The Psychological Symptom Cluster Among Women with Breast Cancer Before and During Adjuvant Therapy

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Women with breast cancer commonly experience multiple psychological symptoms (i.e., fatigue, depressive symptoms, anxiety) that cluster together throughout their cancer diagnosis and treatment trajectory. Individuals differ substantially in their experience and trajectory of psychological symptoms. A number of factors may contribute to these differences in symptom experience, including demographic and clinical characteristics. In addition, given the contribution of the hypothalamic-pituitary-adrenal (HPA) axis to these contemporaneous symptoms, individual differences in genes that regulate the HPA activity may play a role. This dissertation study aimed to (1) characterize the clustering of psychological symptoms over time among postmenopausal women with early stage breast cancer during the first 18 months of adjuvant therapy, (2) identify distinct subgroups of women with breast cancer based on their experience of a cluster of psychological symptoms , and (3) assess whether distinct demographic and clinical characteristics and variation in genes regulating the HPA axis predict symptom trajectory subgroup membership. This study used symptom and genetic data from postmenopausal women with early stage breast cancer followed from baseline (pre-adjuvant therapy) to 18 months post-initiation of adjuvant therapy. Results showed that most symptom clusters (i.e., psychological, neurocognitive, weight, musculoskeletal, vasomotor, urinary, and sexual) existed before adjuvant therapy and were relatively stable through the first 18 months of adjuvant therapy. The gastrointestinal symptom cluster only appeared at 6 months. Fatigue and symptoms of depression and anxiety clustered

together as a psychological symptom cluster over the 18-month period. Two distinct symptom subgroups ("all low" and "all high") were identified based on the trajectories of fatigue, depressive symptom and anxiety. The "all low" subgroup had stable low severity of fatigue and depressive symptom and a linear decreasing pattern for anxiety over time. The "all high" subgroup had stable high severity of fatigue and depressive symptom and a quadratic pattern for anxiety over time. Women who were younger in age, had less education, and who received chemotherapy had greater likelihood of being in the "all high" symptom subgroup. Variation in genes regulating the HPA axis (i.e., FKBP5 rs9394309, NR3C2 rs5525, CRHR1 rs12944712) were associated with membership in the "all high" symptom subgroup. The results of this study may help to identify women with breast cancer who are at increased risk for psychological symptoms, facilitating the development of individualized and preemptive interventions to better manage their symptoms during adjuvant therapy.

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Preface

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1.0 PROPOSAL INTRODUCTION AND SPECIFIC AIMS

Breast cancer is the most common cancer among women in the United States. In 2018, it was estimated that 266,120 women in the United States were diagnosed with invasive breast cancer (Siegel, Miller, & Jemal, 2018). Approximately 80% of women with breast cancer have hormone receptor positive disease (Lumachi, Santeufemia, & Basso, 2015), and a minimum of 5 years of aromatase inhibitor (AI) therapy is recommended for postmenopausal women with hormone receptor positive, early-stage breast cancer with or without chemotherapy (Rugo et al., 2016).

Many women with breast cancer experience "psychological" symptoms, such as fatigue, depressive symptoms, anxiety and sleep disturbances, which may have a detrimental impact on their functional status and quality of life (QOL) (Garreau, DeLaMelena, Walts, Karamlou, & Johnson, 2006). These psychological symptoms have been reported before and during cancer treatment and can persist years after completion of therapy among women with breast cancer (Albusoul, Berger, Gay, Janson, & Lee, 2017a; Denieffe, Cowman, & Gooney, 2014; Roiland & Heidrich, 2011). Rather than studying single symptoms, emphasis over the past 15 years has focused on symptom clusters. A symptom cluster has been defined as two or more symptoms that co-occur together (Kim, McGuire, Tulman, & Barsevick, 2005). Increasing evidence shows that fatigue, depressive symptoms, anxiety and sleep disturbances usually clustered together among women with breast cancer (Bower et al., 2011; Doong et al., 2015; Ho, Rohan, Parent, Tager, & McKinley, 2015). To date, most symptom cluster studies have used cross-sectional designs and selected predetermined symptoms by identifying the most common symptoms among heterogeneous samples of women with breast cancer receiving differing types of treatment, such as chemotherapy and radiation therapy (Xiao, 2010). Furthermore, most

symptom cluster studies among women with breast cancer have limited their follow-up assessment to one year or less during or after treatment (Albusoul, Berger, Gay, Janson, & Lee, 2017b; Ho et al., 2015; Langford et al., 2016). Few studies have examined how the psychological symptom cluster change over time during long-term endocrine therapy or incorporating a comprehensive assessment of symptoms specific to the experience of postmenopausal women with breast cancer. The trajectory of the psychological symptom cluster during long-term endocrine therapy and factors that may aggravate or alleviate this symptom cluster experience in women with breast cancer has not been fully described. It is also not clear whether there are subgroups of women who are at higher risk for the psychological symptom cluster and whether there are demographic and clinical factors (i.e., age, marital status, income, education level, treatment characteristics, stage of disease) or genotypic factors (i.e., variations in polymorphisms) that may influence the symptom cluster subgroup membership over time. Thus, identifying the psychological symptom cluster associated with adjuvant therapy over time and determining the factors that are related to the psychological symptom cluster trajectories are critical steps in symptom management and ultimately improving women's QOL.

Although the reason for the clustering of the psychological symptoms remains unclear. It is widely suggested that cytokines may play a role, acting on the central nervous system to induce sickness behaviors (Cleeland et al., 2003). Women with breast cancer experience high levels of stress from cancer diagnosis and throughout undergoing cancer treatment (i.e., surgery, chemotherapy, radiation therapy) with the activation of inflammatory response and are at high risk for developing psychological symptoms (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). Peripheral levels of pro-inflammatory mediators are controlled by a number of physiological pathways. Key among them is the hypothalamic-pituitary-adrenal (HPA) axis, which has a

complex and bidirectional relationship with the immune system (Chrousos, 1995). Activation of this pathway and subsequent modulation of levels of pro-inflammatory mediators may contribute to individual differences in vulnerability to clusters of psychological symptoms. In support of this possibility, research shows that disrupted HPA axis activity has been linked with psychological symptoms among cancer patients. Hoyt and his colleagues found that sleep disruption and depressive symptom were related to disrupted cortisol activity (Hoyt, Bower, Irwin, Weierich, & Stanton, 2016). Similarly, another study showed that a symptom cluster of pain, depressive symptom, and fatigue was associated with cortisol and adrenocorticotropic hormone levels among women with breast cancer (Thornton, Andersen, & Blakely, 2010). Prolonged activation of the HPA axis may lead to glucocorticoid receptor resistance and influence the down-regulation of inflammation (Miller et al., 2008). Based on this evidence, variations in genes regulating the HPA axis may influence the heterogeneous experience of symptom clusters among cancer patients.

Therefore, the purpose of this study was to characterize the psychological symptom cluster over time using a comprehensive assessment of symptoms experienced by postmenopausal women with early stage breast cancer during the first 18 months of adjuvant therapy (AI therapy with or without chemotherapy), identify distinct subgroups of women with breast cancer based on their experience of the psychological symptom cluster, and assess whether distinct demographic and clinical characteristics and variation in genes regulating the HPA axis are associated with subgroup membership. Results of this study may help to identify women at higher risk of the psychological symptom cluster during adjuvant therapy. Ultimately, these results may guide effective symptom cluster assessment and serve as a foundation for development of personalized interventions to manage symptoms effectively among women with breast cancer receiving adjuvant therapy.

The specific aims of the proposed study were:

Aim 1: To identify symptom clusters at four time points from baseline (pre-adjuvant therapy) to the first 18 months of adjuvant therapy in postmenopausal women with early stage breast cancer. Exploratory factor analyses were performed at four time points to identify symptom clusters using the data from a study of cognitive function and other symptoms in postmenopausal women receiving the AI, anastrozole, for early stage breast cancer (R01-CA107408). Symptoms were comprehensively evaluated in postmenopausal women with breast cancer pre-adjuvant therapy and at 6-month intervals up to 18-months post-initiation of adjuvant therapy. *We hypothesized that by conducting a comprehensive assessment of symptoms at regular intervals, unique symptom clusters and stable symptoms within the psychological symptom cluster would be identified among women with breast cancer during adjuvant therapy. Symptoms were considered stable if they were identified in the same symptom cluster at least three follow-up assessments.*

Aim 2: To identify distinct subgroups of women with breast cancer based on the severity of the stable symptoms within the psychological symptom cluster from baseline (pre-adjuvant therapy) to the first 18 months of systemic adjuvant therapy. *We hypothesized that at least two distinct subgroups of women with breast cancer would be identified based on temporal pattern of symptom severity trajectories across the set of symptoms for the psychological symptom cluster.*

Aim 3: To explore the relationship between the demographic and clinical factors (age, marital status, employment status, education level, treatment of chemotherapy, stage of disease) and genotypic factors (variations in polymorphisms related to HPA axis disturbance) and predicted subgroup membership based on the severity of the

psychological symptom cluster among women with breast cancer from baseline (pre-adjuvant therapy) to the first 18 months of adjuvant therapy.

1.1 BACKGROUND

1.1.1 Breast cancer prevalence and treatment options

Breast cancer is the most common cancer among women in the United States. In 2018, it was estimated that 266,120 women in the United States would be diagnosed with invasive breast cancer (Siegel et al., 2018). Approximately 80% of women with breast cancer have hormone receptor positive disease (Lumachi et al., 2015). Due to clear benefits in disease-free survival and reduced recurrence, a minimum of five years of third-generation AIs (anastrozole 1 mg tablet once daily, letrozole 2.5 mg tablet once daily or exemestane 25mg tablet once daily) is recommended for postmenopausal women with hormone receptor positive, early stage breast cancer (Buzdar, Robertson, Eiermann, & Nabholtz, 2002; Rugo et al., 2016).

1.1.2 Sickness behaviors and inflammation

Farmers have long recognized that sick animals behave differently from other animals, showing increased lethargy, and reduced interaction with other animals. In the 1960s, Miller systematically evaluated sickness behaviors in animals and suggested that a "factor X" produced by sick animals acted in the brain to cause sickness behavior (Holmes & Miller, 1963). In the 1980s, Hart proposed that sickness behavior was an adaptive response to infection and it was important to host defenses

(Hart, 1988). Later, it was shown that infectious pathogens stimulated mononuclear phagocytic cells and produced a protein (i.e., pro-inflammatory cytokines) to cause sickness behaviors (Kent, Bluthé, Kelley, & Dantzer, 1992). These findings suggested a connection between the immune system and brain. In the 1990s, pathways by which peripheral pro-inflammatory cytokines can access the brain were identified, including neural and humoral routes (Banks, Kastin, & Gutierrez, 1994). In the neural pathway, different afferent nerves (vagal nerve and trigeminal nerve) are activated by cytokines and project to different regions of the brain. In the humoral pathway, circulating cytokines reach the brain through circumventricular organs, leaky regions in the blood–brain barrier or communicate with the brain directly through brain parenchymal cells (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008).

Pro-inflammatory cytokines levels are usually higher among cancer patients as a result of disease processes and cancer treatment. Research shows that interleukin-6 (IL-6), IL-8, IL-10, and tumor necrosis factor alpha (TNF-α) are involved in breast cancer development and metastasis induction (Esquivel-Velázquez et al., 2015). Moreover, it has been reported that breast cancer survivors have increased levels of IL-6 and TNF-α after cancer treatment, including surgery, chemotherapy and radiation therapy (Alfano et al., 2017).

In the last 15 years, the cytokine-induced model of sickness behavior has been applied to cancer populations as a proposed mechanism of the depressive symptoms, anxiety, fatigue, and sleep disturbances that patients often experience (Cleeland et al., 2003). Pain, fatigue, sleep disturbances, anxiety and depressive symptoms commonly cluster among women with breast cancer (Denieffe, Cowman, & Gooney, 2014; Dodd, Cho, Cooper, & Miaskowski, 2010; Doong et al., 2015; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Gehrman, Garland, Matura, & Mao, 2016; Golan-Vered & Pud, 2013; Jaremka et al., 2013; Kim, Barsevick, Beck,

& Dudley, 2012; Kim, McDermott, & Barsevick, 2014; Langford et al., 2016; Li, Gao, Yu, Zhu, & Cao, 2017; Liu et al., 2009; Liu et al., 2012; Moskowitz, Feuerstein, & Todd, 2013; Payne, Piper, Rabinowitz, & Zimmerman, 2006; Sanford et al., 2014; So et al., 2009; Starkweather et al., 2013; Thornton et al., 2010). Among these psychological symptoms, fatigue has been well studied among women with breast cancer. Higher levels of the pro-inflammatory cytokines of IL-6, IL-1ra, and TNF-α were associated with fatigue among breast cancer survivors (Bower, Ganz, Aziz, Fahey, & Cole, 2003; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006). Building on evidence that cytokines contribute to the cluster of sickness behaviors that accompany infectious disease, it has been proposed that the inflammation that accompanies cancer diagnosis and treatment results in similar symptom clusters. Indeed, evidence shows that pro-inflammatory cytokines and cytokine gene polymorphisms are associated with the "psychological" symptom cluster among cancer patients (Doong et al., 2015; Illi et al., 2012; Reyes-Gibby et al., 2013; Starkweather et al., 2013).

1.1.3 Neuroendocrine pathway and symptoms

Different pathways are involved in the control of peripheral levels of inflammation and the HPA axis is one of the primary pathways. Activation of the HPA axis begins with the secretion of corticotropin-releasing factor (CRF) from the hypothalamus CRF binds to the receptors on the anterior pituitary gland and stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH) into peripheral circulation. Finally, when ACTH binds to the receptors on the adrenal cortex, cortisol or glucocorticoid is released. To maintain systemic homeostasis, glucocorticoids can regulate their own production through negative feedback on hypothalamus and pituitary gland (Bonfiglio et al., 2011). Peripheral levels of cortisol play an important role in the control of innate

inflammatory responses by activating glucocorticoid receptors within immune cells. Activation of glucocorticoids receptors results in down-regulation of inflammatory gene transcription and the decreased production and release of pro-inflammatory cytokines (Xavier, Anunciato, Rosenstock, & Glezer, 2016). Under conditions of chronic stress, however, the glucocorticoid receptors become less sensitive to the action of cortisol, possible as a result of prolonged exposure to heightened levels (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). In this situation, activation of the HPA axis is less effective at down-regulating inflammation, and prolonged elevation of peripheral inflammatory mediators is observed. In support of this, consistent data shows and an association of distress with elevated levels of pro-inflammatory cytokines, such as IL-6, TNF-α, and C-reactive protein (CRP) (Doong et al., 2015; Oliveira Miranda et al., 2014; Starkweather, Lyon, & Schubert, 2013; Young, Bruno, & Pomara, 2014).

The disrupted HPA axis has been linked with "psychological" symptoms among cancer patients. Hoyt and his colleagues have found that sleep disruption and depressive symptom were related to disrupted cortisol activity (Hoyt et al., 2016), which implies that HPA axis is the possible underlying mechanism of these symptoms. Another study also found that a symptom cluster of pain, depressive symptom, and fatigue is associated with increased levels of cortisol and adrenocorticotropic hormone among women with breast cancer (Thornton, Andersen, & Blakely, 2010).

1.1.4 Cancer treatment, inflammation and the HPA axis

Research shows that chemotherapy and radiation therapy can increase inflammation in patients with breast cancer because of treatment-related damage to tissue (Grivennikov, Greten, & Karin, 2010). Moreover, the HPA axis can be suppressed by chemotherapy and radiation therapy among

cancer patients (Schmiegelow et al., 2003), which may contribute to increased inflammation. Other factors, such as psychological stress related to cancer diagnosis and cancer treatment, can induce inflammation and disrupt the HPA axis as well (Powell, Tarr, & Sheridan, 2013; Spiegel, Giese-Davis, Taylor, & Kraemer, 2006). Although no study has evaluated the influence of endocrine therapy on inflammation and the HPA axis among women with breast cancer, a significant body of work suggests that higher levels of estrogen have anti-inflammatory effects (Kovats, 2015) and can stabilize the function of the HPA axis (De Nicola, Saravia, Beauquis, Pietranera, & Ferrini, 2006). It is still controversial whether estrogen directly regulates the HPA axis or indirectly regulates the HPA axis through the immune system.

Thus, we propose that as a result of cancer treatments and chronic psychological stress, the HPA axis and innate immune inflammatory response are activated, which have complex and bi-directional communications. Prolonged activation of the HPA axis may lead to decreased glucocorticoid receptor sensitivity and thus increased levels of inflammatory mediators. Therefore, the innate immune system and neuroendocrine system interact together to influence CNS function, and ultimately may contribute to the onset of psychological symptoms (see Figure 1).

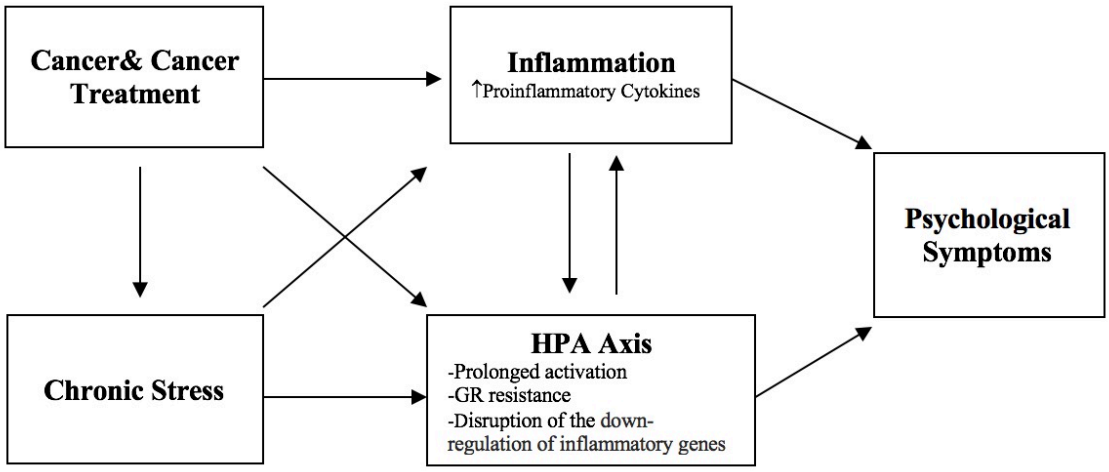

Figure 1 Relationship Among Breast Cancer and Cancer Treatment, Stress, Inflammation, HPA Axis, and Psychological Symptoms

1.2 LITERATURE REVIEW

Two literature reviews were conducted related to 1) the phenotype of the psychological symptom cluster and 2) the biology and impact of genetics related to the HPA axis on the psychological symptom cluster. Three literature databases, PubMed, PsycINFO, and CINAHL, were searched for each review. The terms “breast cancer” and “symptom clusters” or “concurrent symptoms” or “coexisting symptoms” or “multiple symptoms” or “co-occurring symptoms” were used for the review of phenotype of the psychological symptom cluster. A review of functional SNPs of genes associated with the HPA axis in the general population was conducted. Search terms “single nucleotide polymorphism”, “gene” and “HPA axis” were used for the review of functional SNPs of genes associated with the HPA axis in the general population.

1.2.1 Review of phenotype of the psychological symptom cluster

1.2.1.1 Identification of symptom clusters and methodological issues

One of the most common identified symptom clusters among women with breast cancer has been a psychological symptom cluster (Denieffe, Cowman, & Gooney, 2014; Dodd, Cho, Cooper, & Miaskowski, 2010; Doong et al., 2015; Gaston-Jahansson, Fall-Dickson, Bakos, & Kennedy, 1999; Gehrman, Garland, Matura, & Mao, 2016; Golan-Vered & Pud, 2013; Jaremka et al., 2013; Kim, Barsevick, Beck, & Dudley, 2012; Kim, McDermott, & Barsevick, 2014; Langford et al., 2016; Li, Gao, Yu, Zhu, & Cao, 2017; L. Liu et al., 2009; Liu et al., 2012; Moskowitz et al., 2013; Payne, Piper, Rabinowitz, & Zimmerman, 2006; Sanford et al., 2014; So et al., 2009; Starkweather et al., 2013; Thornton, Anderson, & Blakely, 2010). This symptom cluster has been named differently across studies, such as "psychoneurological symptoms" (Kim, McDermott, & Barsevick, 2014; Starkweather et al., 2017), "psychological symptoms" (Langford et al., 2016; Carmen W Sullivan et al., 2018), "emotional symptoms" (Sarenmalm, Browall, & Gaston-Johansson, 2014), "behavioral symptoms" (Bower, 2008; Fagundes, LeRoy, & Karuga, 2015) and "treatment-related symptoms" (Albusoul, Berger, Gay, Janson, & Lee, 2017; Kim, Barsevick, Tulman, & McDermott, 2008). There has been a great deal of variability in the symptoms which constitute the psychological symptom cluster among women with breast cancer. These variations can be attributed to heterogeneous samples across studies and differences in study designs, measurement and analytic approaches.

1.2.1.2 Samples of previous studies

Most previous symptom cluster studies have used a heterogeneous sample combining premenopausal and postmenopausal women with early stage of breast cancer. Only four studies

evaluated symptom clusters exclusively in postmenopausal women (Ho et al., 2015; Sarenmalm, Browall, & Gaston-Jahansson, 2014; Sarenmalm, Ohlen, Jonsson, & Gaston-Johansson, 2007; Roiland & Heidrich, 2011). Sixteen studies evaluated symptom clusters among women receiving adjuvant treatment (chemotherapy, radiation therapy and/or endocrine therapy) (Dodd, Chi, Cooper, & Miaskowski, 2010; Gaston-Jahansson, Fall-Dickson, Bakos, & Kennedy, 1999; Ho et al., 2015; Jaremka et al., 2013; Sarenmalm, Browall, & Gaston-Johansson, 2014; Sarenmalm, Ohlen, Jonsson, & Gaston-Johansson, 2007; Kim, Barsevick, Tulman, & McDermott, 2008; Kim, Barsevick, Beck, & Dudley, 2012; Kim et al., 2009; Kim, McDermott, & Barsevick, 2014; Marshall et al., 2016; Moskowitz, Feuerstein, & Todd, 2013; Roiland & Heidrich, 2011; So et al., 2009; Thornton et al., 2010; Wilmoth, Coleman, & Wahab, 2009), six studies evaluated women before or after surgery (Bender, Ergÿn, Rosenzweig, Cohen, & Sereika, 2005; Denieffe, Cowman, & Gooney, 2014; Doong et al., 2015; Kenefick, 2006; Li, Gao, Yu, Zhu, & Cao, 2017; Starkweather et al., 2013), 14 studies evaluated women receiving chemotherapy (Albusoul, Berger, Gay, Janson, & Lee, 2017; Browall, Brandberg, Nasic, Rydberg, Bergh, Rydén, Xie, Eriksson, & Wengström, 2017; Byar, Berger, Bakken, & Cetak, 2006; Golan-Vered & Pud, 2013; Gwede, Small, Munster, Andrykowski, & Jacobsen, 2008; Hsu et al., 2017; Langford et al., 2016; Liu et al., 2009; Liu et al., 2012; Payne et al., 2006; Phligbua et al., 2013; Sanford et al., 2014; Starkweather et al., 2017; Sullivan et al., 2018), and one study examined women undergoing radiation therapy (Matthews, Schmiege, Cook, & Sousa, 2012). While there are reports of studies examining different symptoms among women with breast cancer during endocrine therapy (Ganz, Petersen, Bower, & Crespi, 2016; Rosenberg, Stanton, Petrie, & Partridge, 2015), only two studies have evaluated symptom clusters among women with breast cancer before or during endocrine therapy (Glaus et al., 2006; Kidwell et al., 2014). Kidwell et al. (2014) indicated that a cluster of

sleep quality, concentration, fatigue, anxiety and depressive symptom was present before AI therapy and these pre-treatment symptoms may negatively influence adherence to AI therapy. Glaus et al. (2006) found that menopausal symptoms (i.e., hot flashes/sweats, tiredness, weight gain, vaginal dryness, decreased sexual interest) and fatigue clustered together among women with breast cancer during endocrine therapy. Since AI therapy is the mainstay of endocrine therapy for postmenopausal women with hormone receptor positive disease, and experts emphasize the importance of homogenous samples in terms of cancer treatment in symptom clusters research as a research priority (Barsevick, 2016; Miaskowski, 2016), more studies are needed to identify the unique symptom clusters experienced by postmenopausal women during AI therapy.

1.2.1.3 Methodologies in previous studies

To date, there have been two main approaches to examine symptom clusters (Miaskowski, 2016). One approach is to select predetermined symptoms by identifying the most common symptoms experienced from previous studies. Correlations among symptoms, using concurrent symptoms and identification of subgroups of patients with similar symptom experiences were commonly used to identify "clusters of symptoms" or "clusters of patients" in this approach. Dodd et al. (2010) used cluster analysis and identified four subgroups based on a pre-determined symptom cluster of pain, fatigue, sleep disturbances, and depressive symptom. The other approach is to examine a comprehensive list of symptoms which may be experienced and identify clusters through analytic techniques such as exploratory factor analysis (EFA), or identification of subgroups of patients with similar symptom experiences. Using this analytic strategy, Kim et al. (2008) identified psychoneurological and upper gastrointestinal (GI) symptom clusters from 20 symptoms commonly experienced by women with breast cancer. Subsequently, Kim et al. (2014) identified three subgroups of women based on their experience of the psychoneurological cluster

using the same sample from previous study. Browall et. al (2017) identified physical, GI and emotional symptom clusters among women with breast cancer during chemotherapy. Subgroups of patients with similar symptom experiences can be identified from a comprehensive list of symptoms with this second approach by using group-based trajectory modeling or latent class growth analysis. Gwede et. al (2008) identified “high-symptom burden” and “low symptom burden” subgroups using 23 symptoms experienced by women with breast cancer.

