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Potential Epigenetic Mechanism(s) Associated With the Persistence of Psychoneurological Symptoms in Women Receiving Chemotherapy for Breast Cancer: A Hypothesis

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Abstract

Due to recent treatment advances, there have been improvements in the proportion of women surviving a diagnosis of breast cancer (BC). However, many of these survivors report persistent adverse side effects following treatment, such as cognitive dysfunction, depressive symptoms, anxiety, fatigue, sleep disturbances, and pain. Investigators have examined circulating levels of inflammatory markers, particularly serum cytokines, for a potential causal relationship to the development/persistence of these psychoneurological symptoms (PNS). While inflammatory activation, resulting from perceived stress or other factors, may directly contribute to the development of PNS, we offer an alternative hypothesis, suggesting that these symptoms are an early step in a cascade of biological changes leading to epigenetic alterations at the level of deoxyribonucleic acid (DNA) methylation, histone modifications, and/or chromatin structure/chromosomal instability. Given that epigenetic patterns have plasticity, if this conjectured relationship between epigenomic/acquired genomic alterations and the development/persistence of PNS is confirmed, it could provide foundational knowledge for future research leading to the recognition of predictive markers and/or treatments to alleviate PNS in women with BC. In this article, we discuss an evolving theory of the biological basis of PNS, integrating knowledge related to inflammation and DNA repair in the context of genetic and epigenetic science to expand the paradigm for understanding symptom acquisition/persistence following chemotherapy.

Keywords

epigenetic, cognitive, methylation

In 2012, a total of 226,870 women were expected to receive a diagnosis of breast cancer (BC) in the United States (Siegel, Naishadham, & Jemal, 2012). Most of these women will have been diagnosed in the early stages of the disease (Stages I and II) and 90% can expect to survive at least 5 years due to improvements in adjuvant chemotherapy and targeted hormonal therapies. However, these treatments and, perhaps, the cancer, itself, contribute to a number of distressing short-term and long-term life-altering and debilitating side effects that may persist in some women long after active treatment has ended. In particular, the administration of adjuvant chemotherapy is frequently associated with multiple co-occurring distressing symptoms (Dodd, Cho, Cooper, & Miaskowski, 2010; Goedendorp, Gielissen, Verhagen, Peters, & Bleijenberg, 2008). Research has linked depressive symptoms, anxiety (Badger, Segrin, Dorros, Meek, & Lopez, 2007), fatigue (Berger, Wielgus, Hertzog, Fischer, & Farr, 2010), sleep disturbances (Lee,

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Cho, Miaskowski, & Dodd, 2004), and pain (Utne, Miaskowski, Bjordal, Paul, & Rustoen, 2010; Valeberg et al., 2008) as a symptom cluster prominent across cancer types and stages. BC patients and survivors have also frequently noted the symptom of cognitive dysfunction, commonly referred to as chemobrain, during active treatment and, for some, after the completion of treatment as a seemingly long-lasting phenomenon (reviewed in Wefel, Vardy, Ahles, & Shagan, 2011). Cognitive dysfunction in cancer patients has, in fact, been a topic of intense research (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008). Collectively, these symptoms can be described as psychoneurological symptoms (PNS) and often result in a significant decline in quality of life by contributing to adverse health outcomes over the active treatment period and into survivorship. PNS are associated with decreased functional status and work limitations (Hansen, Feuerstein, Calvio, & Olsen, 2008) as well as unemployment and early retirement (Mehnert, 2011).

With this growing awareness that cancer survivors may develop both short-term and long-term effects from cancer and its treatments, it is important that we increase our understanding of the molecular mechanisms leading to these side effects. In this article, we present an evolving theory of the biological basis of PNS, suggesting that their development and persistence may reflect a cascade of cellular and molecular events. We offer evidence supporting this hypothesis along with a discussion of how the knowledge of acquired epigenetic perturbation(s), if present, could be exploited to develop future, practical biomarkers for identifying women who are at an elevated risk of developing these potentially debilitating treatment-associated symptoms, with the ultimate goal of designing therapies to alleviate these symptoms.

PNS

The interrelationship of PNS in patients with cancer has led researchers to question whether or not at least some of these symptoms might share a common biological etiology and whether they could be collectively treated (Cleeland et al., 2003). The theoretical guidance from the symptom cluster literature presupposes that commonly occurring symptoms in patients with cancer share a common biological mediator. Inflammation, along with its systemic effects, is a likely candidate for a shared mechanism of not only the development, initiation, and progression of cancer (Mantovani, Allavena, Sica, & Balkwill, 2008) but also the commonly experienced symptoms in individuals with cancer. Epidemiological evidence points to a connection between inflammation and a predisposition for the development of cancer (Coussens & Werb, 2002; Mantovani et al., 2008). In addition, inflammatory processes are central to the pathogenesis of depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008) and other symptoms in the cluster including pain, fatigue, sleep disturbances (Raison, Capuron, & Miller, 2006), and cognitive dysfunction (Roberts et al., 2010).

Support for the premise that inflammatory activation is an early or initiating step in the cascade of events leading to PNS comes from investigations showing cytokine-induced sickness behaviors in animal models and select human studies (Raison et al., 2006). The phrase *sickness behaviors* describes the subjective complaints of patients that may accompany a variety of conditions associated with inflammatory response, such as infectious diseases and cancers. Investigators have suggested that these behaviors (such as lethargy, depression, and fatigue) are actually caused by perturbations in the levels of cytokines acting in the brain (Bower, Ganz, Aziz, & Fahey, 2002; Dantzer et al., 2008; Kelley et al., 2003). The sickness behavior model is relevant to cancer in that chemotherapy has been associated with higher levels of interleukins in both humans and animal models, and researchers have noted cytokine elevations in cancer survivors with severe and persistent fatigue after treatment (Bower et al., 2002). Collectively, these findings indicate that the dysregulation of cytokines may be related to PNS in cancer patients and survivors before, during, and after active treatment. However, these studies, which have generally limited their foci to single symptoms and single markers of inflammation, have not resulted in a clear agreement regarding biological mechanisms of PNS, nor have they led to the development of effective therapeutic interventions.

