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REVIEW ARTICLE

Behavioral Symptoms in Patients With Breast Cancer and Survivors

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ABSTRACT

Behavioral symptoms are a common adverse 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 after treatment. Patients need accurate information about the occurrence of these adverse effects as well as assistance with symptom management. This review considers four of the most common behavioral sequelae of breast cancer, namely 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.

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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 as survivors 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 (Table 1). These symptoms are among the most common adverse 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]

FATIGUE

Prevalence

Fatigue is increasingly recognized as one of the most common and distressing adverse 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 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 2 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 adverse 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 continues 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]

On the basis of patient reports, cancer-related fatigue is more severe, more enduring, and more disabling than normal fatigue caused by lack of sleep or overexertion.[14] Indeed, studies have confirmed that the intensity and duration of fatigue experienced by breast cancer patients and survivors are significantly greater than in healthy controls and

Table 1. Prevalence, Assessment, and Treatment of Behavioral Disturbances in Breast Cancer Patients and Survivors

Symptom	Prevalence Range (%)	Assessment	Treatment
Fatigue	25-99 on treatment; 20-35 off treatment	Self-report	Exercise; psychosocial interventions (education, stress management, cognitive-behavioral therapy, supportive expressive group therapy); pharmacotherapy? (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); pharmacotherapy? (effective in general population but 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); pharmacotherapy
Cognitive disturbance	16-75	Self-report; objective neuropsychological testing	Psychosocial interventions? (preliminary evidence for cognitive-behavioral therapy)

cause 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, adverse 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 suggest 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 (ie, 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 breast cancer populations,[10,15,24] 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,[10,25] highlighting the role of socioeconomic factors as determinants of fatigue. They are also more likely to have comorbid medical problems and a higher body mass index.[10,12,25]

In terms of biologic mechanisms, anemia likely contributes to fatigue in a subset of patients (ie, 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[26] and chemotherapy.[27] There is also evidence that inflammatory processes play a role in post-treatment fatigue. Relative to nonfatigued survivors, breast cancer survivors with persistent fatigue show elevations in circulating markers of proinflammatory cytokine activity and increased production of proinflammatory cytokines after lipopolysaccharide stimulation, as well as alterations in the cellular immune system.[28-31] Together, these changes suggest an inflammatory basis for persistent fatigue in breast cancer survivors.

Alterations in hypothalamic-pituitary-adrenal (HPA) axis function have been documented in fatigued breast cancer survivors, including lower levels of morning serum cortisol,[29] flattened diurnal cortisol slopes,[32] and a blunted cortisol response to acute psychosocial stress.[33] 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.[28] The biologic underpinnings of cancer-related fatigue are an important focus for future research. Figure 1 illustrates the overlap between symptoms of fatigue, depression, and sleep disturbance in breast cancer and summarizes the key factors that may contribute to problems in these domains.

Assessment and Treatment

Fatigue is a subjective phenomenon, and self-report measures are currently the gold standard for fatigue assessment. The majority of

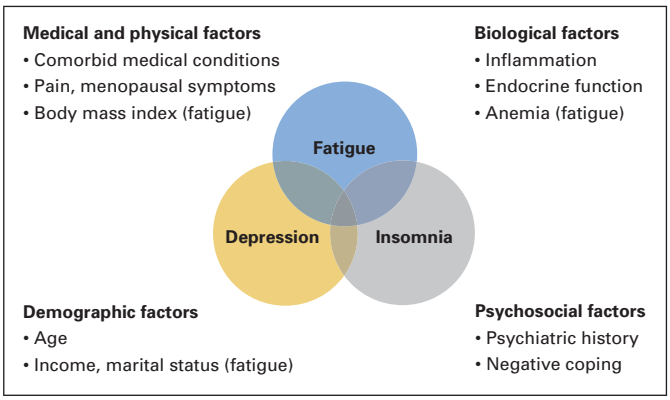

Fig 1. Fatigue, depression, and sleep disturbance frequently co-occur in breast cancer patients and survivors. A variety of factors may contribute to the development and persistence of these symptoms. The key factors associated with these symptoms in the empirical literature are summarized here.

