Inflammatory Markers, Metabolic Profile, and Psychoneurological Symptoms in Women with Breast Cancer: A Literature Review

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Abstract
Breast cancer is one of the most prevalent cancers in women. The improvement in breast cancer treatment has significantly increased the proportion of survival rate for women with breast cancer. Despite the advancement in breast cancer treatment, a great proportion of survivors suffer from co-occurring psychoneurological symptoms which impact their quality of life. The most frequently reported psychoneurological symptoms among women with breast cancer are depressive symptoms, anxiety, fatigue, sleep disturbances, and pain. These symptoms usually appear as a cluster. Inflammatory activation and serum metabolic alterations have been associated with the etiology of cancer and with various chronic neurocognitive disorders. However, to date, no studies considered the combined effects of inflammatory markers and metabolites in the development of psychoneurological symptoms in women with breast cancer especially those who were treated with chemotherapy. Further clarification of the relationships between the inflammatory markers, serum metabolic alterations, and psychoneurological symptoms in women with breast cancer should be pursued.

Introduction And Background
Breast cancer is one of the most prevalent cancers in women. According to the American Cancer Society (2020), it is expected that more than 276,480 women in the United States of America will be diagnosed with invasive breast cancer [1]. Most of these diagnosed women were projected to be in early stages (I and II) and to survive for more than five years due to the advancement in chemotherapy treatments [2].

The improvement in breast cancer treatment has significantly increased the proportion of survival rate for women, however, despite the advancement in treatment, a great proportion of breast cancer survivors suffer from co-occurring psychoneurological symptoms which may have an adverse impact on their quality of life [3-5]. The primary goal of the study is to determine the relationships among inflammatory markers, metabolites changes, and the development, persistence, and severity of the psychoneurological symptoms across time in breast cancer women treated with chemotherapy.

Review

Methods
For this paper, PubMed and Web of Science were used to locate related literature. The database was searched without any prior inclusion or exclusion criteria for all peer-reviewed articles published till May 31, 2021. In general, there are few studies in this field that were matched with our four descriptors (e.g. psychoneurological symptoms, breast cancer, inflammatory markers, and metabolic profile). Searching processes resulted in nine pertinent studies in the best scenario given that all the Medical Subject Headings (MeSH) terminologies related to the descriptors were used during the searching process. Due to the limited number of articles in searching of the database, we targeted references that were indexed in the two best recent articles related to this phenomenon which finally led to thirteen studies. Most of these studies were about psychoneurological symptoms in women with breast cancer with a majority of studies that enrolled women who were treated with chemotherapy. The first two authors extracted data from all peer-review articles in a standard form includes citation (authors, year), purpose, study design, sample size and characteristics, summary for selected variables (therapies, psychoneurological symptoms, inflammatory markers, and other factors), findings and/or limitations. Narrative analyses considered study design and data quality and validity.

Results and discussion
Eighteen articles were grouped into five categories. The first category includes two studies that proposed a new theoretical model that might explain this phenomenon. The second category includes four studies that
investigated the psychoneurological symptoms as an isolated symptom. The third group has six studies that examined psychoneurological symptoms as a cluster of symptoms. The fourth category consists of four studies that examined the relationship between inflammatory markers and psychoneurological symptoms. Finally, the fifth category includes only two articles that described the metabolic profile in a patient with breast cancer. The findings under the five categories were described in the following sections and further information was provided in Table 1.