For the “predetermined symptoms” approach, although there is evidence and background to support the appearance of a predetermined set of symptoms and their shared biological mechanisms, given the fact that symptoms may change over time and different symptoms can be associated with different treatments, some important symptoms may be overlooked. The second approach is more empirically-based and reliable because it takes into consideration a comprehensive list of symptoms that may be experienced. More symptom clusters may be found compared to the approach using a predetermined set of symptoms. Therefore, more studies with larger sample sizes are needed to identify symptom clusters using a comprehensive list of symptoms.

1.2.1.4 Changes in symptom cluster over time

Evidence documenting how symptom clusters change over time is inconsistent across studies. An increasing number of studies have found that symptom clusters are dynamic over time during and after the conclusion? of treatment (Albusoul, Berger, Gay, Janson, & Lee, 2017; Hsu et al., 2017; Kenefick, 2006; Sanford et al., 2014; Starkweather et al., 2017). For example, symptoms clusters were more changeable over the first six months after initiating chemotherapy in women with breast cancer (Starkweather et al., 2017). Symptom distress declined slowly from discharge to six months post-discharge, after surgery (Kenefick, 2006). Other studies have found that the psychological

symptom cluster is relatively stable over time with minor changes in the number of symptoms and the specific symptoms within each symptom cluster (Kim et al., 2009; Sullivan et al., 2018). Most longitudinal studies of symptom clusters are among women with breast cancer during chemotherapy. The literature has not featured any studies that examined changes in the psychological symptom cluster over time during long-term AI therapy.

1.2.1.5 Identification of subgroup membership and their correlates

It is not clear whether subgroups of women with breast cancer exist based on their experience of the psychological symptom cluster during long-term AI therapy (with or without chemotherapy). Among women with breast cancer, the variability of the experience of psychological symptom cluster has been reported between individuals during other treatments. For example, different patient subgroups (all low, mild, moderate, all high) were found based on the experience of pain, fatigue, sleep disturbances, depressive symptom among women with breast cancer during receiving chemotherapy (Kim, McDermott, & Barsevick, 2014). However, no studies to date have examined subgroups of women who are at risk for higher severity of psychological symptom cluster during AI therapy.

Once subgroups are identified, it is important to understand individual susceptibility to symptoms by identifying the demographic, clinical and genotypic factors related to membership in those symptom cluster subgroups. This critical information may be used to identify women who are at high risk for greater symptom severity and help nurses to provide personalized symptom management care. Research suggests that previous cancer treatment, pre-treatment symptom severity, chemotherapy use, advanced disease stage, younger age, higher education level, lower income, less likely to be employed and less likely to be married are associated with higher severity of symptom clusters (Dodd, Cho, Cooper, & Miaskowski, 2010; Gehrman,

Garland, Matura, & Mao, 2016; Kim, Barsevick, Tulman, & McDermott, 2008; Kim, Barsevick, Beck, & Dudley, 2012; Kim et al., 2009; Langford et al., 2016; Liu et al., 2009). All the above studies examining the demographic and clinical factors associated with the psychological symptom cluster were among women with breast cancer receiving chemotherapy, radiation therapy or after surgery. To date, no studies have examined the demographic, clinical and genotypic factors associated with the psychological symptom cluster among women with breast cancer receiving endocrine therapy.

1.2.2 Review on biology and impact on genetics on the psychological symptom cluster

The mechanisms underlying the psychological symptom cluster among women with breast cancer are not entirely clear. For the past 15 years, researchers have explored the mechanism of cancer symptoms using the cytokine-induced sickness behavior model (Cleeland et al., 2003). It is widely proposed that inflammation plays a role in the induction of sickness symptoms. Given the role of the HPA axis in the modulation of inflammatory processes, we propose that the disruption of HPA axis may also contribute to the experience of symptoms. Only two studies have evaluated the relationship between hormones related to the HPA axis and symptom clusters among breast cancer patients. The psychological symptom cluster has been shown to be positively associated with HPA biomarkers and neuroendocrine hormones (Payne et al., 2006; Thornton et al., 2010). Payne et al. (2006) conducted a pilot study among 22 women with breast cancer receiving chemotherapy and found a positive association between HPA biomarkers (melatonin, bilirubin, cortisol, serotonin) and fatigue, sleep disturbances, and depressive symptoms. Later, Thoronto et al. (2010) evaluated the sympathetic nervous system and HPA axis, and found that four neuroendocrine hormones (cortisol, adrenocorticotropic hormone,

epinephrine, norepinephrine) were positively related to a symptom cluster of pain, fatigue and depressive symptom. Additional research is warranted to confirm this mechanism. Thus, it is important to explore the biological mechanism related to the disrupted HPA axis underlying the psychological symptom cluster among women with breast cancer receiving adjuvant therapy.

In 2016, NINR established a National Institutes of Health Symptom Science Model (Cashion & Grady, 2015) to lead symptom science and emphasize the importance of implementation of genomics and "omics science" in developing strategies for personalized symptom prediction and management. Based on the evidence that genetic variability in cytokine genes may influence the experience of psychological symptoms among cancer patients (Doong et al., 2015;Illi et al., 2012), and genetic variability related to the HPA axis may influence the experience of depressive symptoms, anxiety and sleep disturbance in other populations (Buttenschøn et al., 2017; Jiang et al., 2016; Suzuki et al., 2014), more studies are needed to clarify additional biological mechanisms and explore the impact of genetic variability related to the HPA axis on the psychological symptom cluster in women with breast cancer.

Based on knowledge that the HPA axis plays a key role in the control of peripheral levels of proinflammatory mediators that communicate with the central nervous system to coordinate comorbid psychological symptoms, we focused only on genes and SNPs that directly relate to the HPA axis. A review of functional SNPs of genes associated with the HPA axis in the general population was conducted. Search terms "single nucleotide polymorphism", "gene" and "HPA axis" were used in the initial search, which identified 33 genes and 118 SNPs. We then employed a review of the literature to arrow our examination of genes to those that play a role in HPA regulation (Arnett, Muglia, Laryea, & Muglia, 2016). Genes related to glucocorticoid receptors (NR3C1, FKBP5), mineralocorticoid receptor (NR3C2), and corticotropin-releasing hormone

(CRHR1, CRHR2, CRHBP) were identified. Finally, a list of 51 functional SNPs in these 6 genes were selected (See Table 1).

Table 1 Proposed Single Nucleotide Polymorphisms Associated with the Hypothalamic Pituitary Adrenal Axis

Gene	Name	Function	SNP
NR3C1	Glucocorticoid receptor, GR	Receptor for glucocorticoids, function as a transcription factor that binds to glucocorticoid response elements, and as a regulator of other transcription factors; affects immune and inflammatory responses, reproduction, central nervous system, cardiovascular function, cellular proliferation and differentiation in target tissues (Siamatras & Stratakis, 2016); regulates negative feedback of the HPA axis (Laryea, Muglia, Arnett, & Muglia, 2015); NR3C1 mutation can cause glucocorticoid resistance (Vitellius et al., 2016). Polymorphisms in NR3C1 are associated with depression (Schatzberg et al., 2014).	rs41423247
			rs258747
			rs10482605
			rs1800445
			rs6191
			rs258813
			rs33388
			rs10052957
			rs6198
			rs6195
			rs6189
			rs6190
			rs1866388
			rs8192496
			rs2267715
CRHR2	Corticotropin Releasing Hormone Receptor 2	High affinity for CRH, binds to both CRH and urocortin. CRH involved in coordinating the endocrine, autonomic, and behavioral responses to stress and appetitive behaviors (RefSeq, 2011). Activation of CRHR2 is related to anxiety, and memory deficit under stress (Todorovic et al., 2007).	rs2284218
			rs255098
			rs3779250
FKBP5	FK506 Binding Protein 5	Co-chaperone of hsp90 and modulates GR sensitivity. Polymorphisms in FKBP5 are associated with differences in GR sensitivity, stress hormone system regulation (Binder, 2009), and mood disorders (O'Leary et al., 2013).	rs1360780
			rs3800373
			rs9470080
			rs4713916
			rs9296158
			rs9394309
			rs3777747
			rs17542466
			rs2766533
			rs9380526
			rs9394314

			rs2817032
			rs2817040
			rs7753746
			rs4713902
			rs7748266
			rs7757037
CRHR1	Corticotropin Releasing Hormone Receptor 1	Binds CRH, major regulators of HPA axis following chronic stress (Ramot et al., 2017). The encoded protein is essential for the activation of signal transduction pathways that regulate diverse physiological processes including stress, reproduction, immune response and obesity (RefSeq, 2016).	rs17689918
			rs28364032
			rs4458044
			rs242924
			rs1768996
			rs12944712
			rs12938031
			rs4792887
			rs1396862
			rs878886
			rs17763104
			rs110402
			rs242948
			rs1876828
			rs17689882
			rs12936511
			rs242939
			rs1876831
NR3C2	Mineralocorticoid receptor, MR	Receptor for both mineralocorticoids (MC) and glucocorticoids (GC). Binds to mineralocorticoid response elements (MRE) and transactivates target genes. Variation in NR3C2 and polymorphisms are associated with depression (Vinkers et al., 2015), cognitive abilities (Keller et al., 2017), blood pressure and hypertension (van Leeuwen et al., 2010).	rs5525
			rs4835488
			rs10213471
			rs17484245
			rs7694064
			rs2070951
			rs10473984
CRHBP	Corticotropin Releasing Hormone Binding Protein	Regulating glucocorticoid reactivity in response to stress; prevents inappropriate activation of CRH by binding the CRH complex; regulates physiological reactions, metabolic function and oncogenesis (Borowski et al., 2015; Nan, Dorgan, & Rebbeck, 2015)	rs7718461
			rs1875999

1.3 PRELIMINARY STUDY

Symptom Clusters in Women with Breast Cancer Before Adjuvant Therapy (Li, Sereika, & Bender, 2018)

This was a secondary analysis of symptom data collected at baseline (before adjuvant therapy) from an IRB approved prospective repeated measures study of cognitive function in postmenopausal women receiving the AI, anastrozole, for early stage breast cancer (R01-CA107408) (Bender et al., 2015). To identify the symptom clusters prior to initiation of adjuvant therapy (baseline), the secondary analysis included 334 postmenopausal women with breast cancer who would receive AI therapy only (n=212) and who would receive chemotherapy followed by AI therapy (n=122). We used information on 47 symptoms collected prior to adjuvant therapy, obtained from a comprehensive battery of symptom assessment tools. Following identification of the prevalence of individual symptoms, distinct symptom clusters were determined by conducting exploratory factor analysis using principal axis factoring as the extraction method with the promax rotation method. The most prevalent individual symptoms were perceived cognitive impairment (98.8%), followed by anxiety symptoms (97.6%), depressive symptoms (83.9%), fatigue (81.5%), general aches and pains (73.7%), and breast sensitivity (72.2%). Five distinct symptom clusters were identified: neurocognitive, musculoskeletal, psychological, hormonal, and urinary (see Table 2).

Table 2 Symptoms within each symptom cluster before adjuvant therapy

Symptom Cluster	Symptoms in the Cluster	Symptom Cluster	Symptoms in the Cluster
Neurocognitive	Difficulty concentrating	**Psychological**	Fatigue
	Easily distracted		Tendency to take naps
	Forgetfulness		Avoidance of social affairs
	Perceived cognitive function		Depressive symptoms
	Excitability		Tension-anxiety
Musculoskeletal	General aches and pains Joint Pain	**Urinary**	Difficulty with bladder control at other times

	Muscle stiffness Pain		Difficulty with bladder control when laughing or crying
		Hormonal	Hot flashes
			Night sweats

Distinct symptom clusters were present among women with breast cancer before adjuvant therapy. Results of this study suggests that the psychological symptom cluster, which consists of fatigue, depressive symptoms, tension-anxiety, tendency to take naps, and avoidance of social affairs, was highly prevalent and existed among women with breast cancer before they began adjuvant therapy. This preliminary study provided the foundation for our investigation of the psychological symptom cluster and change in this symptom cluster over the first 18 months of adjuvant therapy. Furthermore, it is critical to examine whether baseline symptom severity is associated with the severity of symptom clusters or AI discontinuation at after 12 months and 18 months of AI therapy for future studies.

1.4 THEORETICAL FRAMEWORK

The Symptoms Experience Model (SEM) proposed by Armstrong (2003) is a comprehensive theory that is useful in guiding research about symptom clusters and it will be used to guide this study focusing on the identification of symptom clusters, and the predictors and subgroup membership of the predicted psychological symptom cluster trajectories (see Figure 2). In this model, symptom is conceptualized as the "perception of the frequency, intensity, distress, and meaning occurring as symptoms are produced and expressed" (Armstrong, 2003, p602). According to Armstrong (2003), symptoms are usually "being influenced by the occurrence attributes of other symptoms" and seldom occur alone. Women with breast cancer may experience multiple symptom clusters with disease or treatment. Consistent with this model, we

measured symptom frequency/prevalence and symptom severity experienced by women with breast cancer during AI therapy.

The SEM has three components, antecedents, symptoms/symptom clusters, and consequences. Antecedents can be categorized into demographic (i.e., age, marital status, race and education), clinical (i.e., stage of disease, pre-treatment symptom severity, whether received chemotherapy) and genotypic (i.e., polymorphisms of genes related to HPA axis disturbance) factors. Consequences include adjustment to illness, quality of life, mood, functional status, disease progression and survival. From the SEM's perspective, symptoms are multidimensional with different frequencies, intensities and distress levels. Multiple symptoms may occur together, and antecedents, symptoms and consequences can influence and interact with each other.

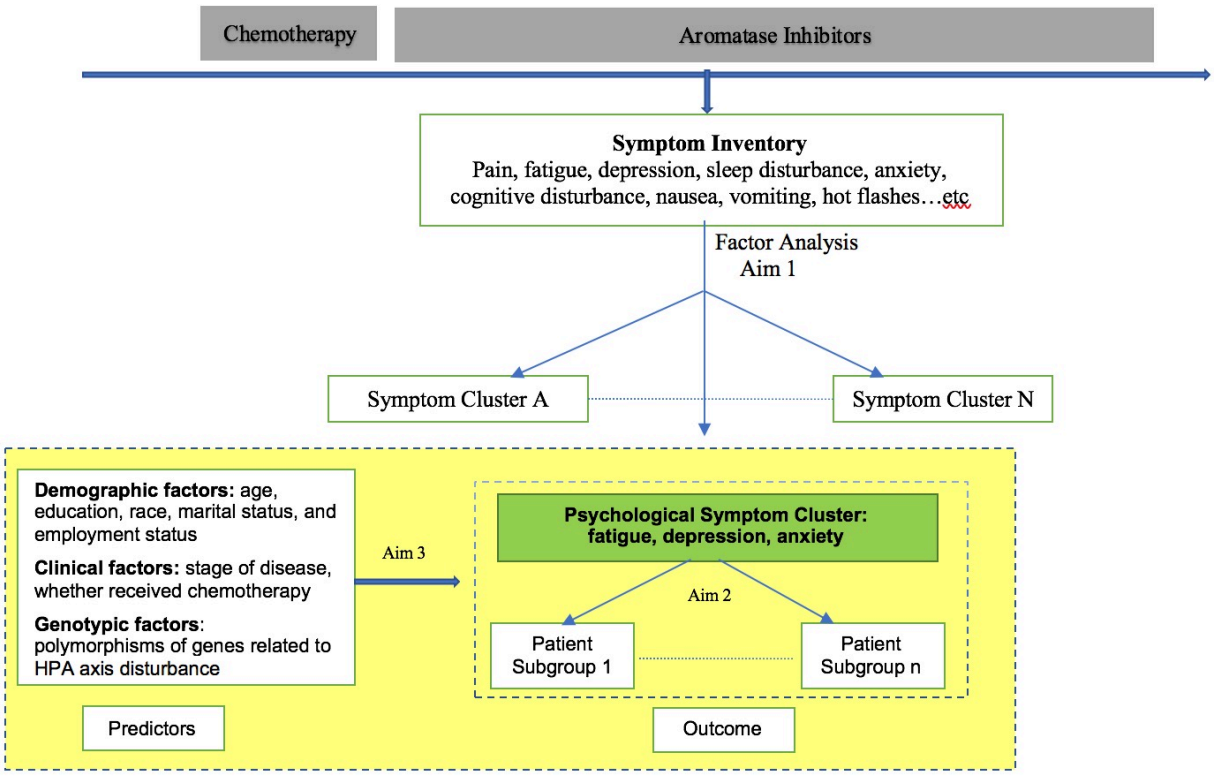

Figure 2 Conceptual Framework of the Proposed Dissertation Study

1.5 SIGNIFICANCE AND INNOVATION

1.5.1 Significance

In the United States, the median age at diagnosis among women with breast cancer is 62 years (American Cancer Society, 2015), which means that most women with breast cancer are postmenopausal at diagnosis. AI therapy is the mainstay of endocrine therapy for postmenopausal women with hormone receptor positive disease (Rugo et al., 2016).

Great emphasis has been placed on symptom cluster research within last 15 years. Women with breast cancer usually experience multiple co-occurring symptoms or symptom clusters with treatment (Nguyen et al., 2011). The psychological symptom cluster, which usually comprises fatigue, depressive symptoms, anxiety and sleep disturbances, has been reported before and during cancer treatment among women with breast cancer (Ho et al., 2015; Kim, Barsevick, Tulman, & McDermott, 2008). This symptom cluster has a negative impact on women's functional status and can compromise their QOL (Dodd, Miaskowski, & Paul, 2001). However, most symptom cluster studies have evaluated this cluster during chemotherapy and radiation therapy among women with breast cancer. Few studies have conducted a comprehensive assessment of co-occurring symptom clusters during adjuvant endocrine therapy, especially AI therapy. Little evidence exists regarding subgroups of women who may be at greater risk for higher severity of the psychological symptom cluster during AI therapy and the demographic, clinical, and genotypic factors that characterize them. Identifying patterns of symptom presentation during AI therapy and individuals who are most vulnerable to severe symptom clusters can facilitate preemptive interventions to manage symptoms together and ultimately improve adherence to AI therapy and QOL for patients.

This proposed study will also help us determine the demographic, clinical and genotypic risk factors associated with the psychological symptom cluster. The results of this work will (1) help nurses and healthcare providers to identify and screen women with breast cancer who are at higher risk of greater severity of psychological symptom cluster and (2) serve as a foundation for the development of individualized interventions to better manage those symptoms effectively among women with breast cancer receiving adjuvant therapy. The association between genes, polymorphisms and symptoms will provide further support for the role of HPA axis mechanism in the clustering of psychological symptoms.

This study fits well with the mission of National Institute of Nursing Research (NINR) in 2016—promoting personalized health strategies and examination of the underlying mechanisms of symptoms experienced by individuals with cancer (Grady, 2017) and the call from NINR for Symptom Cluster Characterization in Chronic Conditions (PA-17-462). Moreover, symptoms in the psychological symptom cluster are aligned with the top priority symptoms (i.e., fatigue, pain, sleep disturbance, cognitive impairment, chemotherapy-induced peripheral neuropathy and psychological distress) identified by the Oncology Nursing Society (Knobf et al., 2015).

1.5.2 Innovation

The proposed study is innovative because it will be the first study to extend the description of symptom clusters over time, identify subgroups of women based on their experience of the psychological symptom cluster and explore its demographic, clinical factors and genotypic predictors among women with breast cancer from pre-adjuvant therapy through the first 18 months of adjuvant therapy (AI therapy with or without chemotherapy). It uses a more reliable and empirically sound approach to identify symptom clusters by evaluating 48 symptoms that

may be experienced by women receiving adjuvant therapy with a broad symptom assessment. Most previous studies have used selected predetermined symptoms based on the most common symptoms reported in the literature; therefore, some important symptoms may be overlooked. Lastly, it will be the first study to explore the association between variations in gene polymorphisms related to the HPA axis disturbance and trajectory subgroup membership based on the intensity of the psychological symptom cluster among women with breast cancer.

1.6 RESEARCH METHODS

1.6.1 Study design

This is an analysis of existing symptom data and newly generated genomic data from a prospective cohort repeated measures study of cognitive function in postmenopausal women receiving the AI, anastrozole, for early stage breast cancer (R01-CA107408) (Bender et al., 2015). The current study will include two groups of postmenopausal women with early stage breast cancer who have completed surgery: women who were prescribed either anastrozole therapy only (AnastOnly) and women prescribed chemotherapy followed by anastrozole therapy (ChemoAnast). Symptom data were collected every 6 months from baseline (pre-adjuvant therapy) to 18-months post initiation of adjuvant therapy (see Table 3). Genetic data were collected via blood or saliva samples.

Table 3 Symptom Assessments by Time Point

Group	Pre-chemo	Chemotherapy	Pre-AI	6 Months AI	12 Months AI	18 Months AI
ChemoAnast	X (baseline)	Yes	X	X	X	N/A
AnastOnly	N/A	No	X (baseline)	X	X	X

Note: All women with breast cancer completed the baseline assessment after primary surgery but prior to any adjuvant therapy. For women in the ChemoAnast group, baseline is before chemotherapy. For women in the

AnastOnly group, baseline is before anastrozole therapy. Women in the ChemoAnast group completed follow-up symptom assessments after chemotherapy but prior to anastrozole therapy, 6, and 12 months after the initiation of anastrozole. Women in the AnastOnly group completed follow-up symptom assessments at 6, 12, and 18 months after the initiation of anastrozole therapy.
Note: AI: aromatase inhibitor; AnastOnly: women prescribed anastrozole therapy only; ChemoAnast: women prescribed chemotherapy followed by anastrozole therapy.

1.6.2 Setting and recruitment

Women with breast cancer were recruited from the Breast Cancer Program of the Hillman Cancer Institute, consisting of Magee-Women's Hospital, Hillman Cancer Center, and Shadyside Hospital from 2005 to 2015. The original study was approved by the University of Pittsburgh Institutional Review Board, all participants provided written informed consent. This study will be sent to the University of Pittsburgh Institutional Review Board to obtain approval.

A total of 354 women with breast cancer (127 ChemoAnast and 227 AnastOnly) were enrolled in the study. Inclusion criteria included: (1) women newly diagnosed with stage I, II or IIIA breast cancer; (2) ≤75 years of age; (3) postmenopausal; (4) scheduled to receive chemotherapy plus anastrozole or anastrozole alone; (5) able to speak and read English; and (6) completed a minimum of 8 years of education. Exclusion criteria included: (1) self-report of hospitalization for psychiatric illness within the last 2 years; (2) prior diagnosis of neurologic illness, such as stroke, multiple sclerosis, dementia syndrome, or Parkinson’s disease, or of HIV-related dementia, or chronic fatigue syndrome; 3) prior diagnosis of cancer; or 4) clinical evidence of distant metastases.

1.6.3 Sample size justification

This study was a secondary analysis of data and blood/saliva samples collected from women with breast cancer receiving AI therapy who participated in the AIM study and hence the sample size for this study is fixed. For Specific Aim 1 to identify symptom clusters for women with breast cancer receiving AI therapy, the recommendation of minimum sample size in exploratory factor analysis is 100 (MacCallum, Widaman, Zhang, & Hong, 1999), with the criteria "100 = poor, 200 = fair, 300 = good, 500 = very good, ≥1000 = excellent" (Comrey & Lee, 2013) and the participant-to-variable ratio being at least 5 (MacCallum et al., 1999). The sample size was sufficient to conduct the EFA at baseline (N=354, 354/48=7.4) and 6 months (N=288, 288/48=6). Even though based on the rule of thumb, we lost some precision to conduct the EFA at 12 (N=205, 205/48=4.2) months and 18 (N=162, 162÷48=3.4) months, the minimum sample size for exploratory factor analysis is also dependent on other factors, such as the communality of the variables, size of factor loadings, and degree of over determination of the factor (MacCallum et al., 1999; Preacher & MacCallum, 2002). To increase the precision to conduct the EFA, we made sure the communality of the variables should be greater than 0.60, symptom-total correlations must be greater than 0.25 (Ferketich, 1991), a minimum of two variables per factor and each factor should have loadings higher than 0.40 (Browne, 2001). Participants who have symptom data for at least two time points from baseline (T0) to 18 months (T3) after adjuvant therapy (N=292) were included to measure within-person symptom trajectories for Specific Aim 2. Literature on trajectories of psychological symptoms or symptom clusters among women with breast cancer suggest that the number of subgroups based on similarities in their experience of symptom clusters may range from two to five (Avis, Levine, Case, Naftalis, & Zee, 2015; Bidstrup et al., 2015; Comrey & Lee, 2013; Donovan, Gonzalez, Small, Andrykowski, & Jacobsen, 2013; Park, Chun,

Jung, & Bae, 2017; Sanford et al., 2014). Among different depressive or anxiety symptom trajectory studies, linear or quadratic polynomial trajectories are the most common trajectories identified. A minimum trajectory group size of 47 is required to estimate a reliable quadratic trajectory (Avis, Levine, Case, Naftalis, & Zee, 2015; Murphy et al., 2015; Rottmann et al., 2016), which is 16% (47/292=16%) of the sample size available for this proposed study. Thus the sample size is much higher than the recommended group membership probability of 5% based on the group size of 292 (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009). Since the suggested number of subgroups ranged from two to five, we had sufficient sample size to estimate maximum of five quadratic trajectories.

For Specific aim 3, data was analyzed in an exploratory manner using logistic regression among women with breast cancer who also have a genetic sample and symptom data (n=167).

1.6.4 Measures

1.6.4.1 Demographic and clinical characteristics

Self-reported demographic (e.g., age, race, education level, occupation type, marital status) and clinical (disease stage, and types of treatments) characteristics of participants were collected at baseline.