Although a biological model that includes inflammation as an initiating step leading to PNS has partial empirical support, the evidence, to date, is not sufficient to conclude that peripheral inflammatory mechanisms are a complete or sufficient mechanism for treatment-related symptoms or persistent symptoms in survivors. Since most inflammatory molecules, such as cytokines, are relatively short lived, the mechanism(s) for how these changes could lead to long-term symptoms that persist and are embedded in an individual's biological memory beyond the time of chemotherapy treatment has been enigmatic (Esteller, 2008). One possible means for "biologically remembering" the effects of BC and/or its treatments would be deoxyribonucleic acid (DNA)-based changes in the individual's somatic (nonreproductive) cells. These acquired changes could result from either epigenomic modifications (which encompass alterations in DNA methylation patterns, modifications of histone proteins, and/or changes in chromatin structure; Feinberg et al., 2010) or genomic changes (which include, but are not limited to, telomere attrition, and acquired chromosomal instability).

Evidence for Epigenetic Alterations in BC and/or Its Treatment

Researchers have conjectured that epigenetic changes are highly relevant to the development of chronic health problems because they account for interactive relationships among environment, genetic background, and disease (Ptak & Petronis, 2008). An epigenetic alteration is defined as one "resulting from changes in a chromosome without alterations in the DNA sequence" (Collado-Hidalgo, Bower, Ganz, Irwin, & Cole, 2008). Thus, epigenetic modifications cause a change in gene activity without altering the underlying DNA sequence. Simplistically, one can liken the activity of the human genome to the wiring of a house (Figure 1). Appliances may be turned on or off in response to an environmental need (e.g., darkness

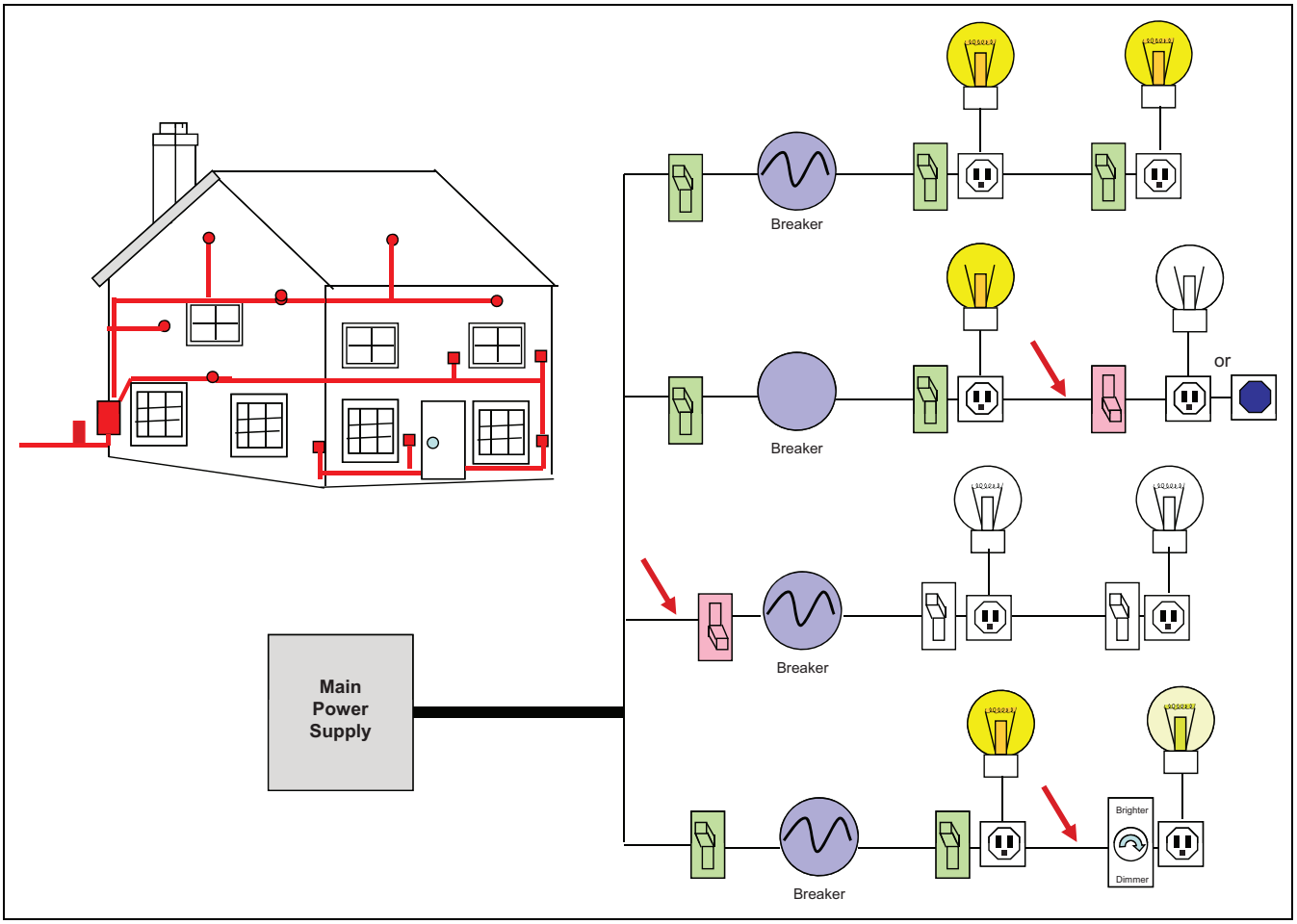

Figure 1. Schematic analogy of the types of epigenetic changes that could occur in response to chemotherapy treatment for breast cancer. Simplistically, one can liken the activity of the genome to the wiring of a house (top left diagram). Although wiring is available to all outlets for appliance/lights usage in a home, one typically turns them on or off in response to need, with the exception of some "housekeeping" appliances (i.e., refrigerator, etc.) that are continuously active. In the schematic representation shown on the right, the typical scenario may be to have activity for multiple regions or genes (Row 1; illustrated by both lights being on). Changes in functionality could impact a single gene (Row 2) or multiple genes in a network (e.g., if a breaker flips as shown in Row 3). These alterations can be complete (on or off) or they can be partial (i.e., dimmer switch as shown in the bottom row).

