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A Conceptual Model of Psychoneurological Symptom Cluster Variation in Women with Breast Cancer: Bringing Nursing Research to Personalized Medicine

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Abstract

Personalized medicine applies knowledge about the patient's individual characteristics in relation to health and intervention outcomes, including treatment response and adverse side-effects, to develop a tailored treatment plan. For women with breast cancer, personalized medicine has substantially improved the rate of survival, however, a high proportion of these women report multiple, co-occurring psychoneurological symptoms over the treatment trajectory that adversely affect their quality of life. In a subset of these women, co-occurring symptoms referred to as symptoms clusters, can persist long after treatment has ended. Over the past decade, research from the field of nursing and other health sciences has specifically examined the potential underlying mechanisms of the psychoneurological symptom cluster in women with breast cancer. Recent findings suggest that epigenetic and genomic factors contribute to inter-individual variability in the experience of psychoneurological symptoms during and after breast cancer treatment. While nursing research has been underrepresented in the field of personalized medicine, these studies represent a shared goal; that is, to improve patient outcomes by considering the individual's risk of short- and long-term adverse symptoms. The aim of this paper is to introduce a conceptual model of the individual variations that influence psychoneurological symptoms in women with breast cancer, including perceived stress, hypothalamic-pituitary-adrenocortical axis dysfunction, inflammation, as well as epigenetic and genomic factors. The proposed concepts will help bring nursing research and personalized medicine together, in hopes that this hitherto neglected and understudied area of biomedical research convergence may ultimately lead to the development of

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Conflict of Interest

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more targeted clinical nursing strategies in breast cancer patients with psychoneurological symptoms.

Keywords

Breast cancer; epigenetics; genetics; hypothalamic-pituitary-adrenal axis; personalized medicine; psychoneuroimmunology; psychoneurological symptoms; symptom clusters

1. Introduction

Although advances in treatment have substantially increased rates of survival for women with breast cancer (BCA), the women often report a number of distressing symptoms that worsen over the course of treatment, and may persist in survivorship [1, 2]. These distressing symptoms can prohibit recovery of pre-diagnosis levels of function and life satisfaction. This is a significant and global health care concern because a majority of BCA survivors are young (< 64 years of age) and these women comprise the largest group of cancer survivors in the world [3]. The most common, severe, and distressing symptoms that co-occur throughout the treatment trajectory and after treatment include depressive symptoms, anxiety, cognitive dysfunction, fatigue, sleep disturbance, and pain. This set of symptoms, which has been termed the psychoneurological (PN) symptom cluster [4], has been reliably associated with reduced quality of life [5–7]. Research to identify the physiological mechanisms underlying these co-occurring symptoms has been ongoing in the hope that it may lead to the development of more targeted symptom management strategies.

Several studies have found an association between symptoms and dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis [8–10]. In addition, studies using a cytokine-induced “sickness behavior” framework have provided some evidence for the association of inflammation with physical and emotional symptoms commonly experienced by women with BCA [11–13]. More recently, research focused on variability in symptom severity and persistence led to investigations focused on the contributions of genetic factors and epigenetic modifications that occur due to psychosocial stressors, the disease process and treatment [14, 15].

Personalized medicine applies knowledge about the patient’s individual characteristics that influence patient outcomes, including treatment response and adverse side-effects, to develop a tailored treatment approach. While nursing research has been underrepresented in the field of personalized medicine, these studies represent a shared goal that crosses disciplines; that is, to improve patient outcomes by considering the individual’s risk of short- and long-term adverse symptoms.

The aim of this paper is to introduce a conceptual model of the individual characteristics that influence psychoneurological symptoms in women with breast cancer, including perceived stress, hypothalamic-pituitary adrenocortical axis dysfunction, inflammation, as well as epigenetic and genomic factors. Genetic variants and epigenetic modifications will be described for each of the candidate mechanisms proposed to influence variability in the symptom experience.

2. Individual Characteristics that Influence Psychoneurological Symptoms

Over the past decade, research from the field of nursing and other health sciences have examined potential underlying mechanisms of the psychoneurological (PN) symptom cluster in women with breast cancer. Collectively, these studies suggest that both psychosocial and biological characteristics of the individual are important in understanding the risk of

experiencing PN symptoms during treatment and in survivorship. The individual characteristics of women with BCA and related mechanisms that contribute to PN symptoms are discussed.