1.6.4.2 Symptoms

A comprehensive battery of measures was used to assess the symptoms that participants experienced before and every 6 months through the first 18 months of adjuvant therapy. To standardize the scaling of symptom scores among the instruments used, the symptom scores will be transformed to a 0-100 scale. Of the 47 symptoms evaluated, 42 symptoms were assessed

with the Breast Cancer Prevention Trial (BCPT) Symptom Checklist (Stanton, Bernaards, & Ganz, 2005), while the remaining 6 symptoms (fatigue, changes in sleep pattern, anxiety symptoms, general pain, depressive symptoms, and perceived cognitive impairment) were assessed using the Profile of Mood States (McNair, Lorr, & Droppleman, 1992) (POMS; fatigue, anxiety), Brief Pain Inventory-Short Form (Cleeland & Ryan, 1994) (BPI; pain), Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) (BDI-II; depressive symptoms), and Patient's Assessment of Own Functioning (Chelune, Heaton, & Lehman, 1986) (PAOFI; perceived cognitive ability).

Two subscales of the POMS (Fatigue/Inertia subscale and Tension/Anxiety subscale) were used to measure fatigue and anxiety. The POMS is a self-report measure of mood states, with 65 items rated on a 5-point Likert scale format from 0 (not at all) to 4 (extremely) (McNair et al., 1992). The POMS-Fatigue/Inertia subscale has 7 items, with a test-retest reliability of .66 and internal consistency of .94 (McNair et al., 1992). The POMS-Tension/Anxiety subscale has 9 items, with an internal consistency of .92 and test-retest reliability of .70 (McNair et al., 1992). Higher average fatigue and anxiety subscale scores (range 0-4) indicate greater severity of fatigue and anxiety.

The BPI-short form was used to measure pain. The BPI consists of 9 items assessing pain intensity, pain relief treatment or medication and pain interference (Cleeland & Ryan, 1994). It has well-established reliability and validity to assess pain among patients with cancer (Caraceni, 2001; Tittle, McMillan, & Hagan, 2003). For this study, 4 items related to pain intensity ranging from 0 (no pain) to 10 (pain as bad as you can imagine) were used. Higher average pain intensity scores indicate severe pain.

The BDI-II, is a 21-item, self-report measure of depressive symptom severity and items are rated on a 4-point Likert scale from 0 (no symptom) to 3 (severe symptom) (Beck et al., 1996). High reliability and validity have been demonstrated for the BDI (Wang & Gorenstein, 2013). The BDI-II measures somatic symptoms (items 15-21) and mood/cognitive symptoms (items 1-14) (Thombs et al., 2010). For this study, a total score of items 1-14 was used to measure depressive symptoms to avoid the influence of other treatment-related symptoms. Higher total scores of the 14 items indicate more severe depressive symptoms. Item 16 from BDI-II (changes in sleep pattern) was used to measure the severity of changes in sleep pattern.

The PAOFI, is a 33-item self-report measure of subjective perceived cognitive impairment, rated on a 6-point scale range from 0 (almost never) to 5 (almost always) (Chelune et al., 1986). The PAOFI has been used in studies among women with breast cancer (Ganz et al., 2014; Pullens, De Vries, & Roukema, 2010), with evidence for construct validity and reliability (Bell, Terhorst, & Bender, 2013). Higher average scores indicate poorer perceived functioning.

The BCPT is a self-report measure of symptoms related to endocrine therapy comprised of subscales including cognitive symptoms, musculoskeletal pain, vasomotor symptoms, gastrointestinal symptoms, dyspareunia, bladder control, weight concerns, and gynecologic symptoms (Stanton, Bernaards, & Ganz, 2005). It has 42 items rated on a 5-point Likert scale, from 0 (not at all) to 4 (extremely). Higher scores of each item indicate greater symptom severity. Only 41 BCPT items were used in this study, item 33 (tendency to take naps) was deleted for the analysis because of its strong correlations with fatigue and depressive symptoms.

1.6.4.3 Genotype data

Among participants who provided a blood sample (n=283), genomic deoxyribonucleic acid (DNA) was extracted from white blood cells by the simple salting-out method (Miller, Dykes, & Polesky,

1988). If blood was unavailable, DNA was extracted from saliva using prepIT•L2P (Genotek, 2016). Samples were genotyped using the iPLEX MassArray platform with proven accuracy (>99.7% concordance rate). As shown in Table 1, a total of 51 functional SNPs were selected for analysis. To control quality for genetic association analysis, SNPs with call rates of <95% or Hardy-Weinberg Equilibrium p-values of <.05 were excluded.

1.6.5 Data analysis

1.6.5.1 Descriptive statistics

Data was analyzed using SAS 9.4 (SAS Institute, North Carolina). Given a variable's level of measurement and data distribution, appropriate descriptive analyses were used to summarize the demographic, clinical, genetic characteristics and the prevalence of each symptom and the mean symptom severity score.

To describe central tendency for ratio variables (e.g., age, education level), mean and standard deviation (SD) were used for normally distributed variables. If the normality assumption was not satisfied, median and interquartile range (IQR) were used. For describing nominal variables, we used frequency and percentage and the mode to summarize central tendency and the range to summarize the variability. We used symptom severity score to describe symptoms. The symptom severity score was calculated as the mean of the symptom score.

1.6.5.2 Data screening procedures

Outliers were assessed by frequency distribution, z-scores and the Mahalanobis Distance. For continuous variables, univariate outliers can be identified by transforming the data into z-

scores. If z-score is greater than +3.29 or less than -3.29, a case can be considered as a univariate outlier (Tabachnick, Fidell, & Ullman, 2007). Multivariate outliers can be identified using Mahalanobis Distance (Mahalanobis, 1936), if the value for the Mahalanobis distance was significant beyond $p<0.001$. For categorical variables, we looked at frequency distribution and examined whether there were sparsely populated categories.

For the treatment of missing data, first, we explored the data and checked the amount of missing data by looking at the percentage of cases having any missing data, distribution of univariate, multivariate, and bounded missing data. Then, the pattern of missing data was checked by exploring the occurrence of missing data by variable and by participant and their combination at each time point and over time points. From these results, we could identify univariate missing or multivariate missing, missing completely at random (MCAR), missing at random (MAR) or missing not at random. If an observation was missing not at random, and if that participant was missing more than 50% of items within one symptom scale, we deleted that participant. For cases of MAR and MCAR, multiple imputation was used to handle missing data for EFA. Missing values were estimated multiple times based on the amount of the missing data. Estimates from analyses from each completed dataset were pooled into one estimate.

Group-based trajectory modeling (GBTM) handles missing data by fitting the model using maximum likelihood estimation. Data were assumed MAR for GBTM. Since we have up to four time points for each participant. We included those who had data collected at two or more times, and exclude those with fewer than two.

Multiple underlying assumptions were checked before the analysis, such as independence, linearity, multicollinearity, and homoscedasticity. Independence is a primarily a design issue. To check independence between participants, we can go back to the study design and check whether

participants are independent of each other. If data were collected from family members or in a time trend, the assumption of independence was violated.

Linearity was assessed by inspecting simple bivariate scatterplots of predictors and dependent variables. Multicollinearity occurs when variables are highly correlated (Hahs-Vaughn, 2016). Tolerance test or variance inflation factors (VIF) were used to assess for multicollinearity. The recommended maximum VIF value is 5 (Rogerson, 2001). The assumption of homoscedasticity is a necessary condition for the assumption of normality (Tabachnick, Fidell, & Osterlind, 2001). This assumption was examined by scatterplots of variables. Points are about the same distance from the line in a consistent pattern suggest variances are constant. If homoscedasticity was not found, then transformations (variance of stabilizing) of variables were considered.

1.6.5.3 Aim-specific data analysis strategies

Aim 1: EFA was conducted using principal axis factoring (PAF) as the extraction method with the promax rotation method to identify symptom clusters from the 48 symptoms, as it is expected that factors would be correlated (Henoch, Ploner, & Tishelman, 2009). Compared with other extraction methods, PAF is a more conceptually appropriate and is the commonly used method to identify symptom clusters without normal distribution assumption of the symptom data (Skerman, Yates, & Battistutta, 2009). To increase clinical significance and have sufficient variation for EFA, symptoms with a prevalence less than 20% were excluded from the analysis. Reliability estimates, the internal consistency was examined among symptoms with a prevalence greater than 20% using Cronbach's α. To measure sampling adequacy for exploratory factor analysis, the Kaiser-Meyer-Olkin (KMO) statistics, and Bartlett's test of sphericity were computed. KMO test measures the sampling adequacy of each variable by calculating the

proportion of variance among variables, with desired value higher than 0.80 (Cerny & Kaiser, 1977). Bartlett's test of sphericity measures whether correlation matrix for the data is an identity matrix (Tabachnick & Fidell, 2001). If the p-value from the Bartlett's test of sphericity was less than 0.05, it indicated that the dataset was suitable for factor analysis. The eigenvalues, the scree plots, and amount of variance explained for each factor, or cluster from the EFA were used to determine the number of extracted clusters. The minimum factor loading of an item considered meaningful in this analysis was 0.40 (Browne, 2001). To be define a symptom cluster, at least two symptoms must load together, the Cronbach α must be greater than 0.60, and the symptom-total correlations must greater than 0.25 (Ferketich, 1991). Separate EFAs were performed at the four specific time points. By conducting EFAs at four time points, we were able to examine the stability of symptom clusters from pre-adjuvant therapy until 18 months of adjuvant therapy. Symptoms were considered stable when they present in the same symptom cluster at least three time points.

Aim 2: Group-based multi-trajectory modeling was used to classify women with breast cancer into subgroups with "similar" psychological symptom cluster trajectories over the 18-month course of adjuvant therapy. The SAS macro PROC TRAJ (Jones, 2014) was used to perform this analysis. First, based on our prior knowledge of symptom clusters trajectory studies (Avis, Levine, Case, Naftalis, & Van Zee, 2015; Donovan et al., 2013), models with two to five subgroups will be fitted. To identify the optimal number of subgroups among trajectory models, we used the following the criteria for model selection: (1) biggest Bayesian Information Criterion (BIC) value, (2) average posterior probabilities (AvePP) of class membership should exceed 0.7 for all subgroups, (3) the odds of correct classification should exceed 5 for all subgroups, and (4) close correspondence between the estimated probability of group membership

and the proportion classified in that group (Nagin & Odgers, 2010). Maximum likelihood estimation was used to estimate model parameters. The parameters of the unconditional multi-trajectory modeling included the probability of membership in each subgroup's trajectory, and the regression coefficients of each subgroup's trajectory (i.e., intercept, linear, quadratic). The significance level was at 0.05.

Aim 3: Binary logistic regression analysis was used to explore the association between genotypic and phenotypic predictors and predicted psychological symptom cluster membership separately. Assumptions of independence, *linearity in the logit* for continuous variables, *nonadditivity* and no serious multicollinearity were checked first in order to perform multinomial logistic regression. Hardy-Weinberg equilibrium and linkage disequilibrium were assessed by PLINK 1.0.7. For each SNP, additive, dominant and recessive models were assessed in the model. The genetic model with the lowest p-value obtained from the three genetic association tests were selected for each SNP.

The phenotypic characteristics of age, marital status, employment status, education, stage of disease and whether chemotherapy was received were evaluated as potential predictor variables. Univariate logistic regression analyses were first be used to identify possible phenotypic predictor variables with those predictor variables having $p < 0.10$ be included in the multivariable model.

To explore the genetic associations with predicted trajectory subgroup membership, a total of 51 SNPs among the 6 candidate genes that passed all quality control filters were included in the analyses. Bivariate analyses were performed for each SNPs. Possible SNPs with $p < 0.10$ identified in the bivariate analyses were evaluated in the final model with the control of phenotypic characteristics. Each significant SNP adjusted for phenotypic characteristics were

reported separately in the final presentation of the results. Covariate-adjusted odds ratios (ORs) and 95% confidence interval were reported to estimate the magnitude and precision of the association between predictor variables and subgroup membership. For all the phenotypic and genotypic models, $p < 0.05/i$ (i is the number of subgroups) was interpreted as significant, using Bonferroni correction for post-hoc pairwise contrasts. Chi-square goodness of fit test and residual analysis were used to assess the model fit of the logistic regression model.

2.0 SUMMARY OF STUDY

There are significant gaps in our understanding of the psychological symptom cluster experienced by women with breast cancer receiving adjuvant therapy with regard to the following issues: (1) it is not clear what the stable core symptoms are comprising the psychological symptom cluster and their trajectories experienced by women with breast cancer during adjuvant therapy, especially for long-term AI therapy; (2) it is not clear whether distinct subgroups of women with breast cancer exist based on the severity of the psychological symptom cluster they experience during adjuvant therapy; and (3) it is not clear whether there are demographic (i.e., age, education, employment status, marital status), clinical (i.e., disease stage, whether received chemotherapy) or genotypic (i.e., variation in polymorphisms) pre-therapy factors that may be associated with predicting subgroup membership within the psychological symptom cluster based on the symptom experience during adjuvant therapy.

Based on the gaps identified about the psychological symptom cluster, this dissertation research has (1) identified symptom clusters at four time points from baseline (pre-adjuvant therapy) to 18 months of adjuvant therapy in postmenopausal women with early stage breast cancer; (2) identified distinct subgroups of postmenopausal women with early stage breast cancer based on the severity of the stable symptoms within the psychoneurological symptom cluster from baseline (pre-adjuvant therapy) to the first 18 months of adjuvant therapy; and (3) explored demographic and clinical factors (age, marital status, education level, treatment characteristics, stage of disease) and genotypic factors (variations in polymorphisms related to HPA axis function) associated with the subgroup membership of the trajectories of the psychological symptom cluster. In regard to genetic factors, the current study focused on genes and

polymorphisms known to regulate activity of the HPA axis in light of evidence that dysregulation of this system and associated inflammation may contribute to the experience of psychoneurological symptoms.

Three manuscripts were developed related to this dissertation project during the course of PhD training. We conducted a study to identify core symptoms of the psychological symptom cluster from the first two manuscripts. In the first manuscript, entitled "Impact of chemotherapy on symptoms and symptom clusters in postmenopausal women with breast cancer prior to aromatase inhibitor therapy", we identified and compared differences in symptom and symptom clusters between postmenopausal women with early stage breast cancer who did and did not receive chemotherapy prior to AI therapy. This manuscript was submitted to the *Journal of Clinical Nursing*. In this study, seven distinct symptom clusters were revealed in both groups prior to AI therapy: cognitive, musculoskeletal, psychological, vasomotor, weight, sexual and urinary, with additional gastrointestinal symptom cluster been identified in women who received chemotherapy. Women who received chemotherapy prior to AI therapy experienced higher severity of symptoms and greater number of symptom clusters than women who did not receive chemotherapy. This study showed the existence of the psychological symptom cluster and provided the foundation for our investigation of the psychological symptom cluster and examination of the stability of this symptom cluster over the first 18 months of adjuvant therapy. The second manuscript, entitled "Stability of symptom clusters in women with breast cancer during the first 18 months of adjuvant therapy", was submitted to the *Journal of Pain and Symptom Management*. This article reported on the identification and evaluation of the changes in symptom clusters in women with breast cancer from pre-adjuvant therapy to 18 months after initiation of adjuvant therapy. Most symptom clusters (i.e., psychological, neurocognitive, weight,

musculoskeletal, vasomotor, urinary, and sexual) existed before adjuvant therapy and were relatively stable through the first 18 months of therapy. Core stable symptoms (i.e., fatigue, depressive symptoms, and anxiety) within the psychological symptom cluster were also identified in this manuscript. To better understand the inter-individual differences of the psychological symptom cluster, we identified subgroups of women who experienced higher severity of the psychological symptom cluster during adjuvant therapy and explored associations between demographic and clinical characteristics and variation in genetic polymorphisms related to HPA axis function and predicted symptom subgroup membership based on multi-trajectory modeling. Results of this analysis were reported in the third manuscript, "Genes involved in the HPA axis and a symptom cluster of fatigue, depressive symptoms and anxiety in women with breast cancer during 18 months of systemic adjuvant therapy". This manuscript was submitted to *Psycho-oncology*. Two distinct symptom subgroups ("all low" and "all high") were identified based on the trajectories of fatigue, depressive symptoms and anxiety. The "all low" subgroup had stable low severity of fatigue and depressive symptoms and a linear decreasing pattern for anxiety over time. The "all high" subgroup had stable high severity of fatigue and depressive symptoms and a quadratic pattern for anxiety over time. Younger age, less education and treatment with chemotherapy were associated with greater likelihood of being in the high symptom subgroup. Polymorphic variation in genes related to the HPA axis (i.e., FKBP5 rs9394309, NR3C2 rs5525, CRHR1 rs12944712) also predicted risk for high severity of psychological symptoms.

In summary, this dissertation project has contributed to *filling several gaps* in the literature about the psychological symptom cluster among postmenopausal women with early stage breast cancer. Stable symptoms (i.e., fatigue, depressive symptoms, anxiety) clustered within the psychological symptom cluster and their trajectories during 18 months of adjuvant therapy were

identified. Subgroups of women who have higher severity of the psychological symptoms were identified based on symptoms trajectories. Phenotypic and genotypic predictors related to the subgroup membership let us better understand the inter-individual differences of symptoms experienced by women with breast cancer. Results of this study will help healthcare providers screen women with breast cancer and identify those who are at increased risk for psychological symptoms, facilitating the development of preemptive and individualized interventions to manage symptoms and improve quality of life during cancer treatment.

2.1 CHANGES TO PROPOSAL

Several changes were made to this dissertation proposal after the comprehensive examination and dissertation overview and have been approved by all committee members. The detailed information about the aforementioned changes is listed below.

2.1.1 Changes to final gene list

Due to budgetary limitations and the design of iPlex, we deleted 11 SNPs from the original gene list. Table 4 contains the final list of SNPs for candidate gene analysis.

Table 4 Final List of SNPs for Candidate Gene Analysis

Gene	SNPs
CRHR2 (Corticotropin Releasing Hormone Receptor 2)	rs8192496
	rs255098
	rs3779250
NR3C1 (Glucocorticoid receptor)	rs41423247
	rs258747
	rs10482605

	rs180044
	rs6191
	rs258813
	rs33388
	rs10052957
	rs6198
	rs6189
	rs6190
FKBP5 (FK506-binding protein 5)	rs1360780
	rs3800373
	rs9470080
	rs4713916
	rs9296158
	rs9394309
	rs3777747
	rs17542466
	rs2766533
	rs9380526
	rs9394314
	rs2817032
	rs2817040
	rs7753746
	rs4713902
	rs774826
	rs7757037
NR3C2 (mineralocorticoid receptor)	rs5525
	rs4835488
	rs10213471
	rs2070951
CRHB (Corticotropin releasing hormone binding protein)	rs10473984
	rs7718461
	rs1875999
CRHR1 (Corticotropin Releasing Hormone Receptor 1)	rs17689918
	rs4458044
	rs242924
	rs1768996
	rs12944712
	rs12938031
	rs4792887

	rs1396862
	rs17763104
	rs110402
	rs242948
	rs1876828
	rs17689882
	rs12936511
	rs242941

2.1.2 Additional analysis of symptom clusters

Originally, symptom clusters were identified in a mixed population of two cohorts of women. Based on suggestions from the dissertation committee members, factor analysis was performed separately for women in ChemoAnast and AnastOnly groups at each time point. Due to the limited sample size, the "comparisons" that were accomplished over time and between the two treatment cohorts are purely descriptive. Results showed that at baseline and 18 months, fatigue and changes in sleep patterns clustered together with other psychological symptoms in AnastOnly group. These two symptoms stood out as a unique symptom cluster in ChemoAnast group. The GI symptom cluster was identified at 6 months in ChemoAnast group only. At 12 months, fatigue and depressive symptoms clustered with musculoskeletal symptoms in AnastOnly group. Separate exploratory factor analyses for each cohort allowed us to better understand different experience of symptom clusters between the two treatment groups and gave us insights that the appearance of the GI symptom cluster was not related to AI therapy.

2.2 STUDY STREGTH AND LIMITATIONS

This study examined a comprehensive list of symptoms which may be experienced by women with breast cancer. Several previous studies have examined symptom clusters comprised of pre-determined set of symptoms (Denieffe et al., 2014; Ho et al., 2015; Sanford et al., 2014). However, given the fact that symptoms may change over time and that different symptoms can be associated with different treatments, some important symptoms may have been overlooked using this approach. The advantage of presenting participants with a more comprehensive list of possible reportable symptoms reduces the potential for selection bias. Our approach is more empirically-based and reliable because it takes into consideration a comprehensive list of symptoms that may be experienced. In addition, this is the first study to evaluate changes in symptom clusters among women with breast cancer from pre-adjuvant therapy up to 18 months after starting adjuvant therapy. Our longitudinal study allows us better understand the changes in symptom clusters over time during chemotherapy and AI therapy. Few studies have included the baseline (pre-adjuvant therapy) time point. This is the first symptom cluster study to include the pre-adjuvant therapy time point among women with breast cancer. Having this baseline assessment helped us identify whether the symptom clusters existed before adjuvant therapy or appeared after therapy. Lastly, this is the first study to evaluate variation in genes and polymorphisms related to the HPA axis and the severity of the psychological symptom cluster over time among women with breast cancer. Variation in genes and polymorphisms related to the HPA axis can be used as clinical biomarkers to identify patients who may be at greater risk of more severe fatigue, depressive symptoms and anxiety.

There are some important limitations to acknowledge in this study. First, 97.0% of the women in this study were Caucasian. Thus, the generalizability of the study results is limited due

to the racial homogeneity of the sample. Secondly, the recommended sample size in EFA is at least 300, based on the criteria "100 = poor, 200 = fair, 300 = good, 500 = very good, ≥1000 = excellent (MacCallum et al., 1999). Our sample (n=354) was sufficient to conduct the factor analysis at baseline and 6 months (n=288); however, we lost some precision to conduct EFA at the later follow-up time points due to study attrition (n=205 at 12 months, n=156 at 18 months). Additionally, our sample was not of sufficient size to accommodate multiple testing of the associations between polymorphisms in the HPA axis related genes and predicted subgroup membership of the psychological symptom cluster. However, this exploratory study does lay the initial groundwork for future larger scale studies to confirm the relationships between phenotypic and genotypic predictors and the predicted subgroup membership. Future research which includes a larger more diverse study population is needed confirm the findings of this study. Thirdly, the dimensions of symptoms (i.e., occurrence, severity, and distress) can influence the results of the symptom cluster. We identified symptom clusters using only symptom severity scores. One study showed that different types of symptom clusters may emerge when using severity versus distress as the dimension evaluated (Suwisith et al., 2008). Other studies have provided evidence that using occurrence and severity ratings would produce similar numbers and types of symptom clusters (Kim et al., 2009; Sullivan et al., 2017). Therefore, future research is needed to examine different dimensions of the symptoms when identifying symptom clusters. Lastly, other predisposing factors, such as demographic and clinical characteristics, personality, general health, menopausal status, and duration of menopause can influence the severity of symptoms among women with breast cancer (Bower et al., 2019; Lockefeer & De Vries, 2013; Mazor et al., 2018). Future research is needed to compare the symptom experience of healthy women and consider the influence of

personality, general health, menopausal status and duration of menopause on the symptom experience of women with breast cancer.

2.3 FUTURE DIRECTIONS

This dissertation project has filled gaps in the literature about the psychological symptom cluster among women with breast cancer receiving adjuvant therapy. However, many questions remain unanswered in the symptom cluster research among oncology patients. The following areas still warrant consideration in future research: (1) study population; (2) assessment of symptom clusters; (3) methods to identify symptom cluster; (4) mechanisms underlying symptom clusters; and (5) individual symptom variability and personalized symptom management.

2.3.1 Study population

It is unknown whether symptom clusters differ depending upon on the type of cancer diagnosis, stage of cancer and types of cancer treatment received. We still need to understand whether symptom clusters are affected by disease or treatment. Therefore, future studies can identify symptom clusters and symptom cluster trajectories across cancer diagnoses and cancer treatment. For example, study is needed to evaluate symptom clusters among women with ovarian cancer and breast cancer. A study can be conducted among a mix of patients with different cancers to evaluate differences or similarities in symptom clusters during chemotherapy. In addition, with the significant progress of immunotherapy and targeted therapies in the past decade, research is needed

to assess and manage symptoms and symptom clusters associated with immunotherapy or targeted therapies used in the treatment of cancer.

2.3.2 Assessment of symptom clusters

To identify symptom clusters from a comprehensive symptom assessment, additional research is needed to determine the optimal number and types of symptoms to assess for oncology patients. Research is needed to summarize and identify the core symptoms to assess for each types of cancer. Even though some assessment instruments contain a broad range of symptoms, some symptoms can still be overlooked in each instrument. For example, the BCPT symptom checklist assesses 42 symptoms (Stanton et al., 2005); however, it does not include fatigue, anxiety, general pain, and depressive symptoms. The Memorial Symptom Assessment Scale evaluates 32 symptoms on four dimensions (Portenoy et al., 1994); however, it does not include weight gain and hot flashes. These overlooked symptoms are commonly experienced and important symptoms to assess for some types of cancer patients (i.e., breast cancer).

In addition, symptoms are multidimensional with different frequencies, and levels of intensity and distress. This study only examined the existence and composition of symptom clusters based on symptom severity scores. In addition to symptom severity, other symptom dimensions (i.e., occurrence, distress) can be used to characterize symptoms.

To date, most symptom cluster research collected data from self-reported symptom instruments. Few studies have evaluated symptom clusters from electronic health records. Further studies are needed to confirm these symptom clusters in a larger population, possibly using electronic health records. Natural language processing and text mining can be used to collect patient-authored symptom data from electronic health records (Dreisbach, Koleck, Bourne, &

Bakken, 2019). Electronic health records will allow us to assess a broad range of symptoms with more symptom assessment time points. Wearable devices and smart phone technology can also be used to collect real-time data and better evaluate the dynamic changes of symptoms.

