The Psychoneurologic Symptom Cluster and Its Association With Breast Cancer Genomic Instability

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OBJECTIVES: To phenotype the psychoneurologic (PN) symptom cluster in individuals with metastatic breast cancer and associate those phenotypes with individual characteristics and cancer genomic variables from circulating tumor DNA.

SAMPLE & SETTING: This study included 201 individuals with metastatic breast cancer recruited in western Pennsylvania.

METHODS & VARIABLES: A descriptive, cross-sectional design was used. Symptom data were collected via the MD Anderson Symptom Inventory, and cancer genomic data were collected via ultra-low-pass whole-genome sequencing of circulating tumor DNA from participant blood.

RESULTS: Three distinct PN symptom phenotypes were described in a population with metastatic breast cancer: mild symptoms, moderate symptoms, and severe mood-related symptoms. Breast cancer *TP53* deletion was significantly associated with membership in a moderate to severe symptoms phenotype ($p = 0.013$).

IMPLICATIONS FOR NURSING: Specific cancer genomic changes associated with increased genomic instability may be predictive of PN symptoms. This finding may enable proactive treatment or reveal new therapeutic targets for symptom management.

KEYWORDS symptom science; breast cancer; cancer genomics; cell-free DNA

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Severe symptoms are associated with breast cancer and its treatment and can lead to decreased quality of life (Hamer et al., 2017). Between 28% and 52% of individuals with metastatic breast cancer experience the psychoneurologic (PN) symptom cluster, which includes pain, fatigue, sleep disturbance, anxiety, depression symptoms, and changes in cognitive function (Albusoul et al., 2017; Niklasson et al., 2017; Starkweather et al., 2013; Sullivan et al., 2018). A systematic review of multiple studies indicates that the PN symptom cluster occurs across the treatment trajectory (So et al., 2021). These symptoms may be present at the time of diagnosis or before the initiation of therapy, and pretreatment symptom severity may be predictive of the symptom experience throughout treatment (Fox et al., 2020; Grayson, Sereika, et al., 2023; Li et al., 2020; Tometich et al., 2019). Precision health research will enable the prediction of patients who are at highest risk for experiencing the PN symptom cluster and explain underlying biologic mechanisms. Accurate symptom prognostication may allow for more proactive symptom interventions, as opposed to reactive treatments once individuals report symptoms.

The National Cancer Institute (n.d.) defines *genomic instability* as the tendency of cancer cells to accumulate mutations and gross genomic anomalies such as chromosome number aberrations. Significant interactions exist between cancer genomic instability and systemic inflammation (Hanahan & Weinberg, 2011; Kawanishi et al., 2017). Inflammation, in turn, has been associated with the severity and occurrence of PN symptoms (Jehn et al., 2012; Ji et al., 2017; Khosravi et al., 2019; Mark et al., 2017; Schmidt et al., 2016). This leads to the hypothesis that cancer genomic instability may be predictive of the PN symptom cluster