Chapter 5
Symptoms: Fatigue and Cognitive Dysfunction

Julienne E. Bower and Patricia A. Ganz

Abstract Fatigue and cognitive complaints commonly occur during adjuvant chemotherapy treatment of breast cancer. Fatigue is also associated with radiation therapy, and can occur with surgery alone. Both of these symptoms may persist beyond the initial treatment of breast cancer and they have taken on greater prominence with the growing number of breast cancer survivors. These symptoms are most troublesome when patients try to resume their pre-illness activities (e.g., work, household responsibilities) and find that they are limited. Recovery may take months to years, but in some women these symptoms persist indefinitely and can be very distressing. In this chapter we review what is known about the etiology and biology of these two common symptoms, discuss potential interventions, and describe future research challenges.

Keywords Fatigue • Cognitive complaints • Breast cancer • Chemotherapy • Radiation therapy • Inflammation

Overview of the Problem

Fatigue and cognitive complaints are two of the most common and distressing symptoms reported by women with breast cancer. After two decades of research on cancer-related fatigue, we have a good understanding of the characteristics, prevalence, and course of this symptom and are beginning to elucidate mechanisms, risk factors, and effective treatments among women with breast cancer (Bower et al. 2000, 2006; Bower 2005, 2014). We also have a growing appreciation of the complexity of fatigue, which shows significant inter-individual variability in its severity

J.E. Bower (✉)
Departments of Psychology and Psychiatry/Biobehavioral Sciences, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, CA, USA
e-mail: jbower@ucla.edu

P.A. Ganz
UCLA Schools of Medicine and Public Health, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA
e-mail: pganz@mednet.ucla.edu

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and expression. In parallel, cognitive complaints emerged as a frequent post-treatment problem in the late 1990s, particularly in women who received high-dose chemotherapy (Ganz 1998; van Dam et al. 1998). Our understanding of the etiology, characteristics, prevalence, and course of cognitive difficulties is not as advanced as the knowledge-base related to fatigue; however, recent advances in neuroimaging have accelerated our understanding of the impact of breast cancer treatments on cerebral functioning. Importantly, research that the authors have jointly conducted over the past decade has begun to identify a common biology for both of these clinical symptoms that is associated with inflammation. In this chapter, we will briefly review descriptive research on cancer-related fatigue and treatment associated cognitive changes in breast cancer patients, provide an overview of research on mechanisms, and highlight key issues to be addressed in future research.

Description of Cancer-Related Fatigue

Research on cancer-related fatigue began with qualitative descriptions of this symptom in the late 1980s and then progressed to more quantitative examination of its prevalence, course, and correlates. Studies conducted with breast cancer patients have documented increases in fatigue during treatment with radiation (Irvine et al. 1998) and with chemotherapy (Jacobsen et al. 1999), although chemotherapy-induced fatigue is somewhat more severe. Fatigue typically improves in the year after treatment completion, although a significant minority of patients continue to experience fatigue for months or years after successful treatment (Bower et al. 2000; Cella et al. 2001). In a survey study we conducted with almost 2000 breast cancer survivors who were between 1 and 5 years post-diagnosis, we found that one-third reported elevated fatigue (Bower et al. 2000). In a follow-up study with this sample, we found that 20 % of study participants continued to report elevated fatigue up to 10 years after breast cancer diagnosis (Bower et al. 2006). Fatigue has a negative impact on work, social relationships, mood, and daily activities and causes significant impairment in overall quality of life during and after treatment among women with breast cancer (Andrykowski et al. 1998; Bower et al. 2000; Broeckel et al. 1998; Curt et al. 2000). Fatigue also predicted shorter recurrence-free and overall survival in a sample of breast cancer patients (Groenvold et al. 2007).

Patient reports suggest that cancer-related fatigue is more severe, more persistent, and more debilitating than "normal" fatigue caused by lack of sleep or overexertion and is not relieved by adequate sleep or rest (Poulson 2001). Indeed, studies have confirmed that the intensity and duration of fatigue experienced by cancer patients and survivors is significantly greater than healthy controls and causes greater impairment in quality of life (Andrykowski et al. 1998; Cella et al. 2002; Forlenza et al. 2005; Jacobsen et al. 1999). Cancer-related fatigue is multidimensional and may have physical, mental, and emotional manifestations including generalized weakness, diminished concentration or attention, decreased motivation or interest to engage in usual activities, and emotional lability (Cella

et al. 2001). Fatigue is strongly correlated with depressive symptoms as well as sleep disturbance, pain, and cognitive function, although patients experience fatigue as a distinct and central symptom.