2.1 Perceived Stress

Seminal research on symptom clusters in women with BCA derived from the perspective of psychoneuroimmunology (PNI) to describe the relationships among multiple psychological stressors encountered during treatment and their reported symptoms [8–13, 16]. An important goal of PNI is to explain the effect of perceived stress on psychosocial-behavioral, neuro-immune and environmental interactions and the underlying mechanisms that influence health outcomes. We have expanded upon the tenets of PNI to incorporate genetic and epigenetic candidate mechanisms of symptoms in the conceptual model (Figure 1).

The individual's genome provides a blueprint for the coordination of neuroendocrine-immune interactions [17]. Variability in the stress response system can occur due to genetic polymorphisms that alter neuroendocrine-immune signaling pathways, thereby leading to disruption in homeostatic regulation and increased vulnerability to persistent symptoms [18–20]. The epigenome contributes another layer of variability by regulating the genes that are “turned on” or “turned off” [21]. Although epigenetic patterns are inherited, modifications can occur in response to extreme or prolonged psychological stress [22, 23] and in association with cancer development and progression [24].

Recent studies on gene-environment interactions demonstrate how genetic variants that regulate the stress response system can influence persistent symptoms. The FK506 binding protein 5 (*FKBP5*) gene codes for the protein that binds to glucocorticoid receptors and modulates glucocorticoid sensitivity [25]. In addition to regulating the nuclear factor kappa-beta (NF_κB) pathway, *FKBP5* is involved in the processes of tumorigenesis and chemoresistance. Polymorphisms of the *FKBP5* gene were recently shown to predict anxiety and depression in newly diagnosed patients with cancer who reported high levels of perceived stress [26]. In adults with a history of childhood trauma, DNA methylation of one of the *FKBP5* polymorphisms was found to increase the risk of developing psychiatric disorders, including symptoms of post-traumatic stress disorder [27].

Chronic stress is associated with low-grade inflammation fostered by immune cells that have acquired resistance to cortisol [28]. NF_κB plays a significant role in stress-induced cortisol resistance in addition to regulating the expression of cytokines, inducible nitric oxide synthase, cyclooxygenase 2, growth factors and inhibitors of apoptosis [29]. Activation of the NF_κB pathway contributes to tumorigenesis and protects tumor cells from apoptosis by oxidative stress thereby providing a mechanism of cellular immortality [30]. Chronically high levels of perceived stress are associated with increased expression of nuclear factor kappa-B (NF_κB) in monocytes, decreased expression of glucocorticoid receptors and fatigue in BCA survivors and caregivers [31, 32].

2.2 Hypothalamic-pituitary-adrenocortical axis dysfunction

Stressful events in childhood and genetic factors have been associated with increased HPA axis responses due to hyperactivity of the corticotropin releasing hormone (CRH) system [33]. A history of childhood trauma was associated with increased CRH concentrations in cerebrospinal fluid along with increased mRNA expression of CRH and CRH receptor type 1 [34, 35]. In addition, CRH polymorphisms and elevated CRH levels are associated with enhanced stress responses to psychosocial stressors [36] and depressive symptoms [37]. An enhanced stress response could lead to cortisol resistance and inflammation, thereby promoting an environment conducive to tumorigenesis [29, 30] Current studies are

evaluating whether enhanced stress responses increase the risk of BCA in women with and without a positive family history.

Cortisol receptors provide substantial variability in the HPA response and are likely the most studied component of the HPA axis. Genetic variants of the two central corticosteroid receptors, high-affinity mineralocorticoid receptor (MR) and the lower-affinity glucocorticoid receptor (GR), modify HPA axis responses at several levels [38]. Both receptors regulate corticosteroid-mediated feedback on the HPA axis and deficits in the activity of either one may alter the response to cortisol, resulting in an increased or decreased stress response. Specifically, the GR polymorphism *TthIII* (rs10052957) is associated with higher basal cortisol levels, while *N363S* (rs6195) and *BclI* site (rs41423247) polymorphisms result in increased cortisol sensitivity [39]. Conversely, polymorphisms in *NR3C1-1* (rs10482605), *ER22/23EK* (rs6189/6190), and *A3669G* (rs6198), result in decreased cortisol sensitivity [40]. The MR polymorphisms *-2G/C* (rs2070951) and *I180V* (rs5522) also result in decreased cortisol sensitivity [38].

