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Behavioral symptoms in breast cancer patients and survivors: Fatigue, insomnia, depression, and cognitive disturbance

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Abstract

Behavioral symptoms are a common side effect of breast cancer diagnosis and treatment and include disturbances in energy, sleep, mood, and cognition. These symptoms cause serious disruption in patients' quality of life and may persist for years following treatment. Patients need accurate information about the occurrence of these side effects as well as assistance with symptom management. This review considers four of the most common behavioral sequelae of breast cancer: fatigue, sleep disturbance, depression, and cognitive impairment. Research on the prevalence, mechanisms, and treatment of each symptom is described, concluding with recommendations for future studies.

Introduction

With advances in detection and treatment, the number of women who survive breast cancer has increased significantly in recent years. Five-year survival rates have climbed to 96%, resulting in an estimated 2 million North American women living in the aftermath of breast cancer.[1] As survival times increase, addressing the impact of breast cancer and its treatment on long-term outcomes has become increasingly important.[2] In particular, better understanding and management of cancer-related symptoms is critical for reducing suffering in cancer survivors.[3]

This review focuses on behavioral disturbances experienced by breast cancer patients, including fatigue, sleep problems, depression, and cognitive disturbance. These symptoms are among the most common side effects of breast cancer diagnosis and treatment, and may endure for months or years after treatment completion. Behavioral symptoms cause significant disruption in patients' quality of life and may also have implications for treatment adherence, morbidity, and mortality. Indeed, some patients report that treating behavioral symptoms such as fatigue is as important as treating the cancer itself.[4] Because depression has received considerable attention in previous reviews, this paper highlights more recent research on fatigue, sleep problems, and cognitive disturbance.

Fatigue

Prevalence

Fatigue is increasingly recognized as one of the most common and distressing side effects of cancer treatment.[5] Prevalence estimates of fatigue during treatment range from 25% to 99% depending on the study sample and method of assessment; in the majority of studies, 30% to

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60% of patients report moderate or severe fatigue symptoms.[5,6] Using a syndrome approach to characterize fatigue, a recent study found that 26% of breast cancer patients undergoing radiation or chemotherapy met criteria for fatigue "caseness", as defined by the presence of fatigue or diminished energy and five additional symptoms for at least two weeks that caused clinically significant distress or impairment.[7]

The course of fatigue during breast cancer treatment has been reasonably well characterized, particularly relative to other behavioral side effects. Longitudinal studies have shown an increase in fatigue symptoms among breast cancer patients undergoing radiation therapy or chemotherapy, although fatigue is typically more pronounced and more disruptive during chemotherapy.[8] For most women, energy improves in the year after treatment completion.[9] However, a significant minority continue to experience fatigue for years after successful treatment.[10,11] Studies of long-term breast cancer survivors suggest that approximately one-quarter to one-third experience persistent fatigue for up to 10 years after cancer diagnosis.[12,13]

Based on patient reports, cancer-related fatigue is more severe, more enduring, and more disabling than "normal" fatigue due to lack of sleep or overexertion.[14] Indeed, studies have confirmed that the intensity and duration of fatigue experienced by breast cancer patients and survivors is significantly greater than healthy controls and causes greater impairment in quality of life.[15,16] Effects may extend beyond quality of life: in one recent report, subjective reports of fatigue predicted shorter recurrence-free and overall survival in breast cancer patients.[17]

Mechanisms

Several factors are thought to contribute to cancer-related fatigue, including direct effects of cancer, side effects of cancer treatment, psychosocial factors, comorbid physical symptoms, and comorbid medical conditions.[18] Studies conducted with breast cancer patients have highlighted the importance of several of these pathways. Psychosocial factors are strongly correlated with fatigue among breast cancer patients and survivors, particularly depressive symptoms.[19] Although the majority of research linking depression and fatigue is cross-sectional, emerging data from longitudinal studies suggests that depression may increase the risk for significant fatigue during and after cancer treatment.7,12 However, there is also evidence that fatigue occurs independently from depression.20,[21] Coping strategies may influence cancer-related fatigue, particularly the tendency to catastrophize (i.e., react to fatigue with negative self-statements and negative thoughts about the future) in response to fatigue symptoms.[7,22,23] Finally, fatigue is correlated with sleep disturbance and pain in cancer populations10,[15], although the causal links between these symptoms have not been determined.

Demographic and medical factors are also associated with fatigue in breast cancer patients. Fatigued patients have a lower income and are less likely to be married[10,24], highlighting the role of situational factors as determinants of fatigue. They are also more likely to have comorbid medical problems and a higher body mass index.[10,12,24]

In terms of biological mechanisms, anemia likely contributes to fatigue in a subset of patients (i.e., women undergoing chemotherapy) but does not account for the majority of fatigue symptomatology. There is growing interest in the role of inflammatory factors as mediators of cancer-related fatigue. Studies have shown a positive association between markers of inflammation and fatigue symptoms in breast cancer patients undergoing treatment with radiation[25] and chemotherapy.26 There is also evidence that inflammatory processes play a role in post-treatment fatigue. Relative to non-fatigued survivors, breast cancer survivors with persistent fatigue show elevations in circulating markers of

proinflammatory cytokine activity and increased production of proinflammatory cytokines following LPS stimulation, as well as alterations in the cellular immune system.[27–30] Together, these changes suggest an inflammatory basis for persistent fatigue in breast cancer survivors.

Alterations in HPA axis function have also been documented in fatigued breast cancer survivors, including lower levels of morning serum cortisol [28], flattened diurnal cortisol slopes [31], and a blunted cortisol response to acute psychosocial stress.[32] One possibility is that impairment in glucocorticoid regulation of inflammatory processes may contribute to fatigue. Indeed, there is preliminary evidence that enhanced proinflammatory cytokine production in fatigued cancer survivors may stem in part from decreased cortisol response to challenge.[27] The biological underpinnings of cancer-related fatigue are an important focus for future research.

Assessment and Treatment

Fatigue is a subjective phenomenon, and self-report measures are currently the gold standard for fatigue assessment. The majority of studies have used self-report inventories to assess various dimensions of fatigue, including intensity, duration, and interference with functioning. There is no agreed-upon definition of cancer-related fatigue, although a clinical syndrome has been proposed to identify patients experiencing more severe and debilitating fatigue.[11] National Comprehensive Cancer Network (NCCN) guidelines suggest that scores of 4 and above on a 0 – 10 point scale indicate moderate to severe fatigue and merit additional attention.

When the etiology of fatigue can be identified, treatment can be directed at the underlying cause. For example, anemic patients may benefit from treatment with erythropoietin, which leads to increases in hemoglobin and concurrent improvements in fatigue and physical function.[33] In the majority of cases, however, the mechanisms underlying fatigue are unknown, and non-specific treatments are indicated.