triggers the need for lighting). Similarly, genes may be turned on and off, via epigenetic modifications, in response to an environmental or exposure-related trigger, with this stimulus being termed an *epigenator*. Continuing with our analogy, to correct the need for light, one must turn on a lamp in a particular location (e.g., a lamp in a downstairs kitchen will not meet the need for light in an upstairs bedroom). Although wiring is available to all outlets for appliance/lights usage in a home, one typically turns them on or off in response to need, with the exception of some "housekeeping" appliances (e.g., refrigerator, etc.) that are continuously active. In the schematic representation (on the right of Figure 1), the typical scenario may be to have activity for multiple regions or genes (Row 1; illustrated by both lights being on). Changes in functionality could impact a single gene (Row 2), or multiple genes in a network (e.g., if a breaker flips as shown in Row 3). These alterations can be complete (on or off) or they can be partial (i.e., dimmer switch as shown in the schematic representation, bottom row). The biological change involved in identifying the specific location for implementing epigenetic changes, termed the *initiator* event, is based on the underlying DNA sequences of the chromatin to be altered. Finally, the resulting response to the environmental stimulus (in our example, keeping the light turned on) is accomplished through the action of the *maintainer*, which for epigenetics is a persistent biological change that sustains an altered chromatin state (Collado-Hidalgo et al., 2008). Given that the maintainers are the persistent, or long-term, biological marks that sustain epigenetic alterations, most biological assays rely on the assessment of these markers to detect the presence of epigenetic changes (Gupta, Nagarajan, & Wajapeyee, 2010).

In Table 1, we summarize the results of studies in which investigators have identified perturbations in a variety of epigenetic markers related to BC and PNS for the following types of epigenetic/genetic alterations: (1) DNA methylation and hydroxymethylation, (2) histone modifications, and (3) chromatin structural alterations as well as chromosomal instability.

Table 1. Summary of Genomic and/or Epigenomic Changes Associated with Breast Cancer, Chemotherapy, and/or Psychoneurological Symptoms.

Finding	References[a]
1. BC has been associated with the acquisition of DNA methylation changes	
DNA methylation	
Altered epigenetic patterns have been observed in BC tumors and allow for recognition of distinct prognostic groups	Dedeurwaerder et al. (2011[b]), Fang et al. (2011), Huang, Nayak, Jankowitz, Davidson, and Oesterreich (2011[b]), Jovanovic et al. (2010[b]), Parrella (2010[b]), Veeck and Esteller (2010[b])
DNA methylation profiles have allowed for the recognition of an immune component in a subset of breast tumors	Dedeurwaerder et al. (2011)
BRCA1 methylation alterations have been seen in a portion of sporadic cases of BC tumors but have not been consistently observed	Bosveil et al. (2012), Butcher and Rodenhiser (2007)
Focused BRCA1 promoter methylation status in blood has been used to attempt to predict a woman's risk of developing BC, with varying results	Al-Moghrabi et al. (2011), Iwamoto et al. (2011)
Genome-wide DNA methylation profiles in blood have been associated with risk of developing BC	Terry et al. (2011)
Epigenetic changes have been implicated as a factor in disparities for cancer risk associated with socioeconomic status	Mohammed et al. (2012)
Stress	
Environmentally induced oxidative stress may induce changes in the 5-hydroxymethylation status of DNA	Chia et al. (2011)
Epigenetic alterations have been observed in response to a variety of stress situations and have been associated with psychiatric conditions as well as the function of neural and other tissues	Mathews et al. (2011), Mehler (2008[b]), Schmidt et al. (2011), Toyokawa et al. (2012)
2. BC and/or the effects of chemotherapy are associated with the acquisition of histone modifications	
EZH2 levels are elevated in BC tumors and it is thought that this histone methyltransferase may be an important early step in initiating a cascade of biological changes in cancer cells, including epigenetic alterations	Bachmann et al. (2006), Collett et al. (2006), Ding et al. (2006), Gonzalez et al. (2009), Grzenda, Ordog, and Urrutia (2011[b]), Kleer et al. (2003), Raaphorst et al. (2003), Rush et al. (2009), Schlesinger et al. (2006), Simon and Lange (2008[b]), Viré et al. (2006), Tsang and Cheng (2011[b])
EZH2 is frequently elevated in inflammatory BC and is predictive of a worse clinical outcome	Gong et al. (2011)
EZH2 is thought to mediate repression of DNA repair	Chang et al. (2011), Stefansson and Esteller (2011)
Reductions in histone (H3 and H4) acetylation lead to significant decreases in brain-derived neurotrophic factor gene expression and perturbations in hippocampus signaling/presence of dendritic spine	Zeng et al. (2011)
Chemotherapy agents adversely affect neural progenitor cell proliferation and are associated with epigenetic (histone) modifications in the hippocampus and prefrontal cortex of the brains of rats	Briones and Woods (2011)
3. BC, stress, or direct effects from chemotherapy lead to the acquisition of telomere alterations and/or chromosomal instability	
Telomeres	
BC	
Chromosomes from epithelial breast cells having shorter telomeres had higher frequencies of chromosomal instability	Diehl et al. (2011), Pampalona, Soler, Genescà, and Tusell (2010)
The value of lymphocyte telomere length as a biomarker for predicting BC risk is controversial	De Vivo et al. (2009), Gramatges et al. (2010), Kim et al. (2011), Pooley et al. (2010), Shen et al. (2007), Zeng et al. (2011)
Stress and inflammation	
Higher anticipatory threat appraisals have been associated with shortened telomere length	O'Donovan et al. (2012)
Cumulative inflammatory response and/or chronic pain/stress have been associated with telomere attrition	Epel (2009[b]), Epel et al. (2004), O'Donovan et al. (2011, 2012), Sibille et al. (2012), Strub et al. (2008)
Progressive telomere shortening has been observed in microglial rat cells, which are mitotically active	Flanary and Streit (2004)

(continued)

Table 1. (continued)