2.3.3 Methods to identify symptom clusters

In addition to EFA and GBTM, other novel machine learning methods can be used to identify different dimensions of symptom clusters in future studies. For example, network analysis could be used to identify co-occurring symptoms and symptom clusters based on different dimensions of specific symptoms (Papachristou et al., 2019). Bayesian network analysis can be used to identify causal relationships between co-occurring symptoms and determine the "trigger" symptom (Xu et al., 2018). Other clustering algorithms (i.e., k-means, Hierarchical Agglomerative Clustering, Spectral-Clustering) can be used to identify symptom clusters and subgroups of patients based on symptom experience (Papachristou et al., 2016).

2.3.4 Mechanisms that underlie symptom clusters

This study explored the correlation between variation in genes and polymorphisms related to HPA axis and the experience of the psychological symptom cluster among women with early-stage breast cancer. Genetic variation in HPA axis sheds light on the mechanisms underlying the psychological symptoms, which suggests that dysregulation of the HPA axis and glucocorticoid receptor sensitivity may play a role in fatigue, depressive symptoms, and anxiety. To advance our understanding of the dysregulation of the HPA axis underlying the psychological symptom cluster, longitudinal studies are needed to examine biomarkers related to the function of the HPA axis and

the neuroendocrine system. Future research is needed to evaluate the underlying genetic and epigenetic mechanism for the psychological symptom cluster. For example, studies can examine how epigenetic changes of the genes related to the HPA axis and GR receptors contribute to psychological symptoms among cancer patients during cancer diagnosis and cancer treatment trajectory. Thus, pharmacological or psychosocial interventions that target the functions of the HPA axis could be developed to further manage the symptoms.

In addition to the dysregulation of the HPA axis, research is needed to explore other possible common mechanisms of different symptom clusters, such as changes in the central nervous system, circadian rhythm disruption, sympathetic nervous system activation, tissue damage and their interaction with inflammation and the immune system. It is also interesting to identify whether common mechanisms exist across different symptom clusters (i.e., psychological, hormonal, GI, and cognitive).

2.3.5 Individual symptom variability and personalized symptom management

Results of this study emphasize the need for personalized symptom management. Genetic features, demographic and clinical characteristics can be used to personalize the prediction of the risk for psychological symptoms among women with breast cancer. Future studies are needed to examine more molecular, genetic, demographic, clinical and behavioral factors (i.e., acute and chronic stress during cancer treatment, family history, early life trauma, physical activity, and personality) and the severity of symptom clusters, not only limited to the psychological symptom cluster. The integration of big data (i.e., phenotypic, genotypic and molecular data) and machine learning with predictive models can help us identify and predict who may have a higher risk of developing severe

symptom profiles based on predisposing and precipitating factors. Therefore, personalized interventions can be developed to reduce patients' symptom burden effectively.

3.0 DATA-BASED MANUCRIPT

3.1 IMPACT OF CHEMOTHERAPY ON SYMPTOMS AND SYMPTOM CLUSTERS IN POSTMENOPAUSAL WOMEN WITH BREAST CANCER PRIOR TO AROMARASE INHIBITOR THERAPY

3.1.1 Abstract

Women with breast cancer often experience multiple concurrent symptoms during aromatase inhibitor (AI) therapy. The burden of symptoms prior to AI are associated with nonadherence to cancer treatment. To date, few studies have comprehensively explored the symptoms and symptom clusters occurring prior to AI therapy. The purpose of this study was to examine and compare the differences in symptoms and symptom clusters between postmenopausal women with early stage breast cancer who did and did not receive chemotherapy prior to AI therapy. This was a secondary analysis of a prospective repeated measures study. The sample comprised postmenopausal women (N=339) with breast cancer who would receive AI therapy with or without chemotherapy. We collected information on 48 symptoms after surgery or chemotherapy but before AI therapy from different symptom assessment tools. Mann-Whitney U tests were used to compare the differences in the severity of symptoms between groups. Exploratory factor analysis (EFA) was conducted to determine symptom clusters. Overall, this study indicates the presence of symptoms among women with breast cancer prior to AI therapy, with higher severity of symptoms and greater number of symptom clusters for women who received chemotherapy. Results showed that the most severe symptoms among women with breast cancer prior to AI therapy were: breast sensitivity,

unhappy with the appearance of my body, general aches and pain, joint pain and muscle stiffness. Women who received chemotherapy prior to AI therapy experienced significantly higher severity of 22 symptoms than women who did not receive chemotherapy. Through EFA seven distinct symptom clusters were revealed in both groups: cognitive, musculoskeletal, psychological, vasomotor, weight, sexual and urinary, with an additional gastrointestinal symptom cluster identified in women who received chemotherapy. Nurses should assess and be aware of symptoms and symptom clusters existed prior to AI therapy and manage them in advance.

3.1.2 Introduction

Approximately 75% of women with breast cancer have estrogen receptor (ER) positive disease. A minimum of 5 years of aromatase inhibitor (AI) therapy is recommended for postmenopausal women with ER-positive early-stage breast cancer with or without chemotherapy (Burstein, Lacchetti, & Griggs, 2016). During AI therapy, 94% of women experience multiple concurrent symptoms or adverse effects, such as fatigue, hot flashes, insomnia, cognitive problems and musculoskeletal pain (Aiello Bowles et al., 2012; Garreau et al., 2006). One third of women with breast cancer do not adhere to AI therapy, primarily because of symptoms they experience during treatment (Henry et al., 2012). It has been suggested that some of these symptoms may be present prior to AI therapy rather than be a result of this treatment (Kidwell et al., 2014). Furthermore, evidence suggests that pre-treatment symptoms positively symptom burden among breast cancer patients during cancer treatment (Liu et al., 2009), and relates to the discontinuation of AI treatment (Kidwell et al., 2014). Thus, identifying symptoms present prior to AI therapy may be helpful in managing symptoms in advance, which is a critical step in improving symptom experience during treatment and adherence to AI therapy.

3.1.3 Background

There has been growing interest in symptom cluster research within the last 15 years, since patients usually experience multiple co-occurring symptoms, also known as symptom clusters, during and after treatment, or due to the disease itself (Nguyen et al., 2011). According to Miaskowski (2016), “a priori” and “de novo” are the two common approaches to conceptualizing symptom clusters. A prior studies of women with breast cancer identify different subgroups of women based on predetermined symptoms (Sanford et al., 2014; Ho et al., 2015). Whereas, de novo studies administer several symptom assessments and identify different clusters of symptoms that develop during the treatment course (Browall, Brandberg, Nasic, Rydberg, Bergh, Rydén, Xie, Eriksson, & Wengström, 2017; Roiland & Heidrich, 2011). Most symptom cluster studies have evaluated symptom clusters during the short time treatment period (i.e., chemotherapy or radiation therapy) among women with breast cancer (Albusoul, Berger, Gay, Janson, & Lee, 2017; Hsu et al., 2017; Sullivan et al., 2018). To date, few studies have evaluated symptom clusters prior to AI therapy. One study evaluated a symptom cluster of sleep quality, concentration, fatigue, anxiety and depressive symptom among women with breast cancer prior to AI initiation (Kidwell et al., 2014). Another study comprehensively assessed symptoms among both pre- and postmenopausal women with breast cancer prior to the initiation of tamoxifen and AI therapy (Ganz et al., 2016). These studies either evaluated symptom clusters from limited number of predetermined symptoms or only evaluated the severity of separate symptoms separately prior to AI therapy among women with breast cancer. None of them compared the symptom and symptom cluster experiences among postmenopausal women with early stage breast cancer who did and did not receive chemotherapy prior to AI therapy. The severity of pre-treatment symptoms may vary from individual to individual, influenced by

previous treatment received and different demographic characteristics, physical health, and disease status. It is important to identify women who are at risk for severe symptom profiles and manage symptoms in advance. It is possible that women who received chemotherapy prior to AI therapy may have severe symptom profiles than women who did not receive chemotherapy. Therefore, the objective of this study was to measure a broad scope of symptoms to access and compare the severity of pre-treatment symptoms and the composition and type of symptom clusters between postmenopausal women with early stage breast cancer who did and did not receive chemotherapy prior to AI therapy.

3.1.4 Methods

3.1.4.1 Study design

This was a secondary analysis of symptom data from an Institutional Review Board approved prospective repeated measures study of cognitive function in postmenopausal women receiving the AI, anastrozole, for early stage breast cancer (R01-CA107408) (Bender et al., 2015). The current investigation included two cohorts of women with early stage breast cancer who had completed surgery: women prescribed anastrozole therapy only (AnastOnly Group) and chemotherapy and anastrozole therapy (ChemoAnast Group).

3.1.4.2 Setting and sample

A total of 339 women with breast cancer were enrolled in the study. Women with breast cancer were recruited between 2005 and 2015 from the Comprehensive Breast Care Program of the UPMC Hillman Cancer Institute from Magee-Women's Hospital, Hillman Cancer Center, and Shadyside Hospital. Inclusion criteria were women who were: (1) newly diagnosed with stage I,

II or IIIA breast cancer; (2) ≤75 years of age; (3) postmenopausal; (4) scheduled to receive chemotherapy plus anastrozole or anastrozole only as post-surgical follow-up therapy; and (5) able to speak and read English; and (6) who had completed a minimum of 8 years of education. Exclusion criteria included: (1) self-report of hospitalization for psychiatric illness within the last 2 years; (2) prior diagnosis of neurologic illness, such as stroke, multiple sclerosis, dementia syndrome, or Parkinson's disease or of HIV-related dementia or chronic fatigue syndrome; 3) prior diagnosis of cancer; or 4) clinical evidence of distant metastases.

3.1.4.3 Procedures

Following written informed consent, women in the ChemoAnast group completed a demographic, clinical characteristics and symptom assessment at enrollment after surgery but before chemotherapy (T0), and symptom data were collected again after chemotherapy but before the initiation of AI therapy (T1). Women in the AnastOnly group completed a demographic, clinical characteristics and symptom assessment at enrollment after surgery and before the initiation of AI therapy (T0). The study flow diagram is displayed in Figure 3. For this study, we compared the severity of symptoms and number of types of symptom clusters at T0 for AnastOnly group and T1 for ChemoAnast group.

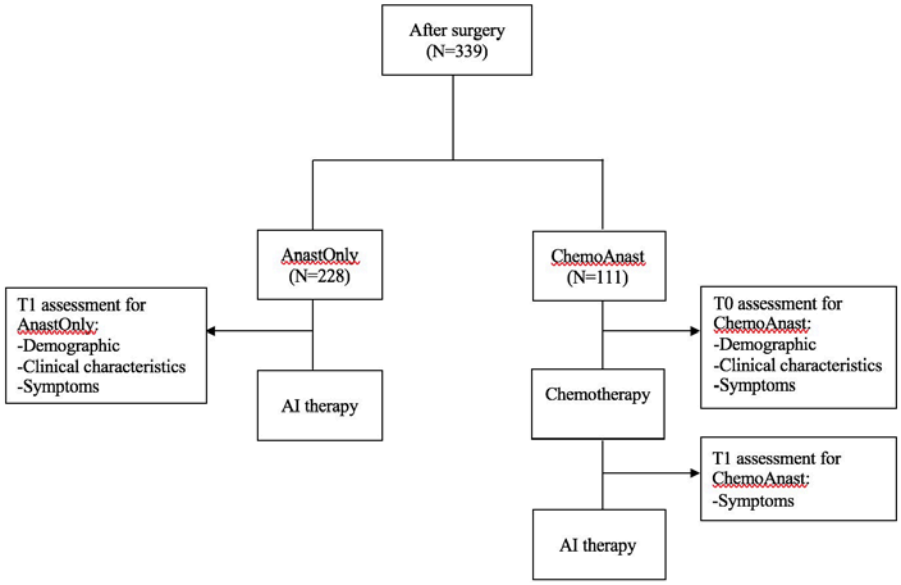

Figure 3 Study Flow Diagram

3.1.4.4 Measurement

Socio-demographic information (e.g., age, race, education level etc.) and clinical characteristics (e.g., stage of disease, treatment etc.) were recorded at baseline.

Of the 48 symptoms evaluated, 42 symptoms were assessed with the Breast Cancer Prevention Trial (BCPT) Symptom Checklist (Stanton et al., 2005). Since the BCPT symptom checklist did not include fatigue, anxiety, general pain, depressive symptoms, changes in sleep patterns and perceived cognitive impairment, we assessed 6 more symptoms using the Profile of Mood States (POMS; fatigue, anxiety) (McNair et al., 1992), Brief Pain Inventory-Short Form (BPI; pain) (Cleeland & Ryan, 1994), Beck Depression Inventory-II (BDI-II; depressive symptoms) (Beck et al., 1996), and Patient's Assessment of Own Functioning (PAOFI; perceived cognitive ability) (Chelune et al., 1986).

The BCPT is a self-report measure of symptoms related to endocrine therapy comprised of subscales including cognitive symptoms, musculoskeletal pain, vasomotor symptoms,

gastrointestinal symptoms, dyspareunia, bladder control, weight concerns, gynecologic symptoms (Stanton et al., 2005). It has 42 items rated on a 5-point Likert scale, from 0 (not at all) to 4 (extremely). The Cronbach's alpha was 0.895 in this study.

Two subscales of the POMS (Fatigue/Inertia subscale and Tension/Anxiety subscale) were used to measure fatigue and anxiety. POMS is a self-report measure of mood states, with 65-items rated on a 5-point Likert scale format from 0 (not at all) to 4 (extremely) (McNair et al., 1992). POMS-Fatigue/Inertia subscale has 7 items, the Cronbach's alpha in this study was 0.945. POMS-Tension/Anxiety subscale has 9 items, the Cronbach's alpha in this study was 0.799.

Pain was measured with the BPI-short form which consists of 9 items related to pain intensity, pain relief treatment or medication and pain interference (Cleeland & Ryan, 1994). The Cronbach's alpha was 0.915 in this study. For this study, 4 items related to pain severity were used.

The BDI-II is a 21-item, self-report measure in which depressive symptom severity is rated on a 4-point Likert scale from 0 (no symptom) to 3 (severe symptom) (Beck et al., 1996). The Cronbach's alpha was 0.838 in this study. Higher average scores of 21 items indicate more severe depressive symptomatology. For this study, a total score of items 1-14 (cognitive/affective scores) was used to measure depressive symptoms to avoid the influence of other treatment related symptoms. Higher total scores of the 14 items indicate more severe depressive symptoms. Item 16 from BDI-II (changes in sleep pattern) was used to measure the severity of changes in sleep pattern.

The PAOFI, a 33-item self-report measure of subjective perceived cognitive impairment, is rated on a 6-point scale range from 0 (almost never) to 5 (almost always) (Chelune et al., 1986). The Cronbach's alpha was 0.916 in this study. Higher average score (range 0-5) of 33 items indicate poorer perceived functioning.

Symptom severity score was calculated as the mean of the symptom scores of participants

who experienced this symptom. To standardize the scaling of symptom severity scores among the instruments used, the symptom severity scores were transformed to a 0–100 scale. Following formula was used for our data transformation: X'=[X-min(X)]/ [max(X)-min(X)] × 100, where X is the particular symptom in its original scaling.

3.1.4.5 Statistical analysis

Data were analyzed using IBM® SPSS® Statistics Version 25 (IBM Corp., Armonk, NY). Data were first screened for missing data (amount and pattern), outliers, normality, etc. Based on the patterns of missing data, appropriate strategies (i.e., multiple imputations) were used. Given a variable's level of measurement and data distribution, student t test and chi-square test statistics were used to summarize and compare the demographic and clinical characteristics between groups. Since the symptom data did not follow a normal distribution, Mann-Whitney U tests were used to compare the mean symptom severity score by treatment groups.

To identify symptom clusters from the 48 possible individual symptoms, exploratory factor analysis (EFA) was conducted using principal axis factoring as the extraction method. The promax rotation method was used to identify components (i.e., "symptom clusters") from the 48 symptoms, since it was expected that the factors would be correlated (Henoch et al., 2009). To increase statistical robustness, have sufficient variation for EFAs and make clinically meaningful results, symptoms with prevalence less than 20% prevalence were excluded from the analysis. Cronbach's α was examined to assess internal consistency. To establish the appropriateness of conducting an EFA, the Kaiser-Meyer-Olkin (KMO) statistic, and Bartlett test statistics were computed to measure sample adequacy. Eigenvalues, scree plots, and the amount of variance explained for each component from the EFA were used to determine the number of extracted components. The minimum factor loading of an individual symptom considered meaningful in this analysis was 0.40

(Browne, 2001). For items with cross-loadings, items were dropped if the difference between the primary loading and the secondary loading was less than 0.2. To define a symptom cluster, at least two symptoms must have loaded together, with the Cronbach α of the symptoms loading on the symptom cluster being greater than 0.60, and the correlation between the individual symptom and the symptom cluster greater than 0.25 (Ferketich, 1991). To compare the number and type of symptom clusters between two subgroups, we used the criteria developed by Kirkova and Walsh (Kirkova & Walsh, 2007). To conclude that both groups showed the same symptom cluster, "at least 75% of the symptoms within a cluster should be present, including the most prominent or important symptom" (Kirkova & Walsh, 2007, p.1012). For example, if only two possible symptoms were present in a symptom cluster, both groups should endorse both symptoms. If three possible symptoms were present in a symptom cluster, at least two important symptoms should be present in both groups.

To identify symptom clusters for women with breast cancer prior to any adjuvant therapy, the recommended minimum sample size for EFA is at least 100 (MacCallum et al., 1999), with the criteria "100 = poor, 200 = fair, 300 = good, 500 = very good, ≥1000 = excellent" (Comrey & Lee, 2013), and the subjective-to-variable ratio is at least 5 (MacCallum et al., 1999). For 48 symptoms, the recommended sample size based on the rule of thumb for is 48×5=240. Therefore, our sample (N=339) is large enough to conduct the EFA (339÷48=7.1, which is higher than 5).

3.1.5 Results

3.1.5.1 Sample characteristics

The demographic and clinical characteristics of the sample are summarized in Table 5. All the patients were postmenopausal women with early-stage breast cancer who underwent surgery, with

a mean age of 61 (SD=6.2) years old. Most patients were Caucasian (96.5%), with a mean of 15 years of education (SD=2.8), currently employed (70.4%), and married (67.8%). Except for age, stage of breast cancer and surgery type (p<.05), there were no significant differences in demographic and clinical characteristics between women in the ChemoAnast group and women in the AnastOnly group. Women received chemotherapy prior to AI therapy were significantly younger (p <.001), had more severe disease status (p <.001), and were more likely to have mastectomy (p =.016) than women in the AnastOnly group.

Table 5 Sample Demographic and Clinical Characteristics (N=339)

Characteristic	**Mean (SD) or n (%)**			**Test statistic, p-value**[†]
	Total (N=339)	**ChemoAnast (n=111)**	**AnastOnly (n=228)**	
Age (years)	61.2 (6.2)	59.3 (5.5)	62.1 (6.3)	t=3.993, p=<.001
Education (years)	14.9 (2.8)	15.0 (2.9)	14.8 (2.7)	
Employment status				
Currently employed	238 (70.4%)	81 (73.0%)	157 (68.9%)	
Unemployed	101 (29.6%)	30 (27.0%)	71 (31.1%)	
Married/partnered				
Yes	231 (67.8%)	79 (71.2%)	152 (66.7%)	
No	108 (32.2%)	32 (28.8%)	76 (33.3%)	
Race				
White	329 (96.5%)	107 (96.4%)	222 (97.4%)	
African American	10 (3.5%)	4 (3.6%)	6 (2.6%)	
Stage of breast cancer				
I	227 (66.6%)	42 (37.8%)	185 (81.1%)	U=6668.5, p=<.001
IIA	70 (20.5%)	35 (31.5)	35 (15.4%)	
IIB	24 (7.0%)	17 (7.2)	7 (3.1%)	
IIIA	18 (5.3%)	19 (5.7)	1 (0.4%)	
Surgery				
Mastectomy	48 (14.1%)	23 (20.7%)	25 (11.0%)	χ^2=5.846, p=.016
Lumpectomy	278 (81.5%)	81(73%)	197 (86.4%)	χ^2=9.126, p=.003
Radiation therapy				
Yes	240 (70.8%)	85 (94.4%)	155 (68.0%)	
No	19 (5.6%)	5 (5.6%)	14 (6.1%)	
Missing data	80 (23.6%)	21 (18.9%)	59 (25.9%)	

Note: AI: aromatase inhibitor; AnastOnly: women prescribed anastrozole therapy only; ChemoAnast: women prescribed chemotherapy and anastrozole therapy; SD: standard deviation;

[†]*P* value are from the student t test or Mann-Whitney U test for continuous variables and Pearson x^2 tests for categorical variables, only *P*<.05 is listed in the table.

3.1.5.2 Symptom severity score between two groups

The severity score for each symptom prior to AI therapy among women with breast cancer in ChemoAnast and AnastOnly groups are shown in Table 6. The most severe symptoms among women in the ChemoAnast group after chemotherapy but prior to AI therapy were: general aches and pains (M=34.5, SD=24.4), unhappy with the appearance of my body (M=33.3, SD=31.1), joint pains (M=33.0, SD=27.0), changes in sleep patterns (M=31.5, SD=25.5), and muscle stiffness (M=29.5, SD=26.8). The most severe symptoms among women in the AnastOnly group prior to AI therapy were: breast sensitivity (M=37.1, SD=30.2), unhappy with the appearance of my body (M=29.2, SD=28.7), general aches and pains (M=29.2, SD=23.6), joint pains (M=28.2, SD=26.5) and hot flashes (M=20.9, SD=27.0).

Women in the ChemoAnast group experienced higher severity of symptoms than women in the AnastOnly group. Compared with women in the AnastOnly group prior to AI therapy, women in the ChemoAnast group experienced significantly lower severity of breast sensitivity (p =.01), but significantly higher severity of weight loss (p=0.047), genital itching (p=.029), changes in sleep pattern (p =.02), constipation (p =.02), avoidance of social affairs (p =.02), early awakening (p =.013), dry mouth (p =.01), perceived cognitive impairment (p =.01), muscle stiffness (p =.005), difficulty concentration (p =.003), fatigue (p =.001), forgetfulness (p <.001), easily distracted (p =<.001), numbness (p <.001), weight gain(p <.001), swelling of hands or feet (p <.001), blind spots (p <.001), diarrhea (p <.001), dizziness (p <.001), decreased appetite (p <.001), and nausea (p <.001) after chemotherapy but prior to AI therapy.