Description of Cognitive Complaints After Breast Cancer Treatments

The first reports of cognitive complaints associated with breast cancer treatments began with the more widespread use of adjuvant chemotherapy, accentuated by the adoption of high dose adjuvant chemotherapy (Phillips and Bernhard 2003). In an early review of this problem (Phillips and Bernhard 2003), Phillips and Bernhard note the strong association of post-treatment cognitive impairment with adjuvant chemotherapy, primarily in cross-sectional studies, with lack of clarity regarding the extent to which premature menopause or adjuvant tamoxifen may have contributed to patient reported complaints. In addition, they raise the question regarding the extent to which these complaints overlap with psychological factors. In a cross-sectional study from a clinical trial comparing neuropsychological tests and quality of life in women who had received either high dose or standard dose adjuvant chemotherapy, those exposed to the high dose chemotherapy were 8.2 times more likely to have cognitive impairment than breast cancer patients who did not receive chemotherapy, and 3.5 times higher than patients receiving standard adjuvant chemotherapy (van Dam et al. 1998). These results were not affected by depression, fatigue, or time since treatment, and suggested a dose response effect for the neuropsychological changes. These women were in their 40s and almost all became menopausal and were receiving tamoxifen. A neurophysiological study done in a subgroup of these patients also reflected changes consistent with a dose effect (Schagen et al. 2001). Additional studies, with small numbers of patients, and with cross-sectional designs (reviewed by Phillips and Bernhard), suffered from similar limitations in being able to determine causal attribution of neurocognitive test abnormalities to chemotherapy exposure, change in menstrual status, or use of tamoxifen. These studies and others (Castellon et al. 2004, 2005) also failed to find significant relationships between self-reported cognitive complaints and neurocognitive testing, and raised the issue of anxiety and depression as confounding factors.

Given these emerging findings, and lack of consensus about how best to study this increasing clinical problem, a group of investigators working in the field came together in April 2003, spurred on by patient advocates who were becoming alarmed about increasing reports of cognitive impairment after treatment. This workshop led to a report (Tannock et al. 2004) that summarized the state of current research, including a number of longitudinal investigations underway or planned, designed to identify prospective changes in cognitive function associated with chemotherapy treatments. In addition, there was a call for more studies to elucidate mechanisms, as well as the addition of assessments in the setting of clinical trials. Breast cancer survivors and advocates emphasized the impact of cognitive impairment on quality

of life and recovery after treatments. Subsequently, this group of investigators, supported in part by funding from an advocate organization, formed the International Cognition and Cancer Task Force, which has met every second year, and has provided a forum for scientific discussion that has moved the field forward substantially (Vardy et al. 2008; Wefel et al. 2011).

Several excellent reviews summarize the findings with regard to cognitive impairment after breast cancer (Ahles 2012; Ahles et al. 2012; Jim et al. 2012). Most studies confirm only subtle changes in cognitive function after exposure to adjuvant chemotherapy on neurocognitive testing, most often manifest as a failure to demonstrate improvement with repeated testing (practice effects) that are seen in control subjects. The domains most often affected as shown in a meta-analysis are verbal ability and visuo-spatial ability (Jim et al. 2012). However, classification of neurocognitive tests into specific domains varies across papers. Other studies have identified processing speed as an affected domain, especially in association with aging and tamoxifen (Ahles et al. 2010). Abnormalities associated with cerebral function have also been corroborated in a series of brain imaging studies in breast cancer patients studied longitudinally, prior to and after chemotherapy administration (Deprez et al. 2011, 2012; McDonald et al. 2010, 2012). Most recently, there is convincing evidence that self-reported cognitive complaints are also manifested in cerebral imaging changes in breast cancer patients (Deprez et al. 2012, 2014; Kesler et al. 2011). Our own studies have demonstrated that about 20 % of non-depressed, younger post-treatment early stage breast cancer patients have higher memory and executive function cognitive complaints than healthy controls, and that this is associated with both chemotherapy and radiation treatments as well as significant differences in domain specific verbal memory and executive function neurocognitive performance (Ganz et al. 2013b). In further studies of this same group of patients, we have found that the initiation of endocrine therapy is associated with increased language and communication complaints (Ganz et al. 2014). For this group of patients, there was a strong association of these complaints with past hormone therapy, as well as an interaction between past hormone therapy and breast cancer targeted endocrine treatment. Further work needs to be done to understand the relative contribution of endocrine therapy to post treatment cognitive complaints. However, overall, these data suggest that patient reports of cognitive difficulties are genuine and reflect changes in brain function that can be identified with sensitive neuroimaging procedures. What are the best self-report tools to capture these complaints, and how to separate them from fatigue and depressive symptoms that may overlap, is an important future research question (discussed below).

The pattern and trajectory of cognitive complaints and clinical cognitive decline post-treatment may be influenced by multiple factors and are dependent on initial cognitive reserve, influence of acute and chronic anxiety (as at time of diagnosis and with initial treatments), followed by changes in hormonal mileu as well as influenced by potential direct toxicities of treatments, and persistent elevations of inflammatory markers. Underlying this may be genetic susceptibility to cognitive decline from known markers (i.e. APOE4) as well as other factors (Ahles 2012; Ahles et al. 2012; Mandelblatt et al. 2014).

The major obstacle associated with more regularly assessing cognitive function as a treatment toxicity or for symptom management, has been the perceived burden of assessing cognitive function with extensive batteries of neurocognitive tests. However, the emerging research demonstrating the validity of self-reported complaints may help to advance the regular assessment of this treatment toxicity along with other patient reported outcomes.

Mechanisms for Fatigue and Cognitive Dysfunction: Focus on Inflammation

Fatigue in breast cancer patients is multi-factorial and may be influenced by a variety of demographic, medical, psychosocial, and biological factors. We have found that younger, unmarried women who have a lower household income report higher levels of fatigue (Bower et al. 2000), suggesting that contextual factors (e.g., absence of partner who can provide instrumental and emotional support) may influence the experience of this symptom. Other potential contributing factors include medical comorbidities, medications, nutritional issues, physical symptoms, and physical deconditioning, among others (Mitchell 2010). For example, we found that heart disease was a significant predictor of persistent post-treatment fatigue in a large sample of breast cancer survivors (Bower et al. 2006). However, fatigue often occurs in patients who are otherwise healthy and have few if any of these contributing factors, suggesting that other processes may also be at work. Of note, treatment-related factors (e.g., type of treatment, dose-intensity) are not consistently associated with fatigue, particularly in the post-treatment period.