To our knowledge, there have not been any studies evaluating the influence of CRH or cortisol receptor polymorphisms on BCA symptoms. However, some studies support the notion that alterations in cortisol secretion and glucocorticoid receptor sensitivity may increase the risk of experiencing persistent symptoms. Lower levels of morning cortisol and flattened diurnal variation of cortisol have been reported in BCA survivors with persistent fatigue [41]. In addition, cortisol dysregulation and reduced levels of serotonin were described in women with BCA who reported symptoms of fatigue, depression, and sleep disturbances [9, 42].

2.3 Pro- and anti-inflammatory cytokines

The observation of adaptive behaviors to infection in animals was initially described by Hart, who coined the term “sickness behaviors” [43]. This set of behaviors, which includes fever, fatigue, loss of appetite, hypersomnia, and depression, has been compared to symptoms observed in patients with cancer [44]. Similar symptom clusters are reported in human studies with experimental stimulation of pro-inflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF- α) [45, 46] and with treatment involving interleukins [47, 48].

Elevated levels of pro-inflammatory cytokines have been reported in patients with cancer who report distressing symptoms prior to treatment [12, 49, 50] suggesting that the tumor microenvironment may influence symptoms via stimulation of cytokines. Tumor cells release norepinephrine which induces increased production of proinflammatory cytokines by tumor-associated macrophages (TAMs) [14]. In addition, breast cancer treatment with surgery, chemotherapy, radiation and hormone therapy is associated with elevated levels of proinflammatory cytokines [51]. IFN- γ , administered for the treatment of a variety of cancers, is associated with fatigue, depression and cognitive dysfunction mediated by activation of indolamine (IDO) which generates cytotoxic kynurenine metabolites [13]. Sustained elevation of IDO during BCA treatment was recently reported among women with early-stage BCA [27].

A subgroup of women with BCA report severe persistent symptoms over the treatment trajectory and in survivorship. Several studies have been conducted to explore the influence of cytokine polymorphisms on symptom patterns in patients with cancer. Both an IL-6 polymorphism and TNF- α promoter polymorphism were associated with sleep disturbance and fatigue in 288 persons with cancer and their care providers [52, 53]. In addition, Collado-Hidalgo *et al.* [54] found a significant relationship between promoter polymorphisms in IL-1beta and persistent fatigue in BCA survivors. Another recent study of

fatigue in BCA survivors reported up-regulation of NF- κ B genes associated with pro-inflammatory transcription factors [55]. Several genes encoding pro-inflammatory cytokines (IL-1A, IL-1B, IL-6, Oncostatin M) and chemokine signaling pathways (CXCL2, CXCR5, CCL20) were also found to be upregulated.

Polymorphisms of genes that regulate inflammation have also been linked with variability in pain perception. The influence of 59 SNPs in 37 inflammation genes on pain severity was recently investigated in 667 newly diagnosed persons with lung cancer [56]. Three SNPs with functional effects on nociceptive transmission were found to be significantly associated with pain severity (*PTGS2* [rs5275], *TNFA* [rs1800629], and *NFKBIA* [rs8904]). In the general population and in specific pain syndromes functional polymorphisms of sensory nerve calcium channels are associated with increased pain perception [57].

Although less studied, anti-inflammatory genetic polymorphisms and their interactions with other polymorphisms may play a role in vulnerability to symptom development and persistence. Gene variants of IL1-receptor 2, IL-10 and TNF- α were associated with depressive symptom trajectories in 167 oncology patients [58]. Along with age and performance status, the polymorphisms predicted membership in a resilient versus subsyndromal classification.

2.4 Oxidative Stress and Telomere Shortening

Breast cancer and treatment with chemotherapy may also contribute to symptom development and persistence through their influence on oxidative stress and telomere shortening. Telomeres are non-coding segments of DNA at the end of chromosomes that prevent the loss of genetic data and protect them from fusing together during cell division [59]. During each cell division a cell loses 30 to 200 base pairs resulting in a gradual decline in telomere length over time, however, factors such as oxidative stress and chemotherapy can accelerate telomere shortening [60]. When the telomere gets shortened to a certain length, this signals senescence and the cell undergoes apoptosis, better known as programmed cell death.