Finding	References[a]
Interventions to reduce stress have been associated with increased telomere lengths and/or less attrition	Biegler, Anderson, Wenzel, Osann, and Nelson (2012), Peres (2011), Puterman et al. (2010)
Chemotherapy and other treatments	
Several chemotherapeutic agents lead to shortening of telomeres through a variety of mechanisms	Hewitt et al. (2012), McCormick and Silva (2006), Walker et al. (2012[b])
Changes in leukocyte telomere lengths have been observed in posttreatment specimens compared to pretreatment specimens in women with or without stem cell transplants	Schroeder et al. (2001)
Chromosomes from mesenchymal stem cells showed shortened telomeres and other attributes of "aging" following exposure to chemotherapeutic agents	Buttiglieri et al. (2011)
Related conditions	
Memory loss and compromised cognitive function have been associated with leukocyte telomere attrition for several conditions	Martin-Ruiz et al. (2006), Valdes et al. (2010), Yaffe et al. (2011)
Telomere attrition has been observed in people having depression, mood disorders, cardiovascular disease, atherosclerosis, diabetes, dementia, Alzheimer's disease, primary caregiver status to chronically ill family members, social stress, and numerous other health conditions	Aviv and Aviv (1998), Cherkas et al. (2006), Damjanovic et al. (2007), Effros (2011), Epel (2009[b]), Fitzpatrick et al. (2007), Humphreys et al. (2012), Kume et al. (2012), Parks et al. (2009), Serrano and Andres (2004[b]), Simon et al. (2006), Wikgren et al. (2012)
Chromosomal instability (micronuclei)	
BC	
Infiltrating ductal carcinoma tumor specimens have an increased frequency of micronuclei, which is correlated with tumor grade	Goel, Bhatia, and Dey (2011), Samanta, Dey, and Nijhawan (2011)
Increased frequency of micronuclei and other measures of chromosomal instability have been seen in lymphocytes of women with BC compared to controls, but results have varied between studies	Aristei et al. (2009), Cardinale, Bruzzi, and Bolognesi (2012[b]), Djordjevic et al. (2010), Elsendoorn et al. (2001), Miloševic-Santos et al. (2010), Varga et al. (2006), Wang et al. (2006)
Folate levels appear to influence lymphocyte micronuclei values in women with and without BC	Wang et al. (2006)
Chemotherapy	
Increased frequency of micronuclei and other measures of chromosomal instability in lymphocytes have been found following therapy compared to baseline values in women with BC, with individual differences being noted	Aristei et al. (2009), Elsendoorn et al. (2001), Miloševic-Djordjevic et al. (2010)
Effect(s) of different therapy regimens on chromosomal instability or breakage varies between studies	Aristei et al. (2009), Miloševic-Djordjevic et al. (2010)
Chemotherapy-induced increases in chromosomal abnormalities in lymphocytes persist for months after treatment	Bilban-Jakopin and Bilban (2001), Elsendoorn et al. (2001)
Age-related changes and complex diseases	
Acquired chromosomal aberrations have been observed to occur in an increased frequency in patients having Alzheimer's disease, Parkinson's disease, schizophrenia, heart disease, autoimmune conditions, atherosclerosis, and numerous other conditions	Aviv and Aviv (1998[b]), Iourov et al. (2008b[b]), Jackson-Cook (2011[b]) Wojda and Witt (2003[b]), Yurov et al. (2008)
Somatic mosaicism for DNA copy number alterations and loss of heterozygosity has been associated with an increased risk of developing cancer	Jacobs et al. (2013)

Note. BC = breast cancer; BRCA1 = breast cancer susceptibility gene one; DNA = deoxyribonucleic acid; EZH2 = enhancer of zeste 2.
[a]The references cited are representative of published studies in the field, but the list is not exhaustive.
[b]Review article.

DNA Methylation and Hydroxymethylation Alterations

DNA methylation occurs when a methyl group ($-CH_3$) is added to one of the four DNA bases (cytosines) in a DNA molecule (Jones & Liang, 2009; Miranda & Jones, 2007). This process, which is catalyzed by enzymes called DNA methyltransferases (Carey, Marques, & Reik, 2011), usually results in the repression of gene transcription (turning genes "off"; Mazzio & Soliman, 2012). Hydroxymethylation is an alternative

modification that can be found on cytosine bases (Kriaucionis & Heintz, 2009; Tahiliani et al., 2009). Research has not yet fully elucidated the biological role of hydroxymethylation, but investigators have hypothesized that it is associated with gene activity (rather than inactivity, as with methylation) and have observed the process in several different tissues, including neural (brain) tissue (Jin, Wu, Li, & Pfeifer, 2011). Methylation changes have been consistently observed in cells from BC tumors as well as in BC cell lines (Table 1). Overall, BC tumor cells have shown significantly increased levels of global DNA hypomethylation (leading to gene activation) as well as hypermethylation in targeted regions of DNA (leading to gene inactivation/repression) when compared to normal tissues (Wilson, Power, & Molloy, 2007). These genome-wide methylation patterns, or "signatures," have allowed for improvements in pathologists' ability to stratify patients by disease progression risk and have led to the recognition of an immune component to the BC tumors in a subset of patients (Dedeurwaerder et al., 2011). However, researchers have noted heterogeneity (between-patient differences) in the utility of single-gene methylation patterns, such as those seen for BC susceptibility gene one (BRCA1), in evaluating BC tumors (Bosveil et al., 2012; Butcher & Rodenhiser, 2007).

In addition to better characterizing BC tumors, epigeneticists have explored the potential for using lymphocyte epigenetic signatures to identify a woman's risk of developing BC a priori. The results of these projections have yielded varied outcomes, with some groups reporting significant odds ratios, while others (primarily based on assessments of just one gene) have found them to have no clear predictive value (Al-Moghrabi, Al-Qasem, & Aboussekhra, 2011; Iwamoto, Yamamoto, Taguchi, Tamaki, & Noguchi, 2011; Terry, Delgado-Cruzata, Vin-Raviv, Wu, & Santella, 2011). Excitingly, recent reports of associations between genome-wide lymphocyte epigenetic patterns and socioeconomic status and/or environmental exposures have shown promise for explaining the well-recognized, but poorly understood, disparity in adult cancer risk related to low socioeconomic status in childhood, even when that status is reversed in adulthood (Mohammed, Springfield, & Das, 2012).

In women with BC, stress associated with the diagnosis of cancer and the ensuing lifestyle disruptions and existential threats may further compound the biological disruptions related to cancer by triggering endocrine stress-response mechanisms through the hypothalamic–pituitary–adrenal axis and the autonomic nervous system (Sephton & Spiegel, 2003). Stress-related inflammation also elicits perturbations in the regulation/expression of several genes, including (but not limited to) those regulating nuclear factor-κB, interleukin-1β, interleukin-6, and tumor necrosis factor-α (Bartsch & Nair, 2006; Miller, Chen, & Parker, 2011). Further, stress may also lead to the disruption of neuroendocrine and immune circadian rhythms (Sephton & Spiegel, 2003), causing disruptions in sleep and metabolic and endocrine functions (Dedert et al., 2012). Researchers have also consistently observed that individuals experiencing stress acquire alterations in the methylation patterns of their lymphocytes (Mathews et al., 2011; Mehler, 2008; Toyokawa, Uddin, Koenen, & Galea, 2012).