| Publication (author, date) | Study Purpose | Study Design | Sample Size | Demographics: Age Stage Race | Therapy: Chemotherapy (CTX), Radiation Therapy (RTX) | PNS: Cluster (C), or Selected Symptom (SS) | Instruments measure PNS | Variables: Inflammatory Markers (IM) Metabolic Profiles (MP) Others | Major Findings |
|---------------------------|---------------|--------------|-------------|----------------------------|-----------------------------------------------|-------------------------------------------------|-------------------------|---------------------------------------------------|------------------|
| Category 1: Theoretical/Conceptual models |
| Lyon et al., 2014[6] | To discuss new hypothesis for the biological basis of PNS through integration of inflammation and DNA repair (genetic and epigenetic) to understand symptoms development and persistence after chemotherapy treatment. | Theoretical: new theory | NA | AN | | | | IM: cytokines | Other: Genetics | The epigenetic changes may involve DNA methylation or histone modifications, possibly through perturbations in the protein enhancer of zeste 2 (EZH2). Both telomerase shortening and the epigenetics changes may lead to chromosomal instability and development of the psychoneurological symptoms. |
| Starkweather et al., 2013a[7] | To discuss new conceptual model for the biological basis of PNS through integration of inflammation and genetic and epigenetic to understand symptoms development and persistence after chemotherapy treatment. | Theoretical: Conceptual Model | NA | NA | | | | IM Other: Genetics | A proposed theoretical model for the PNS in women with breast cancer, including perceived stress, hypothalamic-pituitary-adrenal cortical axis dysfunction, inflammation, epigenetic, and genomic factors. |
| Category 2: PNS as an isolated symptom |
| Aboalela et al., 2015[8] | To determine if the exposure to chemotherapy, radiation, and perceived stress cause chromosomal instability and if it has a role in the development and sustainability of PNS associated with breast cancer. | Longitudinal-1 year (4 points) | 71 | 51.3 years Stages (I to IIIA) 49 Caucasian, 22 Black African | CTX, RTX | SS: Stress | Perceived Stress Scale (PSS) | Other: Genetics | The impact of perceived stress on micronuclear/cytome frequencies was detected across all visits, with the highest levels of stress being reported at baseline. Also, the acquired micronuclear/ cytoplasm abnormality frequencies were detected for race & tumor type. |
| Wu et al., 2014[9] | To examine the longitudinal associations between depressive symptoms and stress hormones. | Longitudinal-1 year (4 points) | 227 | 50.58 years Stages (I to II) 204 White, 23 Non-White 23 | CTX, RTX | SS: stress, depression | Perceived Stress Scale (PSS) Epidemiological Studies Depression | Other: Hormones: Cortisol, ACTH, epinephrine, non-epinephrine | Depressive symptoms were inversely associated to cortisol levels but were positively correlated to rate of change in cortisol. Neither ACTH, epinephrine nor... |
| Category 3: PNS as a cluster of symptoms |
|----------------------------------------|
| To examine the recurrence of depression and anxiety in breast cancer. | Longitudinal – 1 year (2 points) | 51-64 years Stage not provided Race not provided | Not provided | SS: depression & anxiety | Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (DSM-IV and GAD) | None |
| To report the differences in fatigue, physical and psychological symptoms during chemotherapy administration over 1 year. | Longitudinal, descriptive design embedded in a pilot intervention study | Baseline: average of 54.3 years and a range of 40-65 years Stage I-II All Caucasian | CTX (Chemotherapy) | SS: fatigue, physical symptoms (pain, appetite, sleep disturbance, fatigue, bowel patterns, concentration, and appearance), anxiety | Piper Fatigue Scale (PFS); Anxiety Experience Scale (SES) and Depression Scale (HADS) | None |
| To recognize and compare subgroups with different patterns of change in PNS clusters. | Secondary data analysis (3 points) from RCT | Age with mean of 54.6 years and range between 30-81 years Stage IV and recurrence cancer: 104 Caucasian, 147 Caucasian | CTX, RTX | C: depressed mood & cognitive disturbance, fatigue, insomnia, and pain | Depression and confusion subscales of the (POMS-SF); General Fatigue Scale (GFS); Consequence of symptoms was measured by the Functional Performance Inventory (FFI) | None |
| To determine the association between neuroendocrine-immune models and the frequent concurrency of PNS (pain, depression, and fatigue). | Cross-sectional observational study | 53 ≤11 years Stage IV and recurrence cancer: 93 Caucasian, 11 African American | CTX, RTX | C: pain, depression, & fatigue | Brief Pain Inventory (BPI); Center for Epidemiological Studies Depression Scale (CES-D); Fatigue Symptom Inventory (FSI) | Other: Latent variable analysis indicated neuroendocrine levels ( cortisol, ACTH, epinephrine, and norepinephrine), preexisting pain, depression and fatigue, while controlling for important disease and demographic variables. |
| To explore the relationship between pre- | | | | | Sleep Quality Index (PSQI); Multidimensional Fatigue | All women reported worse sleep, more fatigue and more depressive symptoms during treatment compared with |
| (So et al., 2009)[5] | Treatment cluster categories and longitudinal profiles symptoms during the course of chemotherapy. Prospective longitudinal study (7 points) | Age with mean of 51.1 ± 9.1 years and a range between 34–79 years Stages I-II:55 Caucasian, 21 Non-Caucasian | CTX | C: sleep, fatigue, depression | Symptom Inventory—Short Form (BFI-SF) |
| --- | --- | --- | --- | --- | --- |
| (Kim et al., 2009) | To examine the symptom cluster of fatigue, pain, anxiety, and depression and its effect on the QOL of women with breast cancer that were receiving chemotherapy/ radiation. Descriptive Study 215 | Age with mean of 51.65 ± 10.36 years and a range between 29-66 years Stages I-II: Chinese ethnicity | CTX, RTX | C: Fatigue, pain, anxiety, & depression | Chinese versions of the Brief Fatigue Inventory (BFI-C) (Starkweather et al., 2008) (Bender et al., 2008) (So et al., 2009) (Liu et al., 2009) |
| (Kim et al., 2009)[14] | To examine treatment-related symptom clusters and the effect of demographic/clinical variables on symptom clustering in women with breast cancer during treatment. Secondary data analysis (4 points) from RCT 282 | Age with mean of 50.21 ± 12.1 ± years and a range between 30-83 years Stages (0 to IV): 258 Caucasian, 24 Non-Caucasian | CTX, RTX | C: PNS cluster: depressed mood & cognitive disturbance, fatigue, insomnia, and pain, Upper GI cluster: nausea, vomiting, decreased appetite | Depression and confusion subscales of the POMS-SF, General Fatigue Scale (GFS), Pittsburgh Sleep Quality Index—Short Form (PSQI) One item asking about pain-intensity (1-4 Likert) |
| (Bender et al., 2005)[2] | To identify and compare symptom clusters across 3 phases of the disease. Secondary data analysis (pooled analysis from 3 independent studies) 154 (Study 1: 41, Study 2: 88, Study 3: 26) | Study 1: Age: 42.3 ± 5.3 years Stage: I-II Race not provided Study 2: Age: 55.3 ± 4.1 ± years Stage: I-II Race not provided Study 3: Age: 55.2 ± 12.1 ± years Stage IV Race not provided | CTX, RTX | C: Anxiety, Depression, Anger, Vigor, Fatigue, & Confusion | POMS |
| Category 4: PNS and inflammatory markers | To explore clusters of PNS and inflammation (levels of C-RP) over time in a cohort of women with early-stage breast cancer. Prospective longitudinal study (5 points) 75 | Age with an average of 51.52 ± 10.34 years and a range between 23–71 years Stage: I, IIA, IIB, IIIA 53 Caucasian, 22 African American | CTX | C: cognitive, depression, anxiety, fatigue, sleep disturbance | CNS Vital Signs to measure cognitive impairment, global cognition, affective symptoms, and cognitive efficiency. The Brief Fatigue Inventory (BFI) General Sleep Disturbance Scale (GSDS) The Brief Inflammatory Symptom Inventory (BISI) (Starkweather et al., 2017)|