Behavioral and psychological interventions have demonstrated efficacy in reducing fatigue among breast cancer patients and survivors. A growing number of trials have examined the effects of physical exercise on fatigue and other aspects of quality of life in cancer patients, and have yielded consistently positive results.[34] Indeed, a recent meta-analysis of exercise trials conducted with breast cancer patients and survivors concluded that exercise is associated with significant improvements in fatigue.[35] Positive effects have been seen with different exercise regimens, including home-based walking programs[36], supervised training on cycle ergometers[37], and even print materials and step pedometers.[38] Exercise interventions have also shown positive effects on immune parameters in breast cancer patients, including reductions in inflammatory markers[39], suggesting one potential mechanism for intervention efficacy.

Psychosocial interventions are also associated with improvements in cancer-related fatigue. For example, an educational group intervention designed to provide information about cancer and ways to manage the disease and treatment-related side effects had positive effects on vitality, physical functioning, and health-related role limitations in women undergoing treatment for breast cancer [40], with the beneficial effects of treatment on vitality maintained over a 3-year follow-up.[41] Other forms of group therapy, such as supportive expressive group therapy, have shown beneficial effects on fatigue among women with metastatic disease.[42] Patient administered treatments have also demonstrated positive effects on fatigue, including a self-administered form of stress management training[43] and a peer-modeling video designed for women who had recently completed treatment.[44]

The majority of these trials have not specifically focused on cancer-related fatigue, nor have they selectively recruited fatigued patients. Thus, their feasibility and efficacy among women with more severe fatigue has not been determined; indeed, one major barrier to participation in exercise programs among cancer patients is fatigue.[45] One recent trial examined the efficacy of a cognitive-behavioral therapy (CBT) designed for cancer survivors with severe fatigue, including breast cancer survivors.[46] This treatment focused on factors that may perpetuate fatigue, including poor coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue, dysregulation of sleep and activity, and low social support. Survivors in the intervention condition showed clinically significant improvements in fatigue severity and functional impairment relative to wait-list controls that were sustained for 2 years after treatment.47 Similar, though more modest effects were seen with a brief educational intervention focusing on fatigue management.48 Other promising approaches for treating cancer-related fatigue include yoga and mindfulness-based stress reduction, both of which are feasible for individuals with more severe fatigue symptoms.49

Pharmacologic treatments for cancer-related fatigue have been investigated in several trials, including erythropoietin (for chemotherapy-induced anemia), antidepressants, and psychostimulants. As noted above, treatment with erythropoietin leads to increases in hemoglobin and concurrent improvements in fatigue and physical function among cancer patients with anemia.[33] However, as most fatigued patients are not anemic, erythropoietin is unlikely to be a viable treatment for most cases of cancer-related fatigue.

Two randomized controlled trials have evaluated the efficacy of antidepressants for fatigue in breast cancer patients.[50,51] In both trials, paroxetine was effective in reducing depression but had no effect on fatigue. Results for psychostimulants are inconclusive; open-label studies conducted with fatigued breast cancer patients and others have shown improvements in fatigue[52,53], but a double-blind randomized trial with fatigued patients showed no difference between methylphenidate and placebo (both groups showed improvements in fatigue).[54] To the extent that inflammatory processes are involved in cancer-related fatigue, use of cytokine antagonists may be a promising direction for intervention efforts. Several recent trials have demonstrated that TNF blockade with etanercept is safe in patients with advanced cancer, although effects on fatigue are mixed.[55–57]

Insomnia

Prevalence

An emerging literature suggests that reports of difficulty sleeping are common among breast cancer patients and survivors. Sleep problems have been reported before [80], during [81], and after cancer treatment with radiation and/or chemotherapy[81–84] and among women with both early-stage and metastatic disease.[85] The prevalence of subjective sleep complaints ranges from 20% to 70%, depending on the study and method of assessment. In the largest study conducted to date with 300 breast cancer survivors, 51% complained of sleep problems and 19% met diagnostic criteria for insomnia.[82] Insomnia is a clinical syndrome characterized by complaints of difficulty with initiating or maintaining sleep, or nonrestorative sleep, which last for at least one month and cause clinically significant distress or impairment in important areas of functioning. Fifty-five percent of the women who met criteria for insomnia in this study reported that breast cancer either caused or aggravated their sleep problems, supporting the role of cancer diagnosis and treatment as a precipitating factor for sleep disturbance.

Longitudinal studies focusing on sleep in breast cancer patients are lacking, and there is little information about the course and duration of these problems during and after treatment.

Moreover, few studies have compared sleep in breast cancer patients to non-cancer controls. One small study found that women with a history of breast cancer had significantly shorter sleep duration than healthy controls, although overall sleep quality was similar in the two groups.[84] Another found no difference in sleep quality between breast cancer patients and women presenting for physical exams for general medical conditions.[81] Studies using polysomnography to assess objective sleep parameters in breast cancer patients have also yielded inconsistent results. [86,87]

The literature on sleep problems associated with breast cancer is in its infancy. Initial evidence indicates that sleep problems are common among breast cancer patients and that the prevalence of insomnia is 3 to 5-fold higher than rates in the general population, although controlled studies are required to determine the degree to which sleep problems in breast cancer patients and survivors differ from women with no cancer history. Sleep disturbance causes significant disruption in women's quality of life and is associated with problems with daytime fatigue, depressed mood, pain, and general ability to function.[80,81]

Mechanisms

There is a wealth of literature on insomnia in the general population that can inform our understanding of sleep problems in cancer patients. Savard and Morin[88] distinguish between three types of factors that can influence insomnia: enduring factors that *predispose* an individual for sleep problems, acute factors that *precipitate* the onset of sleep problems, and factors that *perpetuate* the maintenance of sleep problems. *Predisposing* factors that increase risk for insomnia in the general population include female gender, advancing age, personal or family history of insomnia, and multiple concomitant health problems.[89] Co-occurrence of another psychiatric disorder, particularly depression or anxiety, may also increase risk for insomnia, although it is unlikely that the prevalence of sleep problems in cancer patients is entirely due to these disorders.

A key *precipitating* factor for sleep problems in breast cancer patients may be the occurrence or exacerbation of menopausal symptoms caused by chemotherapy or hormonal therapy. Subjective reports of vasomotor symptoms are positively correlated with sleep complaints in breast cancer survivors [83,84], and there is preliminary evidence that an objective measure of hot flashes is associated with less efficient, more disrupted sleep.[90] Other precipitating factors relevant for breast cancer patients include pain and the stress of cancer diagnosis and treatment itself. Biological changes associated with cancer and its treatment may also play a role, including alterations in proinflammatory cytokines and the HPA axis.[91]

Perpetuating factors that increase risk for enduring sleep problems in the general population include maladaptive sleep habits and dysfunctional cognitions about sleep.[88] In particular, spending more time in bed, napping during the day, and having an irregular sleep-wake schedule may desynchronize the sleep-wake cycle and lead to persistent problems with sleep. Having unrealistic expectations about sleep, inaccurate appraisals of sleep difficulties, misattributions of daytime impairments, and misconceptions about the causes of insomnia may also perpetuate sleep problems. The degree to which these factors influence fatigue in breast cancer patients is an important topic for future research.