A variety of biological mechanisms for cancer-related fatigue have been proposed and investigated over the past two decades (Barsevick et al. 2010; Morrow et al. 2002). These include anemia, cytokine dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, five hydroxy tryptophan (5-HT) neurotransmitter dysregulation, and alterations in adenosine triphosphate and muscle metabolism, among others (Barsevick et al. 2010). With respect to cognitive function, Ahles and Saykin (2007) reviewed potential mechanisms for the development of cancer-related cognitive changes, which included endocrine factors (reductions in estrogen and testosterone), DNA damage and telomere length, cytokine dysregulation and disruption in the blood brain barrier. The mechanism that is common across both conditions is cytokine dysregulation, and specifically inflammation.

The possibility that inflammatory processes may be involved in the etiology of cancer-related fatigue and cognitive problems draws from basic research on neural-immune signaling. This body of work has demonstrated that peripheral inflammatory cytokines can signal the central nervous system to generate symptoms of fatigue and other behavioral changes (Dantzer et al. 2008; Haroon et al. 2012; Miller et al. 2008) (see Fig. 5.1). Signals from the peripheral immune system are conveyed to the central nervous system through several routes, including direct neural activation via the afferent vagus nerve, transport of peripheral cytokines across

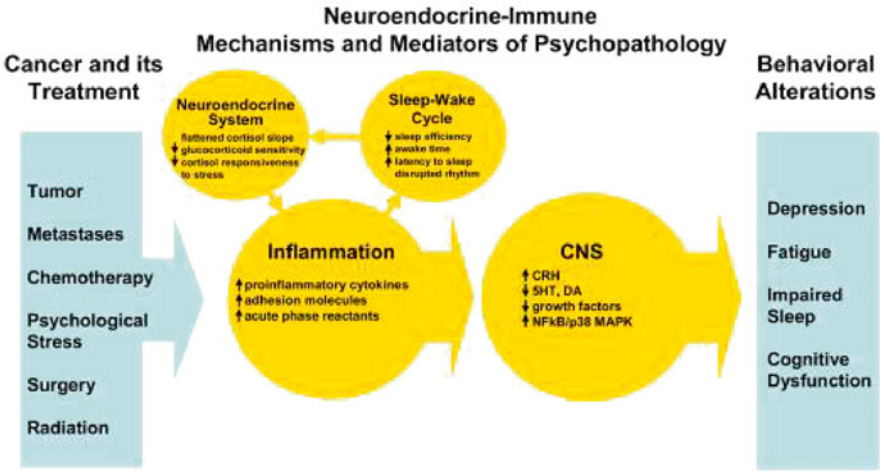

Fig. 5.1 Model for explaining the influence of cancer and its treatments on common behavioral alterations including fatigue and cognitive dysfunction [Reproduced with permission from Miller et al. (2008)]

the blood-brain barrier via carrier molecules, and interaction of circulating cytokines with brain cytokine receptors in areas that lack a functional blood-brain barrier (i.e., circumventricular organs) and with brain vascular endothelial cells that release second messages to stimulate cytokine production in the brain (Irwin and Cole 2011). Cytokine signaling leads to changes in neural activity, physiological processes (e.g., fever), and behavior, including changes in energy/fatigue and cognitive function (Miller et al. 2013). In animal models, induction of pro-inflammatory cytokines leads to decreased motor activity (presumably a behavioral manifestation of fatigue) and altered cognition, as well as reduced food and water intake, social withdrawal, and anhedonia.

These behavioral changes have been collectively described as "sickness behavior" and are thought to represent a motivational shift designed to facilitate recovery and prevent the spread of infection (Dantzer and Kelley 2007; Irwin and Cole 2011). In humans, pharmacologic doses of cytokines given for treatment of cancer or hepatitis C are associated with significant increases in fatigue, cognitive problems, and other markers of sickness (depressed mood, sleep disturbance) (Capuron et al. 2000; Kirkwood 2002; Valentine et al. 1998). Experimental studies of cytokine induction in healthy individuals have documented similar effects, with subjects reporting increased fatigue and cognitive disturbance following endotoxin administration that are correlated with elevations in circulating concentrations of pro-inflammatory cytokines (Reichenberg et al. 2001; Spath-Schwalbe et al. 1998). Further, pharmacologic agents that block the pro-inflammatory cytokine TNFα lead to reduced fatigue among individuals with inflammatory conditions (Tyring et al. 2006), and in

pilot studies with cancer patients (Monk et al. 2006) (though fatigue can also be a side effect of these agents in certain patient populations). Together, this evidence provides a strong biological rationale for inflammation as a potential mechanism underlying cancer-related fatigue and cognitive disturbance.