Most participants reported mild-to-moderate levels of fatigue and pain. 21% and 36% of patients had anxiety or depression, respectively. Significant associations between 4 symptoms indicated presence of the symptom cluster. Patients who received chemotherapy had a poorer QOL.
To assess the relationships between cytokines to cognitive function over 2 years in early-stage breast cancer.

Prospective, longitudinal study (3 points)

Age with an average of 51.92 ± 10.34 years and a range between 23–71 years Stage: I, IIA, IIB, IVA, IVB, Caucasian, 22 African American

CTX: C: cognitive, CNS: Vital Signs to measure cognitive

BMI: C-reactive protein (CRP), M: Metabolites

Over time, there were associations between the patterns of cytokines and domain-specific cognitive functioning. It was found that cytokines from different classes were associated with cognitive performance and such associations were not limited to only prototypical cytokines.

To examine how symptom cluster subgroups distribute and associate with peripheral cytokine levels.

Secondary data analysis from cross-sectional study

Age with an average of 47.7 ± 7.7 and a range between 27–60 Stages: I–III BC Caucasians, 20 African American

CTX: C: Fatigue, & sleep disturbances, Depression, Pain severity & interference

BMI: cytokines

A significant difference between the high and low composite symptom score subgroups was found for interleukin IL-6 and IL-7.

To compare cytokine levels and patterns between women with breast cancer and the control group.

Cross-sectional

Positive biopsy

Age 58.7 ± 5.2 years Stages: I, IIA, IIB, IVA 13 White, 6 Black

BMI: cytokines

Compared with women without breast cancer, women with breast cancer had significantly higher levels of all systemic measured cytokines with an exception for granulocyte colony-stimulating factor (GCSF) and interferon-gamma (IF-γ). Three cytokines (GCSF, IL-6, and IL-17) were able to discriminate between the breast cancer and control groups.

To assess the associations between metabolic pathway and metabolomics (hypothalamus) and the psychoneurological symptoms before and after chemotherapy.