In summary, the pioneering studies investigating methylation patterns in BC have shown that changes are clearly present in BC tumors, with the results of recent genome-wide studies suggesting that methylation alterations are also acquired in lymphocytes in response to environmental exposures. Furthermore, studies have shown that these perturbations in methylation patterns persist for years (Toyokawa et al., 2012).

Histone Modifications

In vertebrates, the packaging of DNA into chromatin is dependent on four core histone proteins (called Histone 2A, Histone 2B, Histone 3, and Histone 4). These histones and DNA form a complex that provides the basic organizational structure for chromatin (Kouzarides, 2007). The "tail" portion of these histone proteins contains numerous amino acid residues that can be modified, with the location and types of modifications influencing how tightly the DNA is compacted, as well as serving to recruit other proteins that are essential for mediating the methylation of DNA (Arrowsmith, Bountra, Fish, Lee, & Schapira, 2012; Greer & Shi, 2012). Methylation is also one type of modification that can occur in histones. Researchers have hypothesized that the protein enhancer of zeste 2 (EZH2) is involved in the early "decision" steps leading to histone methylation, chromatin condensation, and gene silencing (Schlesinger et al., 2006; Viré et al., 2006). Although research has not fully resolved (Rush et al., 2009), the specific role EZH2 plays in initiating histone methylation, and perhaps DNA methylation as well (Viré et al., 2006), findings have shown that the expression of EZH2 is significantly altered (often overexpressed) in BC tumors, allowing the protein to serve as a prognostic indicator for BC tumor cell progression (Bachmann et al., 2006; Collett et al., 2006; Ding, Erdmann, Chinnaiyan, Merajver, & Kleer, 2006; Gong et al., 2011; Kleer et al., 2003; Raaphorst et al., 2003; Viré et al., 2006). Researchers have also noted that EZH2 silences the expression of several DNA repair genes. Its amplification/overexpression in tumor cells, then, may impair these cells' ability to repair DNA, thus predisposing them to metastasis (Chang et al., 2011; Stefansson & Esteller, 2011). As we noted above for DNA methylation, studies of histone modifications associated with BC in humans have primarily focused on tumor tissue. However, investigators have also completed studies of somatic cells, with Briones and Woods (2011) showing that histone alterations were induced in the brain cells of rats following exposure to chemotherapeutic agents. Moreover, brain cells in rats have consistently shown perturbations of gene expression, along with changes in brain cell function and structure, following the acquisition of histone modifications.

Chromatin Structural Alterations and Chromosomal Instability

A third type of epigenetic modification involves alterations in chromatin structure. Active genes tend to be localized to loosely compacted DNA (termed euchromatin), whereas

inactive genes tend to be found in tightly condensed DNA (called heterochromatin; Quivy et al., 2004). One chromatin structure that has been implicated in BC is the telomere or the end of the chromosome. Telomeres are normally heterochromatic and are interesting ribonuclear structures in that they are epigenetically regulated (through histone modifications). They can also influence gene expression via epigenetic mechanisms. In humans, telomeres consist of tandem copies of a hexameric sequence (TTAGGG) bound by numerous associated proteins, which form a protective cap-like structure important for ensuring chromosomal stability and regulating how many times a cell can divide (Jovanovic, Rønneberg, Tost, & Kristensen, 2010; O'Sullivan & Karlseder, 2010). Telomeres can shorten, which is a genetic change rather than an epigenetic alteration since the underlying DNA is altered. Alternatively, the protective telomeric structure or cap may become compromised, which is an epigenetic change since the underlying DNA is not altered. If either of these telomeric alterations occurs, the neighboring chromatin structure becomes more open or "relaxed," thereby allowing for transcription of genes adjacent to subtelomeric regions (an epigenetic change). Multiple investigators have observed telomere shortening in BC tumors (Diehl et al., 2011) as well during the early stages of mammary carcinogenesis (Meeker & Argani, 2004). Furthermore, data are accumulating to indicate that several exposure factors can result in telomere shortening in normal body cells. These exposures include (but are not limited to) stress, mainstay chemotherapeutic agents used in the treatment of BC, and inflammation (Epel, 2009; Epel et al., 2004; Hewitt et al., 2012; McCormick & Silva, 2006; O'Donovan et al., 2011, 2012; Sibille et al., 2012; Strub, Depcrynski, Elmore, & Holt, 2008; Walker et al., 2012). Research has also revealed associations between telomere shortening and many age-related health conditions (Aviv & Aviv, 1998; Humphreys et al., 2012; Kume et al., 2012; Martin-Ruiz et al., 2006; Simon et al., 2006; Valdes et al., 2010; Wikgren et al., 2012). However, the potential utility of the telomere as a biomarker for recognizing women at risk of developing BC is controversial, with some investigators identifying a clear association between telomere attrition and risk of BC, and others finding no relationship (De Vivo et al., 2009; Gramatges, Telli, Balise, & Ford, 2010; Kim et al., 2011; Pooley et al., 2010; Shen et al., 2007; Zheng et al., 2010).

One consequence of telomere shortening is chromosomal instability, which is a genetic change. Chromosomal aberrations, which can be identified using both conventional metaphase chromosome analysis and the micronucleus assay (which is a high throughput means for accurately quantifying chromosomal instability) are hallmark findings in many tumors and are not limited to BC (Janssen & Medema, 2012). In addition to tumor-specific chromosomal abnormalities, investigators have shown a significantly increased frequency of acquired chromosomal anomalies present in a variety of body cells from individuals with cancer. Researchers completed most of these assessments using noninvasively obtained tissues such as lymphocytes and buccal mucosa (Aristei et al., 2009; Cardinale, Bruzzi, & Bolognesi, 2012; Elsendoorn et al., 2001; Miloševic-Djordjevic, Grujicic, Vaskovic, & Marinkovic, 2010; Santos et al., 2010; Varga et al., 2006; Wang et al., 2006). The frequency of these acquired chromosomal aberrations increases in response to chemotherapy (Aviv & Aviv, 1998; Iourov, Vorsanova, & Yurov, 2008b; Jackson-Cook, 2011; Wojda & Witt, 2003; Yurov et al., 2008). Though research has not yet fully determined the causes for these acquired somatic cell chromosomal abnormalities, age, telomere attrition, genetic makeup, diet, and environmental exposures can all be contributing factors (Jackson-Cook, 2011; Kirsch-Volders et al., 2011). Investigators have identified an increased frequency of acquired chromosomal abnormalities in a wide range of complex health problems in addition to cancer, leading to speculation that the abnormalities play a contributory/causal role in the development of these conditions (Table 1).