Studies of Inflammation and Fatigue in Cancer Patients

In the cancer context, investigators have proposed that tumors and the treatments used to eradicate them can activate the pro-inflammatory cytokine network, leading to symptoms of fatigue and cognitive disturbance (Cleeland et al. 2003; Miller et al. 2008; Seruga et al. 2008). In the pre-treatment period, the tumor itself may be a source for pro-inflammatory cytokines (Aggarwal et al. 2009; Coussens and Werb 2002) while during treatment, cytokines may be produced in response to tissue damage from surgery, radiation, or chemotherapy (Aggarwal et al. 2009; Stone et al. 2003). The inflammatory response may persist well after treatment completion as the host tries to deal with persisting pathogenesis and alterations in homeostasis.

A growing number of studies have examined the association between circulating markers of inflammation and fatigue during and after breast cancer treatment. In a study of breast cancer patients assessed prior to chemotherapy (but after surgery), fatigue was associated with elevations in CRP, a marker of systemic inflammation (Pertl et al. 2013). In a study of breast and prostate cancer patients undergoing radiation therapy, we found that patients reported increases in fatigue that were correlated with increases in circulating inflammatory markers (CRP, IL-1 receptor antagonist) (Bower et al. 2009). Similarly, increases in fatigue were correlated with increases in the inflammatory cytokine IL-6 among breast cancer patients undergoing chemotherapy (Liu et al. 2012). Documenting an association between inflammatory markers and on-treatment-related fatigue is complicated by dynamic changes in the cellular immune system and inflammation that occur during the acute phase of cancer treatment. Investigators have found more reliable associations between inflammatory activity and fatigue after treatment completion. In a series of cross-sectional studies with breast cancer survivors, we have documented elevations in inflammatory markers among women who report elevated fatigue at 1 month (Bower et al. 2011b), 2 years (Collado-Hidalgo et al. 2006), and 5 years (Bower et al. 2002) post-treatment. Consistent with these results, several other groups have found significant elevations in CRP among breast cancer survivors with persistent fatigue (Alexander et al. 2009; Alfano et al. 2012; Orre et al. 2011). At the molecular level, leukocytes from fatigued breast cancer survivors show increased expression of genes encoding proinflammatory cytokines and other mediators of immunologic activation, as well increased activity of proinflammatory NF-κB/Rel transcription factors, which might structure the observed differences in the expression of inflammation-related genes (Bower et al. 2011a).

Studies of Inflammation and Cognitive Function in Breast Cancer Patients

In parallel to the studies of fatigue, there are increasing reports that have focused on the potential role of inflammation in the etiology of cognitive impairment after breast cancer. Early reviews of potential mechanisms identified inflammation as a possible etiology (Ahles and Saykin 2007) and studies in rodents provide strong support for inflammatory mechanisms (Seigers and Fardell 2011). While some chemotherapeutic agents may cross the blood brain barrier and cause direct toxicity (e.g., especially the CMF regimen, with methotrexate and fluorouracil), the mechanism by which both chemotherapy and radiation cause injury is likely through the production of reactive oxygen species and tissue damage, that result in systemic inflammation as well as stimulation of local microglial inflammation within the brain. Indeed, several studies of breast cancer patients have demonstrated relationships between systemic levels of inflammation and brain imaging structural and metabolic changes (Kesler et al. 2013b; Pomykala et al. 2013). Animal models studies support these findings (Seigers et al. 2013), and an inflammatory basis of cognitive changes associated with cancer treatments would be consistent with age related cognitive changes of which this may be a manifestation (Ahles 2012). Since only a subgroup of patients with breast cancer appear to be vulnerable to cognitive difficulties, as with age-related variation in cognitive decline, similar host factors and susceptibilities may be relevant (see below).

To develop an understanding of the potential role of inflammation and cognitive dysfunction in women with breast cancer, we recruited a cohort of women with newly diagnosed breast cancer who had completed primary adjuvant chemotherapy and/or radiation therapy, but enrolled prior to the start of endocrine therapy if planned. The Mind Body Study (MBS) cohort of 191 patients was less than 66 years of age, and excluded women with significant depressive symptoms, history of central nervous system disorders, conditions with chronic inflammation, or with use of immunosuppressive therapy (see details in Bower et al. 2011b; Ganz et al. 2013a, b). We observed post-treatment elevations of soluble TNFα receptor II (sTNFR2) levels at study enrollment that declined over the subsequent 12 months of follow-up, with elevations only noted in the patients who had received chemotherapy (Ganz et al. 2013a). We should note that there was a parallel association between fatigue and sTNFR2 in this same sample at the baseline assessment (Bower et al. 2011b), and we see the co-occurrence of these two symptoms in the longitudinal follow-up of this sample (unpublished data). The changes in TNF over the 12 months were correlated with self-reported memory complaints, as well as changes in PET scan glucose metabolism in a small subgroup of patients, with normalization of metabolism in the inferior frontal gyrus as TNF levels decreased between baseline and 12 months later. More detailed evaluation of sTNFR2 and other proinflammatory cytokines in the PET scan study are reported separately in an additional publication, where we observed positive correlations between metabolism in the medial prefrontal cortex and anterior temporal cortex with both memory complaints and cytokine

markers only in patients who received chemotherapy (Pomykala et al. 2013). Of note, Kesler et al. (2013b) have found an association between decreased hippocampal volume on MRI in breast cancer survivors and elevated TNFα and IL-6, along with decreased verbal memory performance on cognitive testing, in comparison to a healthy control group.