Table 6 Symptom Mean Severity Scores Reported by Postmenopausal Women treated for Early Stage Breast Cancer

Symptom	**Symptom Severity[†] Mean± SD with 95% CI**				**Mean difference between groups (95%CI)**
	Total	**ChemoAnast (T1)**	**AnastOnly (T1)**	**p-value[‡]**	

Breast sensitivity/ tenderness	32.5 (30.1)	23.0 (27.6)	37.1 (30.2)	0.010	-14.1[-20.6, -7.6]
Unhappy with the appearance of my body	30.9 (29.5)	33.3 (31.1)	29.7 (28.7)	0.374	3.6 [-3.3, 10.5]
General aches and pains	30.9 (23.9)	34.5 (24.4)	29.2 (23.6)	0.060	5.4 [-0.1, 10.9]
Joint pains	29.7 (26.7)	33.0 (27.0)	28.2 (26.5)	0.089	4.8 [-1.3, 11.0]
Muscle stiffness	24.0 (25.0)	29.5 (26.8)	21.3 (23.6)	0.005	8.2 [2.3, 14.1]
Changes in sleep patterns	23.8 (26.5)	31.5 (25.5)	20.0 (26.2)	0.020	11.5 [5.6, 17.4]
Fatigue	23.8 (23.5)	28.9 (23.8)	21.4 (23.1)	0.001	7.5 [2.1, 12.9]
Early awakening	23.4 (26.7)	27.9 (27.1)	21.2 (26.3)	0.013	6.7 [0.6, 12.9]
Hot flashes	21.7 (27.1)	23.2 (27.3)	20.9 (27.0)	0.432	2.3 [-3.9, 8.5]
Tendency to take naps; stay in bed	21.2 (24.8)	25.7 (27.6)	19.1 (23.1)	0.046	6.6 [0.6, 12.6]
Anxiety	19.0 (15.0)	19.0 (13.0)	19.0 (15.9)	0.420	0 [-3.3, 3.1]
Pain	18.5 (21.5)	20.9 (23.8)	17.3 (20.2)	0.367	3.6 [-1.6, 8.8]
Forgetfulness	18.4 (20.9)	24.8 (24.4)	15.2 (18.2)	<.001	9.5 [4.4, 14.7]
Vaginal dryness	18.2 (25.3)	20.9 (28.5)	16.9 (23.5)	0.349	4.1 [-2.1, 10.3]
Night sweats	18.0 (25.7)	19.8 (27.6)	17.1 (24.8)	0.465	2.7 [-3.4, 8.8]
Difficulty concentrating	17.8 (20.0)	22.7 (22.5)	15.5 (18.3)	0.003	7.3 [2.4, 12.1]
Easily distracted	16.0 (20.0)	21.4 (22.2)	13.3 (18.2)	<0.001	8.1 [3.3, 12.9]
Headaches	15.6 (19.7)	15.8 (20.8)	15.6 (19.0)	0.768	0.2 [-4.5, 4.7]
Dry month	14.7 (24.6)	20.9 (28.3)	11.7 (22.0)	0.010	9.3 [3.2, 15.3]
Numbness, tingling	13.9 (22.7)	23.2 (27.5)	9.4 (18.4)	<0.001	13.8 [8.1, 19.5]
Difficulty with bladder control at other times	13.7 (21.8)	15.3 (20.6)	12.9 (22.4)	0.091	2.4 [-2.5, 7.2]
Weight gain	12.9 (19.8)	18.0 (24.9)	10.5 (16.4)	<0.001	7.4 [2.3, 12.6]
Swelling of hands or feet	12.7 (21.4)	23.0 (26.6)	7.7 (16.3)	<0.001	15.3 [9.9, 20.7]
Constipation	12.7 (20.7)	15.5 (22.4)	11.3 (19.7)	0.020	4.2 [0.7, 9.1]
Short temper	12.6 (18.0)	14.2 (19.0)	11.9 (17.5)	0.230	2.3 [-1.9, 6.5]
Avoidance of social affairs	12.5 (21.2)	17.3 (23.1)	10.2 (19.8)	0.020	7.1 [2.1, 12.2]
Difficulty with bladder control when laughing or crying	12.4 (22.3)	13.7 (23.0)	11.7 (21.9)	0.469	2.0 [-3.2, 7.2]
Perceived cognitive impairment	12.3 (9.3)	15.0 (10.4)	11.0 (8.5)	0.010	3.9 [1.7, 6.1]
Blind spots	11.3 (20.8)	20.7 (26.7)	6.6 (15.3)	<0.001	2.7 [8.7, 19.4]
Pain with intercourse	10.8 (22.7)	10.4 (21.4)	11.1 (23.4)	0.917	-0.6 [-5.8, 4.5]
Excitability	9.7 (16.0)	11.3 (16.1)	8.9 (16.0)	0.106	2.4 [-1.3, 6.0]
Ringing in ears	9.1 (20.1)	9.2 (19.6)	9.1 (20.4)	0.792	0.1 [-4.4, 4.7]

Diarrhea	8.4 (16.9)	11.7 (20.7)	6.8 (14.4)	<0.001	4.9 [0.6, 9.2]
Nausea	8.1 (16.9)	13.3 (21.3)	5.6 (13.6)	<0.001	7.7 [3.3, 12.1]
Decreased appetite	8.0 (16.9)	12.4 (21.6)	5.9 (13.6)	<0.001	6.5 [2.1, 10.9]
Genital itching	6.7 (15.1)	9.7 (19.4)	5.3 (12.2)	0.029	4.4 [0.4, 8.4]
Weight loss	6.5 (14.8)	9.0 (17.8)	5.3 (12.9)	0.047	3.7 [0.4, 7.0]
Dizziness	5.4 (14.1)	7.7 (15.4)	4.4 (13.3)	<0.001	3.4 [0.2, 6.5]
Depressive symptoms	5.3 (8.2)	5.8 (7.4)	5.1 (8.5)	0.115	0.7 [-1.0, 2.5]
Difficulty breath	5.3 (14.4)	7.4 (15.7)	4.2 (13.7)	0.052	3.2 [-0.2, 6.5]
Cold sweats	5.2 (16.2)	7.9 (19.1)	3.8 (14.4)	0.051	4.0 [-.4, 7.7]
Tendency toward accidents	4.3 (11.2)	5.2 (12.7)	3.8 (10.4)	0.332	1.3 [-1.4, 4.1]
Chest pain	3.6 (10.5)	3.9 (10.8)	3.4 (10.3)	0.710	0.5 [-2.0, 2.9]
Vaginal discharge	2.9 (9.5)	3.2 (10.2)	2.9 (9.2)	0.999	0.3 [-2.0, 2.6]
Cramps	2.0 (9.3)	2.7 (9.7)	1.6 (9.1)	0.163	1.1 [-1.1, 3.2]
Vomiting	1.8 (8.4)	2.5 (10.1)	1.4 (7.5)	0.203	1.1 [-1.1, 3.2]
Feelings of suffocation	1.5 (8.3)	1.6 (7.7)	1.4 (8.5)	0.519	0.2 [-1.7, 2.0]
Vaginal bleeding	0.3 (2.7)	0.2 (2.4)	0.3 (2.9)	0.740	-0.1 [-0.7, 0.5]

Note: AnastOnly: women prescribed anastrozole therapy only; ChemoAnast: women prescribed chemotherapy and anastrozole therapy; SD: standard deviation; CI: confidence interval; T0: after surgery and before the initiation of chemotherapy; T1: before the initiation of AI therapy for women in the AnastOnly group, after chemotherapy but prior to AI therapy for women in the ChemoAnast group

† Symptom severity was presented in a descending order; symptom severity was calculated based on the standardized scaling (0 to 100).

‡ *p* values are from Mann-Whitney U test

3.1.5.3 Differences in symptom clusters between groups

An eight-factor solution was identified from the EFA among women in the ChemoAnast group after chemotherapy and prior to the initiation of AI therap. Based on the symptoms in these clusters, we labelled them cognitive, musculoskeletal, psychological, vasomotor, weight, gastrointestinal (GI), urinary and sexual. Women in the AnastOnly group had seven similar symptom clusters prior to the initiation of AI therapy, except that the GI symptom cluster was not identified (see Table 7). Symptoms comprising some of the clusters differed between groups. For the cognitive symptom cluster, the total number of symptoms was 5 and the percent agreements were 100% for both groups. It consisted of symptoms including “easily distracted”, “perceived

cognitive impairment", "difficulty concentrating", and "forgetfulness". For the musculoskeletal symptom cluster, the total number of symptoms ranged from 4 to 5 and the percent agreement was 80% for ChemoAnast group and 100% for AnastOnly group. It consisted of "joint pain", "general aches and pains", and "general pain interference" for ChemoAnast group, with additional "swelling of hands" for AnastOnly group. For the "psychological" symptom cluster, the total number of symptoms ranged from 4 to 5 and the percent agreement was 80% for ChemoAnast group and 100% for AnastOnly group. "Fatigue", "anxiety", "depressive symptoms" and "avoidance of social affairs" clustered together as a "psychological" symptom cluster in the ChemoAnast group. In addition to these four symptoms, "changes in sleep pattern" clustered together with them in the AnastOnly group. The "urinary" symptom cluster consisted of "difficulty with bladder control when laughing or crying" and "difficulty with bladder control at other times" and the percent agreements were 100% for both groups. The "vasomotor" symptom cluster consisted of "hot flashes" and "night sweats" and the percent agreements were 100% for both groups. The "sexual" symptom cluster consisted of "vaginal dryness" and "pain with intercourse" and the percent agreements were 100% for both groups. The "weight" symptom cluster consisted of "weight loss" and "decreased appetite" and the percent agreements were 100% for both groups. The "GI" symptom cluster consisted of "nausea" and "diarrhea", and the percent agreement was 100% for ChemoAnast group and 0% for AnastOnly group.

Table 7 Symptom Clusters with Cluster Loadings†

Symptom Cluster and Individual Symptom	**Cluster Loading AnastOnly(n=228)**	**Cluster Loading ChemoAnast (n=111)**
Cognitive		
Difficulty concentrating	.884	.889
Easily distracted	.816	.826
Forgetfulness	.763	.883
Perceived cognitive (PAOFI)	.530	.726
Musculoskeletal		

Joint Pain	.926	.959
General aches and pains	.925	.814
Muscle stiffness	.721	.614
Pain (BPI)	.634	.693
Swelling of hands or feet	.456	-
Psychological		
Depressive symptoms (BDI-II)	.868	.733
Anxiety (POMS)	.602	.674
Fatigue (POMS)	.508	.438
Avoidance of social affairs	.590	.419
Change in sleep pattern (BDI-II)	.506	-
Urinary		
Difficulty with bladder control when laughing or crying	.899	.851
Difficulty with bladder control at other times	.820	.787
Vasomotor		
Hot flashes	.851	.833
Night sweats	.859	.806
Sexual		
Pain with intercourse	.731	.859
Vaginal dryness	.583	.769
GI		
Diarrhea	-	.879
Nausea	-	.579
Weight		
Weight loss	.731	.701
Decreased appetite	.729	.846
Total variance explained	71.4%	74.3%

Note: BCPT: AnastOnly: women prescribed anastrozole therapy only; ChemoAnast: women prescribed chemotherapy and anastrozole therapy; GI: gastrointestinal; BCPT: Breast Cancer Prevention Trial; BDI-II: Beck Depression Inventory-II; BPI: Brief Pain Inventory; PAOFI: Patient's Assessment of Own Functioning; POMS: Profile of Mood States.

[†]Of 33 symptoms with >20% prevalence, 16 did not co-occur with at least one other symptom, have a factor loading >.4, or symptom-total correlations > .25 (breast sensitivity, unhappy with the appearance of my body, early awakening, headaches, short temper, constipation, weight gain, dry mouth, excitability, numbness, vomiting, decreased appetite).

3.1.6 Discussion

To our knowledge, this is the first study to examine and compare differences in the severity of symptoms and symptom clusters between women with breast cancer who did or did not receive chemotherapy prior to AI therapy using a comprehensive list of symptoms. To date only two studies have comprehensively examined patient-reported symptoms among women with breast cancer prior to AI therapy (Ganz et al., 2016; Kidwell et al., 2014). Kidwell et al. (2014) reported the rate of occurrence of depression, anxiety, sleep quality, fatigue, cognitive, musculoskeletal pain and vaginal dryness among postmenopausal women with breast cancer after chemotherapy and before AI therapy. Ganz and her colleagues (2016) measured the severity of endocrine therapy (ET)-related symptoms after chemotherapy and before ET to 12 months after the initiation of ET among pre-and postmenopausal women with breast cancer. This study found that cognitive problems, musculoskeletal pain, and hot flashes were the most severe symptoms among women with breast cancer prior to AI therapy. Taken together, the results of these studies suggest that a number of symptoms exist prior to AI therapy. Because the symptom dimension assessed by Kidwell et al. (2014) and the population in the study by Ganz el al. (2016) were different from the symptom dimension and population in our study, some caution should be taken when comparing the results of these studies.

3.1.6.1 Differences in symptom severity score between two groups

In general, women who received chemotherapy prior to AI therapy experienced more severe symptoms compared to women who did not receive it. In this study, the severity of 10 symptoms (i.e., forgetfulness, easily distracted, weight gain, numbness, decreased appetite, nausea, diarrhea, swelling of hands or feet, blind spots, dizziness) were significantly higher in the

ChemoAnast group than women in the AnastOnly group (p<.001). Most of these symptoms, such as decreased appetite, nausea, diarrhea, and difficulty breathing, have been reported among women with breast cancer during chemotherapy (Hsu et al., 2017; Carmen W Sullivan et al., 2018). Our results add to the evidence that chemotherapy may exacerbate the severity of some symptoms experienced prior to AI therapy. It is possible that higher severity of these symptoms may be partially attributed to the influence of chemotherapy. However, in addition to receiving chemotherapy prior to AI therapy, research shows that women who are younger, have less education, have lower income, and have a higher comorbidity profile are more likely to experience higher severity of symptoms (S. H. Doong et al., 2015). In this study, women in the ChemoAnast group were younger, had greater stage of disease and were more likely to have received a mastectomy compared with the women in the AnastOnly group. Thus, more studies are needed to comprehensively identify predictors (i.e., treatment of chemotherapy, demographic and clinical characteristics, general health) of the pre-treatment symptom experience among women with breast cancer.

It was also interesting to note that breast sensitivity was more severe in the AnastOnly group. A meta-analysis showed that breast pain after surgery is associated with younger age, radiation therapy, axillary lymph node dissection and it is not related to type of surgery or chemotherapy (Wang et al., 2016). In this study, women in the AnastOnly groups were younger than the ChemoAnast group, which could be one of the factors associated with higher severity of breast sensitivity.

3.1.6.2 Differences in symptom clusters between two group

The EFA results showed that the GI symptom cluster was only identified among women who received chemotherapy after surgery and prior to AI therapy. This symptom cluster has been

documented among women with breast cancer during and after chemotherapy, but with different specific symptoms within the symptom cluster. For example, Sullivan et al. (2018) identified that nausea and diarrhea clustered with lack of appetite, weight loss, change in the way food tastes, dry month, and abdominal cramps one week after chemotherapy. However, two weeks after chemotherapy, nausea clustered with feeling bloated, weight gain, and difficulty sleeping. Albusoul et al. (2017) assessed symptom clusters among women with breast cancer before, during and after chemotherapy and found that the GI symptom cluster was present before and during chemotherapy, but it no longer existed one month after chemotherapy. These results suggest that the GI symptom cluster persists several weeks after chemotherapy; however, it is not clear whether the GI symptom cluster is transient or how long it persists. Further research is warranted to fully understand the time course of GI symptoms after chemotherapy.

3.1.6.3 Similarity in symptom severity score between two groups

Our results showed that there were no differences in the severity of some symptoms between the two groups, including psychological (i.e., depressive symptoms, anxiety), musculoskeletal (i.e., joint pain, general aches and pains), sexual (i.e., pain with intercourse, vaginal dryness), vasomotor (i.e., hot flashes, night sweats) and urinary (i.e., difficulty with bladder control when laughing or crying) symptoms. This finding suggests that these symptoms are common among women with breast cancer prior to AI therapy regardless of whether they received chemotherapy or not. These symptoms may be related to natural menopausal changes, general health status, breast cancer and/or surgery prior to the initiation of AI therapy.

Consistent with the results of our study, Marino et al. (2016) found that adjuvant chemotherapy does not influence the severity of vasomotor, and sexual symptoms among women with breast cancer, except for pain with intercourse. However, some studies suggest that

chemotherapy is associated with worsening vasomotor symptoms (Bernhard et al., 2007; Savard, Savard, Quesnel, & Ivers, 2009). These inconsistencies may be due to differences in samples across studies in terms of menopausal status and cancer treatments been received. More studies are needed to confirm the influence of chemotherapy on vasomotor and sexual symptoms among postmenopausal women with breast cancer prior to AI therapy.

3.1.6.4 Similarity in symptom cluster between two groups

Fatigue, anxiety, depressive symptoms and avoidance of social affairs clustered together in the ChemoAnast group, with additional symptom of changes in sleep pattern in the AnastOnly group. Findings from this study and other studies suggest that the psychological symptom cluster is present at the time of cancer diagnosis and can persist after surgery regardless of treatment received (Denieffe, S. Cowman, et al., 2014; Ho et al., 2015; Kidwell et al., 2014; Stacy D. Sanford et al., 2014). Since it is the most common symptom cluster experienced by women with breast cancer, more studies are warranted to understand the underlying mechanisms and evaluate the trajectory of the psychological symptom cluster during AI therapy.

For the cognitive symptom cluster, similar to this study, Bender et al. (2005) identified a perceived cognitive impairment symptom cluster consisting of problem with memory and loss of concentration. However, in other studies, some cognitive symptoms were found to cluster with other symptoms, such as outlook (Matthews et al., 2012), pain, shortness of breath and vomiting (Hsu et al., 2017). These differences can be explained by different cancer treatments patients received and different statistical methodologies used across studies. Since poor cognitive function pre-exists AI therapy in some women with breast cancer (Bender et al., 2015), it is important to assess and manage cognitive problems prior to AI therapy. Future research is

needed to develop and test the efficacy of useful interventions to manage cognitive problems specifically prior to AI therapy.

For the musculoskeletal symptom cluster, general aches, joint pain, muscle pain were also reported among women with breast cancer in Marshall et al. (2016) and Roiland et al. (2011). Meanwhile, evidence suggests that general pain prior to AI therapy can predict higher severity of joint pain, fatigue and sleep disturbance among women with breast cancer during AI therapy (Shi et al., 2013). Management of musculoskeletal symptoms in advance of AI therapy may prevent worsening of symptoms with treatment. For example, physical activity, such as walking, has been shown to improve musculoskeletal symptoms among women with breast cancer receiving AI therapy (Nyrop et al., 2014).

Vasomotor, urinary and sexual symptom clusters were present prior to AI therapy among women with breast cancer in both groups. No study has identified these symptom clusters prior to AI therapy, however, these symptom clusters have been identified at different assessment timepoints. Sullivan et al. (2018) identified the same vasomotor symptom cluster, consisting of hot flashes and night sweats, among women with breast cancer one week before chemotherapy. Vasomotor symptoms (i.e., hot flashes, night sweats), and sexual symptoms (i.e., vaginal dryness) also cluster together as a menopausal symptom cluster among women with breast cancer during chemotherapy and radiation therapy (Marshall et al., 2016).

The limitations of this study are important to acknowledge. First, 97.0% women in this study were Caucasian. Thus, the generalizability of the study results was limited due to the racial homogeneity of the sample. Secondly, some symptoms, such as sleep disturbances, were measured in a very limited manner. In this study, only one item was used to assess sleep disturbances. A more comprehensive assessment of sleep disturbance may result in this symptom being featured

more prominently in the psychological symptom cluster. In addition, we only compared differences in symptom experience between treatment groups, we did not take all host factors into consideration. Other factors, such as demographic and clinical characteristics, personality, general health and comorbidities, menopausal status, duration of menopause, and genetic differences can influence the severity of symptoms prior to AI therapy as well. Future studies are needed to build a comprehensive model and consider the contribution of general physical health, personality, menopausal status, duration of menopause to the symptom experience reported by women with breast cancer prior to AI therapy.

3.1.7 Conclusion

It is of great significance to identify and compare the differences in the severity of symptoms and symptom clusters between postmenopausal women with early stage breast cancer who did and did not receive chemotherapy prior to AI therapy. Nurses should be aware that women who receive chemotherapy prior to AI therapy may experience specific severe chemotherapy related symptoms and symptom clusters. Psychological, musculoskeletal, sexual, urinary and vasomotor symptoms are common among women with breast cancer prior to AI therapy regardless of treatment with chemotherapy. Since symptoms may change over the course of AI therapy, additional research is warranted to evaluate the change of symptoms and symptom clusters over the course of AI therapy, and to evaluate the predictive relationship between symptom severity at baseline and symptom severity during AI therapy and adherence to AI therapy.

Findings from our study provided a guide to assessment of symptoms in women with breast cancer prior to AI therapy. Nurses should be aware that women with breast cancer may experience cognitive, musculoskeletal, psychological, vasomotor, weight, sexual and urinary symptoms prior

to AI therapy. It is important for nurses to screen for these symptoms and manage them in advance. Knowing pre-treatment symptoms may be helpful in managing symptoms before treatment, since the burden of pre-treatment symptoms may be associated with worse symptoms during treatment and ultimately influence treatment adherence and women's QOL. Furthermore, it is critical to educate patients about the symptom experience prior to AI therapy and teach them about symptom management strategies. Research shows that higher symptom management self-efficacy can reduce symptom distress among cancer patients (Liang et al., 2016). Early behavioral interventions (i.e., physical exercise, music therapy, acupuncture, mind-body therapies) can be provided to manage those symptoms prior to the initiation of AI therapy (Greenlee et al., 2017).

3.2 STABILITY OF SYMPTOM CLUSTERS IN WOMEN WITH BREAST CANCER DURING THE FIRST 18 MONTHS OF ADJUVANT THERAPY

3.2.1 Abstract

Women with breast cancer treated with aromatase inhibitor (AI) therapy experience multiple concurrent symptoms or symptom clusters. These symptoms are the most commonly reported reason for nonadherence to cancer therapies. Therefore, understanding of the symptom experience and identifying symptom clusters before and during AI therapy are important for the development of interventions to improve clinical outcomes. The aim of this study was to identify symptom clusters experienced by women with breast cancer treated with AI therapy from pre-adjuvant therapy up to 18 months of adjuvant therapy using a comprehensive symptom assessment. Forty-six symptoms were evaluated in postmenopausal women with breast cancer

(N=354) who received AI therapy or chemotherapy followed by AI therapy (ChemoAnast). Symptoms were assessed at four semi-annual time points with the Breast Cancer Prevention Trial Symptom Checklist, Patient's Assessment of Own Functioning Inventory, Brief Pain Inventory, Beck Depression Inventory-II, and Profile of Mood States Tension/Anxiety and Fatigue/Inertia subscales. Exploratory factor analyses were conducted at each time point to identify symptom clusters. Four stable symptom clusters (i.e., musculoskeletal, vasomotor, urinary, sexual) and three relatively stable symptom clusters (i.e., psychological, neurocognitive, weight) were identified across the 18-month follow-up period. The gastrointestinal symptom cluster only appeared at after 6 months of adjuvant therapy (post-chemotherapy) in ChemoAnast group. This is the first study to examine symptom clusters over the 18 months of adjuvant therapy among postmenopausal women with early stage breast cancer. These findings may help guide symptom assessment and management in women with breast cancer during adjuvant therapy.

3.2.2 Introduction

In the United States, approximately 80% of women with breast cancer have hormone receptor positive disease (Lumachi et al., 2015). According to the ASCO guideline (Burstein et al., 2018), AI therapy for 5 years is the mainstay of endocrine therapy for postmenopausal women with hormone receptor positive breast cancer.

The symptom experience after a cancer diagnosis may differ depending upon where patients are on the continuation of care. Symptoms may be related to menopausal status, pre-existing symptoms related to comorbidities, cancer and cancer treatment received (Bodai & Tuso, 2015; Bower et al., 2014). Once women begin adjuvant therapy, preexisting symptoms may be

exacerbated or change over time (Ganz et al., 2016). The most common symptoms associated with AI therapy are exacerbation of menopausal symptoms, musculoskeletal symptoms, and changes in cognitive function (Cella & Fallowfield, 2008; Rosenberg et al., 2015). Nonadherence to AI therapy is a challenging issue for both patients and clinicians. The overall AI therapy discontinuation rate is up to 50%, with 5%-25% being nonadherent in the first two years of treatment (Murphy, Bartholomew, Carpentier, Bluethmann, & Vernon, 2012). Symptoms related to endocrine therapy are the most common reasons for nonadherence among women with breast cancer (Aiello Bowles et al., 2012). With the increasing emphasis on survivorship needs of women with breast cancer, it is critical for healthcare providers to understand the burden of these symptoms, which influence adherence to treatment and compromise quality of life (QOL) (Chim et al., 2013; Ganz et al., 2016; Simon, Latreille, Matte, Desjardins, & Bergeron, 2014).

Rather than study symptoms in isolation, research has focused on symptom clusters during chemotherapy and radiation therapy (Albusoul, Berger, Gay, Janson, & Lee, 2017; Hsu et al., 2017; Sullivan et al., 2018). However, few studies have assessed symptom clusters prior to adjuvant therapy or examined the long-term symptom burden of endocrine therapy, as most studies limit follow-up to less than one year post-therapy initiation (Cuzick, Sestak, Cella, & Fallowfield, 2008; Gallicchio, Calhoun, & Helzlsouer, 2017; Ganz et al., 2016). Little is known about how symptom clusters change over time from pre-adjuvant therapy and through AI therapy, or whether symptom clusters are a response to treatment or are preexisting. Accordingly, the goal of the current study was to conduct a comprehensive assessment of symptoms and identify symptom clusters that are present at four time points from pre-adjuvant therapy up to 18 months of adjuvant therapy among postmenopausal women with breast cancer.

We also compared symptom clusters between two cohorts of women who received chemotherapy plus AI therapy and women who received AI therapy only.

3.2.3 Methods

3.2.3.1 Study design

This secondary analysis used symptom data from a prospective cohort, repeated measures study of cognitive function in postmenopausal women receiving anastrozole, an AI, for early stage breast cancer (R01-CA107408) (Bender et al., 2015). All women completed surgery and received either (1) anastrozole therapy only (AnastOnly) or (2) chemotherapy followed by anastrozole therapy (ChemoAnast). All women with breast cancer completed the baseline assessment after primary surgery but prior to any adjuvant therapy. Symptom data were collected every 6 months from pre-adjuvant therapy (baseline) to 18 months post-baseline (see Table 8).

Table 8 Time Points for Symptom Assessment

Group	Pre-chemo	Chemotherapy	Pre-AI	6 Months AI	12 Months AI	18 Months AI
ChemoAnast	X	Yes	X	X	X	N/A
AnastOnly	N/A	No	X	X	X	X

Note: All women with breast cancer completed the baseline assessment after primary surgery but prior to any adjuvant therapy. For women in the ChemoAnast group, baseline is before chemotherapy. For women in the AnastOnly group, baseline is before anastrozole therapy. Women in the ChemoAnast group completed follow-up symptom assessments after chemotherapy but prior to anastrozole therapy, as well as 6 and 12 months after the initiation of anastrozole. Women in the AnastOnly group completed follow-up symptom assessments at 6, 12, and 18 months after the initiation of anastrozole therapy.
Note: AI: aromatase inhibitor; AnastOnly: women prescribed anastrozole therapy only; ChemoAnast: women prescribed chemotherapy and anastrozole therapy.

3.2.3.2 Sample and setting

Women with breast cancer were recruited from the Breast Cancer Program of the UPMC Hillman Cancer Center. This study was approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent. A total of 354 women with breast cancer were enrolled in the study. Women were eligible for this study if they were newly diagnosed

with early stage breast cancer, postmenopausal, less than 75 years old, scheduled to receive chemotherapy plus anastrozole or anastrozole alone, were able to speak and read English, and had a minimum of 8 years of education. Women were excluded if they had self-report of hospitalization for psychiatric illness, prior diagnosis of neurologic illness or cancer, or clinical evidence of distant metastases.

3.2.3.3 Measurement

Self-reported demographic and clinical characteristics from the medical record of participants were collected at baseline. Symptoms were measured by the Breast Cancer Prevention Trial (BCPT) symptom checklist, which includes cognitive, vasomotor, musculoskeletal pain, gastrointestinal, dyspareunia, bladder control, weight concerns, and gynecologic symptom subscales (Stanton et al., 2005). The measure assesses the severity of 42 bothersome symptoms whether the symptoms were bothersome on a 5-point Likert scale, from 0 (not at all) to 4 (extremely).