Hypothesized Model for a Biological Cascade Involving Inflammation, Epigenetic, and/or Genetic Changes in the Development and/or Persistence of PNS

We have integrated the existing knowledge about cancer and epigenetics to develop a hypothesis to explain the development and persistence of PNS following cancer treatment (Figure 2). We posit that the chemotherapy treatment (and possibly the cancer itself) initiates a cascade of biological changes that include inflammation and epigenetic and genetic alterations. Specifically, we propose that epigenetic alterations arise either in response to inflammatory activation or as a direct consequence of chemotherapy. The induced inflammatory activation/epigenetic alterations may lead directly to cellular changes but can also result in telomere attrition, with potential gene-by-environment interactions influencing an individual's response. The proposed epigenetic changes may involve DNA methylation or histone modifications, possibly through perturbations in EZH2. Since EZH2 is important for DNA repair, alterations in its expression could lead to chromosomal instability. Similarly, epigenetic alterations and telomere shortening could lead to chromosomal instability. Each of these factors, acting either singly or in concert, could lead to cellular changes or may act synergistically.

The types of cellular responses arising as a consequence of these epigenetic and/or genetic changes could include cell death/cellular senescence, as well as true (due to aneuploidy) or functional (via gene expression changes) genetic imbalances. Each of these alterations would be expected to interfere with the cell's metabolic activities and could contribute to the development of PNS. For example, if true or functional genetic imbalances occur in neural tissue, the cells may no longer be capable of completing normal responses, thereby blocking the transmission of intercellular signals necessary for normal neural function. Support for this conjecture comes from the observation that enzymes involved in histone methylation (gene expression) are important components in learning and memory processes (Day & Sweatt, 2011; Lubin, Gupta, Parrish, Grissom, & Davis, 2011). Furthermore, researchers have shown that individuals

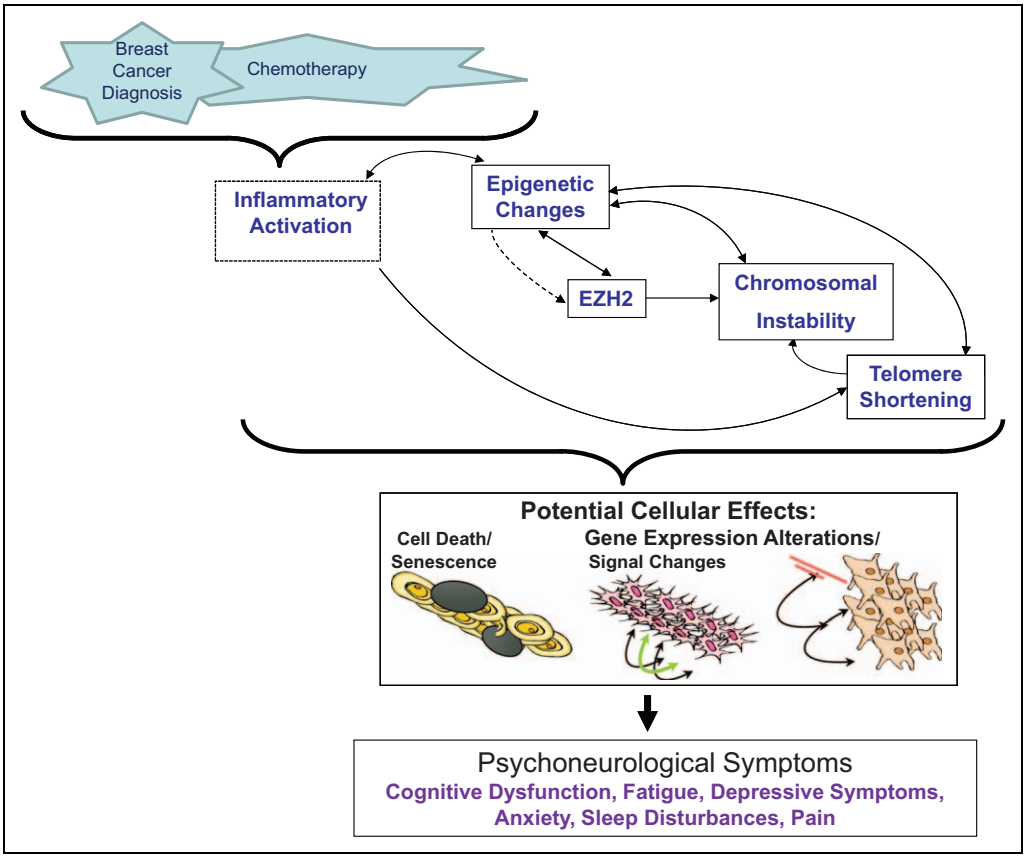

Figure 2. Cascade of hypothesized biological changes leading to psychoneurological symptoms (PNS) in women having breast cancer treated with chemotherapy. Breast cancer and chemotherapy lead to inflammatory activation and may also directly induce epigenetic, telomeric, and/or chromosomal changes. Briefly, the induced inflammatory activation may cause epigenetic changes as well as telomere attrition. Alternatively, epigenetic alterations may occur first, leading to inflammatory activation. These epigenetic changes may involve DNA methylation or histone modifications, possibly through perturbations in the protein enhancer of zeste 2 (EZH2). Changes in EZH2 expression could lead to chromosomal instability as well as other DNA methylation alterations. Telomere shortening, as well as epigenetic alterations, could also directly lead to chromosomal instability. Each of these factors, acting either singly or in concert, could lead to cellular changes. These induced cellular changes could then lead to the presentation and/or persistence of PNS. CRP = C-reactive protein; DNA = deoxyribonucleic acid; E × G interactions = environment × genetic interactions.

having a variety of health and/or psychiatric conditions (including but not limited to Alzheimer's disease, Parkinson disease, and schizophrenia) have higher levels of acquired chromosomal abnormalities (genetic imbalance) than age-matched controls in both organ-specific tissues (e.g., brain cells in people having psychopathology) and peripheral tissues (most frequently peripheral blood; Faggioli, Vijg, & Montagna, 2011; Iourov, Vorsanova, & Yurov, 2008a, 2008b; Kingsbury et al., 2005). If the cells experience senescence or death in response to the acquired epigenetic/genetic changes, the proliferative potential of the tissue would be compromised, with the effects potentially leading to physiological alterations that could culminate in phenotypic consequence. Briones and Woods (2011), for example, reported cognitive impairment in response to chemotherapy-induced decreases in cellular proliferation in rats.