Host Factors that May Increase Risk for Fatigue

Although cancer-related fatigue is common, it does not affect all patients (see Table 5.1). Clinicians have no doubt observed that certain patients are more susceptible to fatigue, and empirical studies have now documented considerable variability in reports of fatigue before, during, and after treatment. This variability was nicely illustrated in a longitudinal prospective study of breast cancer patients who were followed for 6 months after cancer treatment (Donovan et al. 2007). Using growth mixture modeling, two groups of patients were identified on the basis of their fatigue scores. One group, which comprised approximately 30 % of the sample, reported consistently low levels of fatigue across the assessment period, including in the immediate aftermath of treatment. The other group reported elevated fatigue at treatment completion, which declined over the assessment period but remained significantly higher than the low fatigue group. Of note, disease- and treatment-related factors did not determine group membership in this study; instead, body mass index and coping strategies were significant predictors of group membership. Other studies have similarly found no evidence that cancer-related fatigue is associated with

Table 5.1 Host factors associated with fatigue and cognitive dysfunction

Fatigue
Pre-treatment fatigue
Pre-treatment sleep disturbance
History of depression
Loneliness
Early life stress
Physical inactivity
High body mass index
Catastrophizing coping style
Genetic factors (e.g., SNPs in inflammation-related genes)
Neuroendocrine dysregulation
Cognitive dysfunction
Pre-treatment diminished cognitive reserve, low educational status
History of head trauma
Comorbid conditions (e.g., diabetes, vascular disease)
Genetic factors (e.g., *APOE-4*, *COMT*, SNPs in inflammation-related genes)
Older age (?)

type of cancer treatment, particularly in the post-treatment period. Together, these findings strongly suggest that host factors play an important role in the development and persistence of cancer-related fatigue.

Longitudinal studies have begun to identify predictors of cancer-related fatigue. These include pre-treatment fatigue, pre-treatment sleep disturbance, history of depression, loneliness, early life stress, physical inactivity, and body mass index (Bower 2014). In addition, patients who engage in negative thoughts or "catastrophize" about their fatigue (e.g., I tell myself I don't think I can bear the fatigue any more), report elevated fatigue during and after treatment. Thus, psychosocial and behavioral factors may set the stage for more severe and persistent cancer-related fatigue. Importantly, some of these factors are amenable to intervention, including physical inactivity, high BMI, and catastrophizing.

Genetic factors have also been linked to cancer-related fatigue. Most of the studies in this area have taken a candidate gene approach, focusing on single nucleotide polymorphisms (SNPs) in inflammation-related genes including *IL1B*, *IL6*, and *TNF* given evidence linking circulating inflammatory markers and fatigue. We examined whether polymorphisms in these genes were associated with fatigue within 1 month after treatment, using data from breast cancer survivors enrolled in the MBS study. Consistent with hypotheses, we found that women with the "high expression" versions of these genes reported higher levels of fatigue (Bower et al. 2013a). Similarly, in a small sample of breast cancer survivors assessed several years after treatment, polymorphisms in *ILB* and *IL6* were associated with persistent post-treatment fatigue (Collado-Hidalgo et al. 2008). There is also preliminary evidence that polymorphisms in inflammation-related genes are associated with fatigue among patients undergoing radiation therapy, including many breast cancer patients (Aouizerat et al. 2009; Miaskowski et al. 2010).

Alterations in the HPA axis may contribute to cancer-related fatigue, either directly or through effects on inflammatory processes. We found that breast cancer survivors with persistent fatigue had a flatter diurnal cortisol slope (with elevated levels of cortisol in the evening) as well as blunted cortisol responses to psychosocial stress that were correlated with alterations in inflammatory activity (Bower et al. 2005a, b, 2007) Further, genome-wide transcriptional profiling of leukocytes from fatigued breast cancer survivors showed a marked down-regulation of genes with response elements for the glucocorticoid receptor, suggesting a state of functional GR resistance which may contribute the tonic upregulation of NF-κB observed in fatigued survivors (Bower et al. 2011a). Fatigue is also associated with alterations in the autonomic nervous system in breast cancer survivors, including lower heart rate variability (an indicator of parasympathetic activity) and elevated norepinephrine (an indicator of sympathetic activity) (Crosswell et al. 2014; Fagundes et al. 2011). Importantly, because all of these studies have been cross-sectional investigations of breast cancer survivors, it is impossible to determine whether neuroendocrine alterations play a causal role in the development and persistence of this symptom, or arise as a consequence of fatigue and inflammatory activity.

Longitudinal studies that examine risk factors for cancer-related fatigue are still quite limited and few have followed patients from pre-treatment in to the post-treatment period; fewer still have examined mechanisms that underlie effects of these risk factors on fatigue. To advance research in this area, longitudinal studies are required that track patients before, during, and after treatment and include comprehensive assessment of biobehavioral risk factors and underlying mechanisms. This approach will facilitate the identification of distinct trajectories of fatigue, risk factors for fatigue onset and persistence, and the mechanisms that underlie their effects, paving the way for targeted interventions.