Assessment and Treatment

Diagnosis of an insomnia syndrome is made by clinical interview. Hyponotic medications are the most commonly used treatment for insomnia, including benzodiazepines, benzodiazepine receptor antagonists, antidepressants, and anti-histamines. Empirical studies of benzodiazepines and benzodiazepine receptor antagonists indicate that they are effective

in improving various aspects of sleep, although no trials have evaluated the efficacy of these medications in cancer populations nor has their long-term efficacy been determined.[86] Drawbacks of these medications include their adverse side effects and risk for tolerance and dependence. In addition, in the context of breast cancer, there is the potential for interactions with cancer treatments and potential reluctance by patients to take additional medications.

Behavioral therapies have demonstrated efficacy in the treatment of insomnia, including insomnia secondary to medical conditions, supporting their use among breast cancer patients. Positive effects of cognitive-behavioral therapy (CBT) and other behavioral treatments have been demonstrated in several meta-analyses[92,]93, including one focusing on middle-aged and older adults94, who represent the majority of breast cancer patients. Indeed, a comparative meta-analysis found that behavioral therapies are at least as effective and longer-lasting than pharmacotherapy in treating insomnia.95

There is preliminary evidence that CBT may also be effective for improving sleep in breast cancer patients. A randomized controlled trial of CBT for women with insomnia caused or exacerbated by breast cancer found significant improvement in subjective sleep complaints, as well as improvements in mood and quality of life, compared to wait-list controls.96 Effects were maintained up to 12 months after treatment completion. Changes in objective polysomnographic sleep measures were observed in an initial, single-arm pilot trial of this intervention97, but not in the larger RCT.[96] Other behavioral therapies (i.e., sleep hygiene, relaxation, and sleep scheduling) also show promise for treating sleep problems in cancer patients[98–]100, as do mind-body approaches including mindfulness meditation 101,102 and yoga[103].

Depression

Prevalence

Depression is perhaps the best studied behavioral side effect of cancer treatment. Among women with breast cancer, the prevalence of depression ranges from 1.5% to 50%, depending on the sample and particularly the definition of depression and method of assessment.[104] The majority of studies find that 20 – 30% of women experience elevated depressive symptoms, although the prevalence of major depressive disorder may be considerably lower. Major depressive disorder is a clinical syndrome that lasts for at least two weeks and causes significant impairment in normal functioning. One recent study that utilized a structured clinical interview to diagnose depression found that 9% of ambulatory breast cancer patients met criteria for major depression.[105]

Psychological distress and depressive symptoms are typically highest in the first 6 months after cancer diagnosis and then decline over time as women adjust to initial shock of diagnosis and acute effects of cancer treatment.[106] Large-scale studies of disease-free breast cancer survivors find rates of depressive symptoms that are comparable to women in the general population[107,108], although a subset of women may continue to experience depression for years after treatment.

As might be expected, depression has a detrimental effect on all aspects of quality of life in cancer patients and is associated with poorer medical adherence and more barriers to cancer care, including lack of understanding of treatment recommendations and worries about treatment side effects.[109] There is also evidence of increased morbidity and possibly, mortality in depressed cancer patients.[110,111] As such, depression represents an important target for timely identification and treatment.

Mechanisms

There are a number of factors that can influence depression in breast cancer patients. Psychosocial factors appear to be the strongest predictors of depressive symptoms in this population, including history of depression, poor social functioning, occurrence of other stressful life events, use of avoidant coping strategies, and pessimism. [108,112–115] Physical factors, including pain, physical disability, and other symptoms, also show modest associations with depression.[108] In contrast, objective aspects of cancer diagnosis and treatment are not consistently associated with depressive symptoms, including stage of disease, type of treatment received, and tamoxifen use.[108,116] These findings suggest that the occurrence of depression in breast cancer patients is more strongly influenced by social and personality factors of the patient, rather than severity of the disease or treatment regimen.

Biological factors may also play a role in cancer-related depression. For example, there is preliminary evidence of alterations in autonomic regulation and HPA axis activity among depressed women with metastatic breast cancer,117 as well as elevations in proinflammatory cytokines in depressed patients with breast, pancreatic, and esophageal cancers.[118] However, the degree to which these changes drive increases in depression in breast cancer patients has not been determined. Changes in biological systems may play a more minor role among women with early-stage breast cancer relative to women with advanced disease and other patient populations (e.g., pancreatic cancer patients), given the site and localized nature of their tumors.

Assessment and Treatment

Although a clinical interview is required for diagnosis of major depression, screening can be accomplished by asking patients a few simple questions. For example, Chochinov[119] reports that a single-item question, “Are you depressed most of the time?”, has high sensitivity and specificity for detecting depression among cancer patients. A brief self-report questionnaire, the PHQ-9, also has high sensitivity for detecting major depression and has been validated in the general population.[120,121]

Psychological interventions are effective in treating depression in the general population[122], and there is compelling evidence that psychosocial approaches are also effective in improving depressive symptoms among cancer patients.[123–125] In trials conducted with breast cancer patients, positive effects on depressive symptoms have been seen with educational and nutritional interventions[126], cognitive-behavioral therapy[127], and supportive-expressive group therapy [128,129], among others. Shorter-term treatments that focus on providing information about breast cancer and its treatment and managing disease-related stress may be particularly helpful for newly diagnosed patients, whereas interventions that emphasize support and emotional expression may be more useful for women with advanced stage disease. In general, psychological interventions appear to be most effective for those who are distressed[127,129], although it is important to note that the majority of these trials were preventative and did not selectively recruit women with elevated depression; thus, their efficacy for treating clinically significant depression has not been determined.