Samples taken from prospective, longitudinal study (2 points: prior to initial CTX, and 1-2 week after the final CTX initiation)

Age 58.7 ± 5.2 years Stages: I, IIA, IIB, IVA 13 White, 6 Black

BMI: cytokines

Levels of PNS (pain, fatigue, and depression) increased after chemotherapy. This study found symptoms of pain and fatigue were strongly associated with global and several targeted metabolites. Concerning the tryptophan pathway, this study found women after chemotherapy had a higher level of pain and fatigue and a significantly higher concentration of kynurenine and indole-3-propionic acid.

To determine whether plasma metabolic phenotype allows differentiating breast cancer.

Cross-sectional study

Breast Cancer Age: the average of age was 58 ± 11 years and a range between 24–86 years for training cohort, and average of age of 60 ± 12 years and a range between 40–71 for the validation cohort. Stage I not provided. For both groups Race not provided for both groups. Lung Cancer Age: the average of age was 61 ± 10 years and a range between 43–75 years

NA

The 1H-NMR Spectroscopy technique was able to classify 96% of patients with breast cancer and 93% of patients with lung cancer based on their metabolic profile. Results were cross validated. Metabolite
between breast and lung cancer.

### TABLE 1: Summary for studies of PNS in women with breast cancer.

PNS: psychoneurological symptoms, NA: not applicable.

#### Conceptual/Theoretical Model: Psychoneurological Symptoms in Breast Cancer

Historically most of the studies in this field were designed to study this phenomenon based on the concept of dysfunction in the pathway of the hypothalamic-pituitary-adrenocortical axis (HPA). Starkweather et al. (2013a) and Lyon et al. (2014) proposed a new conceptual model to explain the variation of psychoneurological symptoms in women with breast cancer, and this model includes HPA and another three concepts: inflammation, epigenetic, and genomic factors [6,7]. In women with breast cancer, the telomerase shortening and the epigenetics changes may lead to chromosomal instability and development of the psychoneurological symptoms [6].

Nowadays this model is the cornerstone for most of the recent studies funded by the National Institute of Health (NIH) since it’s incorporating constructs from the parent model ‘Symptom Science Model’ that was developed by NIH [21]. The two primary constructs adopted in this model from the Symptom Science Model were the biomarkers identification and symptom cluster. This model includes concepts of genetic and inflammatory markers under the construct of biomarkers identification; however, it didn’t consider metabolites or metabolic profiles as one of the biomarkers in its design.

#### Psychoneurological Distress as an Isolated Symptom in Breast Cancer

Articles under the second category had investigated the co-occurrence of psychoneurological distress as an isolated symptom in women with breast cancer. This group includes four longitudinal studies that were conducted over one year. Aboalela et al. (2015) reported that perceived stress was detected in overall patient visits, and it was associated with an impact on chromosomal stability during the treatment period with the highest level of stress being reported at the baseline of the study [8]. Wu et al. (2014) found depressive symptoms were negatively associated with cortisol level but not covaried with adrenocorticotropic hormone (ACTH), epinephrine, and norepinephrine [9].

Hill et al. (2011) reported the occurrences of depressive episodes in two-thirds and the general anxiety episodes in 40% of the patient during the first year after diagnosis [10]. Byar et al. (2006) reported results consistent with the findings in Aboalela et al. (2015) and Hill et al. (2011) studies in terms of anxiety and depression. Anxiety was the highest at baseline while depression was the highest during the fourth chemotherapy cycle. Also, Byar et al. (2006) found that pain and sleep disturbances were the most intense, frequent, and distressing symptoms over the other symptoms [4].

This category is characterized by longitudinal studies with adequate samples. Studies in this category examined psychoneurological symptoms in women with breast cancer as an isolated symptom, and such concept was reflected in its statistical analyses which were based on the techniques of univariate rather than the multivariate analysis.

#### Psychoneurological Distress as Cluster of Symptoms in Breast Cancer

The third category has six studies that investigated psychoneurological distress as a cluster of symptoms. In this category, findings of these studies were ranked in the following order: (1) two descriptive cross-sectional studies, (2) one longitudinal study, and (3) finally three secondary data analysis studies that were based on randomized clinical trials.

Cross-sectional studies: So et al. (2009) reported the existence of significant correlations between four symptoms (e.g. fatigue, pain, anxiety, and depression), and they interpreted these findings as evidence supporting the presence of symptoms cluster in women with breast cancer [5]. Thornton, Andersen, and Blakely (2010) reported a similar cluster of symptoms (e.g. pain, depression, and fatigue) that was associated with latent variable indicated HPA (e.g. cortisol, ACTH, epinephrine, and norepinephrine) [12].