Host Factors and the Risk for Cognitive Impairment

Less is known about the host factors associated with the risk of cognitive impairment after breast cancer treatments (see Table 5.1). Ahles and Saykin (2007) reviewed potential mechanisms for the development of cognitive changes and these included genetic susceptibility, endocrine factors (reductions in estrogen and testosterone), DNA damage and telomere length, cytokine dysregulation and disruption in the blood brain barrier. Among these mechanisms, genetic susceptibility has been studied by several groups. Ahles has reported on the association of the *APOE-4* allele, found in Alzheimer's disease, with cancer-related cognitive dysfunction in long-term breast and lymphoma survivors treated with chemotherapy (Ahles et al. 2003). In another sample of breast cancer patients followed prospectively, Small et al. (2011) found that patients with the catechol-o-methyltransferase (COMT) genotype Val + allele had greater cognitive difficulties with attention, verbal fluency and motor speed, with an interaction with chemotherapy for attention. COMT-Val + carriers are thought to metabolize dopamine more rapidly and this might be the putative mechanism. In our MBS study, we have found that a genetic risk score of SNPs for *IL1B, IL6*, and *TNF* was significantly associated with memory complaints as well as fatigue (Bower et al. 2013b). Other groups have also found similar associations (Merriman et al. 2013, 2014).

Other contributing factors could be those influences associated with age-related cognitive decline and cognitive reserve may be reduced in individuals with lower education or prior comorbid conditions leading to subclinical brain injury (Ahles 2012; Mandelblatt et al. 2014) (see Fig. 5.2). It is likely that the cognitive complaints that patients report after treatment exposure are a manifestation of having to work harder (recruit more areas of the brain) to retrieve information, multi-task, and perform executive tasks. These are similar to what happens with age-related cognitive decline (Maillet and Rajah 2013). In addition to these factors, age-related vascular disease, diabetes, and hormonal changes may contribute to these problems. However, it is most interesting the manifestations of symptomatic cognitive difficulties are most notable in younger women, similar to what is seen with fatigue. It may be that the everyday demands put upon younger women exacerbate these complaints, whereas older women may be less likely to notice subtle changes in function.

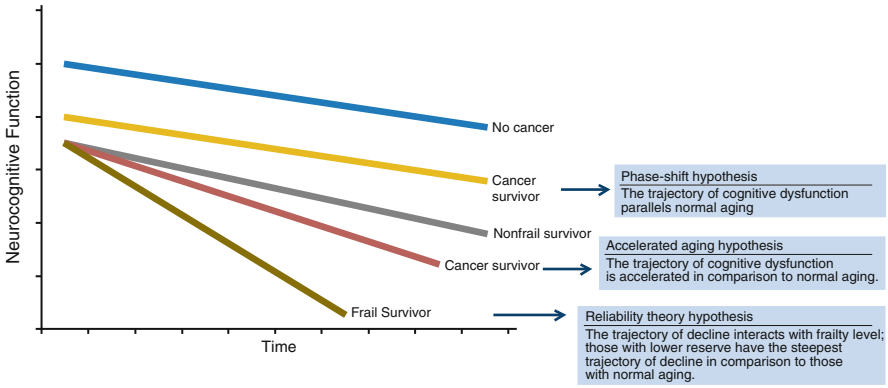

Fig. 5.2 Trajectories of cognitive decline based on theories of aging and frailty phenotype [Adapted from Mandelblatt et al. (2014)]

What Are the Potential Intervention Strategies to Consider for Management of Fatigue or Cognitive Complaints?

Interventions for Cancer-Related Fatigue

A diverse range of treatment approaches have been used to address cancer-related fatigue during and after cancer treatment, including physical activity, psychosocial, mind-body, and pharmacological interventions. Perhaps because the etiology of cancer-related fatigue is multi-factorial and still poorly understood, there is currently no "gold standard" for treatment of this symptom. Still, a number of these approaches have been shown to be beneficial in reducing cancer-related fatigue, as reviewed below. The recently published ASCO Guideline on Fatigue in Cancer Survivors outlines the intervention strategies that should be considered (Bower et al. 2014). A number of randomized controlled trials have examined the effect of exercise on cancer-related fatigue. Overall, meta-analyses of these trials indicate that exercise is effective in reducing fatigue, with effect size estimates ranging from −0.27 to −0.38, indicating a moderate effect (Cramp and Byron-Daniel 2012; Puetz and Herring 2012). Beneficial effects of exercise have been observed in trials conducted with patients during and after treatment, indicating that exercise can be helpful at different stages of the disease trajectory. Aerobic exercise regimens seem to be particularly beneficial. Guidelines from the American College of Sports Medicine (ACSM) recommend that cancer patients and survivors engage in at least 150 min of moderate intensity aerobic activity each week, consistent with recommendations for the general population (Schmitz et al. 2010). ACSM guidelines further recommend that exercise should be tailored to the individual cancer patient to account for exercise tolerance and specific diagnosis, and that patients be closely monitored to safely progress exercise intensity and avoid injury.