Pharmacotherapy should also be considered for the treatment of major depression in breast cancer patients. Antidepressants have been shown to improve depression in physically ill patients[130], supporting their potential efficacy among breast cancer patients. In the few randomized trials conducted to date, paroxetine has been shown to be effective in reducing depressive symptoms in breast cancer patients, even among those who were not depressed at study entry.[50,51]

Cognitive disturbance

Prevalence

Reports of cognitive deficits are common among breast cancer patients during and after chemotherapy. This phenomenon, often referred to as “chemobrain”, has been the focus of empirical research since the 1990s.[58] Cross-sectional studies utilizing objective measures of cognitive function provided initial evidence of cognitive compromise among women treated with chemotherapy relative to non-treated controls, with estimates of cognitive deficits ranging from 16% to 75% depending on the patient population and definition of impairment. Two recent meta-analyses of this literature concluded that women treated with chemotherapy show small to moderate impairments in cognitive function compared to controls or published norms.[59,60] Chemotherapy-related cognitive changes are apparent across multiple cognitive domains, including language, verbal and nonverbal memory, spatial ability, and motor function, suggesting a pattern of generalized cognitive impairment. Deficits appear to be most pronounced among women treated with high-dose chemotherapy[61], although effects are also apparent among women treated with standard dose chemotherapy.[62–65]

More recently, longitudinal studies have emerged that provide a more rigorous test of chemotherapy effects on cognitive functioning.66,67 Several of these studies have included a control group who did not receive chemotherapy to account for practice effects (performance on neuropsychological tests typically improves with repeated administration). In one study, breast cancer patients treated with chemotherapy showed declines on specific measures of memory from pre- to one year post-treatment relative to patients who did not receive chemotherapy.[68] Another found greater cognitive decline among women treated with chemotherapy from pre- to one year post-treatment compared to healthy controls, particularly among those treated with high dose chemotherapy (25 vs. 6.7% impaired at one year post-treatment).69 A study by Jenkins et al. showed reliable cognitive declines in 18% of women treated with chemotherapy at one year post-treatment; however, similar declines were seen in patients who did not receive chemotherapy and healthy controls.70 In this cohort, cognitive effects were most pronounced if treatment resulted in premature menopause, suggesting that particular groups may be at increased risk for chemotherapy-related cognitive impairment.

Follow-up studies conducted with patients after treatment completion suggest that there is improvement in cognitive function over time, although a subset of patients continue to show deficits for up to 10 years after treatment.[71] For example, one study found that 16% of women showed impairment while on chemotherapy, 4.4% showed impairment at one year post-treatment, and 3.6% showed impairment at two years post-treatment.[9]

A small number of studies have utilized neuroimaging techniques to evaluate cognitive changes associated with chemotherapy in breast cancer patients. In a study by Silverman and colleagues[72], PET scans were acquired both at rest and during an activation paradigm using memory-related and control tasks in breast cancer survivors treated with chemotherapy between 5–10 years previously. Significant alterations in cerebral blood flow were observed in regions of frontal cortex and cerebellum during performance of a short-term recall task in chemotherapy-treated patients relative to untreated controls. Resting glucose metabolism was also altered in prefrontal areas, and was correlated with impairments in neurocognitive performance on a short-term memory task. Further, women whose treatment regimens also included tamoxifen had lower basal ganglia activity.

A study by Inagaki and colleagues[73] using structural MRI found that breast cancer survivors treated with chemotherapy within the previous year had smaller volumes of prefrontal,

parahippocampal, cingulate, and precuneus areas relative to untreated controls. These effects were not observed among longer-term survivors, consistent with a previous report by this group. [74] An interesting case study of monozygotic twins showed increases in subjective cognitive problems as well as alterations in brain structure and function in the twin who developed breast cancer and was treated with chemotherapy relative to her nonaffected sister.[75]

Taken together with the neuropsychological testing results, the neuroimaging findings provide compelling evidence that chemotherapy has a negative effect on cognition in a subset of women, and that these effects may persist for years after successful treatment. Although these effects are modest in statistical terms, they may have profound effects on patients' lives and can interfere with work and other activities.[66]

One important difference between research on cognitive problems and research on other behavioral symptoms is that cognitive function is typically assessed using objective measures (see below), which may reflect a different type or level of impairment than that assessed by self-report. Indeed, subjective cognitive complaints are not correlated with objective cognitive performance in breast cancer survivors, but are correlated with subjective reports of fatigue and depressed mood.[65]

Mechanisms

The biological mechanisms underlying effects of chemotherapy on cognitive function are unknown. A recent review article highlighted several candidate mechanisms for chemotherapy-induced cognitive changes, including direct neurotoxic effects, DNA damage and telomere length, inflammation and cytokine deregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms that may render individuals more susceptible to these effects.[76] For example, there is preliminary evidence that women with at least one epsilon 4 allele of APOE may be at greater risk for chemotherapy-related cognitive deficits. [77] There is also evidence that treatment with tamoxifen may increase the incidence and/or extent of cognitive impairment.[65,68] The identification of risk factors that predispose women to cognitive impairment is a critical question for future research, as greater understanding of these factors may influence treatment decisions for certain patients.

Assessment and Treatment

Assessment of cognitive impairment in breast cancer patients requires objective neuropsychological testing, the gold standard for assessment of cognitive function. This type of testing may be particularly important in assessing "chemobrain", as subjective reports of chemotherapy-related cognitive impairment are typically not correlated with objective measures of cognitive function.[65] Performance on neuropsychological tests is compared to a reference group to determine the presence of cognitive compromise. One possible battery for use with breast cancer patients includes measures of premorbid intellectual ability, working memory, learning and memory, information-processing speed and efficiency, spatial and retrieval skills.[58]

Interventions for chemotherapy-related cognitive impairment in breast cancer patients have not yet been developed and evaluated. However, results from a recent pilot study suggest that a cognitive-behavioral approach may be effective. Ferguson and colleagues[78] conducted a single-arm cognitive-behavioral intervention with breast cancer survivors who reported problems with memory and attention several years after chemotherapy. Participants were provided with information about chemotherapy-related cognitive problems, learned how to identify "at risk" situations where cognitive problems might occur, and were trained in the use of compensatory strategies to help manage these situations (e.g., schedule making,

external cueing). There were significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance at post-treatment, 2-month, and 6-month follow-ups. These findings require replication in a randomized controlled trial but suggest that this type of program may be feasible and effective for breast cancer survivors with persistent cognitive impairment. Other potential treatment approaches include methylphenidate, which has been used to improve cognitive function in patients with advanced cancer.[79]

Clinical Applications

Despite the prevalence of behavioral side effects in patients and survivors, these symptoms are typically underreported and undertreated. Patients may feel that these symptoms are an inevitable consequence of cancer treatment; indeed, a study focusing on cancer-related fatigue found that 74% of patients believed that fatigue was a symptom to be endured, and only 50% discussed treatment options with their physicians.{Vogelzang, 1997 286 /id} The first step in addressing behavioral problems is to ask patients about them directly. Simple screening questions such as “Are you feeling fatigued or depressed much of the time?”, or “Are you having trouble falling asleep or staying asleep much of the time?” should help to identify patients who are experiencing problems in these domains. Validated self-report measures are available for evaluation of depressive symptoms (e.g., PHQ-9{Kroenke, 2001 95 /id}) and sleep disturbance (e.g., Pittsburgh Sleep Quality Inventory{Buysse, 1991 230 /id}), although interviews are required for clinical diagnosis of depression and insomnia. Evaluation of cognitive function requires objective neuropsychological testing, which may not track with subjective reports of cognitive impairment.