Fatigue and anxiety were measured using the Profile of Mood States (POMS) by Fatigue/Inertia and Tension/Anxiety subscale, respectively (McNair et al., 1992). The POMS has been used to measure changes in mood in cancer patients (Meek et al., 2000). Symptoms were rated from 0=not at all to 4=extremely. Both POMS subscales have been widely used in cancer patients with adequate internal consistency reliability (Cronbach's α >.87) (Baker, Denniston, Zabora, Polland, & Dudley, 2002).

Pain was measured using 7 items from the Brief Pain Inventory-Short Form (BPI-short) (Cleeland & Ryan, 1994). Patients were asked to indicate their pain intensity on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). Investigators have used BPI to assess pain among patients with cancer with well-established reliability and validity (Caraceni, 2001; Tittle et al., 2003).

Depressive symptom severity was measured using total score of items 1-14 from the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996). Symptom severity scores can range from 0 (no symptom) to 3 (severe symptom). High reliability and validity have been demonstrated for the BDI-II (Wang & Gorenstein, 2013), with strong internal consistency (Cronbach's α=0.93) among cancer patients (Hopko et al., 2007). Changes in sleep pattern was assessed using the score in the sleep item on the BDI-II.

Perceived cognitive impairment was measured by the Patient's Assessment of Own Functioning (PAOFI) (Chelune et al., 1986). Items were rated from 0 (almost never) to 5 (almost always). The PAOFI has been used in studies among women with breast cancer, with adequate internal consistency and construct validity (Bell et al., 2013).

3.2.3.4 Data analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics for the total sample and by two groups of women based on chemotherapy status (chemotherapy plus anastrozole or anastrozole alone). Treatment groups were compared with Mann-Whitney U test for continuous variables, and chi-square test of independence for categorical variables. All analyses were completed using IBM® SPSS® Statistics Version 25 (IBM Corp., Armonk, NY).

Exploratory factor analysis (EFA) was conducted using principal axis factoring (PAF) as the extraction method followed by promax rotation method to identify symptom clusters from the 48 symptoms, since PAF explain the correlations among symptoms and promax rotation assumes that the factors are correlated. To increase clinical significance, symptoms with a prevalence of less than 20% were excluded from the analysis. The minimum factor loading of an item considered meaningful in this analysis was 0.40 (Browne, 2001). To be defined as a symptom cluster, at least two symptoms had to load together, with a Cronbach α greater than 0.60 and symptom-total

correlations greater than 0.25 (Ferketich, 1991). Separate EFAs were performed at the four time points to investigate the stability of the composition of the symptom clusters over time. To explore differences of symptom cluster between two treatment groups, EFAs were conducted separately in ChemoAnast and AnastOnly groups at each of the four time points.

3.2.4 Results

3.2.4.1 Demographic and clinical characteristics of the sample

The demographic and clinical characteristics for the total sample and by treatment group are summarized in Table 9. A total of 354 postmenopausal women with early stage breast cancer were on average 61 years (SD=6.2) of age and 15 years (SD=2.8) of education. Most participants were Caucasian (96.3%), currently employed (70.7%), and married (67.3%). The majority of patients had stage I breast cancer (65.6%) and 81.7% of the sample received lumpectomy. Even though women in the AnastOnly group (M=62.1) were statistically significantly (P<0.001) older than women in the ChemoAnast group (M=59.6), the differences in age were likely not clinically meaningful. In terms of clinical characteristics, women in the AnastOnly group were more likely to have had a lumpectomy (P=0.002), and have a lower disease stage (P<0.001) than women in the ChemoAnast group.

Table 9 Demographic and Clinical Characteristics

Characteristic	Mean (SD) or n (%)			Test Statistic, p value[†]
	Total (n=354)	ChemoAnast (n=127)	AnastOnly (n=227)	
Age (years)	61.2 (6.2)	59.6 (5.4)	62.1 (6.3)	U=11373.5, p<0.001
Education (years)	14.9 (2.8)	14.8 (2.9)	14.8 (2.7)	
Employment status				
Currently employed	251 (70.7%)	94 (74.0%)	157 (68.9%)	
Unemployed/retired/student	104 (29.3%)	33 (26.0%)	71 (31.1%)	
Married/partnered				
Yes	239 (67.3%)	87 (68.5%)	152 (66.7%)	

No	116 (32.7%)	40 (31.5%)	76 (33.3%)	
Race				
White	342 (96.3%)	120 (94.5%)	222 (97.4%)	
African American	13 (3.7%)	7 (4.5%)	6 (2.6%)	
Stage of breast cancer				
I	233 (65.6%)	48 (37.8%)	185 (81.1%)	U=7648.5, p<0.001
IIA	76 (21.4%)	41 (32.3)	35 (15.4%)	
IIB	27 (7.6%)	20 (15.7)	7 (3.1%)	
IIIA	19 (5.4%)	18 (14.2)	1 (0.4%)	
Surgery				
Mastectomy	51 (14.4%)	26 (20.5%)	25 (11.0%)	χ^2=5.993, p=0.014
Lumpectomy	290 (81.7%)	93 (73.2%)	197 (86.4%)	χ^2=9.466, p=0.002

Note: U= Mann–Whitney U; AnastOnly: women prescribed anastrozole therapy only; ChemoAnast: women prescribed chemotherapy and anastrozole therapy.

[†]*P* value are from the student t test or Mann-Whitney U test for continuous variables and Pearson chi-square tests of independence for categorical variables, only those characteristics that demonstrated statistically significant differences (p<.05) between the two treatment groups are reported in the table.

3.2.4.2 Changes in symptom clusters over time

Multiple symptom clusters were identified at four time points (see Table 10). Based on the characteristics of the symptoms loading on a symptom cluster, eight distinct symptom clusters were revealed and were labeled as: *cognitive, psychological, musculoskeletal, vasomotor, urinary, sexual, weight, and gastrointestinal (GI).* All the symptom clusters were present at baseline and lingered over time during AI therapy, except for the GI symptom cluster.

The *musculoskeletal, vasomotor, urinary, sexual* symptom cluster were most stable over time with the same symptoms with the symptom clusters from pre-adjuvant therapy to 18 months. Symptoms in the *musculoskeletal* symptom cluster included general aches, joint pain, muscle stiffness, and general pain intensity. The *vasomotor* symptom cluster consisted of hot flashes and night sweats. The *urinary* symptom cluster comprised difficulty with bladder control when laughing or crying and difficulty with bladder control at other times. The *sexual* symptom cluster consisted of vaginal dryness and pain with intercourse.

The neuro*cognitive, psychological*, and *weight* symptom clusters were relatively stable over time with some changes in symptoms within the symptom clusters at some time points.

Across the first three time points, difficulty concentrating, being easily distracted, forgetfulness, and perceived cognitive disturbance were stable within the *cognitive* symptom cluster, with the addition of dry mouth at 6 months, and symptom excitability, short temper, and tendency toward accidents at 12 months. Fatigue and depressive symptoms were stable within the *psychological* symptom cluster from baseline to 12 months. However, the *cognitive* and the *psychological* symptom cluster merged into a *psychoneurocognitive* symptom cluster at 18 months, which consisted of fatigue, depressive symptoms, anxiety, difficulty concentrating, being easily distracted, forgetfulness, excitability, and short temper. The *weight* symptom cluster, consisting of weight gain and unhappiness with appearance, was stable from 6 months to 18 months. However, these two symptoms were not present at baseline. Instead, weight loss and decreased appetite clustered together at baseline.

The *GI* symptom cluster was not stable over time. It was only observed at 6 months and consisted of nausea and diarrhea. At 12 and 18 months, nausea was not included in the EFA because of its low prevalence (<20%).

Table 10 Symptom Clusters with Factor Loadings at Four Time Points

Baseline	6 Months	12 Months	18 months
Psychological depressive symptoms (0.681), anxiety (0.640), changes in sleep patterns (0.569), avoid of social affairs (0.566), fatigue (0.505),	**Psychological** anxiety (0.843), depressive symptoms (0.811), avoid of social affairs (0.548), fatigue (0.475), short temper (0.402)	**Psychological** fatigue (0.726), changes in sleep patterns (0.575), depressive symptoms (0.439)	**Psychoneurocognitive** excitability (0.884), forgetfulness (0.819), anxiety (0.779), difficulty concentrating (0.729), easily distracted (0.723), depressive symptoms (0.707), fatigue (0.444), short temper (0.443)
Neurocognitive difficulty concentrating (0.899), easily distracted (0.866), forgetfulness (0.747), perceived cognitive disturbance (0.593)	**Neurocognitive** difficulty concentrating (0.937), forgetfulness (0.872), easily distracted (0.854), perceived cognitive disturbance (0.692), dry mouth (0.417)	**Neurocognitive** easily distracted (0.929), difficulty concentrating (0.911), excitability (0.782), perceived cognitive disturbance (0.733), forgetfulness (0.721), short temper (0.578), tendency toward accidents (0.452),	

		anxiety (0.400)	
Musculoskeletal joint pain (0.915), general aches (0.814), muscle stiffness (0.719), general pain (0.535)	**Musculoskeletal** general aches (0.842), joint pain (0.920), muscle stiffness (0.703), general pain (0.456)	**Musculoskeletal** joint pain (0.964), general aches (0.802), muscle stiffness (0.623), general pain (0.500)	**Musculoskeletal** joint pain (0.955), general pain (0.817), muscle stiffness (0.767), general aches (0.603)
Vasomotor night sweats (0.880), hot flashes (0.857)	**Vasomotor** night sweats (0.874), hot flashes (0.865)	**Vasomotor** hot flashes (0.891), night sweats (0.697)	**Vasomotor** night sweats (0.854), hot flashes (0.806)
Bladder difficulty with bladder control when laughing or crying (0.908), difficulty with bladder control at other times (0.818)	**Bladder** difficulty with bladder control at other times (0.858), difficulty with bladder control when laughing or crying (0.750)	**Bladder** difficulty with bladder control at other times (0.834)，difficulty with bladder control when laughing or crying (0.709)	**Bladder** difficulty with bladder control when laughing or crying (0.773), difficulty with bladder control at other times (0.605)
Sexual vaginal dryness (0.833), pain with intercourse (0.554)	**Sexual** vaginal dryness (0.843), pain with intercourse (0.712)	**Sexual** vaginal dryness (0.872), pain with intercourse (0.809)	**Sexual** vaginal dryness (0.846), pain with intercourse (0.771)
Weight decreased appetite (0.803), weight loss (0.600)	**Weight** unhappy with the appearance of my body (0.821), weight gain (0.575)	**Weight** weight gain (0.840), unhappy with the appearance of my body (0.602)	**Weight** weight gain (0.661), unhappy with the appearance of my body (0.606)
N/A	**GI** diarrhea (0.938), nausea (0.694)	**N/A**	**N/A**

3.2.4.3 Differences in symptom clusters between the two groups

Table 11 and 12 showed the symptom clusters among women in ChemoAnast, and AnastOnly groups, respectively. At baseline and 18 months, fatigue and changes in sleep patterns clustered together with other *psychological* symptoms in AnastOnly group. These two symptoms stood out as a unique symptom cluster in ChemoAnast group. The *GI* symptom cluster was identified at 6 months in ChemoAnast group only. At 12 months, fatigue and depressive symptoms clustered with *musculoskeletal* symptoms in AnastOnly group.

Table 11 Table Symptom Clusters at Four Time Points for ChemoAnast Group

Baseline	6 Months	12 Months	18 months

Psychological unhappy with the appearance of my body (0.743), depressive symptoms (0.635), short temper (0.547), avoid of social affairs (0.497), anxiety (0.444)	**Psychological** depressive symptoms (0.737), anxiety (0.713), avoid of social affairs (0.477), fatigue (0.473)	**Psychological** fatigue (0.748), avoid of social affairs (0.663), changes in sleep pattern (0.521)	**Psychoneurological** easily distracted (0.900), excitability (0.832), forgetfulness (0.823), difficulty concentrating (0.787), anxiety (0.730), depressive symptoms (0.488), short temper (0.428)
Neurocognitive difficulty concentrating (0.887), forgetfulness (0.875), easily distracted (0.858), perceived cognitive disturbance (0.613)	**Neurocognitive** forgetfulness (0.968), difficulty concentrating (0.803), easily distracted (0.745), perceived cognitive disturbance (0.735), dry mouth (0.636), excitability (0.517)	**Neurocognitive** difficulty concentrating (0.925), easily distracted (0.991), forgetfulness (0.762), perceived cognitive disturbance (0.704), anxiety (0.604), excitability (0.549), tendency toward accidents (0.465),	
Musculoskeletal joint pain (0.959), general aches (0.834), muscle stiffness (0.517)	**Musculoskeletal** joint pain (0.977), general aches (0.841), muscle stiffness (0.663), general pain (0.645)	**Musculoskeletal** general aches (0.930), joint pain (0.961), muscle stiffness (0.681), general pain (0.645), unhappy with the appearance of my body (0.457),	**Musculoskeletal** joint pain (0.972), general aches (0.879), muscle stiffness (0.758), general pain (0.704), numbness (0.576), swelling of hands or feet (0.520)
Vasomotor night sweats (0.933), hot flashes (0.904)	**Vasomotor** hot flashes (0.809), night sweats (0.804)	**Vasomotor** hot flashes (0.823), night sweats (0.753)	**Vasomotor** night sweats (0.916), hot flashes (0.751)
Bladder difficulty with bladder control when laughing or crying (0.962) difficulty with bladder control at other times (0.821)	**Bladder** N/A	**Bladder** difficulty with bladder control at other times (0.901), difficulty with bladder control when laughing or crying (0.725)	**Bladder** difficulty with bladder control when laughing or crying (0.716), difficulty with bladder control at other times (0.498)
N/A	**Sexual** pain with intercourse (0.828), vaginal dryness (0.804)	**Sexual** vaginal dryness (0.941), pain with intercourse (0.842)	**Sexual** pain with intercourse (0.991), vaginal dryness (0.677)
Weight weight gain (0.628), swelling of hands or feet (0.551)	**Weight** weight gain (0.680) decreased appetite (-0.639), weight loss (-0.550), unhappy with the appearance of my body (0.445)	**Weight** dry mouth (0.606), weight gain (0.593)	**Weight** weight gain (0.732), unhappy with the appearance of my body (0.707)
Sickness changes in sleep patterns (0.721),	N/A	N/A	**Sickness** fatigue (0.876),

fatigue (0.557)			changes in sleep patterns (0.572)
N/A	**GI** Nausea (0.663), Diarrhea (0.860), blind spots (0.456)	N/A	N/A

Table 12 Symptom Clusters at Four Time Points for AnastOnly Group

Baseline	6 Months	12 Months	18 months
Psychological depressive symptom (0.760), avoid of social affairs (0.685), anxiety (0.626), fatigue (0.498) changes in sleep patterns (0.488)	**Psychological** depressive symptom (0.765), avoid of social affairs (0.671), anxiety (0.581), general pain (0.541), decreases appetite (0.515), fatigue (0.505), headaches (0.453)	N/A	**Psychoneurocognitive** excitability (0.945), perceived cognitive disturbance (0.877), depressive symptom (0.762), forgetfulness (0.750), anxiety (0.738), difficulty concentrating (0.559), easily distracted (0.473)
Neurocognitive difficulty concentrating (0.854), easily distracted (0.814), forgetfulness (0.770), perceived cognitive disturbance (0.607), short temper (0.415)	**Neurocognitive** difficulty concentrating (0.961), forgetfulness (0.849), easily distracted (0.844), perceived cognitive disturbance (0.696), blind spots (0.487)	**Neurocognitive** difficult concentrating (0.989), easily distracted (0.913), excitability (0.800), perceived cognitive disturbance (0.761), forgetfulness (0.708), anxiety (0.604), avoidance of social affairs (0.563), tendency toward accidents (0.465)	
Musculoskeletal joint pain (0.906), general aches (0.837), muscle stiffness (0.749), swelling of hands or feet (0.551), numbness (0.448)	**Musculoskeletal** general aches (0.901), joint pain (0.814), muscle stiffness (0.715)	**Musculoskeletal-depressive symptoms** joint pain (0.949), general aches (0.862), muscle stiffness (0.506), fatigue (0.485), general pain (0.416), depressive symptoms (0.408)	**Musculoskeletal** general pain (0.891), joint pain (0.832), muscle stiffness (0.693)
Vasomotor night sweats (0.854), hot flashes (0.835)	**Vasomotor** hot flashes (0.925), night sweats (0.846)	**Vasomotor** night sweats (0.917), hot flashes (0.812)	**Vasomotor** night sweats (0.944), hot flashes (0.807)
Bladder difficulty with bladder control when laughing or crying (0.872), difficulty with bladder control at other times (0.743)	**Bladder** difficulty with bladder control when laughing or crying (0.852), difficulty with bladder control at other times (0.844)	**Bladder** difficulty with bladder control at other times (0.676), difficulty with bladder control when laughing or crying (0.809)	**Bladder** difficulty with bladder control when laughing or crying (0.969), difficulty with bladder control at other times (0.774)
Sexual vaginal dryness, pain with intercourse	**Sexual** vaginal dryness (0.767), pain with intercourse (0.742)	**Sexual** vaginal dryness (0.853), pain with intercourse (0.770)	**Sexual** pain with intercourse (0.832), vaginal dryness (0.726)

Weight weight gain, decreased appetite	**Weight** unhappy with the appearance of my body (0.757), weight gain (0.705)	**Weight** weight gain (0.759), unhappy with the appearance of my body (0.589), dry mouth (0.469)	**Weight** weight gain (0.737), unhappy with the appearance of my body (0.708)

3.2.5 Discussion

This is the first study to evaluate and descriptively compare changes in the composition of symptom clusters among two cohorts of women with breast cancer treated with AI therapy from pre-adjuvant therapy to 18-months adjuvant therapy. We will discuss each symptom cluster separately based on the specific symptoms within the cluster and their stability.

3.2.5.1 Psychological and neurocognitive symptom clusters

In this study, the main symptoms in the psychological symptoms were fatigue, anxiety and depressive symptoms. In other studies, depressive symptoms, anxiety and fatigue also clustered with sleep disturbance, cognitive symptoms, and pain (Kim, Barsevick, Tulman, & McDermott, 2008; Langford et al., 2016; Starkweather et al., 2017). The main symptoms in the neurocognitive symptom cluster are difficulty concentrating, being easily distracted, forgetfulness, and perceived cognitive disturbance. Similar to our finding, Roiland et al. (2011) identified a symptom cluster consisting of balance problems, dizziness, memory problems, and trouble concentrating among breast cancer survivors. In other studies, cognitive symptoms clustered with outlook (worry about future) (Matthews et al., 2012), pain, shortness of breath and vomiting (Hsu et al., 2017).

It was worth noting that that psychological symptoms clustered with neurocognitive symptoms into a psychoneurocognitive symptom cluster at 18 months. Sullivan et al.(2018) also

found that some cognitive symptoms (i.e., difficulty concentrating) clustered with psychological symptoms among women with breast cancer during chemotherapy. These findings suggest that common biological mechanisms may exist between psychological and cognitive symptoms since they are usually highly correlated. Meanwhile, fatigue and changes in sleep patterns did not cluster with psychological symptoms at baseline and 18 months for women in the ChemoAnast group. It suggests that behavioral symptoms (i.e., fatigue, sleep problems) may have different biological mechanisms with psychological and neurocognitive symptoms even though they are usually highly correlated. Prior studies have related higher overall burden of fatigue, sleep problems, depressive symptom, anxiety and pain to increases in levels of systemic inflammation, resulting in the experience of sickness (Wang et al., 2010). Future studies are needed to examine whether psychological, behavioral and neurocognitive symptoms have common or disparate biological mechanisms.

Results from the current study suggest that the psychological and neurocognitive symptom clusters persist for a long time. Healthcare providers should assess patients' psychological symptoms both during cancer diagnosis and during long-term cancer treatment and should integrate mental health with cancer care when needed.

3.2.5.2 Musculoskeletal, vasomotor, urinary and sexual symptom clusters

In this study, the musculoskeletal, vasomotor, urinary and sexual symptom cluster appeared prior to adjuvant therapy and they were stable over the 18 months of adjuvant therapy.

Consistent with the current results, Sullivan et al. (2018) identified the same hormonal symptom cluster, consisting of hot flashes and night sweats among both pre- and post-menopausal women with breast cancer before and during chemotherapy. Night sweats and hot flashes can also cluster with some psychoneurological symptoms (i.e., feeling irritable, difficulty concentrating,

mood swings) before and after chemotherapy (Phligbua et al., 2013). It was interesting to note that fatigue and depressive symptoms clustered together with musculoskeletal symptoms at 12 months post-AI therapy in AnastOnly group. Consistent with this study, previous studies found that general aches, joint pain, and muscle pain clustered together with other symptoms (i.e., fatigue, weakness, headaches) (Marshall et al., 2016; Roiland & Heidrich, 2011). These studies suggest that fatigue and depressive symptoms are highly associated with musculoskeletal symptoms among women with breast cancer. Therefore, it is important to manage fatigue, depressive symptoms and musculoskeletal symptoms together.

Only two studies have reported urinary and sexual symptom clusters among women with breast cancer. Roiland et al. (2011) found that incontinence, increased urination, decreased sex drive, and irritated eyes clustered together among breast cancer survivors. In Yates et al. (2015), urinary problems clustered with sexual problems among younger (<60 years) cancer patients, whereas urinary problems clustered with problems with sexual interest, diarrhea, and irritability among older (≥60 years) cancer patients. Urinary and sexual symptoms merged into one symptom cluster among those studies; however, they were identified as unique symptom clusters in our study. Compared to those two studies, our study has a more homogenous sample in terms of cancer type (breast cancer versus breast, prostate, lung and other cancer) and menopausal status (postmenopausal versus pre- and postmenopausal).

Since these symptom clusters may be attributed to the impact of reduced estrogen with AI therapy or menopause status (Lønning, 1996), more studies are warranted to explore trajectories of these symptom clusters while considering age and menopause status as influential factors.

3.2.5.3 GI symptom cluster

In this study, the GI symptom cluster was only identified at 6 months among women in the ChemoAnast group. The appearance of the GI symptom cluster was not related to AI therapy. Although we did not record the exact date of completion of chemotherapy in this group, the results raise the possibility that symptoms of nausea and vomiting resulting from chemotherapy lingered weeks after chemotherapy and present prior to AI therapy. More studies are needed to confirm the duration of the GI symptom cluster after chemotherapy.

The GI symptom cluster has been reported in other studies as well. However, symptoms within the GI symptom cluster varied across studies. Kim et al. (2008) identified that nausea and vomiting clustered with decreased appetite among women with breast cancer 48 hours after chemotherapy. In Sullivan et al. (2018) study, nausea sometimes clustered with weight loss, weight gain, lack of appetite, and diarrhea as a nutritional symptom cluster and sometimes clustered with feeling bloated and abdominal cramps as a GI symptom cluster. Hsu et al. (2017) found that nausea clustered with emotional symptoms and peaked at 3 to 5 days during chemotherapy and gradually decreased till the end of 21-day chemotherapy cycle. Future research is needed to evaluate the relationship between GI, nutritional and emotional symptoms among women with breast cancer.

3.2.5.4 Weight symptom cluster

The symptoms within the weight symptom cluster changed from baseline to 6 months and then were stable over time after AI therapy was initiated. At baseline, weight loss and decreased appetite clustered together. This result was consistent with Sullivan et al. (2018) study which showed that weight gain clustered with weight loss and decreased appetite one week prior to chemotherapy, then disappeared during and after chemotherapy. In the current study, weight gain and unhappy with the appearance clustered together from 6 months to 18 months. Few studies have identified

weight gain and unhappiness with appearance, as these two symptoms are not included in most symptom scales, such as the Memorial Symptom Assessment Scale (Portenoy et al., 1994). This study indicates the need to include weight gain and satisfaction with appearance in future symptom research. More studies are needed to confirm the weight symptom cluster among women with breast cancer during AI therapy.

3.2.5.5 Limitations

Some limitations are important to consider in this study. First, 96% of our sample was Caucasian. The racial homogeneity of the sample may influence the study result. Secondly, the recommended sample size for EFA is at least 300, with the criteria "100 = poor, 200 = fair, 300 = good" (MacCallum et al., 1999). Our sample (N=354) is sufficient to conduct exploratory factor analysis at baseline. However, our sample size is not sufficient to conduct exploratory factor analysis separately for women in the ChemoAnast (n=127) group and women in the AnastOnly (n=227) group. The comparisons that were accomplished over time and between the two treatment cohorts were purely descriptive and exploratory. Future efforts are needed to expand the study in larger, more racially diverse sample. Lastly, differences in the dimensions of symptoms (i.e., occurrence, severity, distress) may influence clustering of symptoms. We only identified symptom clusters using a symptom severity score. Future research is needed to examine different dimensions of symptoms when identifying symptom clusters.

3.2.6 Conclusion

We identified four stable symptom clusters with the same symptoms within the symptom clusters from pre-adjuvant therapy to 18 months post adjuvant therapy (i.e., musculoskeletal, vasomotor,

urinary, sexual), and three relatively stable symptom clusters with some changes in symptoms within the symptom clusters at some time points (i.e., psychological, neurocognitive, weight) among postmenopausal women with early stage breast cancer. These symptom clusters exist prior to any adjuvant treatment and persist for the first 18 months of adjuvant therapy. The GI symptom cluster only appeared at 6-month time point of adjuvant therapy in ChemoAnast group (i.e., post chemotherapy). It is important for health care providers to educate women with breast cancer that many symptom clusters may already exist before adjuvant therapy, the presence of these symptom clusters may relate to menopause, general health status, cancer pathophysiology, or other demographic or clinical characteristics, but symptoms are not all sue to the effect of adjuvant therapy. Adjuvant therapy may exacerbate these preexisting symptoms. Further studies are needed to confirm these findings by evaluating trajectories of the stable symptom clusters and identifying predictors related to these symptom clusters.

