were included. Trials involving a combination of pharmacological therapy and interpersonal dialogue were excluded, as were trials involving couples, family members or group formats. In the end, the review was based on 1249 people who took part in clinical trials to test psychosocial interventions.

The reviewers noted considerable variation in the style and delivery of psychosocial interventions—e.g. one or two discussions vs. ongoing contact; telephone vs. face-to-face interventions, etc. They said that the statistically combined results may be limited and susceptible to criticism because of this. They also concluded that risk screening would help to identify and target patients who are at most risk of emotional difficulties and, therefore, most in need of support, along with consideration of a range of possible intervention types to suit identified needs.

Stress reduction: influences on breast cancer recurrence and survival

In that chronic stress can impair immune system function, alter cellular signaling, promote inflammation, and stimulate blood vessel growth, it seems plausible that pre-existing and newly-added stress can enrich the tumor microenvironment and help to foster tumor recurrence, growth, and metastasis.[49]

An early prospective study of 208 white women with breast cancer, diagnosed 1958-1960, asked participants about objective and subjective stress and social support in the five years prior to diagnosis. The group was followed over 20 years. The relationships between stress and survival were examined for three age groups: 15-45, 46-60, and 61 and older. Objective stress was related to survival in the older group while subjective stress was related to survival in the youngest group. Neither was related to survival in women aged 46-60. When women aged 46-60 were eliminated from the analysis, stress and social involvement accounted for twice as much variance in survival as the stage of cancer at the time of diagnosis.[50]

A case-control study of 50 women with recurrent breast cancer reported that women with recurrent disease were nearly six times as likely to have experienced severe, stressful life events—including death of a spouse or child, divorce, or otherwise severe breakdown in family relationships—since their initial treatment, compared with 50 women whose breast cancer was in remission.[51] Less severe stressful events were associated with a two-fold increased risk of recurrence.

Many clinicians and investigators have wondered if stress reduction might not only improve the quality of life for breast cancer survivors but also reduce the risk of recurrence and lengthen time of survival. In 1984, Morgenstern and colleagues published one of the first studies that statistically evaluated the impacts of psychotherapeutic interventions on breast cancer survival.[52] It was a small retrospective study of 34 women with breast cancer and matched controls. The intervention consisted of group discussions, meditation, and mental imagery using drawings. Analysis showed a modest, statistically-insignificant survival benefit. In 1993 this group published a larger study finding no survival benefit of a weekly program of individual counseling, patient peer support, family therapy, and direction in relaxation, positive mental imagery, and meditation.[53]

Investigators have also prospectively examined the effect of supportive group therapy on survival in women with metastatic breast cancer.

- In 1989 Spiegel and colleagues reported the results of a prospective study of patients with metastatic breast cancer, showing that 50 women who had received weekly group therapy and who used self-hypnosis for pain management in addition to routine care survived an average of 18 months longer than 36 women who received routine care.[54] It was a small study, and when the same group attempted to replicate their findings with a larger number of participants, they found no added survival benefit with supportive-expressive psychotherapeutic interventions in the group analysis. However, a subgroup of women with ER negative tumors who participated in the intervention survived significantly longer than their counterparts who did not.[55] It's important to recognize that conventional breast cancer therapy was rapidly improving during this time period so that any benefits of psychotherapeutic interventions were likely to be more difficult to see and may well have been most beneficial in women with the most treatment-resistant disease.

- A recent randomized controlled trial of supportive-expressive group therapy, added to three classes in relaxation therapy in both the intervention and control groups, among 485 women with metastatic breast cancer at baseline, found that the intervention reduced and prevented depression, reduced hopeless-helplessness and trauma symptoms, and improved social functioning. It did not improve survival.[56]

- In another randomized controlled trial of 235 women with metastatic breast cancer, designed to replicate the work of Spiegel, et al., 158 participated in weekly supportive-expressive group therapy, while 77 did not.[57] All women received educational material and otherwise appropriate medical and psychosocial care. The group therapy intervention did not prolong survival but significantly improved mood and reduced pain perception, particularly in women who were more distressed at the outset of treatment.

- One long-term prospective study has examined the effects of a group psychosocial intervention on survival and recurrence in 227 women with non-metastatic breast cancer.[58] Women were randomized to standard care or 4 months of weekly group-based intervention and 8 months of monthly sessions. The intervention included relaxation and stress reduction exercises, coping skills training, and health behavior change related to diet and exercise. Intervention participants showed a significant reduction in overall and breast cancer-specific mortality as well as 45 percent reduced risk of cancer recurrence at an average of 11 years follow-up. Those who did experience recurrence were cancer free for an average of six months longer, after controlling for multiple variables. Among those who died from breast cancer, me-

dian survival time in the intervention group was 1.3 years longer. The psychosocial intervention caused alterations in some stress-related immune processes that could help to explain improved general health and altered disease course.[59] This study also shows the value of more comprehensive interventions, which not only help to reduce stress but also improve diet, exercise, sleep, and social support.[60] These will be further discussed in chapter 8.

Adding psycho-social interventions to routine cancer care increasingly shows a variety of benefits. Improved quality of life and reduced stress- and treatment-related symptoms are well documented in women with metastatic and non-metastatic breast cancer. Psycho-social interventions may independently contribute to delayed recurrence and improved survival for at least some people, particularly those with non-metastatic disease at the outset and perhaps for those with most treatment-resistant disease. The most beneficial designs of interventions, their timing, and identification of subgroups of individuals who will benefit most continue to be clarified.[61]

Body-mind-spirit; mindfulness-based stress reduction

Variations on body-mind-spirit interventions are increasingly employed as a component of conventional breast cancer therapy. Mindfulness is a way of paying attention—of consciously being aware of our experience, in the present moment, without judgments.[62] Mindfulness exercises use techniques like walking and breathing meditation, yoga, mindful movement, and psychological education. The intent is to help individuals become more aware of their thoughts and feelings so that instead of being overwhelmed by them, they manage them better.