If patients do report problems in a particular domain, physicians should evaluate potential medical causes for these symptoms. For example, women who report significant fatigue should be evaluated for anemia and alterations in thyroid function.{Kumar, 2004 506 /id} Medications may also influence fatigue, sleep, mood, and cognitive function and should be carefully evaluated in patients and survivors. If a medical cause cannot be identified (which may occur in the majority of cases), patients should be provided with information about the symptom that includes options for treatment. It is important for patients to recognize that treatments *are* available and to receive appropriate referrals. Educational materials can be found online and at resource centers for cancer patients and their families. Women who are experiencing more severe and persistent symptoms that impair their normal functioning may benefit from referral to a mental health professional for further evaluation and individualized treatment.

Behavioral symptoms frequently co-occur, so that a woman who is fatigued may also report problems with sleep, mood, and cognitive function. To that extent that a primary or underlying symptom can be identified, this may help in targeting treatment. For example, antidepressants have been shown to be efficacious in reducing depression but not cancer-related fatigue.{Morrow, 2003 327 /id} However, there is overlap in the recommended treatments for each symptom, and exercise, education, and other nonspecific interventions may have beneficial effects across domains.

Conclusions

Results from this emerging literature indicate that behavioral symptoms are common in breast cancer patients and survivors. There is evidence that fatigue, sleep disturbance, depression, and cognitive impairment are elevated in patients relative to healthy controls, and that these symptoms may persist for months or years after successful treatment in a substantial minority of women. Behavioral disturbances cause serious disruption in patients’

quality of life and require careful attention from physicians. A number of treatment options are available for managing behavioral symptoms in breast cancer patients. In particular, behavioral and psychological interventions have demonstrated efficacy in improving fatigue and depressive symptoms, with promising preliminary results for sleep and cognitive disturbance.

To date, research on behavioral comorbodities in cancer patients has primarily focused on documenting the prevalence of these symptoms and in some cases, assessing correlates and potential treatments. There are a number of important questions to be addressed in the next generation of research.[131] Prospective studies are needed to document the course of symptoms during and after treatment. In some cases, it may be difficult to obtain a true "baseline", as the stress of diagnosis (and possibly effects of the tumor itself) may lead to elevations in behavioral symptoms before treatment onset; still, evaluating effects of primary and adjuvant therapies is critical for elucidating the trajectory of behavioral changes. These studies would also benefit from inclusion of an appropriate control group, given the prevalence of fatigue, cognitive and sleep disturbance, and depressive symptoms in midlife women with no cancer history.

Identification of risk factors for symptom development and persistence is critical. It appears that behavioral disturbances are particularly prominent in a subgroup of patients, but the characteristics of these women have not yet been elucidated. A recent study used growth mixture modeling to identify subgroups of women reporting low vs. high fatigue after cancer treatment and to characterize women in the high fatigue group, who had a higher body mass index and were also more likely to catastrophize in response to fatigue symptoms.[24] This type of analysis provides extremely useful information about vulnerable women and potential treatment targets (e.g., CBT for catastrophizing coping style). Studies in this area may find it helpful to distinguish between predisposing factors, precipitating factors, and perpetuating factors for cancer-related symptoms, similar to research on insomnia.[88] Identifying relevant risk factors will facilitate the delivery of targeted interventions to those most in need.

Determining the mechanisms for behavioral changes in cancer patients and survivors is another important area for research. Little is currently known about the underlying etiology of cancer-related behavioral problems, although there is emerging evidence that cytokine dysregulation may play a role in fatigue and possibly other behavioral changes. A related issue is whether these symptoms are independent, or whether they share common biological and/or behavioral underpinnings. Subjective complaints are typically correlated with each other, including fatigue, depressive symptoms, sleep disturbance, and subjective reports of cognitive impairment. This may suggest a common etiology, or simply that experiencing problems in one area (e.g., sleep) may lead to disturbances in others (e.g., energy, mood). The co-occurrence of these symptoms, their shared and unique predictors, and implications for treatment merits focused attention in future studies.[132]

References

1. Jemal A, Murray T, Ward E, et al. Cancer Statistics, 2005. CA Cancer J Clin 2005;55:10–30. [PubMed: 15661684]
2. Ganz PA. Why and how to study the fate of cancer survivors: observations from the clinic and the research laboratory. Eur J Cancer 2003;39:2136–2141. [PubMed: 14522370]
3. Patrick DL, Ferketich SL, Frame PS, et al. National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15–17, 2002. J Natl Cancer Inst 2003;95:1110–1117. [PubMed: 12902440]

4. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5:353–360. [PubMed: 11040270]
5. Lawrence DP, Kupelnick B, Miller K, et al. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004;32:40–50. [PubMed: 15263040]
6. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. Eur J Cancer 2002;38:27–43. [PubMed: 11750837]
7. Andrykowski MA, Schmidt JE, Salsman JM, et al. Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. J Clin Oncol 2005;23:6613–6622. [PubMed: 16170168]
8. Donovan KA, Jacobsen PB, Andrykowski MA, et al. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. J Pain Symptom Manage 2004;28:373–380. [PubMed: 15471655]
9. Fan HG, Houede-Tchen N, Yi QL, et al. Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. J Clin Oncol 2005;23:8025–8032. [PubMed: 16258100]
10. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18:743–753. [PubMed: 10673515]
11. Cella D, Davis K, Breitbart W, et al. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol 2001;19:3385–3391. [PubMed: 11454886]
12. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer 2006;106:751–758. [PubMed: 16400678]
13. Servaes P, Gielissen MF, Verhagen S, et al. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. Psychooncology 2006;16:787–795. [PubMed: 17086555]
14. Poulson MJ. Not just tired. J Clin Oncol 2001;19:4180–4181. [PubMed: 11689589]
15. Andrykowski MA, Curran SL, Lightner R. Off-treatment fatigue in breast cancer survivors: a controlled comparison. J Behav Med 1998;21:1–18. [PubMed: 9547419]
16. Jacobsen PB, Hann DM, Azzarello LM, et al. Fatigue in women receiving adjuvant chemotherapy for breast cancer: characteristics, course, and correlates. J Pain Symptom Manage 1999;18:233–242. [PubMed: 10534963]
17. Groenvold M, Petersen MA, Idler E, et al. Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. Breast Cancer Res Treat. 2007
18. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. Br J Cancer 2004;91:822–828. [PubMed: 15238987]
19. Jacobsen PB, Donovan KA, Weitzner MA. Distinguishing fatigue and depression in patients with cancer. Semin Clin Neuropsychiatry 2003;8:229–240. [PubMed: 14613050]
20. Visser MR, Smets EM. Fatigue, depression and quality of life in cancer patients: how are they related? Support Care Cancer 1998;6:101–108. [PubMed: 9540167]
21. Capuron L, Gumnick JF, Musselman DL, et al. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 2002;26:643–652. [PubMed: 11927189]
22. Jacobsen PB, Andrykowski MA, Thors CL. Relationship of catastrophizing to fatigue among women receiving treatment for breast cancer. J Consult Clin Psychol 2004;72:355–361. [PubMed: 15065968]
23. Broeckel JA, Jacobsen PB, Horton J, et al. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 1998;16:1689–1696. [PubMed: 9586880]
24. Donovan KA, Small BJ, Andrykowski MA, et al. Utility of a cognitive-behavioral model to predict fatigue following breast cancer treatment. Health Psychol 2007;26:464–472. [PubMed: 17605566]
25. Wratten C, Kilmurray J, Nash S, et al. Fatigue during breast radiotherapy and its relationship to biological factors. Int J Radiat Oncol Biol Phys 2004;59:160–167. [PubMed: 15093912]
26. Mills P, Adler K, Perez C, et al. Soluble ICAM-1 and fatigue in breast cancer patients in response to chemotherapy. Psychsom Med 2003;65:A22.