Psychosocial interventions are also effective in reducing fatigue, particularly interventions that provide education about fatigue and contributing factors (e.g., physical activity, sleep disturbance) and address dysfunctional fatigue-related thoughts and behaviors. Among women undergoing radiation or chemotherapy for breast cancer, individualized educational and cognitive-behavioral approaches that specifically targeted fatigue buffered the increase in fatigue observed among control patients (Montgomery et al. 2009, 2014; Yates et al. 2005). A brief psychoeducational intervention that provided information about fatigue and modeled adaptive coping strategies (e.g., physical activity) also led to reductions in fatigue among women who had recently completed breast cancer treatment (Stanton et al. 2005). More intensive and targeted treatments have shown benefit for survivors with severe and persistent post-treatment fatigue. These include individual cognitive-behavioral therapy focused on perpetuating factors for persistent fatigue (Gielissen et al. 2006), and a web-based, tailored education program providing information on cancer-related fatigue as well as energy conservation, physical activity, sleep hygiene, distress management, nutrition, and pain control (Yun et al. 2012). Mind-body interventions have also demonstrated efficacy for treating cancer-related fatigue in cancer survivors (see Table 5.2). In particular, specialized programs of acupuncture (Molassiotis et al. 2012), yoga (Bower et al. 2012), and mindfulness (van der Lee and Garssen 2012) led to significant reductions in fatigue among survivors with persistent post-treatment fatigue.

In terms of pharmacologic interventions, there is mixed evidence for the effectiveness of psychostimulants (e.g., methylphenidate) and other wakefulness agents (e.g., modafinil) as treatments for cancer-related fatigue (Minton et al. 2008, 2011). Several large trials of these agents have yielded negative effects, though subgroup analyses suggested that patients with severe fatigue may show some benefit (Jean-Pierre et al. 2010; Moraska et al. 2010). However, there is very limited evidence of their effectiveness in reducing fatigue in patients who are disease free following active treatment. American ginseng may hold promise for treating cancer-related fatigue, particularly among patients undergoing treatment, but more research on this agent is needed (Barton et al. 2013). Of note, very few of the pharmacologic trials have focused specifically on breast cancer patients or survivors.

Interventions for Cognitive Complaints

There have been relatively few studies designed to provide intervention for cognitive dysfunction in cancer survivors, and most of them have been conducted in breast cancer. The first study by Ferguson et al. (2007) was a single arm, individually delivered cognitive behavioral therapy (CBT) approach to memory problems. Due to feasibility and improvements in objective and subjective evaluation, this was expanded to a phase II randomized wait-list controlled trial (Ferguson et al. 2010) that showed trends towards improvement in some aspects of quality of life and memory, but was not definitive. We recently conducted a pilot feasibility trial of a

Table 5.2 Randomized controlled trials of mind-body interventions using cancer-related fatigue as an entry criteria

Author, publication date	Participants	Intervention type	Intervention duration	Control group(s)	Results
Bower (2011)	31 breast cancer survivors with moderate to severe fatigue	Iyengar yoga; group format; focused on postures thought to be effective for reducing cancer-related fatigue (restorative poses, supported back bends, supported inversions)	12 weeks, 2 sessions per week	Health education group	Decrease in fatigue in yoga group vs. controls at post-intervention; group differences maintained over 3 month follow-up
Johns (2014)	35 cancer survivors with moderate to severe fatigue (85.7 % breast)	Mindfulness-based stress reduction; group format; provided training in mindfulness meditation and psycho-education about cancer-related fatigue	7 weeks, 1 session per week	Wait list	Decrease in fatigue in mindfulness group vs. controls at post-intervention; group differences maintained over 1 month follow-up
Molassiotis (2012)	302 breast cancer survivors with moderate to severe fatigue; all post- chemotherapy	Acupuncture; individual sessions; needled 3 standardized points	6 weeks, 1 session per week	Usual care (fatigue information booklet)	Decrease in fatigue in acupuncture group vs. controls at post-intervention
van der Lee (2012)	100 cancer survivors with severe fatigue (58 % breast)	Mindfulness-based cognitive therapy; group format; provided training in mindfulness meditation and using mindfulness to manage automatic negative thoughts about fatigue	9 weeks, 1 session per week	Wait list	Decrease in fatigue in mindfulness group vs. controls at post-intervention; improvement maintained over 6 month follow-up

5 week, group intervention, cognitive rehabilitation program adapted from strategies used in older adults with mild cognitive impairment (Ercoli et al. 2013). This single arm study in 27 breast cancer survivors demonstrated feasibility as well as improvement in self-report and neurocognitive testing up to 6 months post intervention. A small sub-study showed significant normalization of EEG patterns in women who participated in the intervention. Recently, we completed a phase II randomized controlled trial of the same intervention compared to a wait-list control group, and showed highly significant improvements in self-report, neurocognitive tests, and EEG in the intervention group compared to the control group, which was sustained out to 2 months post-intervention, along with improvements in EEG correlating with those who had improved cognitive complaints (Ercoli et al. 2015). These very encouraging findings suggest there is a physiological basis for the improvement in cognitive complaints and test performance.

Other groups have applied computerized technologies to improve cognitive function in breast cancer patients. Kesler et al. (2013a) in a pilot study which randomized 41 breast cancer survivors to a computerized training program focused on executive functioning and memory found significant improvements in those who received the training compared to those who did not. Von Ah et al. (2012) examined a computer-based memory or processing speed training program compared to a wait-list control group of breast cancer survivors. They found that the processing speed training improved that outcome and memory immediately post-intervention and 2 months later. The memory training improved memory performance on neuropsychological testing.