studies have used self-report inventories to assess various dimensions of fatigue, including intensity, duration, and interference with functioning. There is no agreed-on 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 guidelines suggest that scores of 4 or greater on a 0- to 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.[34] In the majority of patients, however, the mechanisms underlying fatigue are unknown, and nonspecific 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.[35] 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.[36] Positive effects have been seen with different exercise regimens, including home-based walking programs,[37] supervised training on cycle ergometers,[38] and even print materials and step pedometers.[39] Exercise interventions have also shown positive effects on immune parameters in breast cancer patients, including reductions in inflammatory markers,[40] 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 adverse effects had positive effects on vitality, physical functioning, and health-related role limitations in women undergoing treatment for breast cancer,[41] with the beneficial effects of treatment on vitality maintained over a 3-year follow-up period.[42] Other forms of group therapy, such as supportive expressive group therapy, have shown beneficial effects on fatigue among women with metastatic disease.[43] Patient-administered treatments have also demonstrated positive effects on fatigue, including a self-administered form of stress management training[44] and a peer-modeling video designed for women who had recently completed treatment.[45]

The majority of these trials have not specifically focused on cancer-related fatigue or selectively recruited fatigued patients. Thus, the feasibility and efficacy of the interventions among women with more severe fatigue have not been determined; indeed, one major barrier to participation in exercise programs among cancer patients is fatigue.[46] One recent trial examined the efficacy of cognitive-behavioral therapy (CBT) designed for cancer survivors with severe fatigue, including breast cancer survivors.[47] 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 on the intervention arm showed clinically significant improvements in fatigue severity and functional impairment relative to wait-list controls that were sustained for 2 years after treatment.[48] Similar, although more modest, effects were seen with a brief educational intervention focusing on fatigue management.[49] 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.[50]

Pharmacologic treatments for cancer-related fatigue have been investigated in several trials, including erythropoietin (for chemotherapy-induced anemia), antidepressants, and psychostimulants. As noted earlier, treatment with erythropoietin leads to increases in hemoglobin and concurrent improvements in fatigue and physical function among cancer patients with anemia.[34] However, because most fatigued patients are not anemic, erythropoietin is unlikely to be a viable treatment for most patients with cancer-related fatigue.

Two randomized controlled trials have evaluated the efficacy of antidepressants for fatigue in breast cancer patients.[51,52] 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,[53,54] but a double-blind randomized trial with fatigued patients showed no difference between methylphenidate and placebo (both groups showed improvements in fatigue).[55] 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 tumor necrosis factor blockade with etanercept is safe in patients with advanced cancer, although effects on fatigue are mixed.[56-58]

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,[24] during,[59] and after cancer treatment with radiation and/or chemotherapy[59-62] and among women with both early-stage and metastatic disease.[63] The prevalence of subjective sleep complaints ranges from 20% to 70%, depending on the study and method of assessment. In one large study conducted with 300 breast cancer survivors, 51% complained of sleep problems, and 19% met diagnostic criteria for insomnia.[60] Insomnia is a clinical syndrome characterized by complaints of difficulty with initiating or maintaining sleep or of nonrestorative sleep, which last for at least 1 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 with sleep in noncancer 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.[62] Another study found no difference in sleep quality between breast cancer patients and women presenting for physical

examinations for general medical conditions.[59] Studies using polysomnography to assess objective sleep in breast cancer patients have also yielded inconsistent results.[64,65]

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 three- to five-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 those in women with no cancer history. Sleep disturbance causes significant disruption in women's quality of life and general ability to function.[24,59]

Mechanisms

Savard and Morin[66] distinguish between three types of factors that can influence insomnia, as follows: 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 sex, older age, medical conditions, personal or family history of insomnia, and co-occurrence of other psychiatric disorders, such as depression or anxiety.[64,66] This suggests that women diagnosed with breast cancer may be at heightened risk for insomnia simply by virtue of their sex and (for older women) their age; those with other medical and/or psychiatric problems may be at particular risk.

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,[61,62,67] and there is preliminary evidence that an objective measure of hot flashes is associated with less efficient, more disrupted sleep.[68] Sleep problems are correlated with fatigue and depressed mood in breast cancer patients and survivors, although it unclear whether these symptoms are a cause of, are a consequence of, or co-occur with sleep disturbance.[10,24,62,67] Other potential precipitating factors include pain and psychological stress associated with cancer or other life events.[67] Biologic changes associated with cancer and its treatment may also play a role in sleep disturbance, including alterations in proinflammatory cytokines and the HPA axis.[69]

Perpetuating factors that increase risk for enduring sleep problems in the general population include maladaptive sleep habits and dysfunctional cognitions about sleep.[66] 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. The degree to which these factors influence insomnia in breast cancer patients is an important topic for future research.