27. Bower JE, Ganz PA, Aziz N, et al. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. Brain Behav Immun 2007;21:251–258. [PubMed: 17008048]
28. Bower JE, Ganz PA, Aziz N, et al. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002;64:604–611. [PubMed: 12140350]
29. Bower JE, Ganz PA, Aziz N, et al. T-cell homeostasis in breast cancer survivors with persistent fatigue. J Natl Cancer Inst 2003;95:1165–1168. [PubMed: 12902446]
30. Collado-Hidalgo A, Bower JE, Ganz PA, et al. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin Cancer Res 2006;12:2759–2766. [PubMed: 16675568]
31. Bower JE, Ganz PA, Dickerson SS, et al. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology 2005;30:92–100. [PubMed: 15358446]
32. Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom Med 2005;67:277–280. [PubMed: 15784794]
33. Cella D, Kallich J, McDermott A, et al. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol 2004;15:979–986. [PubMed: 15151958]
34. Mock V. Evidence-based treatment for cancer-related fatigue. J Natl Cancer Inst Monogr 2004;32:112–118. [PubMed: 15263051]
35. McNeely ML, Campbell KL, Rowe BH, et al. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ 2006;175:34–41. [PubMed: 16818906]
36. Pinto BM, Frierson GM, Rabin C, et al. Home-based physical activity intervention for breast cancer patients. J Clin Oncol 2005;23:3577–3587. [PubMed: 15908668]
37. Courneya KS, Mackey JR, Bell GJ, et al. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol 2003;21:1660–1668. [PubMed: 12721239]
38. Vallance JK, Courneya KS, Plotnikoff RC, et al. Randomized controlled trial of the effects of print materials and step pedometers on physical activity and quality of life in breast cancer survivors. J Clin Oncol 2007;25:2352–2359. [PubMed: 17557948]
39. Fairey AS, Courneya KS, Field CJ, et al. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. Brain Behav Immun 2005;19:381–388. [PubMed: 15922556]
40. Helgeson VS, Cohen S, Schulz R, et al. Education and peer discussion group interventions and adjustment to breast cancer. Arch Gen Psychiatry 1999;56:340–347. [PubMed: 10197829]
41. Helgeson VS, Cohen S, Schulz R, et al. Long-term effects of educational and peer discussion group interventions on adjustment to breast cancer. Health Psychol 2001;20:387–392. [PubMed: 11570653]
42. Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. A randomized outcome study. Arch Gen Psychiatry 1981;38:527–533. [PubMed: 7235853]
43. Jacobsen PB, Meade CD, Stein KD, et al. Efficacy and costs of two forms of stress management training for cancer patients undergoing chemotherapy. J Clin Oncol 2002;20:2851–2862. [PubMed: 12065562]
44. Stanton AL, Ganz PA, Kwan L, et al. Outcomes From the Moving Beyond Cancer Psychoeducational, Randomized, Controlled Trial With Breast Cancer Patients. J Clin Oncol 2005;23:6009–6018. [PubMed: 16135469]
45. Courneya KS, Friedenreich CM, Quinney HA, et al. A longitudinal study of exercise barriers in colorectal cancer survivors participating in a randomized controlled trial. Ann Behav Med 2005;29:147–153. [PubMed: 15823788]
46. Gielissen MF, Verhagen S, Witjes F, et al. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. J Clin Oncol 2006;24:4882–4887. [PubMed: 17050873]
47. Gielissen MF, Verhagen CA, Bleijenberg G. Cognitive behaviour therapy for fatigued cancer survivors: long-term follow-up. Br J Cancer 2007;97:612–618. [PubMed: 17653075]

48. Yates P, Aranda S, Hargraves M, et al. Randomized controlled trial of an educational intervention for managing fatigue in women receiving adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 2005;23:6027–6036. [PubMed: 16135471]
49. Bower JE, Woolery A, Sternlieb B, et al. Yoga for cancer patients and survivors. Cancer Control 2005;12:165–171. [PubMed: 16062164]
50. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. J Clin Oncol 2003;21:4635–4641. [PubMed: 14673053]
51. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 2005;89:243–249. [PubMed: 15754122]
52. Hanna A, Sledge G, Mayer ML, et al. A phase II study of methylphenidate for the treatment of fatigue. Support Care Cancer 2006;14:210–215. [PubMed: 16096772]
53. Bruera E, Driver L, Barnes EA, et al. Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: a preliminary report. J Clin Oncol 2003;21:4439–4443. [PubMed: 14645434]
54. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol 2006;24:2073–2078. [PubMed: 16648508]
55. Monk JP, Phillips G, Waite R, et al. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. J Clin Oncol 2006;24:1852–1859. [PubMed: 16622259]
56. Madhusudan S, Muthuramalingam SR, Braybrooke JP, et al. Study of Etanercept, a Tumor Necrosis Factor-Alpha Inhibitor, in Recurrent Ovarian Cancer. J Clin Oncol 2005;23:5950–5959. [PubMed: 16135466]
57. Madhusudan S, Foster M, Muthuramalingam SR, et al. A Phase II Study of Etanercept (Enbrel), a Tumor Necrosis Factor {alpha} Inhibitor in Patients with Metastatic Breast Cancer. Clin Cancer Res 2004;10:6528–6534. [PubMed: 15475440]
58. Vardy J, Rourke S, Tannock IF. Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. J Clin Oncol 2007;25:2455–2463. [PubMed: 17485710]
59. Falleti MG, Sanfilippo A, Maruff P, et al. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. Brain Cogn 2005;59:60–70. [PubMed: 15975700]
60. Stewart A, Bielajew C, Collins B, et al. A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. Clin Neuropsychol 2006;20:76–89. [PubMed: 16410227]
61. van Dam FS, Schagen SB, Muller MJ, et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst 1998;90:210–218. [PubMed: 9462678]
62. Brezden CB, Phillips KA, Abdolell M, et al. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 2000;18:2695–2701. [PubMed: 10894868]
63. Schagen SB, van Dam FS, Muller MJ, et al. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 1999;85:640–650. [PubMed: 10091737]
64. Tchen N, Juffs HG, Downie FP, et al. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. J Clin Oncol 2003;21:4175–4183. [PubMed: 14615445]
65. Castellon SA, Ganz PA, Bower JE, et al. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. J Clin Exp Neuropsychol 2004;26:955–969. [PubMed: 15742545]
66. Wefel JS, Lenzi R, Theriault RL, et al. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer 2004;100:2292–2299. [PubMed: 15160331]