Telomere damage, including shortening and mutations can result from endogenous and exogenous toxic exposures and lead to p53 activation, a major component of DNA repair. However, p53 activation can also impair mitochondrial function [61]. Mitochondrial dysfunction results in the production of reactive oxygen species (ROS) leading to oxidant stress, which further damages pre- and post-telomeric DNA. This cyclical process of DNA damage and mitochondrial dysfunction ultimately results in cellular and metabolic senescence, apoptosis and metabolic changes that are associated with aging and disease, including cancer. In addition, genetic mutations of the telomerase system, which is classically known to maintain and even lengthen telomeres, have also been shown to play a role in stem-cell homeostasis. Without a healthy stem cell reservoir to replenish somatic cells, functional decline of tissues and organs occurs, thus leading to aging [60].

Telomere shortening may be linked with the symptom experience. Associations among mood disorders, including major depression, oxidative stress and accelerated telomere shortening have been reported [62, 63]. However, when telomeres reach a critical stage of shortening and induce cellular senescence, an altered pattern of gene expression can cause the cell to function aberrantly [59]. Although not directly tested, the accumulation of dysfunctional senescent cells in BCA survivors may play a role in symptom persistence. A recent study testing the effect of a psychosocial counseling intervention in cervical cancer survivors found that a longitudinal decrease in perceived stress was not only associated with increased telomere length in peripheral blood mononuclear cells (PBMCs) but also an increase in the naïve T cell population [64]. The results suggest a potential role for such

interventions in cancer prevention and in patients receiving chemotherapy to reduce the rate of telomere attrition and damage.

2.5 DNA Damage

In addition to telomere shortening, oxidative stress is a common cause of DNA damage resulting in single- or double-strand breaks that can increase the risk of cancer [59]. Evidence of oxidative DNA damage has been reported in PBMCs of women with BCA following chemotherapy. In fact, many chemotherapeutic agents achieve their effect by causing DNA damage to block replication of cancer cells and induce apoptosis. Although the goal is to eradicate tumor cells, the DNA in normal cells can also be affected resulting in many of the side-effects observed. As a plausible mechanism of persistent symptoms in cancer survivors, clinical research studies are underway to examine the relationship between DNA damage and the symptom trajectory [49].

Deficiencies in DNA repair mechanisms that increase BCA risk may also contribute to the symptom trajectory through an accumulation of DNA damaged cells. Ataxia Telangiectasia Mutated (ATM) kinase is a protein that acts a master controller of cell cycle checkpoint signaling pathways that are required for cellular response to DNA damage and genome stability. Methylation of the ATM gene is associated with increased risk of BCA [65]. It was recently reported that miR-18a, a microRNA that functions in transcriptional and post-transcriptional regulation of gene expression, impairs the DNA damage response by downregulating ATM kinase [66]. Promoter CpG methylation of glutathione S-transferase 1 (GSTP1) which results in accumulation of oxygen radicals and DNA damage has also been identified as a biomarker of BCA risk [67]. The DOK-7 protein participates in activating the protein MuSK that maintains acetylcholine receptor (AChR) in the neuromuscular junction. Methylation of *DOK-7* has been associated with an increased risk of BCA [68] and may be a plausible mechanism of fatigue, the most frequently reported symptom over the disease trajectory and in survivorship.

3. Outlook

The body of research on symptom clusters in women with BCA suggests that psychological and biological factors are relevant to understanding the symptom experience and trajectory. The proposed conceptual model provides a framework to guide the generation of hypothesis on the mechanisms of symptom cluster phenotypes in women with BCA. It emphasizes the unique stressors confronted by women with BCA including psychosocial stressors arising from the BCA experience, biological stressors from the tumor microenvironment and environmental stressors related to treatment with surgery, chemotherapy, radiation and hormone therapy. Based on a growing body of evidence, the model incorporates potential contributions of genetic and epigenetic factors on stress responses and vulnerability to symptom phenotypes.

Further research to test the relationships posited by the model and examine other gene-gene and gene-environment interactions is needed to advance predictive accuracy and begin the development of interventions to target the pathways contributing to symptom phenotypes. A deeper understanding of the gene-gene interactions and epigenetic modifications that influence symptoms may provide new methods to predict the most effective treatment with the least risk of symptoms. Eventually this information could be used to provide women with BCA more personalized information on their symptom risk profile, which may assist in decision-making regarding treatment options.

Conclusions

Personalized medicine and nursing research share a common goal of improving patient outcomes in women with breast cancer. Recent studies in nursing and other areas of health science suggest there are individual characteristics that influence the patient's symptom experience during and after breast cancer treatment. Although nursing research has been underrepresented in the field of personalized medicine, this knowledge is prerequisite for providing a personalized approach to symptom management. The proposed concepts help, in part, to bring nursing research and personalized medicine together in hopes that this area of research may ultimately lead to the development of more personalized and targeted symptom management strategies.