Assessment and Treatment

Subjective sleep problems are typically assessed by self-report. Diagnosis of a clinical insomnia syndrome is made by interview, and objective sleep is assessed by polysomnography. Hypnotic medications are the most commonly used treatment for insomnia, including benzodiazepines, benzodiazepine receptor antagonists, antidepressants, and antihistamines. 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 and their long-term efficacy has not been determined.[64] Drawbacks of these medications include their adverse 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 CBT and other behavioral treatments have been demonstrated in several meta-analyses,[70,71] including one focusing on middle-aged and older adults,[72] 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.[73]

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 with wait-list controls.[74] Effects were maintained for up to 12 months after treatment completion. Changes in objective polysomnographic sleep measures were observed in an initial, single-arm pilot trial of this intervention[75] but not in the larger randomized controlled trial.[74] Other behavioral therapies (ie, sleep hygiene, relaxation, and sleep scheduling) also show promise for treating sleep problems in cancer patients,[76-78] as do mind-body approaches including mindfulness meditation[79,80] and yoga.[81]

DEPRESSION

Prevalence

Depression is perhaps the best studied behavioral adverse 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.[82] The majority of studies find that 20% to 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 2 weeks and causes significant impairment in normal functioning. One recent study that used a structured clinical interview to diagnose depression found that 9% of ambulatory breast cancer patients met criteria for major depression.[83]

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 the initial shock of diagnosis and acute effects of cancer treatment.[84] Large-scale studies of disease-free breast cancer survivors find rates of depressive symptoms that are comparable to women in the general population,[85,86] 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 adverse effects.[87] There is also evidence of increased morbidity and, possibly, mortality in depressed cancer patients.[88,89] 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 seem 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.[86,90-93] Physical factors, including pain, physical disability, and other symptoms, also show modest associations with depression.[86] 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.[86,94] These findings suggest that the occurrence of depression in breast cancer patients is more strongly influenced by psychosocial and physical factors, rather than severity of the disease or treatment regimen. As noted earlier, depressed mood is correlated with fatigue and sleep disturbance in the context of breast cancer (Fig 1).[10,24,62,86]

Biologic 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,[95] as well as elevations in proinflammatory cytokines in depressed patients with breast, pancreatic, and esophageal cancers.[96] However, the degree to which these changes drive increases in depression in breast cancer patients has not been determined. Changes in biologic systems may play a more minor role among women with early-stage breast cancer relative to women with advanced disease and other patient populations (eg, 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[97] 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 Brief Patient Health Questionnaire Mood Scale, also has high sensitivity for detecting major depression and has been validated in the general population.[98,99] Self-report measures are often used to assess severity of depressive symptoms in breast cancer populations.

Psychological interventions are effective in treating depression in the general population,[100] and there is compelling evidence that psychosocial approaches are also effective in improving depressive symptoms among cancer patients.[101-103] In trials conducted with breast cancer patients, positive effects on depressive symptoms have been seen with educational and nutritional interventions,[104] CBT,[105] and supportive-expressive group therapy,[106,107] 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 seem to be most effective for those who are distressed,[105,107] although it is important to note that the majority of these trials were preventative and did not selectively recruit women with elevated depression; thus, the efficacy of psychological interventions 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,[108] 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.[51,52]

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.[109] One important difference between research on cognitive disturbance and research on other behavioral symptoms in cancer patients is that cognitive performance is usually assessed using objective measures, which may reflect a different type or level of impairment than that assessed by self-report. Indeed, subjective cognitive complaints are typically not correlated with objective cognitive performance in breast cancer patients but are correlated with subjective reports of fatigue and depressed mood.[110]

Cross-sectional studies using objective measures of cognitive function provided initial evidence of cognitive compromise among women treated with chemotherapy relative to nontreated 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 with controls or published norms.[111,112] 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 seem to be most pronounced among women treated with high-dose chemotherapy,[113] although effects are also apparent among women treated with standard-dose chemotherapy.[110,114-116]