In addition to contributing to the development of PNS through their response to environmental stimuli, epigenetic/genetic alterations could explain the persistence of PNS since epigenetic "marks" and chromosomal alterations can be stably retained for years and through multiple cell divisions in mitotically active cells (Feinberg et al., 2010). Similarly, this phenomenon could explain how epigenetic changes in postmitotic cells, such as neurons, could potentially contribute to long-term, treatment-related symptoms. The plasticity and sensitivity of epigenetic responses to genetic background, different environment influences, and the dynamic interplay between genetics and environment (G × E interaction) could explain why PNS only develop in a subset of women with BC who have had chemotherapy. Thus, epigenetic and chromosomal alterations fully meet the criteria necessary for providing a means to "biologically remember" the effects of chemotherapy (or the cancer itself).

Examples From Pilot Data

To date, there are no published reports directly testing our hypothesized association between the development and/or persistence of chemotherapy-induced PNS and epigenetic alterations, telomere attrition, or chromosomal instability. However, preliminary data from our pilot studies have shown that at least a subset of telomeres have alterations in length following

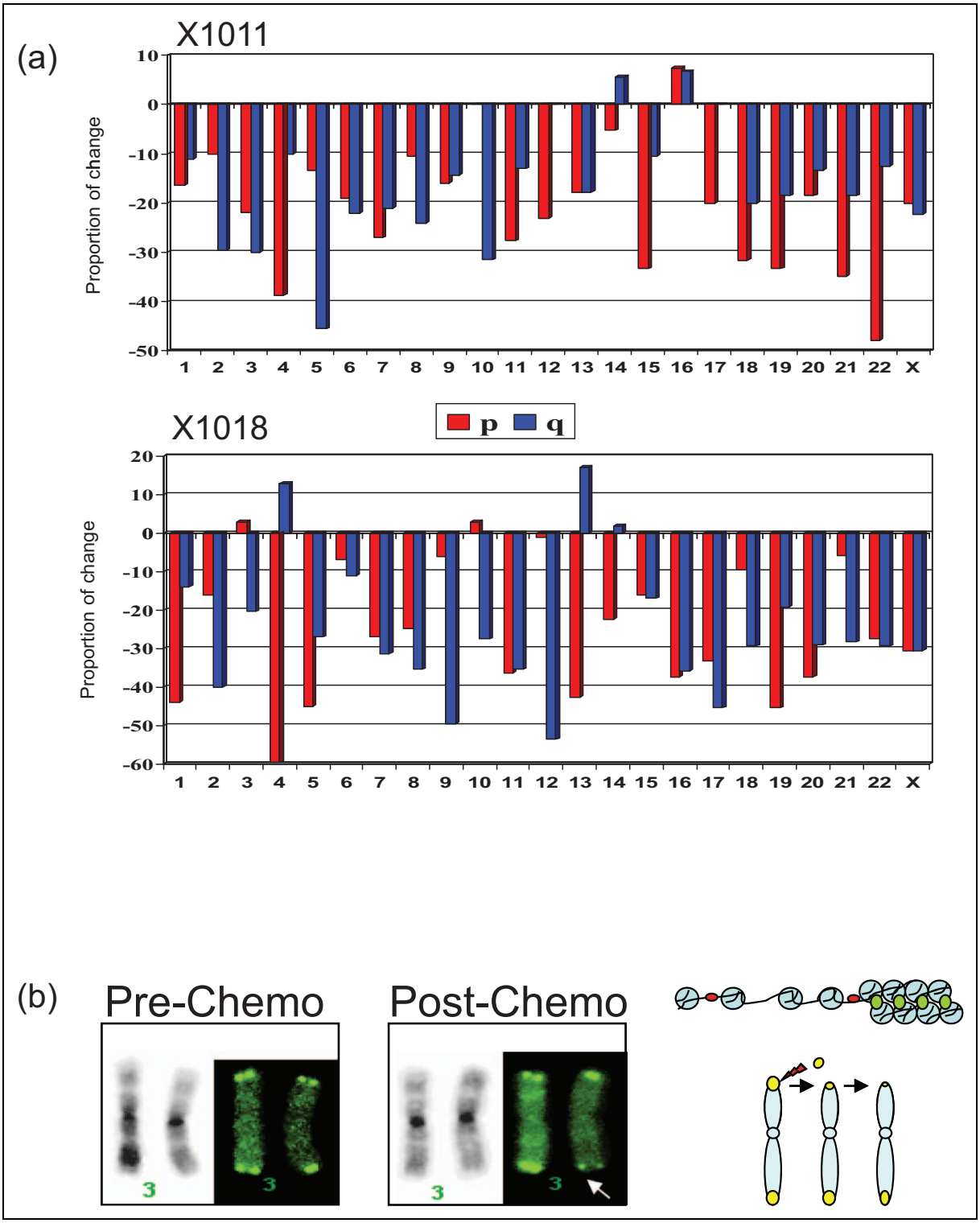

Figure 3. Differential chromosomal and epigenetic alterations acquired following chemotherapy for breast cancer in women evaluated in pilot study. (a) A chromosome-specific fluorescent in situ hybridization methodology was used to assess telomere length variation in lymphocyte chromosomes of two women before and after chemotherapy treatment for breast cancer. Genome-wide chromosome-specific telomere shortening (short arm [p] and long arm [q]) was seen for both women studied (X1011 [top panel] and X1018 [middle panel]), visualized by difference values less than 0. (b) To illustrate the method used for the telomere length determinations, a partial karyotype of the chromosomes 3 from case X1018 is shown (bottom left). Similar telomere intensities are present for the short arm (top of chromosomes), but the telomere was less bright on one of the long-arm telomeres, indicating that shortening occurred (arrow). A schematic illustrating how acquired telomeric shortening could lead to "opening" of nearby chromatin is also shown (bottom right).