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List of Abbreviations

AChR	acetylcholine receptor
ATM	Ataxia Telangiectasia Mutated
BCA	breast cancer
CRH	corticotropin releasing hormone
DNA	deoxyribonucleic acid
GR	glucocorticoid receptor
HPA	hypothalamic-pituitary-adrenocortical
IDO	indolamine
IL	interleukin
MR	mineralocorticoid receptor
mRNA	messenger ribonucleic acid
NF_κB	nuclear factor kappa-beta
PBMCs	peripheral blood mononuclear cells
PN	psychoneurological
PNI	psychoneuroimmunology
SNP	single-nucleotide polymorphism
TAM	tumor-associated macrophages
TNF-α	tumor necrosis factor-alpha

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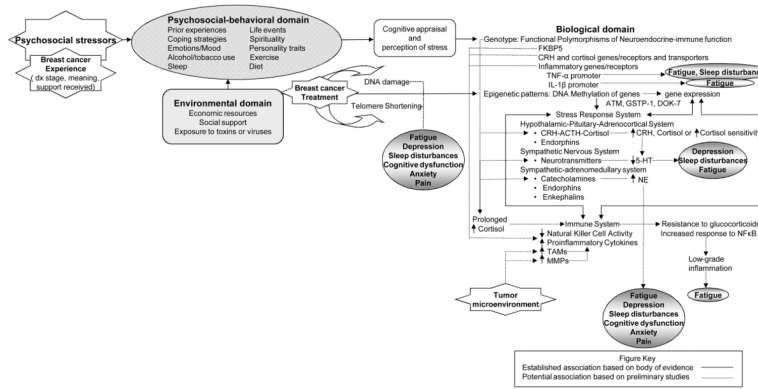


Figure 1. Psychoneuroimmunology Model Integrating Epigenetic and Genomic Factors with a view to personalized medicine in nursing for psychoneurological symptom clusters in women with breast cancer

Genetic polymorphisms that have been associated with specific symptom phenotypes are depicted in the model as well as potential pathways initiated by prolonged stress, BCA treatment and the tumor microenvironment that may lead to symptom clusters. CRH = corticotropin releasing hormone; TNF- α = tumor necrosis factor – alpha; IL-1 β = interleukin 1 – beta; ACTH = adrenocorticotrophic hormone; 5-HT = 5-hydroxytryptamine (serotonin); NE = norepinephrine; TAMs = tumor-associated macrophages; MMPs = matrix metalloproteinases.

Table 1

Genetic polymorphisms associated with psychoneurological (PN) symptom cluster.

Candidate gene; SNP (rs), tSNP numbers, and/or non-SNP polymorphism	PN-based Symptoms	Function	References
<i>HPA Axis Dysfunction: Corticotropin Releasing Hormone and Cortisol genes/receptors; Mineralocorticoid genes/receptors; Monoamine genes/receptors and transporters</i>			
NR3C1; rs10052957, rs6195, rs41423247 rs10482605, rs6189, rs6190, rs6198	Depression Anxiety	Glucocorticoid receptors Increased basal cortisol levels Increased cortisol sensitivity Decreased cortisol sensitivity	[17, 36]
MR; rs2070951, rs5522	Depression	Mineralocorticoid receptor Decreased cortisol sensitivity	[37]
MAOA; functional variable number tandem repeat (VNTR)	Depression	Metabolizes 5-HT and norepinephrine	[18, 19, 59, 60]
SERT (5-HTTLPR); rs25531, rs3794808, functional insertion/deletion	Depression Fatigue Cognitive dysfunction	Serotonin transporter	[18, 37]
<i>Immune Reactivity: Inflammatory genes/receptors</i>			
NFKB; functional insertion/deletion rs8904	Depression, Fatigue Pain	Inflammatory transcription/signaling	[55*, 56]
IL1B -511CT; rs16944	Fatigue	Inflammatory signaling	[54*]
IL-6 -174GC; rs1800795 IL-6 -6101AT; rs4719714	Fatigue	Inflammatory signaling	[52*, 54*]
TNFA -308GA; rs1800629	Fatigue Sleep disturbances Pain	Inflammatory signaling	[53*, 56*]

* research studies that included women with breast cancer