Mindfulness-based stress reduction (MBSR) is a psycho-educational training initially developed by Kabat-Zinn for chronic pain patients and stress-related conditions.[63] It is a group program that can be conducted varying amounts of time—often for 8 weeks, with weekly 2.5-hours sessions and one full retreat day. The participants are given instructions for home practice.

A meta-analysis of nine studies examined the impact of using MBSR on perceived stress, depression, and anxiety in women with breast cancer.[64] Participants in the studies were 45-61 years old and more than 90 percent were Caucasian. Twenty-four studies were left out of the analysis because of inadequate data or other design flaws. The meta-analysis found that the use of MBSR significantly improved participants' mental health by reducing perceived stress, depression and anxiety. The effect was graded as moderate to large based on a scale (the Cohen scale) calculated from the difference of means in two populations, accounting for the standard deviation of the data. Another systematic review and meta-analysis limited to randomized controlled trials and using Cochrane review criteria for study inclusion also

found that the addition of MBSR to standard care significantly reduced depression and anxiety in women with breast cancer compared to standard care.[65]

Several studies examining physiologic changes in breast cancer patients who have participated in MBSR interventions report lower afternoon cortisol levels, a steeper diurnal cortisol pattern compared to controls, improvements in measures of the immune function, and/or reduced pro-inflammatory gene expression.[66,67,68,69]

Social support and stress reduction

Along with other interventions, strong social support can substantially help ameliorate the stress response and improve outcomes in women with breast cancer. Social support has both structural and functional dimensions.[70,71] Structural support refers to the size and complexity of the network of reciprocal relationships that an individual has with friends, relatives, and co-workers. The functional component has to do with what the network actually provides, such as information, tangible contributions and services, and emotional support. It may include information regarding medical care options, financial assistance, transportation, and childcare, along with the perception of being loved, valued, and cared for.

Studies of the impact of social support on cancer survival often distinguish between network size and how it is actually experienced by an individual with cancer. The association with marital status is sometimes examined separately. These studies are challenging because the size and perception of social support can be influenced by age, presence or absence of depression, and socioeconomic status, each of which can independently influence disease outcomes.

A 2010 meta-analysis of 87 studies addressing the association between social networks and cancer survival includes an excellent discussion of some of these challenges.[72] The authors found that having high levels of perceived social support, larger social networks, and being married were associated with decreases in the risk of mortality of 25 percent, 20 percent, and 12 percent, respectively. In subgroup analyses, they reported a stronger association with increased survival for larger network size (number of social contacts) in studies of breast cancer and increased perceived support in studies of lymphoma and leukemia.

Several additional studies are also available:

- In a population-based study of younger women with breast cancer, 584 were followed for up to 12.5 years.[73] The mean age at diagnosis was 44 years, 81 percent were married, and 29 percent were racial/ethnic minorities. They were participants in a psycho-educational intervention project addressing the needs of younger women soon after diagnosis, with evaluation of the association between social

support and disease progression. Although the size of their social network did not make a difference, women who reported increased contact with their social support network post-diagnosis experienced a 69 percent increased survival at up to 12.5 years, compared with those who maintained the same level of contact with relatives and friends. The authors concluded that increasing social contact and support may increase the likelihood of survival by enhancing coping skills, providing emotional support, and expanding opportunities for information-sharing.

- In an evaluation of 2,835 women 46-71 years old from the Nurses' Health Study who were diagnosed with stages one to four breast cancer, social networks were evaluated on three occasions over ten years.[74] Women who were socially isolated before diagnosis had a 66 percent increased risk of all-cause mortality and a two-fold increased risk of breast cancer mortality compared with women who were socially integrated. Women without close relatives, friends, or living children had elevated risks of breast cancer mortality and of all-cause mortality. Participation in religious or community activities or having a close confidant was not related to outcomes. The authors concluded that socially isolated women were likely to have an elevated risk of mortality because of a lack of access to beneficial care-giving from friends, relatives, and adult children.

- A group of 2,264 women, average 58 years old, from the Life After Cancer Epidemiology study who were diagnosed with early-stage, invasive breast cancer between 1997 and 2000, were evaluated for associations between social network size and function and disease progression over an average of 10.8 years of follow up.[75] Socially isolated women did not have an increased risk of recurrence or breast-cancer specific mortality but did experience higher all-cause mortality. Among those with low levels of social support from friends and family, lack of religious/social participation and lack of volunteering were associated with higher all-cause mortality. Small networks and high levels of support were not associated with higher mortality, consistent with other studies showing that the quality of support, independent of network size, has value.

- A population-based, multi-center, case-control study of 4,589 women with invasive breast cancer found that higher scores on a composite measure of social connectedness as determined by the frequency of contacts with family and friends, attendance of religious services, and participation in community activities was associated with a 15–28 percent reduced risk of death from any cause over an average of 5.6 years of follow up.[76] No significant associations were found between social networks and breast cancer-specific mortality. The average age of study participants was 59 years; about 75 percent were post-menopausal.

- An analysis of the association of social networks and survival in 4,530 women, average 64 years old, who were participants in the Women's Health Initiative study, found that in those with high levels of social support, being married was related to lower all-cause mortality.[77] In contrast, among women with high social burdens, those with a higher number of first-degree relatives, including siblings, parents, and children, had higher all-cause and breast cancer-specific mortality. The authors concluded that social relationships may have both beneficial and adverse influences on breast cancer survival, depending on the context of women's relationships.

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