The current findings inform future research by introducing symptoms for assessments and through suggesting shared biological mechanisms. Since AI therapy is usually prescribed for 5 to 10 years, it is critical for health care providers to know the symptom clusters experienced by women receiving this treatment and manage them properly over time in order to improve adherence. This is particularly important given low levels of adherence to this prolonged treatment, with some indication that women stop taking the medication due to ongoing symptoms. Future studies are needed to explore the biological mechanisms underlying each symptom cluster and to identify both phenotypic and genotypic factors that influence the inter-individual differences of the symptom cluster experience.

3.3 GENES INVOLVED IN THE HPA AXIS AND THE SYMPTOM CLUSTER OF FATIGUE, DEPRESSIVE SYMPTOM AND ANXIETY IN WOMEN WITH BREAST CANCER DURING 18 MONTHS OF ADJUVANT THERAPY

3.3.1 Abstract

Fatigue, depressive symptom and anxiety frequently coexist throughout cancer diagnosis and treatment trajectory among women with breast cancer. Research shows that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may contribute to these contemporaneous symptoms. Individual differences in genetics may also contribute to the risk for this psychological symptom cluster via association with HPA axis function. The aims of this study were to (1) identify subgroups of postmenopausal women with distinct experiences with the psychological symptom cluster from pre-adjuvant therapy through the first 18 months after starting adjuvant therapy and (2) explore associations between demographic and clinical characteristics and variation in genetic polymorphisms related to HPA axis function and the predicted symptom trajectory subgroup membership. Genetic data were collected in a subgroup at pre-adjuvant therapy (N=184), and symptom data were collected semi-annually at four time points from baseline to 18-month follow-up (N=292). Group-based multi-trajectory modeling was used to classify women with breast cancer into subgroups with similar psychological symptom cluster trajectories over the course of their adjuvant therapy. Binary logistic regression analysis was used to explore the associations between each genotypic and phenotypic predictor and predicted trajectory subgroup membership. Two distinct symptom subgroups (low and high) were identified based on the trajectories of the psychological symptom cluster of fatigue, depressive symptom and anxiety over the first 18 months of adjuvant therapy. Younger age [OR=0.92, P<0.001], less education [OR=0.86,

P=0.004], and treatment with chemotherapy [OR=1.66, *P*=0.071] were associated with greater odds of being in the high severity psychological symptom cluster subgroup. Polymorphic variations in genes related to the HPA axis (i.e., FKBP5 rs9394309 [OR=3.98, *P*=0.015], NR3C2 rs5525 [OR=2.54, *P*=0.036], CRHR1 rs12944712 [OR=3.99, *P*=0.021]) were also associated with membership in the high severity psychological symptom cluster subgroup. Results of this study may help healthcare providers to screen and identify postmenopausal women diagnosed with early stage breast cancer who are at increased risk for psychological symptoms during adjuvant therapy which includes the AI, anastrozole, facilitating the development of individualized and preemptive interventions to better manage their symptoms.

3.3.2 Introduction

Women with breast cancer commonly experience multiple psychological symptoms throughout their cancer diagnosis and treatment trajectory (Park et al., 2018; Tsaras et al., 2018). According to a systematic review, approximately 39% and 27.2% women with breast cancer will experience long-term depressive symptom and anxiety, respectively, five years after a cancer diagnosis (Maass, Roorda, Berendsen, Verhaak, & de Bock, 2015). Psychological symptoms are highly correlated with somatic symptoms (Leonhart et al., 2017). Increasing evidence shows that fatigue, depressive symptom and anxiety frequently cluster together among women with breast cancer (Bower et al., 2011; Doong et al., 2015; Ho et al., 2015). Results from our previous longitudinal study of symptom clusters among women with breast cancer also suggests that these symptoms form a psychological symptom cluster, with possible concurrent symptoms of “sleep disturbance”, and “cognitive impairment”. These psychological symptoms have a detrimental impact on

cognitive function, adherence to treatment and can compromise the patients' quality of life (QOL) (Biglia et al., 2012; Ng et al., 2015; Pitman, Suleman, Hyde, & Hodgkiss, 2018).

The etiologies of fatigue, and depressive symptom and anxiety are multifactorial. Although the reason for the clustering of these psychological symptoms remains unclear, it is widely suggested that cytokines, which act on the central nervous system, may play a role by inducing sickness behaviors (Cleeland et al., 2003). Women with breast cancer experience high levels of stress from cancer diagnosis and throughout undergoing cancer treatment with the activation of inflammatory response are at high risk for developing psychological symptoms (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). Peripheral levels of proinflammatory mediators are controlled by a number of physiological pathways. Key among them is the hypothalamic-pituitary-adrenal (HPA) axis, which has a complex and bidirectional relationship with the immune system (Chrousos, 1995). Research shows that the HPA axis can be suppressed by chemotherapy and radiation therapy during cancer treatment (Schmiegelow et al., 2003), which may contribute to increased inflammation. Other factors, such as psychological stress related to cancer diagnosis and treatment, can also induce inflammation and disrupt the HPA axis (Marsland, Walsh, Lockwood, & John-Henderson, 2017; Spiegel et al., 2006). Although no study has evaluated the influence of endocrine therapy on inflammation and the HPA axis among women with breast cancer, a significant body of work suggests that higher levels of estrogen has an anti-inflammatory effect (Kovats, 2015), which can stabilize the function of the HPA axis (De Nicola, Saravia, Beauquis, Pietranera, & Ferrini, 2006). The estrogen levels of postmenopausal women with breast cancer are substantially reduced due to the effect of aromatase inhibitor (AI) therapy and the change of menopausal status (Lønning, 1996). Therefore, activation and disruption of the HPA axis during cancer treatment and subsequent modulation of levels of proinflammatory mediators may

contribute to individual differences in vulnerability to clusters of psychological symptoms. In support of this possibility, research shows that disrupted HPA axis activity has been linked with psychological symptoms among cancer patients. Hoyt and colleagues found that sleep disruption and depressive symptom were related to disrupted cortisol activity (Hoyt et al., 2016). Similarly, another study showed that a symptom cluster of pain, depressive symptom, and fatigue was associated with increased level of cortisol and adrenocorticotropic hormone levels among women with breast cancer (Thornton et al., 2010). The regulation of peripheral inflammation by the HPA axis is influenced by both peripheral levels of cortisol and the sensitivity of glucocorticoid receptors (GR) in immune cells to its anti-inflammatory properties (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). A number of genetic polymorphisms have been identified that can influence magnitude of HPA axis activity and sensitivity of GR receptors. Moreover, a number of these polymorphisms (e.g., FKBP5, CRHR1, CRHR2, NR3C1) are associated with a higher risk of post-traumatic stress disorder and depressive disorder (Carvalho, Coimbra, Ota, Mello, & Belangero, 2017; Rao et al., 2016; Watkins et al., 2016). This raises the possibility that variation in genes that regulate activity and sensitivity of the HPA axis may contribute to the experience of comorbid psychological symptoms among women with breast cancer.

To date, studies have focused on the experience of clusters of symptoms among women with breast cancer who are receiving chemotherapy (Kim et al., 2014). Results suggest that symptoms of pain, fatigue, sleep difficulty and depressive symptom cluster within these patients over time. The trajectory of the psychological symptom cluster among women receiving long-term endocrine therapy is less well characterized and factors that may impact risk for these symptoms are poorly understood. Based on evidence that the HPA axis plays a role in the modulation of peripheral inflammatory mediators that can result in sickness and psychological symptoms,

including fatigue, depressive symptom and anxiety, it is possible that genetic polymorphisms that relate to variation in HPA axis function may contribute to risk for the psychological symptom cluster among women with breast cancer.

Accordingly, the purpose of this study is to: (1) identify subgroups of women with breast cancer with distinct experiences with the psychological symptom cluster from baseline through the first 18 months of systemic adjuvant therapy; and (2) explore associations between demographic and clinical characteristics and variation in genetic polymorphisms related to HPA axis function and symptom subgroup membership.

3.3.3 Methods

3.3.3.1 Study design

This is an analysis of existing symptom data and newly generated genomic data from a prospective repeated measures study of cognitive function in postmenopausal women receiving the AI, anastrozole, for early stage breast cancer (R01-CA107408) (Bender et al., 2015). Symptom data were collected every 6 months from baseline (after surgery and pre-adjuvant therapy) to 18-months post initiation of adjuvant therapy. Genetic data were collected from DNA extracted from blood or saliva samples.

3.3.3.2 Sample and setting

Two cohorts of postmenopausal women with early stage breast cancer who had completed surgery were recruited from the Breast Cancer Program of the Hillman Cancer Institute. One group of women was only prescribed anastrozole therapy (AnastOnly) and the other group of women was prescribed chemotherapy followed by anastrozole therapy (ChemoAnast). The original study was

approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent.

Women were included if they were newly diagnosed with stage I, II or IIIA breast cancer, postmenopausal, less than 75 years old, scheduled to receive chemotherapy plus anastrozole or anastrozole alone, abled to speak and read English and had completed a minimum of 8 years of education. Women were excluded if they had self-reported psychiatric illness within the previous 2 years, a prior diagnosis of a neurologic illness or cancer, or clinical evidence of distant metastases. For this analysis, we only included women who had symptom data for at least two of the time points from baseline to 18 months after adjuvant therapy initiation (N=292).

3.3.3.3 Measures

Self-reported demographic information and clinical characteristics from medical records were collected at baseline, including age, race, education level, occupation type, marital status, disease stage, and types of treatments.

3.3.3.4 Symptom measures

Two subscales of the Profile of Mood States (POMS) (Fatigue/Inertia subscale and Tension/Anxiety subscale) were used to measure fatigue and anxiety. The POMS is a self-reported measure of mood states, with 65-items rated on a 5-point Likert scale format ranging from 0 (not at all) to 4 (extremely) (McNair et al., 1992). The POMS-Fatigue/Inertia subscale has 7 items, with a test-retest reliability of 0.66 and internal consistency of 0.94 (McNair et al., 1992). The POMS-Tension/Anxiety subscale has 9 items, with an internal consistency of 0.92 and test-retest reliability of 0.70 (McNair et al., 1992). Higher average fatigue and anxiety subscale scores (range 0-4) indicate a greater severity of fatigue and anxiety.

The Beck Depression Inventory-II (BDI-II), a 21-item, self-reported measure in which depressive symptom severity is rated on a 4-point Likert scale ranging from 0 (no symptoms) to 3 (severe symptoms) (Beck et al., 1996). High reliability and validity have been demonstrated for the BDI (Wang & Gorenstein, 2013). The BDI-II measures somatic symptoms (items 15-21) and mood/cognitive symptoms (items 1-14) (Thombs et al., 2010). For this study, the total score of items 1-14 was used to measure depressive symptom to avoid the influence of other treatment related symptoms. Higher total scores for the 14 items indicate more severe depressive symptoms.

3.3.3.5 Genotypic measures

Among participants who provided a blood sample for genetic analyses(n=184), those providing blood had genomic deoxyribonucleic acid (DNA)was extracted from white blood cells using the simple salting-out method (Miller et al., 1988). If blood was unavailable, DNA was extracted from saliva using prepIT•L2P (Genotek, 2016). Samples were genotyped using the iPLEX MassArray platform which has excellent with proven accuracy (>99.7% concordance rate). To control the quality of genetic data, Hardy-Weinberg p-values of <0.05 and SNPs with call rates of <95% were excluded.

Based on the knowledge that the HPA axis plays a key role in the control of peripheral levels of proinflammatory mediators that communicate with the central nervous system to coordinate comorbid psychoneurological symptoms, we focused only on genes and SNPs that are directly related to the HPA axis. A review of functional SNPs of genes associated with the HPA axis in the general population was conducted. Search terms “single nucleotide polymorphism”, “gene” and “HPA axis” were used in the initial search, which identified 33 genes and 118 SNPs. We employed a review of the literature to narrow our examination of genes to those that play a direct and major role in HPA regulation (Arnett et al., 2016). Although many candidate genes can

influence the function of the HPA axis, genes related to glucocorticoid receptors (NR3C1, FKBP5), mineralocorticoid receptor (NR3C2), and corticotropin-releasing hormone (CRHR1, CRHR2, CRHBP) play an important role in the regulation of HPA axis reactivity (Arnett et al., 2016). Finally, a list of 39 SNPs in these 6 genes that have been associated with HPA regulation in the literature were selected for analysis after quality control (See Appendix A, Table 1).

3.3.3.6 Statistical analysis

Group-based multi-trajectory modeling was used to classify women with breast cancer into subgroups with "similar" psychological symptom cluster trajectories over the course of adjuvant therapy. The SAS macro PROC TRAJ (*SAS 9.4*) (Jones, 2014) was used to perform this analysis. Data screening was performed to make sure the assumption for missing data at random was not violated and the subsample used for the genetic analysis were random samples from the original dataset. First, based on our prior knowledge of symptom clusters trajectory studies (Avis, Levine, Case, Naftalis, & Van Zee, 2015; Donovan, Gonzalez, Small, Andrykowski, & Jacobsen, 2013), two to five subgroups were fitted in the models. To identify the optimal number of subgroups among trajectory models, we used the following the criteria for model selection: (1) highest Bayesian Information Criterion (BIC) and (2) average posterior probabilities (AvePP) of class membership. To assess model adequacy, the following criteria were used: (1) AvePP of assignment should exceed 0.7 for all subgroups, (2) the odds of correct classification (OCC) should exceed 5 for all subgroups, and (3) close correspondence between the estimated probability of group membership and the proportion classified in that group (Nagin & Odgers, 2010). The parameters of the unconditional multi-trajectory modeling included the probability of membership in each subgroup's trajectory and the regression coefficients (b_0 =intercept, b_1 =linear, or b_2 =quadratic) of each subgroup's trajectory. The significance level was set at 0.05.

Binary logistic regression analysis was used to explore the associations between demographic and clinical predictors and predicted trajectory subgroup membership. Univariate analyses were used initially to identify potential significant predictors ($p<0.10$) to include in the multivariable models. Age, marital status, race, education, employment, stage of disease, and treatment of chemotherapy were evaluated as potential predictors.

Binary logistic regression was used to explore the relationship between each genetic model for each SNP (additive, dominant, recessive) and the predicted trajectory subgroup membership. Significant demographic and clinical predictors were included in the binary logistic models at potential covariates. Univariate analyses were initially performed for each SNP. Each possible SNPs with $p<0.10$ identified in the univariate analyses were evaluated one at a time in the multivariate model controlling for significant covariates. Only significant SNPs ($p<0.05$) controlling for covariates were reported in the final results. Goodness of fit, covariate-adjusted odds ratios (ORs) and 95% confidence intervals were reported to estimate the magnitude and precision of the association between predictors variables and predicted subgroup membership.

3.3.4 Results

3.3.4.1 Trajectory of two subgroups

The response profiles/trajectories identified via multi-trajectory modeling for each of the three symptoms are included Table 13 and Figure 4. Two distinct trajectory subgroups (low and high) were identified from multi-trajectory modeling based on the trajectories of fatigue, depressive symptoms and anxiety with best fit based on selection and diagnostic criteria (BIC=-9555.55, $AvePP_{low\ group}$=97.5%, $AvePP_{high\ group}$=95.7%, $OCC_{low\ group}$=11, $OCC_{high\ group}$=77). Approximately 22.6% of women were classified in the high trajectory group. In the high group, self-reports of

fatigue and depressive symptoms remained high from baseline to 18 months ($b_{0,fatigue}$ = 42.487, $b_{0,depressive\ symptom}$ = 12.883). However, significant linear and quadratic effects were also found for anxiety in the high group (b_0 = 51.928, b_1 = -14.536, and b_2 = 2.795). As shown in Figure 4, anxiety was high at baseline, declined from baseline to 6 months and then slightly increased after 12 months. In the low group, self-reports on fatigue and depressive symptoms remained low from baseline to 18 months ($b_{0,fatigue}$ = 12.219, $b_{0,depressive\ symptom}$ = -2.175), whereas anxiety declined linearly from baseline to 18 months (b_0 =15.501, b_1 = -1.282) in the low group. The estimated parameters reported in Table 13 were the intercept, linear and quadratic terms of the latent variable, not the predicted mean on the trajectory plot in Figure 4. Trajectory mean calculation is complex and uses the equation developed by Nagin (2005, p.32), which takes into account the impact of censoring.

Table 13 Group-Based Trajectory Model Profiles

Predicted Trajectory Group Membership	**Symptoms**	**Model Parameter (SE), p-value**		
		Intercept	**Linear**	**Quadratic**
Low Severity (77.37%)	Fatigue	12.22 (0.97), p<.001	N/A	N/A
	Depression symptom	-2.18 (0.59), p<.001	N/A	N/A
	Anxiety symptoms	15.50 (1.14), p<.001	-1.28 (0.42), p=.002	N/A
High Severity (22.63%)	Fatigue	42.49 (1.93), p<.001	N/A	N/A
	Depression symptom	12.88 (1.02), p<.001	N/A	N/A
	Anxiety symptoms	51.93 (5.10), p<.001	-14.54 (4.50), p=.001	2.76 (0.93), p=.003

Note: SE=standard error

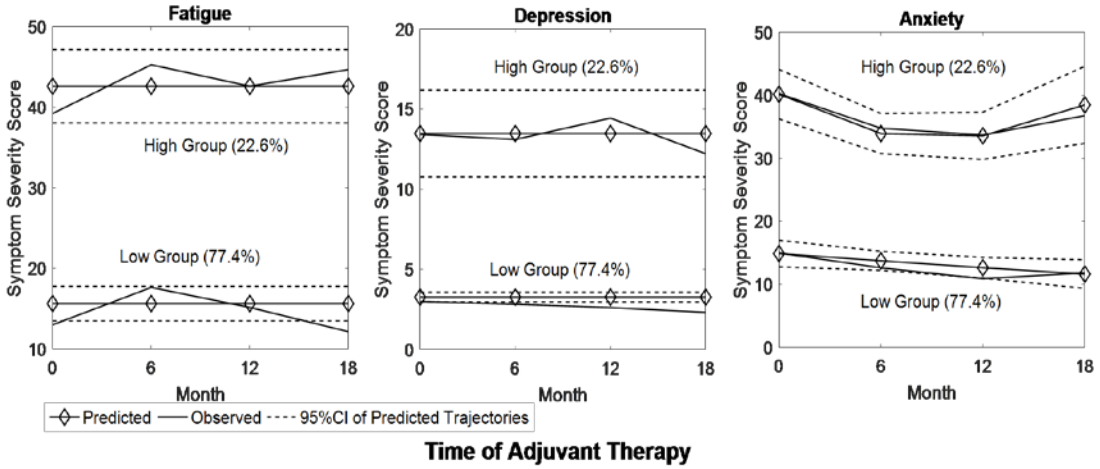

Figure 4 Trajectories of Fatigue, Depressive Symptoms and Anxiety

Table 14 Demographic and Clinical Characteristics Between Predicted Trajectory Subgroup

Characteristic	**Low Group (n=225)**	**High Group (n=67)**	**Univariate**	**Multivariate**
	Mean ± SD		**OR (95%CI)**	
Age (years)	61.92 ± 6.18	58.69 ± 5.28	0.92 (0.87, 0.96)***	0.91 (0.86, 0.95)***
Education (years)	15.15 ± 2.93	14.03 ± 2.24	0.86 (0.77, 0.95)**	0.82 (0.73, 0.92)**
Characteristic	**n (%)**		**OR (95%CI)**	
Race				
White	218 (96.9%)	64 (95.5%)	1.46 (0.37, 5.81)	-
Black†	7 (3.1%)	3 (4.5%)		
Systemic therapy				
Chemotherapy plus AI	80 (35.6%)	32 (48.8%)	1.66 (0.96, 2.88)*	-
AI only†	145 (64.4%)	35 (52.2%)		
Stage of disease				-
I†	144 (64.0%)	42 (63.6%)		
IIA	49 (21.8%)	14 (21.2%)	0.98 (0.49, 1.95)	
IIB	19 (8.4%)	5 (7.6%)	0.90 (0.32, 2.56)	
IIIA	13 (5.8%)	5 (7.6%)	1.32 (0.45, 3.91)	
Currently married/partnered				-
Yes	158 (79.2%)	43 (64.2%)	0.76 (0.43, 1.35)	
No†	67 (29.8%)	24 (35.8%)		
Currently Employed				-
Yes(part-time & full time)	157 (69.8%)	49 (73.1%)	1.18 (0.64, 2.17)	
No†	68 (30.2%)	18 (26.9%)		

Note: *p<0.1, **p<0.01, ***p<0.001, † reference group.
Note: OR=odds ratio; AI=aromatase inhibitor.
Note: Univariate analyses were used initially to identify potential significant predictors (p<0.1). Only significant predictors were included in the multivariable models.

3.3.4.2 Associations between demographic and clinical characteristics and predicted trajectory subgroup membership

Demographic and clinical characteristics of the two predicted trajectory subgroups are shown in Table 14. The initial univariate analysis included age, race, education, marital status, employment status, stage of disease and treatment of chemotherapy. Based on univariate logistic regression age ($p<0.001$), education ($p=0.004$) and treatment of chemotherapy ($p=0.073$) were associated with predicted symptom subgroup membership. Results from the multivariate binary logistic model including only the candidate predictors meeting the screening threshold of $p<0.10$ showed that women in the high group were significantly younger (OR=0.82, $p<0.001$), had less education (OR=0.91, $p=0.001$) than women in the low group.

3.3.4.3 Associations between SNPs and predicted trajectory subgroup membership

Three SNPs associated with glucocorticoid receptor FKBP5, mineralocorticoid receptor NR3C2, and corticotropin-releasing hormone CRHR1 were significant in the binary logistic regression after controlling for age, education, and treatment of chemotherapy (see Table 15). Other covariate-adjusted findings for all of the SNPs used in the analysis are listed in Appendix A Supplement Table 1. In the regression analysis for FKBP5 rs9394309, for women carrying two common A alleles (i.e., AA), the odds of being in the high group membership were 4 times greater than women carrying one or two minor G alleles (i.e., AG+GG). In the regression analysis for NR3C2 rs5525, for women carrying one or two minor A alleles (i.e., GA+AA), the odds of being in the high group membership was 3 times higher than the odds of women carrying two common G alleles (i.e., GG). In the regression analysis for CRHR1 rs12944712, for women carrying one or two minor A alleles (i.e., GA+AA), the odds of being in the high group membership was 4 times larger than for those with two common G alleles (i.e., GG).

Table 15 Multivariate Binary Logistic Regression Models for Genotypic Predictors of Predicted Subgroup Membership

Predictor	OR	SE	95% CI	Z	P Value
FKBP5 rs9394309	3.98	0.57	[1.31,12.08]	5.953	.015*
Age	0.88	0.05	[0.81, 0.96]	7.794	.005*
Education	0.84	0.09	[0.70, 1.01]	3.363	.067
Chemotherapy	2.59	0.49	[1.00, 6.72]	3.837	.051
Overall model fit:	χ^2= 7.704, df=8, p=.463, pseudo R^2 =.147				
NR3C2 rs5525	2.54	.44	[1.06, 3.60]	4.396	.036*
Age	0.89	.04	[0.83, 0.96]	8.594	.003**
Education	0.87	.08	[0.74, 1.01]	3.230	.072
Chemotherapy	1.54	.43	[0.66, 3.60]	1.010	.315
Overall model fit:	χ^2=12.393, df=8, p=.135, pseudo R^2 =.112				
CRHR1 rs12944712	3.88	.59	[1.23, 12.28]	5.331	.021*
Age	0.90	.04	[0.84, 0.97]	6.885	.009**
Education	0.86	.08	[0.84, 0.97]	3.134	.077
Chemotherapy	1.71	.23	[0.72, 4.10]	1.458	.227
Overall model fit:	χ^2=6.614, df=8, p=.579, pseudo R^2 =.123				

Note: * means p<.05, ** means p<.01; SE=standard error; OR=odds ratio; CI=confidence interval.
Note: Low group is the reference group; Genotypic predictors evaluated in the models were FKBP5 rs9394309 (AA versus AG+GG), NR3C2 rs5525 (GA+AA versus GG), and CRHR1 rs12944712 (GA+AA versus GG).
Note: Age, and education are reported in years. Chemotherapy is reported as Yes or No, No is the reference group.

3.3.5 Discussion

This is the first study to explore associations between variability in genes related to the HPA axis and risk for the clustering of fatigue, depressive symptom and anxiety among women with early-stage breast cancer. By using group-based multi-trajectory modeling, we were able to identify subgroups of patients based on multiple psychological symptoms trajectories at the same time. Traditional group-based trajectory modeling can only estimate the trajectory for a single symptom.