Longitudinal study: In 2009, Liu et al. found that breast cancer chemotherapy-treated women reported a
A triad cluster of a symptom (sleep, fatigue, and depression). Also, they found that women who started with a large cluster index continued to experience worse symptoms compared with women who began with a lower cluster index [13].

Secondary data analysis studies: Bender et al. (2005) identified three types of symptom clusters which were co-occurred with the three phases of breast cancer experience [2]. Each cluster was composed of symptoms related to fatigue, mood problems, and perceived cognitive impairment. Kim et al. (2008) reported two distinct clusters: a psychoneurological cluster (depressed mood, cognitive disturbance, fatigue, insomnia, and pain), and an upper gastrointestinal cluster (nausea, vomiting, and decreased appetite) [14].

Kim et al. (2008) reported that demographic and clinical variables were not significantly associated with symptom clusters [14]. Interestingly, this finding was inconsistent with the third study published by the same authors which found that a higher level of education and chemotherapy treatment were significantly associated with a higher and constant pattern of symptom clusters [11].

The third category provides support for the existence of psychoneurological distress as a cluster of symptoms in women with breast cancer. The most commonly reported symptoms in the cluster of psychoneurological symptoms were depressed mood, cognitive disturbance, fatigue, insomnia, and pain.

**Psychoneurological Symptoms and Inflammatory Markers in Breast Cancer**

Inflammatory markers are chemical substances released by human body cells which have an effect on the interaction and communication between cells. Lyon et al. (2008) reported that all systemic cytokines were higher in women with a positive biopsy for breast cancer compared with the women with negative biopsy results [18]. This study was followed by Starkweather et al. (2013b) who reported significant differences between high and low symptoms composite score for IL-6 and IL-7 [17].

The findings in both studies were promising and maybe help to understand the biological mechanisms underlying the development of the psychoneurological symptoms. However, there are many limitations in the two studies. First, psychoneurological symptoms were not investigated in Lyon et al. (2008) study. Second, Starkweather et al. (2013b) study was a secondary data analysis based on an original experiment that did not monitor participants over a long time. The limitations of these two studies were considered by two longitudinal published studies [15,16]. Lyon et al. (2016) found there were significant associations between cognitive performance and cytokines from different classes [16]. Moreover, Starkweather et al. 2017 found that across the time of the study there was an inverse association between levels of C-reactive protein (CRP) and cognitive efficiency [15].

**Psychoneurological Symptoms and Metabolic Profile in Breast Cancer**

Metabolic profile or the metabolic phenotype is a reflection of the end products of cellular processes, and the changes in its concentration either in tissue or the circulation. There are many reported evidence that cancer cell metabolism differs from that of normal cell metabolism [22].

The advances in metabolomics as a biomarker were widely used across different diseases, and it was found to be helpful in the prediction and prognosis of the illnesses. 1H-NMR spectroscopy is one of the noninvasive techniques that can detect more than 100 metabolites. Louis et al. (2016) found that 1H-NMR spectroscopy technique was able to classify 99% of patients with breast cancer based on their metabolic profile [20]. A recent pilot study correlates between global and targeted metabolic phenotypes and the psychoneurological symptoms in women with breast cancer were encouraging [19]. This study found symptoms of pain and fatigue were strongly associated with global and several targeted metabolites [19]. Concerning the tryptophan pathway, this study found women after chemotherapy had a higher level of pain and fatigue and a significantly higher concentration of acetyl-L-alanine, indoxyl sulfate, kynurenine levels, and kynurenine/tryptophan [19].

This category provides support for the existence of a correlation between psychoneurological and the metabolic phenotype. However, these studies were few and in the infancy stage. Thus more studies with various designs were needed. Further, such studies were needed to consider the combined or the simultaneous alteration in inflammatory markers and metabolite and their influence on the development, persistence, and severity of psychoneurological symptoms in women with breast cancer.

Findings of this review were summarized in a proposed model. The proposed theoretical model/framework was developed to explain the phenomenon of development, persistence, and severity of psychoneurological symptoms in women with breast cancer that was treated by chemotherapy (Figure 1).
**Conclusions**

In general, several pieces of evidence support the existence of psychoneurological symptoms as clusters in women with breast cancer. However, to date, no study has considered the combined effects of inflammatory activation and metabolic profile in the development of the psychoneurological symptoms in women with breast cancer. We recommend further studies should shed light on the following phenomenon in that chemotherapy will induce an alteration in the inflammatory markers and serum metabolites among breast cancer women treated with chemotherapy, and such alterations are required for the development, persistence, and severity of the psychoneurological symptoms.

**Additional Information**

**Disclosures**

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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