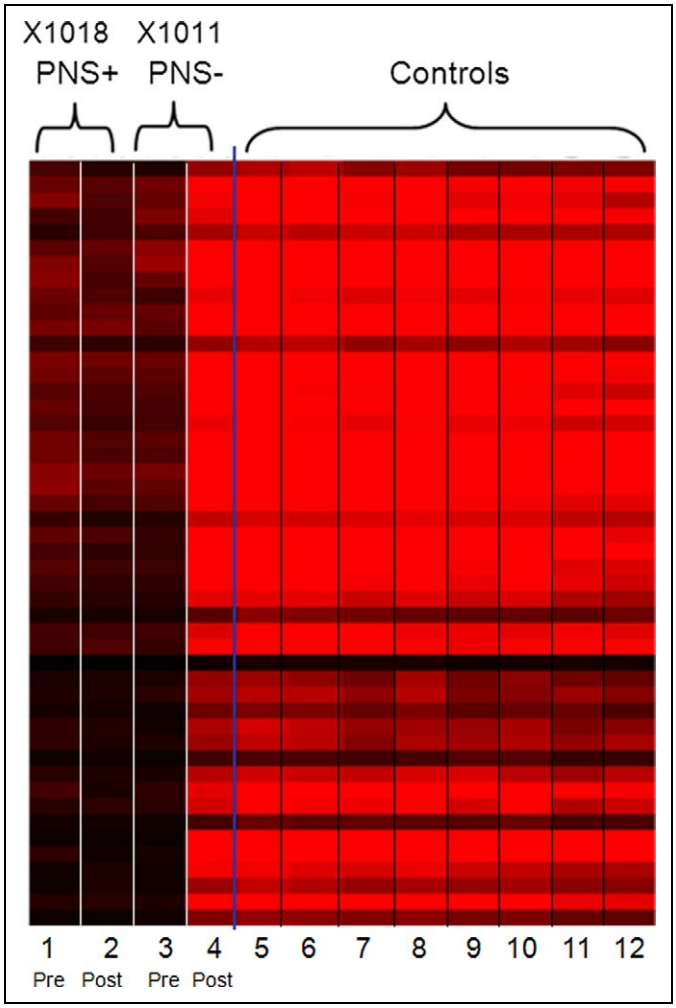

Figure 4. Differences in methylation patterns between women diagnosed with breast cancer and age-matched controls without cancer. This heatmap shows the methylation status of a subset of loci from 12 peripheral blood specimens. Columns 1 (pretreatment) and 2 (15 weeks posttreatment) show values from woman X1018, who had persistent psychoneurological symptoms (PNS). Columns 3 (pretreatment) and 4 (posttreatment) show the values from woman X1011, who did not have persistent PNS. The remaining columns (columns 5–12) are specimens collected from eight different healthy control subjects. Each row (Y axis) represents a different genetic locus, with a total of 48 loci being shown in this subset. The methylation status for each gene/gene region is quantified as a continuous number ranging from 0 to 1, with the value indicated by a shade of red to black, respectively. Both of the pretreatment specimens from the women with a diagnosis of breast cancer (Columns 1 and 3) had a different pattern (black-toned) from those seen in healthy, age-matched controls (Columns 5–12; red-toned patterns). The posttreatment methylation pattern (Column 4) for woman X1011 (no PNS) became more similar to that of the normal controls. In contrast, the posttreatment methylation pattern (Column 2) for woman X018 (who had persistent PNS) remained similar to the pretreatment pattern (dark-toned pattern).

chemotherapy, that epigenetic alterations are present in the leukocytes of women with BC compared to age-matched controls without BC, and that these epigenetic patterns can be altered in some women after chemotherapy (Figures 3 and 4). We used a chromosome-specific fluorescent in situ hybridization (FISH) methodology to assess telomere length variation in lymphocyte chromosomes of two women diagnosed with BC, completing evaluations before treatment and 15 weeks after chemotherapy (Figure 3). We found genome-wide chromosome-specific telomere shortening for both women and noted no clear pattern of chromosome-specific loss.

We also observed differences in methylation patterns (Figure 4) between women having a diagnosis of BC and age-matched controls without BC. Excitingly, our anecdotal assessment of two women receiving chemotherapy for their BC showed that the methylation signature for a subset of genes evaluated in a genome-wide analysis reverted back to a pattern similar to that of the "normal" controls 15 weeks after chemotherapy initiation for a woman who did not develop debilitating side effects. In contrast, a woman who experienced persistent adverse significant side effects maintained an aberrant methylation pattern 15 weeks following the initiation of chemotherapy. We currently have an ongoing longitudinal study of a larger cohort of women receiving treatment for BC to formally test the hypothesis presented in this article.

Implications for the Development of Future Biomarkers for Biobehavioral Research

We predict that our and other researchers' future investigations to test this hypothesized relationship of epigenetic alternations to the development and persistence of PNS will reveal biomarkers that will allow for the identification of individuals having an elevated risk of developing PNS when treated for BC. Given that there are numerous epigenetic mechanisms controlling gene expression within cells, it seems likely that multiple predictive biomarkers will be identified and that these biomarkers may ultimately provide a basis for a personalized medicine approach for empowering women to make informed decisions regarding treatment options. However, in concert with research to examine epigenetic mechanisms, further study of the incidence, prevalence, and co-occurrence of symptoms is needed to reach a consensus on the nature of symptom clusters.

Additional research may also culminate in an understanding of the molecular/cellular basis for PNS development and/or persistence. For example, discovering hypermethylation of DNA in promoter regions of genes implicated in DNA repair as well as neural cell function, memory, and other cognitive functions could guide future studies leading to the recognition of genes underpinning the development of PNS and may also lead to the discovery of biomarkers most amenable to diagnostic testing (i.e., those with a more rapid turnaround time and/or lower cost than a genome-wide platform). The facts that EZH2, a key epigenetic mediator, has been implicated in DNA repair (Stefansson & Esteller, 2011) and that basal levels of acquired chromosomal instability/DNA damage in peripheral blood lymphocytes are higher in a subset of untreated patients having BC compared to healthy women (Parrella, 2010) lend additional credence to our pursuit of these end points as potential predictive biomarkers related to the development of PNS symptoms.

Finally, since epigenetic changes can be reversed (Esteller, 2005; Issa, Shen, & Toyota, 2005; Mehler, 2008; Muotri & Gage, 2006), the recognition of clinically relevant epigenetic alterations could lead to the development of effective therapeutic interventions. By exploiting the knowledge gained about acquired epigenetic changes, researchers could develop targeted interventions to reduce stress, ameliorate symptoms, enhance quality of life, and possibly prevent or reverse the adverse health outcomes associated with BC and its treatment during the acute treatment phase as well as the survivorship period.

Declaration of Conflicting Interests

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