3.3.5.1 Psychological symptom cluster trajectories and phenotypic profiles

In this study, two groups of women (low versus high trajectory) were identified based on reported psychological symptoms trajectories. Depressive symptom and fatigue were generally stable and persistent for both groups. Similar to our finding, Avis et al. (2013) also found that depressive

symptom was stable and low among older women with breast cancer (> 65 years old) when measured 18 months after cancer diagnosis. However, depressive symptom was initially high and significantly decreased after cancer diagnosis among younger women with breast cancer (<65 years old). Bidstrup et al. (2015) identified three subgroups based on depressive symptom trajectories and showed that depressive symptom decreased from baseline (before surgery) to eight months post-surgery. Our results regarding the group trajectory of anxiety from baseline to 12 months were consistent with other trajectory studies, all subgroups had highest anxiety severity at baseline and then slightly decreased or plateaued during cancer treatment (Bidstrup et al., 2015;Saboonchi, Petersson, Wennman-Larsen, Alexanderson, & Vaez, 2015). It is interesting to note that we observed a slight increase in anxiety from 12 months to 18 months in the high group. Additional research is needed to confirm these results and explore the reasons why anxiety increased during this period in the high group. In another fatigue trajectory study, Bower et al. (2018) tracked fatigue for five years after primary treatment (after surgery, chemotherapy and radiation therapy) and identified five trajectory subgroups. The very low and high groups had stable and persistent fatigue; however, linear and quadratic changes were observed in the other groups. Differences in the results of these studies may be due to different sample characteristics, and assessment times. Compared to these studies, our study had an older population (postmenopausal women) and different baseline assessment point (after surgery but before adjuvant therapy). Overall, all these studies provide evidence that depressive symptom, anxiety and fatigue did not disappear but persisted during and long after cancer treatment. Therefore, health care providers should address the psychosocial needs of women from cancer diagnosis and throughout their treatment trajectory.

In terms of phenotypic predictors, the results from our binary logistic regression showed that younger age, less education and treatment of chemotherapy were associated with a higher symptom severity. Consistent with our findings, Doong et al. (2015), reported that higher severity of a cluster of pain, fatigue, sleep disturbance and depressive symptom was inversely associated with age, non-white race, and less education among women with breast cancer. In the Bidstrup et al. (2015) study, younger age and receiving chemotherapy were associated with higher psychological distress, anxiety and depressive symptom among women with breast cancer. It is possible that women with higher education levels may have more information and a better understanding of the disease process and treatment side effects. Therefore, an integrated team of health care providers with expertise in psycho-educational interventions may help oncologists to reduce the burden of depressive symptom and anxiety, especially among younger women with less education (Ram, Narayanasamy, & Barua, 2013). In addition to age, education and treatment characteristics of patients, race, income, disease characteristics (Doong et al., 2015), comorbidity score (Doong et al., 2015), body mass index (Bower et al., 2018), childhood trauma (Han et al., 2016), loneliness (Jaremka et al., 2013), and physical inactivity (Winters-Stone, Bennett, Nail, & Schwartz, 2008) have been shown an associated with fatigue, depressive symptoms and anxiety among women with breast cancer in other studies. It is possible that different phenotypic predictors can interact with each other and influence the symptom experience. For example, established research shows that the accelerated aging that accompanies cancer and cancer therapy may influence cognitive function among cancer patients (Mandelblatt et al., 2013). Future studies are needed to examine the complex relationships between phenotypic predictors and psychological symptoms experienced among women with breast cancer.

3.3.5.2 HPA axis related genes and subgroup membership

It is known that certain genetic polymorphisms can influence the regulation of HPA axis and GR sensitivity (Binder, 2009). Variation of the psychological symptom experience has been hypothesized to stem from some genetic variations in the HPA axis through the regulation of HPA axis function and characterized by hyperactive of the HPA axis, decreased GR sensitivity and enhanced inflammation. In this study, we identified three SNPs of genes associated with HPA axis that were related to the psychological symptom experience.

Women who were heterozygous for the minor A allele of CRHR1 rs12944712 had higher incidence of more severe psychological symptoms. The frequency of A allele in our sample (A=0.44) was higher than the general population (A=0.35). Consistent with our finding, minor A allele of CRHR1 rs12944712 has been linked with major depressive disorder (da Silva et al., 2016), posttraumatic stress symptoms (White et al., 2013), and moderation of the stress-related physical health (Lessard & Holman, 2014) in non-cancer populations. CRHR1 is a G-protein coupled type I CRH receptor, which plays an important role in activation of the HPA axis following stress (Mahon, Zandi, Potash, Nestadt, & Wand, 2013). Other polymorphisms of CRHR1 gene have been associated with increased cortisol reactivity (Sheikh, Kryski, Smith, Hayden, & Singh, 2013), and increased pharmacologically-induced cortisol response among children with maltreatment (Tyrka et al., 2009). These evidences suggest that CRHR1variants can interact with environment to impact cortisol reactivity and stress sensitivity and increase the risk of psychological related symptoms and disorders. Future research is needed to evaluate psychological symptoms with polymorphisms of CRHR1 gene and the interaction with environment (i.e., childhood maltreatment, stressful life events) together among cancer patients.

Women who were homozygous for the common A allele of FKBP5 rs9394309 had a higher severity of psychological symptoms. The frequency of A allele in our sample (A=0.77) can represent the frequency of A allele in the general population (A=0.75). Consistent with our finding, other studies also found that the common A allele of rs9394309 is associated with major depression (Szczepankiewicz et al., 2014), and increased cortisol secretion in non-cancer populations (Velders et al., 2011). Increasing evidence suggests that variation of polymorphisms of FKBP5 (i.e., rs9296158, rs3800373, rs1360780, rs947008, rs755558, rs3800373) are associated with a higher risk of post-traumatic stress disorder (Watkins et al., 2016), musculoskeletal pain (Bortsov et al., 2013), and major depressive disorders (Rao et al., 2016) in non-cancer populations. rs9394309 is located on intro 10 of the FKBP5 gene. The primary role of FKBP5 is to inhibit GR signaling and decrease GR sensitivity by interacting with heat-shock protein 90 (Hsp90) as a co-chaperone (Binder, 2009). Common SNP (rs1360780) in FKBP5 is associated with increased expression of FKBP5, decreased GR sensitivity and less negative feedback of the HPA axis (Zannas, Wiechmann, Gassen, & Binder, 2016), evidenced by increased cortisol response and depressive symptoms (Höhne et al., 2015; Velders et al., 2011). Moreover, increased FKBP5 production promotes NF-κB related inflammation with a positive association with pro-inflammatory cytokines (Zannas et al., 2019). This evidence suggest that variants of FKBP5 seem to modulate GR sensitivity through the role in regulation of HPA axis, resulting in enhanced inflammation and increasing the risk of psychological symptoms. Given the function of FKBP5 in GR signaling and stress response, further research is needed to expand the sample size and examine the variation of polymorphisms, gene expression, epigenetic changes of the FKBP5 gene and the related psychological symptoms among cancer patients.

Women who were heterozygous for the minor A allele of NR3C2 rs5525 had more severe psychological symptoms. The frequency of A allele in our sample (A=0.11) is similar to the frequency of A allele in the general population (A=0.12). NR3C2 is a mineralocorticoid receptor (MR), which is a high-affinity receptor for glucocorticoids, and plays an important role in tonic inhibitory control of the HPA axis activity (ter Heegde, De Rijk, & Vinkers, 2015). Decreased MR expression and functionality in the hippocampus are found in patients with depression (Medina et al., 2013). It has been shown that genetic variation in NR3C2 (i.e., rs5522, rs2070951) can change MR expression and the function of MR protein and are associated with enhanced responses in cortisol secretion (DeRijk et al., 2006). MR activity can influence inflammatory response through regulation of NF-κB and pro-inflammatory cytokine production (Chantong, Kratschmar, Nashev, Balazs, & Odermatt, 2012). This evidence suggests that MR variants may play a role in the development of psychological symptoms characterized by increased inflammation and hyperactivity of the HPA axis with increased cortisol secretion. Little research has identified genetic variation at this locus (rs5525) with psychological symptoms. One study shows that genetic variation in rs5525 is associated with verbal memory performance (Keller et al., 2017). More studies are needed to confirm the association between rs5525 and other psychological related symptoms (i.e., cognitive function, pain, fatigue) among cancer patients.

This evidence suggests that genes involved in regulating the HPA axis and GR sensitivity also associated with susceptibility to psychological symptom trajectories among women with breast cancer. Genetic variation in HPA axis sheds light on the mechanisms underlying the psychological symptoms. Future studies can assess biological biomarkers and epigenetic changes related to the HPA axis to help us better understand the underlying mechanisms of psychological symptoms thus allowing interventions to be developed related to biomarkers to reduce the burden

of symptoms among cancer patients. The results of this study emphasize the need for personalized medical care for symptom management. These genetic feature, demographic and clinical characteristics can be used to personalize the prediction of psychological symptoms among women with breast cancer.

Some limitations of this study are important to acknowledge. First, the majority of our sample was Caucasian women. Therefore, generalizability of the study results is limited due to the racial homogeneity of the sample. Symptom profiles and allele frequencies may be different among different ethnic groups. Secondly, we did not assess the patient's personality, or general physical and mental health status. In addition to cancer diagnosis and cancer treatment, personality, comorbidity, and general health status may contribute to the course of psychological symptoms. Future research is needed to take these factors into consideration and have a healthy age-matched control group for comparison. In addition, because this was an exploratory analysis, our study did not correct for multiple testing of the associations between polymorphisms in HPA axis related genes and the subgroup membership of the psychological symptom cluster. This exploratory study lays the initial groundwork for future studies. Replication in a larger sample is needed to confirm the relationships between phenotypic predictors and the symptom trajectory subgroup membership.

3.3.6 Conclusion

Two distinct symptom subgroups (low and high) were identified based on the predicted trajectories of symptoms of fatigue, depressive symptom and anxiety. Fatigue and depressive symptom were stable high or low over the course of adjuvant therapy. Women experienced highest anxiety before starting any adjuvant therapy. Women of younger age, less education with lesser degree and those

that received chemotherapy had a higher burden of psychological symptoms. Our findings provide new evidence that genetic variation associated with activation and sensitivity to the HPA axis (FKBP5 rs9394309, NR3C2 rs5525, and CRHR1 rs12944712) are associated with the severity of the psychological symptom cluster of fatigue, depressive symptom and anxiety among women with breast cancer. The association between genes, polymorphisms and symptoms provides further support for the role of the HPA axis mechanism in the clustering of psychological symptoms. The results of this study will directly help healthcare providers to identify and screen women with breast cancer and identify those who are at higher risk of more severe psychological symptoms across the first 18 months of adjuvant therapy.

Appendix A SUPPLIMENT MATERIALS

A.1 SUPPLIMENT TABLES

Table 1 Final list of single nucleotide polymorphisms for genetic analysis

Gene	SNP	Alleles	MAF	HWP	p-value	Model
CRHR2	rs255098	A>G	0.38	0.63	0.470	R
	rs3779250	T>C	0.36	0.67	0.206	D
NR3C1	rs41423247	G>C	0.33	0.24	0.557	D
	rs258747	A>G	0.4	n/a	n/a	n/a
	rs10482605	A>G	0.18	0.3	0.193	D
	rs6191	C>A	0.49	0.08	0.257	D
	rs258813	G>A	0.29	0.11	0.478	D
	rs33388	A>T	0.49	0.06	0.469	R
	rs10052957	G>A	0.31	0.54	0.568	R
	rs6198	T>C	0.17	0.12	0.298	R
	rs 6189	C>A	0.03	0.64	0.295	R
	rs6190	C>T	0.02	0.71	0.288	D
FKBP5	rs1360780	C>T	0.29	n/a	n/a	n/a
	rs3800373	A>C	0.26	n/a	n/a	n/a
	rs4713916	G>A	0.28	n/a	n/a	n/a
	rs9296158	G>A	0.29	0.24	0.145	R
	rs9394309	G>A	0.23	0.28	0.015	D
	rs3777747	A>G	0.47	0.45	0.284	R
	rs17542466	A>G	0.15	n/a	n/a	n/a
	rs2766533	G>A	0.42	0.96	0.177	R
	rs9380526	T>C	0.30	n/a	n/a	D
	rs9394314	A>G	0.28	0.76	0.091	D
	rs2817032	T>C	0.28	0.21	0.126	R
	rs2817040	G>A	0.27	n/a	n/a	n/a
	rs7753746	A>G	0.14	0.83	0.209	D
	rs4713902	T>C	0.32	n/a	n/a	n/a
	rs7748266	C>T	0.17	0.97	0.087	D

	rs7757037	G>A	0.34	n/a	n/a	n/a
NR3C2	rs5525	G>A	0.12	0.55	0.036	R
	rs4835488	T>C	0.46	0.43	0.096	R
	rs10213471	G>A	0.14	0.55	0.253	R
	rs2070951	G>C	0.43	0.19	0.755	R
CRHBP	rs10473984	G>T	0.06	0.84	0.977	R
	rs7718461	A>G	0.43	0.22	0.377	D
	rs1875999	T>C	0.35	0.96	0.777	R
CRHR1	rs17689918	G>A	0.20	0.64	0.405	R
	rs4458044	G>C	0.29	0.55	0.126	D
	rs242924	C>A	0.45	0.65	0.068	D
	rs1768996	T>A	0.33	0.1	0.207	R
	rs12944712	G>A	0.46	0.91	0.021	R
	rs12938031	A>G	0.40	0.83	0.308	D
	rs4792887	C>T	0.09	0.98	0.294	R
	rs1396862	C>T	0.21	0.82	0.470	R
	rs17763104	G>A	0.15	0.21	0.740	R
	rs110402	C>T	0.46	0.55	0.102	R
	rs242948	A>C	0.39	0.7	0.065	D
	rs1876828	G>A	0.20	0.66	0.443	D
	rs17689882	G>A	0.20	0.81	0.266	R
	rs12936511	C>T	0.04	0.29	0.889	D
	rs242941	G>T	0.32	0.41	0.160	D

Note: A=additive model; R=recessive model; D=dominant model; HWE=Hardy-Weinberg Equilibrium; MAF=minor allele frequency; SNP=Single Nucleotide Polymorphism. n/a=failed assay or SNP violated Hardy-Weinberg expectations ($p < 0.05$). All models are adjusted for age, education level and treatment of chemotherapy. In all models, p-values from binary logistic regression are reported.

A.2 CONSENT FORMS

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SOURCE OF SUPPORT: **National Cancer Institute**

Why is this research being done?

You are being asked to participate in a research study in which we will examine and compare cognitive function (the ability to maintain attention and remember things) and quality of life in women with breast cancer who take Anastrozole (Arimidex) versus women who do not take this drug. We will also explore whether changes in cognitive function are related to changes in reproductive hormones such as estrogen and progesterone and the amount of anastrozole you take.

Who is being asked to take part in this research study?

You are being invited to take part in this research study for one of the following reasons:

_____ 1) You have recently been diagnosed with breast cancer and will receive chemotherapy followed by Anastrazole (Arimidex).
_____ 2) You have recently been diagnosed with breast cancer and will receive chemotherapy alone (Not followed by Anastrozole).
_____ 3) You have recently been diagnosed with breast cancer and will receive Anastrozole without chemotherapy.
_____ 4) You are a healthy woman and you do not have breast cancer.

A total of 645 postmenopausal women between 18 and 75 years of age are being asked to take part in this study.

What procedures will be performed for research purposes?

If you decide to take part in this research study, you will undergo the following procedures that are not part of your standard medical care:

<u>Experimental Procedures:</u>

If you qualify to take part in this research study, you will undergo the experimental procedures listed below. These procedures will take place in the Outpatients Services of the Breast Care Program at Magee-Womens Hospital, the Clinical Research Center of Magee-Womens Hospital, the Clinical Research Suites at the University of Pittsburgh School of Nursing or at one of the following UPMC Cancer Centers: Hillman Cancer Center; Passavant; Cranberry; Upper St. Clair; Monroeville/Haymaker; Monroeville/Mosside or Moon Township. These procedures may also take place at your residence.

1. You will be asked to complete measures of cognitive function and quality of life. These tests evaluate your attention span, ability to learn and remember what you learn, problem solving skills and your thoughts about your cognitive function and quality of life. In addition, you will be asked to complete questionnaires that ask about your employment history and sleep habits. This will take approximately 90 minutes to 2 hours of your time. The timing of your completion of these measures differs depending upon which study group you are in.

    a) If you will receive chemotherapy followed by Anastrazole (Arimidex) or if you are receiving chemotherapy alone, you will be asked to complete these measures before you begin chemotherapy.

    b) If you will receive Anastrozole alone, you will be asked to complete these measures before you begin Anastrozole alone.

    c) If you are a healthy woman enrolled in the study, you will be asked to complete these measures at a time that is convenient for you.

2. We will also take a small sample (about 2 teaspoonfuls) of blood from a vein in your arm to measure the levels of your reproductive hormones.

<u>Monitoring/Follow-up Procedures:</u>

Procedures performed to evaluate the effectiveness and safety of the experimental procedures are called “monitoring” or “follow-up” procedures. For this study, the follow-up measures consist of the following:

1. You will again be asked to complete measures of cognitive function, quality of life, employment history and sleep habits. This will take approximately 90 minutes to 2 hours of your time.

2. We will also take a small sample (about 2 teaspoonfuls) of blood from a vein in your arm to measure the levels of your reproductive hormones.

The timing and the number of times that you complete these measures differs depending upon which study group you are in as described below.

a) If you will receive chemotherapy or chemotherapy followed by Anastrazole (Arimidex) you will be asked to complete the measures at nine follow-up timepoints. The additional visits will occur at 6 months and then 12 month intervals since your last visit with the AIM Study and will occur at your regular study location. The study timepoints are as follows:

Timepoint 0	Baseline assessment
Timepoint 1	Will occur after you complete chemotherapy and before you start taking Arimidex
Timepoint 2	Will occur 6 months after Timepoint 1
Timepoint 3	Will occur 6 months after Timepoint 2
Timepoint 4	Will occur 6 months after Timepoint 3
Timepoint 5	Will occur 6 months after Timepoint 4
Timepoint 6	Will occur 12 months after Timepoint 5
Timepoint 7	Will occur 12 months after Timepoint 6
Timepoint 8	Will occur 12 months after Timepoint 7
Timepoint 9	Will occur 12 months after the date you stop taking Armidex

b) If you will receive Anastrozole (Arimidex) alone, you will be asked to complete these measures at eight follow-up timepoints. The additional visits will occur at 6 months and then 12 month intervals since your last visit with the AIM Study and will occur at your regular study location. The study timepoints are as follows:

Timepoint 1	Baseline assessment
Timepoint 2	Will occur 6 months after you start taking Arimidex
Timepoint 3	Will occur 6 months after Timepoint 2
Timepoint 4	Will occur 6 months after Timepoint 3
Timepoint 5	Will occur 6 months after Timepoint 4
Timepoint 6	Will occur 12 months after Timepoint5
Timepoint 7	Will occur 12 months after Timepoint 6
Timepoint 8	Will occur 12 months after Timepoint 7
Timepoint 9	Will occur 12 months after the date you stop taking Armidex

c) If you are a healthy woman enrolled in the study, you will be asked to complete these measures at nine follow-up timepoints. The additional visits will occur at 6 months and then 12 month intervals since your last visit with the AIM Study and will occur at your regular study location. The study timepoints are as follows:

Timepoint 0	Baseline assessment
Timepoint 1	Will occur 6 months after your initial Timepoint
Timepoint 2	Will occur 6 months after Timepoint 1
Timepoint 3	Will occur 6 months after Timepoint 2
Timepoint 4	Will occur 6 months after Timepoint 3
Timepoint 5	Will occur 6 months after Timepoint 4
Timepoint 6	Will occur 12 months after Timepoint 5
Timepoint 7	Will occur 12 months after Timepoint 6
Timepoint 8	Will occur 12 months after Timepoint 7
Timepoint 9	Will occur 12 months after Timepoint 8

What are the possible risks, side effects, and discomforts of this research study?

The possible risks of this research study may be due to the completion of the study measures or the blood tests.

Risks of the Completion of the Study Measures: It is possible that during the completion of some of the cognitive function and quality of life measures you may become frustrated or fatigued. In order to alleviate any fatigue which may occur, you are offered breaks during testing periods. You will also be provided with a referral for psychiatric consultation if you choose.

Risks of the Blood Tests: Bruising, bleeding, soreness, or rarely, fainting or infection may occur as a result of the needle sticks to obtain blood from your vein.

What are possible benefits from taking part in this study?

You will likely receive no direct benefit from taking part in this research study.

What treatments or procedures are available if I decide not to take part in this research study?

Because this study does not involve any type of medical treatment, there are no treatments or procedures available if you decide not to take part in this research study.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?

Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study (i.e., Experimental Procedures, or Monitoring/Follow-up Procedures described above). You will be charged, in the standard manner, for any procedures performed for your routine medical care.

Will I be paid if I take part in this research study?

You will be paid if you decide to take part in this research study. You will be paid $50 after the completion of the study measures at each timepoint. Therefore, the total amount that you will be paid differs depending upon the study group you are in as described below.

a) If you will receive either chemotherapy followed by Anastrazole (Arimidex) a total of $500.

b) If you are receiving Anastrozole alone, you will receive a total of $450.

c) If you are a healthy woman enrolled in the study, you will receive a total of $500.

Who will pay if I am injured as a result of taking part in this study?

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

Who will know about my participation in this research study?

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

Will this research study involve the use or disclosure of my identifiable medical information?

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., physician office) records. The information that will be recorded will be limited to your age, race, number of years of education that you have completed and information about your breast cancer diagnosis and treatment.

Who will have access to identifiable information related to my participation in this research study?

In addition to the investigators listed on the first two pages of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators,

for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of five years after final reporting or publication of a project.

May I have access to my medical information that results from my participation in this research study?

In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

Is my participation in this research study voluntary?

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no affect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw, at a future date, my consent for participation in this research study?

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no affect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If I agree to take part in this research study, can I be removed from the study without my consent?

It is possible that you may be removed from the research study by the researchers if, for example, there is a change in the stage of your breast cancer or a change in your breast cancer treatment.

Might I be contacted after I have completed my participation in this study?

We may contact you after you have completed this study if we need more information from you for this study, or if we have other studies in which you may be interested in participating.

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions which I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise."

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

Signature of Person Obtaining Consent _____ Date _____

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

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SOURCE OF SUPPORT: **National Cancer Institute**

New Information:
During the blood draw procedure we would like to obtain an extra 3 cc of blood to store for future genetic testing. If a blood draw does not occur, we will obtain the genetic sample by collecting 2 ml (less than a teaspoon) of your saliva into a vial.

Why is this research study being done?
This project will identify factors that may influence cognitive function among individuals with breast cancer. You are being asked to participate in a research study where we will examine whether inherited factors (genes), or the products of genes, affect cognitive function in individuals with breast cancer. It is the hope that the results of this study may someday lead to better methods to prevent changes in cognitive function related to cancer and cancer treatment.

What procedures will be performed for research purposes?
If you decide to take part in this research study, you will undergo the following procedures that are not part of your standard medical care:

An additional blood sample will be drawn at the same time when blood sampling is being done for the other portion this study. 3 cc of blood (a little more than ½ a teaspoon) will be collected for the purpose of evaluating genes and gene products. It is possible that you will be asked to provide a saliva sample for this purpose if obtaining a blood sample is not possible.

We will save the DNA for future testing of genes and gene products that may be involved with cognition in individuals with breast cancer; however we cannot, at this time, tell you exactly what genes or gene products will be tested. If you agree to participate in the research project, your biological sample and genetic material will be maintained in a -80°C freezer in the Victoria building under the control of the principal investigator of this research project and will be maintained indefinitely.

In the event that we send your genetic sample to a different facility for analysis in the future, none of your identifying information will accompany the sample.

What are the possible risks, side effects and discomforts of this research study?
The blood specimen will be drawn at the same time that other specimens are being drawn, so you will not be subjected to an additional needle stick. The procedure to obtain a saliva sample is painless. Your genetic sample will be stored with only your study ID number attached to it. Information linking these code numbers to your private information will be kept in a separate secure location. It is possible that a breach of confidentiality may occur during study participation. However, every effort is made to ensure that subject confidentiality is maintained. All investigators and are trained in HIPAA policies and procedures and sign confidentiality agreements. Knowledge of your genetic research data could potentially impact your future insurability, employability, or reproduction plans: or have a negative impact on family relationships; and/or result in shame or embarrassment.

Will I be informed of personal results of this genetics study?

You will not be provided with the results of this research study since the genetic data cannot yet be interpreted or applied in a clinically relevant manner. However, should the genetic information become clinically relevant as a result of the availability of new strategies for the prevention or treatment of the respective disease, it will be provided to you.

What are the possible benefits from taking part in this study?
There are no direct benefits to you from taking part in this genetic research.

Is my participation in this study voluntary?
Your participation in this additional blood draw or saliva sample is completely voluntary. Your refusal will not affect your participation in The AIM Study.

May I withdraw, at a future date, my consent for participation in this research study?

You understand that can withdraw from this research study at any time. Your other care and benefits will be the same whether you participate in this research study or not. Any genetic sample obtained from your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Might I be contacted after I have completed my participation in this study?
We may contact you after you have completed this study if we need more information from you for this study, or if we have other studies in which you may be interested in participating.

****

VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions which I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____
Printed Name of Participant

_____ _____
Participant's Signature Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the

individual(s) have about this study have been answered, and we will always be available to address future questions as they arise."

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study
_____	_____
Signature of Person Obtaining Consent	Date

Appendix B INSTITUTIONAL REVIEW BOARD

APPROVAL LETTERS

University of Pittsburgh
Institutional Review Board

Human Research Protection Office
3500 Fifth Avenue, Suite 106
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APPROVAL OF SUBMISSION (Expedited)

Date:	July 1, 2019
IRB:	STUDY18100081
PI:	Hongjin Li
Title:	The Psychological Symptom Cluster Among Women with Breast Cancer Before and During Adjuvant Therapy
Funding:	Name: University of Pittsburgh; Name: Sigma Theta Tau International, Grant Office ID: BU00002077, Funding Source ID: FP00001078
Grant Title:	*<Indicate "None" if there is none.>*
Grant ID:	BU00002077;

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

Approval Documentation

Review type:	Initial Study
Approval Date:	7/1/2019

Determinations:	
Approved Documents:	• Consent form for AIM study, Category: Other; • Consent form for genetic testing, Category: Other; • Reference List.docx, Category: Other;

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Amy Fuhrman.

Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.

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