More recently, longitudinal studies have emerged that provide a more rigorous test of chemotherapy effects on cognitive functioning.[117,118] Several of these studies included a control group who did not receive chemotherapy to account for practice effects (performance on neuropsychological tests typically improves with repeated administration). One study found that breast cancer patients treated with chemotherapy showed declines on specific measures of memory from before treatment to 1 year after treatment relative to patients who did not receive chemotherapy.[119] Women treated with both chemotherapy and tamoxifen showed the broadest pattern of deficits. Another study found greater cognitive decline among women treated with high-dose chemotherapy from before treatment to 6 months after treatment than among healthy controls, although no differences were observed between women treated with standard chemotherapy and controls.[120] A study by Jenkins et al[121] showed reliable cognitive declines in 18% of women treated with chemotherapy at 1 year after

treatment; however, similar declines were observed in patients who did not receive chemotherapy and in healthy controls. In this cohort, cognitive effects were most pronounced if treatment resulted in premature menopause. Overall, these results suggest that particular subgroups of patients 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 continued to show deficits for up to 10 years after treatment.[122] For example, one study found that 16% of women showed impairment while on chemotherapy, 4.4% showed impairment at 1 year after treatment, and 3.6% showed impairment at 2 years after treatment.[9]

A small number of studies have used neuroimaging techniques to evaluate cognitive changes associated with chemotherapy in breast cancer patients. In a study by Silverman et al,[123] positron emission tomography 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 and 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. Furthermore, women whose treatment regimens also included tamoxifen had lower basal ganglia activity.

A study by Inagaki et al[124] using structural magnetic resonance imaging 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.[125] 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.[126]

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.[117] These effects do not seem to be a result of other behavioral disturbances (eg, depression), although these confounds have not been rigorously evaluated.

Mechanisms

The biologic 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 dysregulation, and estrogen or testosterone reduction, as well as genetic polymorphisms that may render individuals more susceptible to these effects.[127] 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.[128] There is also evidence that treatment with tamoxifen may increase the incidence and/or extent of cognitive impairment.[110,119] The identification of risk factors that predispose women to cognitive impairment is a critical question for future research because greater understanding of these factors may influence treatment decisions for certain patients.

Assessment and Treatment

The gold standard for assessment of cognitive function is objective neuropsychological testing. Performance on neuropsychological tests is compared with a reference group to determine the presence of cognitive compromise. One recommended battery for use with breast cancer patients includes measures of premorbid intellectual ability, working memory, learning and memory, information-processing speed and efficiency, and spatial and retrieval skills.[109] Self-report measures are also available for assessment of subjective cognitive complaints, although these do not necessarily track with objective cognitive impairment.[110] It is possible that women may be sensitive to subtle changes in cognitive function that are not picked up by objective tests or that subjective measures are more strongly influenced by other behavioral problems, such as depression or fatigue.

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 et al[129] conducted a single-arm CBT 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 (eg, schedule making, external cueing). There were significant improvements in self-reported cognitive function, quality of life, and standard neuropsychological test performance after treatment and at the 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.[130]

CLINICAL APPLICATIONS

Despite the prevalence of behavioral adverse effects in patients and survivors, these symptoms are typically under-reported and undertreated. Women 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.[131] 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 also available for evaluation of depression (eg, Brief Patient Health Questionnaire Mood Scale[98]) and sleep disturbance (eg, Pittsburgh Sleep Quality Inventory[132]), although interviews are required for diagnosis of clinical depression and insomnia.

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.[133] 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 patients), 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 the 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.[51] However, there is overlap in the recommended treatments for each symptom, and exercise, education, and other nonspecific interventions may have beneficial effects across domains.

DISCUSSION

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 comorbidities 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.[134] 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 because the stress of diagnosis (and possibly the effects of the tumor itself) may lead to elevations in behavioral symptoms before treatment onset; still, evaluating the 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 seems 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 versus 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.[25] This type of analysis provides extremely useful information about vulnerable women and potential treatment targets (eg, 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.[66] 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 biologic 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 (eg, sleep) may lead to disturbances in others (eg, energy, mood). The co-occurrence of these symptoms and their shared and unique predictors merit focused attention in future studies.[135]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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