67. Hurria A, Rosen C, Hudis C, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. J Am Geriatr Soc 2006;54:925–931. [PubMed: 16776787]
68. Bender CM, Sereika SM, Berga SL, et al. Cognitive impairment associated with adjuvant therapy in breast cancer. Psychooncology 2006;15:422–430. [PubMed: 16097037]
69. Schagen SB, Muller MJ, Boogerd W, et al. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. J Natl Cancer Inst 2006;98:1742–1745. [PubMed: 17148777]
70. Jenkins V, Shilling V, Deutsch G, et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. Br J Cancer 2006;94:828–834. [PubMed: 16523200]
71. Ahles TA, Saykin AJ, Furstenberg CT, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol 2002;20:485–493. [PubMed: 11786578]
72. Silverman DH, Dy CJ, Castellon SA, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5–10 years after chemotherapy. Breast Cancer Res Treat 2007;103:303–311. [PubMed: 17009108]
73. Inagaki M, Yoshikawa E, Matsuoka Y, et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. Cancer 2007;109:146–156. [PubMed: 17131349]
74. Yoshikawa E, Matsuoka Y, Inagaki M, et al. No adverse effects of adjuvant chemotherapy on hippocampal volume in Japanese breast cancer survivors. Breast Cancer Res Treat 2005;92:81–84. [PubMed: 15980995]
75. Ferguson RJ, McDonald BC, Saykin AJ, et al. Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. J Clin Oncol 2007;25:3866–3870. [PubMed: 17761972]
76. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 2007;7:192–201. [PubMed: 17318212]
77. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology 2003;12:612–619. [PubMed: 12923801]
78. Ferguson RJ, Ahles TA, Saykin AJ, et al. Cognitive-behavioral management of chemotherapy-related cognitive change. Psychooncology 2007;16:772–777. [PubMed: 17152119]
79. Rozans M, Dreisbach A, Lertora JJ, et al. Palliative uses of methylphenidate in patients with cancer: a review. J Clin Oncol 2002;20:335–339. [PubMed: 11773187]
80. Ancoli-Israel S, Liu L, Marler MR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. Support Care Cancer 2006;14:201–209. [PubMed: 16010529]
81. Fortner BV, Stepanski EJ, Wang SC, et al. Sleep and quality of life in breast cancer patients. J Pain Symptom Manage 2002;24:471–480. [PubMed: 12547047]
82. Savard J, Simard S, Blanchet J, et al. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep 2001;24:583–590. [PubMed: 11480655]
83. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes toward estrogen replacement therapy. J Clin Oncol 1995;13:2737–2744. [PubMed: 7595732]
84. Carpenter JS, Elam JL, Ridner SH, et al. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. Oncol Nurs Forum 2004;31:591–5598. [PubMed: 15146224]
85. Koopman C, Nouriani B, Erickson V, et al. Sleep disturbances in women with metastatic breast cancer. Breast J 2002;8:362–370. [PubMed: 12390359]
86. Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. Sleep Med Rev 2006;10:419–429. [PubMed: 16963293]
87. Silberfarb PM, Hauri PJ, Oxman TE, et al. Assessment of sleep in patients with lung cancer and breast cancer. J Clin Oncol 1993;11:997–1004. [PubMed: 8487063]

88. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol 2001;19:895–908. [PubMed: 11157043]

89. Klink ME, Quan SF, Kaltenborn WT, et al. Risk factors associated with complaints of insomnia in a general adult population. Influence of previous complaints of insomnia. Arch Intern Med 1992;152:1634–1637. [PubMed: 1497397]

90. Savard J, Davidson JR, Ivers H, et al. The association between nocturnal hot flashes and sleep in breast cancer survivors. J Pain Symptom Manage 2004;27:513–522. [PubMed: 15165649]

91. Rich T, Innominato PF, Boerner J, et al. Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer. Clin Cancer Res 2005;11:1757–1764. [PubMed: 15755997]

92. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. Am J Psychiatry 1994;151:1172–1180. [PubMed: 8037252]

93. Murtagh DR, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. J Consult Clin Psychol 1995;63:79–89. [PubMed: 7896994]

94. Irwin MR, Cole JC, Nicassio PM. Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. Health Psychol 2006;25:3–14. [PubMed: 16448292]

95. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. Am J Psychiatry 2002;159:5–11. [PubMed: 11772681]

96. Savard J, Simard S, Ivers H, et al. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: Sleep and psychological effects. J Clin Oncol 2005;23:6083–6096. [PubMed: 16135475]

97. Quesnel C, Savard J, Simard S, et al. Efficacy of cognitive-behavioral therapy for insomnia in women treated for nonmetastatic breast cancer. J Consult Clin Psychol 2003;71:189–200. [PubMed: 12602439]

98. Berger AM, VonEssen S, Khun BR, et al. Feasibilty of a sleep intervention during adjuvant breast cancer chemotherapy. Oncol Nurs Forum 2002;29:1431–1441. [PubMed: 12432414]

99. Berger AM, VonEssen S, Kuhn BR, et al. Adherence, sleep, and fatigue outcomes after adjuvant breast cancer chemotherapy: results of a feasibility intervention study. Oncol Nurs Forum 2003;30:513–522. [PubMed: 12719750]

100. Davidson JR, Waisberg JL, Brundage MD, et al. Nonpharmacologic group treatment of insomnia: a preliminary study with cancer survivors. Psychooncology 2001;10:389–397. [PubMed: 11536417]

101. Carlson LE, Speca M, Patel KD, et al. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. Psychoneuroendocrinology 2004;29:448–474. [PubMed: 14749092]

102. Shapiro SL, Bootzin RR, Figueredo AJ, et al. The efficacy of mindfulness-based stress reduction in the treatment of sleep disturbance in women with breast cancer: an exploratory study. J Psychosom Res 2003;54:85–91. [PubMed: 12505559]

103. Cohen L, Warneke C, Fouladi RT, et al. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. Cancer 2004;100:2253–2260. [PubMed: 15139072]

104. Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Instgr 2004;32:57–71.