There has also been exploration of psychostimulants to improve fatigue (Jean-Pierre et al. 2010) and secondarily cognitive function, but the findings are not conclusive (Kohli et al. 2009). Other investigators have attempted to examine methylphenidate without success, in terms of adequate recruitment to a treatment trial (Mar Fan et al. 2008). Any such therapy would have to have minimal side effects if it is given chronically, and many breast cancer survivors are averse to continue taking medication long-term if it is not truly necessary or very helpful. Thus behavioral strategies have greater appeal.

What Are the Research Challenges Associated with These Two Common Symptoms?

One of the critical challenges in the area of cancer-related fatigue and cognitive dysfunction is determining the underlying mechanisms for these symptoms. Although cross-sectional research has shown a positive association between inflammatory activity and fatigue in cancer patients and survivors, the causal nature of this association has not been determined. In particular, it is unknown whether inflammation causes fatigue (as observed in experimental models of sickness behavior), or whether inflammation is a consequence of fatigue (perhaps due to reductions in physical activity, alterations in sleep, or other behavioral/physiological changes).

One challenge to advancing research in this area is the lack of animal models of cancer-related fatigue (Dantzer et al. 2012). To directly address the causal role of inflammation in a human model, we conducted a small pilot study to evaluate the acute effects of infliximab, a monoclonal antibody against TNF, in five breast cancer survivors with severe, persistent fatigue. Participants completed daily diaries for 2 weeks before and after receiving a single dose of infliximab to assess changes in the severity and duration of daily fatigue. All five women reported reductions in daily fatigue, including a mean 1.9 point decrease in "worst" fatigue from pre- to post-treatment. These preliminary findings are promising and could be pursued in a larger randomized, placebo-controlled trial to determine the causal role of inflammation in cancer-related fatigue. However, anti-cytokine therapies have well-known side effects that may limit their use among women with breast cancer. In addition, given the multi-factorial nature of fatigue, it is likely that only certain women will respond to these (or other) anti-inflammatory agents. Indeed, a recent trial of infliximab for depression found that only those patients with elevated inflammation at treatment onset showed a positive response to this medication (Raison et al. 2013). Similarly, only patients with elevated inflammation are likely to show reduced cancer-related fatigue (and improvements in cognitive function) following anti-inflammatory therapies. Patients whose fatigue is driven by cognitive processes, such as catastrophizing, may be more responsive to cognitive-behavioral therapies, whereas those fatigue is driven by deconditioning may be responsive to exercise. Of course, these treatments may have multiple targets; for example, in our yoga trial with fatigued breast cancer survivors, women in the intervention group reported higher self-efficacy to manage fatigue symptoms and lower inflammatory activity, both of which may have contributed to their reduced fatigue (Bower et al. 2012, 2014). Identifying appropriate treatments for individual patients is an important challenge for future research. In addition, determining the factors that influence fatigue onset vs. persistence may be helpful in determining which type of interventions may be most helpful during vs. after treatment.

Another topic of considerable interest for research on cancer-related fatigue and cognitive disturbance is the intersection of aging and cancer (Dale et al. 2012). Similar biological processes are involved in aging, fatigue, and cognitive function, including inflammation (Mandelblatt et al. 2013). Indeed, cancer and its treatment may accelerate age-related changes in inflammatory activity and other physiological processes, which may contribute to fatigue and cognitive decline, particularly in vulnerable individuals. Cancer patients and survivors who suffer from fatigue and cognitive problems may look biologically "older" than patients without these problems, which may make them more susceptible to age-related declines in physical and mental function. However, few studies have probed the overlap between age-related processes and cancer-related behavioral disturbances. In addition, potential common and specific mechanisms for fatigue and cognitive function have not been carefully examined.

Clinically, in our practice with breast cancer survivors, persistent fatigue and/or cognitive difficulties often co-occur. In some women, one symptom is more prominent than the other. In our various research studies focused on women with cognitive

complaints seeking rehabilitation services, increased fatigue, sleep disturbance and impaired physical function are all self-reported as moderate to severe, even though these complaints are not prominently mentioned. What has been most reassuring to women has been our ability to explain the possible biological factors underlying the development of either persistent fatigue or cognitive complaints, as they frequently feel isolated and rejected by the medical community and even support groups, where other women do not have similar complaints. They are often labeled as being depressed, when they clinically are not, and they are very hard on themselves for not being able to function and work the way they did before their cancer diagnosis and treatment. With the emerging evidence from neuroimaging studies that there are functional cerebral abnormalities associated with breast cancer treatment (especially chemotherapy), it will be critical to develop a better understanding of the natural history of these changes and to determine who is most vulnerable for persistent difficulties that do not resolve or worsen over time. The MBS cohort study is one study, but more are needed. In addition, we need to begin to intervene early in the course of the treatment to try to improve outcomes for women so that they can resume their pre-illness functioning, especially for activities of everyday life which can be compromised in many.

Given the substantial numbers of women who experience persistent fatigue and cognitive difficulties after breast cancer treatment, we can no longer ignore this as a potential toxicity of cancer treatment. Consent forms in clinical trials must address this possibility, and patient reported assessments should be included in clinical trial outcomes. Some of the newer targeted agents, such as everolimus, may have significant impact on fatigue (Baselga et al. 2012) and cognitive difficulties have not been assessed to our knowledge. While we have been successful in reducing the number of women now exposed to adjuvant chemotherapy due to genomic profiles testing, a substantial number will still receive treatments that may cause either fatigue or cognitive difficulties and we need to gather this information to help in management and decision-making regarding treatment.

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