105. Coyne JC, Palmer SC, Shapiro PJ, et al. Distress, psychiatric morbidity, and prescriptions for psychotropic medication in a breast cancer waiting room sample. Gen Hosp Psychiatry 2004;26:121–128. [PubMed: 15038929]

106. Schag CA, Ganz PA, Polinsky ML, et al. Characteristics of women at risk for psychosocial distress in the year after breast cancer. J Clin Oncol 1993;11:783–793. [PubMed: 8478672]

107. Ganz PA, Rowland JH, Desmond K, et al. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. J Clin Oncol 1998;16:501–514. [PubMed: 9469334]

108. Bardwell WA, Natarajan L, Dimsdale JE, et al. Objective cancer-related variables are not associated with depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol 2006;24:2420–2427. [PubMed: 16651649]
109. Ell K, Sanchez K, Vourlekis B, et al. Depression, correlates of depression, and receipt of depression care among low-income women with breast or gynecologic cancer. J Clin Oncol 2005;23:3052–3060. [PubMed: 15860863]
110. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. Biol Psychiatry 2003;54:269–282. [PubMed: 12893103]
111. Gallo JJ, Bogner HR, Morales KH, et al. The effect of a primary care practice-based depression intervention on mortality in older adults: a randomized trial. Ann Intern Med 2007;146:689–698. [PubMed: 17502629]
112. Epping-Jordan JE, Compas BE, Howell DC. Predictors of cancer progression in young adult men and women: avoidance, intrusive thoughts, and psychological symptoms. Health Psychol 1994;13:539–547. [PubMed: 7889909]
113. Stanton AL, Snider PR. Coping with a breast cancer diagnosis: a prospective study. Health Psychol 1993;12:16–23. [PubMed: 8462494]
114. Kissane DW, Clarke DM, Ikin J, et al. Psychological morbidity and quality of life in Australian women with early-stage breast cancer: a cross-sectional survey. Med J Aust 1998;169:192–196. [PubMed: 9734576]
115. Carver CS, Pozo C, Harris SD, et al. How coping mediates the effect of optimism on distress: a study of women with early stage breast cancer. J Pers Soc Psychol 1993;65:375–390. [PubMed: 8366426]
116. Scheier MF, Helgeson VS. Really, disease doesn't matter? A commentary on correlates of depressive symptoms in women treated for early-stage breast cancer. J Clin Oncol 2006;24:2407–2408. [PubMed: 16651643]
117. Giese-Davis J, Wilhelm FH, Conrad A, et al. Depression and stress reactivity in metastatic breast cancer. Psychosom Med 2006;68:675–683. [PubMed: 17012520]
118. Musselman DL, Miller AH, Porter MR, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. Am J Psychiatry 2001;158:1252–1257. [PubMed: 11481159]
119. Chochinov HM. Depression in cancer patients. Lancet Oncol 2001;2:499–505. [PubMed: 11905726]
120. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–613. [PubMed: 11556941]
121. Martin A, Rief W, Klaiberg A, et al. Validity of the Brief Patient Health Questionnaire Mood Scale (PHQ-9) in the general population. Gen Hosp Psychiatry 2006;28:71–77. [PubMed: 16377369]
122. Hollon SD, Stewart MO, Strunk D. Enduring effects for cognitive behavior therapy in the treatment of depression and anxiety. Annu Rev Psychol 2006;57:285–315. [PubMed: 16318597]
123. Devine EC, Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. Oncol Nurs Forum 1995;22:1369–1381. [PubMed: 8539178]
124. Barsevick AM, Sweeney C, Haney E, et al. A systematic qualitative analysis of psychoeducational interventions for depression in patients with cancer. Oncol Nurs Forum 2002;29:73–84. [PubMed: 11817494]
125. Meyer TJ, Mark MM. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. Health Psychol 1995;14:101–108. [PubMed: 7789344]
126. Scheier MF, Helgeson VS, Schulz R, et al. Interventions to enhance physical and psychological functioning among younger women who are ending nonhormonal adjuvant treatment for early-stage breast cancer. J Clin Oncol 2005;23:4298–4311. [PubMed: 15994143]
127. Antoni MH, Lehman JM, Klibourn KM, et al. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. Health Psychology 2001;20:20–32. [PubMed: 11199062]

128. Classen C, Butler LD, Koopman C, et al. Supportive-expressive group therapy and distress in patients with metastatic breast cancer: a randomized clinical intervention trial. Arch Gen Psychiatry 2001;58:494–501. [PubMed: 11343530]

129. Goodwin PJ, Leszcz M, Ennis M, et al. The effect of group psychosocial support on survival in metastatic breast cancer. N Engl J Med 2001;345:1719–1726. [PubMed: 11742045]

130. Gill D, Hatcher S. Antidepressants for depression in medical illness. Cochrane Database for Systematic Reviews 2003:3.

131. Bower JE. Prevalence and causes of fatigue after cancer treatment: the next generation of research. J Clin Oncol 2005;23:8280–8282. [PubMed: 16219929]

132. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. J Natl Cancer Inst Monogr 2004;32:17–21. [PubMed: 15263036]

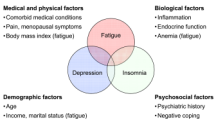

Figure 1.

Fatigue, depression, and sleep disturbance frequently co-occur in breast cancer patients and survivors. A variety of factors may contribute to the development and persistence of these symptoms. The key factors associated with these symptoms in the empirical literature are summarized here.

Table 1

Prevalence, assessment, and treatment of behavioral disturbances in breast cancer patients and survivors

Symptom	Prevalence	Assessment	Treatment
Fatigue	25 – 99% (on tx) 20 – 35% (off tx)	Self-report	Exercise Psychosocial interventions Education, stress management, cognitive behavioral therapy, supportive expressive group therapy Pharmacologic? Mixed evidence for efficacy
Insomnia	20 – 70%	Self-report Interview required for diagnosis of clinical syndrome Polysomnography for objective sleep	Psychosocial interventions Cognitive behavioral therapy Pharmacologic? Effective in general population, not evaluated in breast cancer patients
Depression	1.5 – 50%	Self-report Interview required for diagnosis of clinical syndrome	Psychosocial interventions Education, stress management, cognitive behavioral therapy, supportive expressive group therapy Pharmacologic
Cognitive disturbance	16 – 75%	Objective neuropsychological testing	Psychosocial interventions? Preliminary evidence for cognitive behavioral therapy