Biological Basis for the Clustering of Symptoms

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Objectives: *Identification of biologic pathways of symptom clusters is necessary to develop precision therapies for distressing symptoms. This review examined extant literature evaluating relationships between biomarkers and symptom clusters in cancer survivors.*

Data Sources: *PubMed, CINAHL, Web of Science and Cochrane Library were searched using terms "biological markers" or "biomarkers" and "symptom cluster" or "symptom complex" or "multiple symptoms."*

Conclusion: *Biomarkers related to inflammation (eg, cytokines) were the most studied and showed the most significant relationships with clusters of symptoms. This review suggests that clustering of symptoms related to cancer or cancer therapy is linked to immune/inflammatory pathways.*

Implications for Nursing Practice: *Understanding the etiology of symptom clusters may guide future nursing interventions for symptom management.*

Key Words: *symptom cluster, inflammation, cancer-related symptoms, symptom complex, biological, pathways.*

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Advances in treatment and screening for early detection of cancer have resulted in increased survival for millions of individuals.[1] There are over 14 million cancer survivors living in the United States, and this number is expected to reach 19 million by 2024.[2] Regardless of where one is in the spectrum of cancer survivorship, symptoms are a major concern for individuals and their caregivers. Symptoms may be associated with the stage of the cancer or adverse effects of treatments. Frequency, severity, and the number of co-occurring symptoms contribute to symptom burden, which negatively affects health-related quality of life of cancer survivors.[3]

Although individual symptoms may have unique manifestations clinically, it is hypothesized that co-occurring symptoms may share common biologic underpinnings.[4,5] The etiology behind clustering of symptoms observed in oncology patients is poorly understood. A recent review identified inflammatory pathways to explain the biology of symptom cluster (pain, fatigue, sleep disturbance, and depression) reported by women with breast cancer after treatment.[6]

Cancer and its treatment are known triggers of acute and persistent inflammatory and immune responses,[7-9] as well as influential players in the hypothalamic-pituitary-adrenal axis function.[10-12] It was reported that cancer treatment directly increases the synthesis and release of cytokines from macrophages[13,14] that bind to receptors in target cells and produce additional inflammatory cytokines and chemokines to mount a systemic inflammatory response to counter the cellular damage inflicted by the cancer therapy.[15] This systemic inflammatory response is believed to target inflammatory-responsive neurons in the central nervous system that produces co-occurrence of symptoms to include fatigue, anorexia, cognitive dysfunction, and other cytokine-induced sickness behavior.[16,17]

Inflammatory pathways were also suggested to explain the biology of clustering of symptoms in clinical populations other than cancer. Levels of interleukin (IL)-15 and IL-1 receptor agonist were negatively associated with the clustering of neuropsychiatric symptoms including depression, apathy, agitation, and sleep in individuals with Alzheimer's disease.[18] In women with fibromyalgia, an inflammatory transcriptome profile distinctly delineated subjects complaining of fatigue associated with pain from those reporting fatigue associated with catastrophizing.[19]

The goal of this review is to investigate the biology of clustering of symptoms related to cancer or cancer therapy. Specifically, this review examined studies focusing on relationships of biological markers and the co-occurrence of cancer-related symptoms. Central to the development and implementation of targeted, individualized, symptom management strategies for symptom clusters is to understand the mechanisms undergirding their development and/or persistence.

Methods

An extensive literature search was performed with the assistance of a medical librarian at the University of Florida (Gainesville, FL)using four commonly referenced databases (PubMed, CINAHL, Web of Science, and Cochrane Library). The initial search resulted in 2,656 articles using the search terms listed in Table 1. After removal of duplicates (n = 24), 2,632 articles remained. Articles were included if they were written in English, published between 2005 and 2015 to capture the most recent information, and enrolled only human subjects who were at least 21 years of age. All articles reviewed were studies in which participants had a cancer diagnosis (any type, any stage, receiving any cancer treatment), reported co-occurrence of more than one symptom, and explored the relationship of biological markers and reported symptoms. The 2,632 articles were assessed for relevance to the review by visually examining their titles and abstracts using the inclusion/exclusion criteria which resulted in an additional 2,435 articles being removed. This left 197 articles for consideration. Articles were further excluded if they were reviews, commentaries, editorials, or dissertations, which left 56 articles for full text review. After a thorough review of the full text of the remaining articles, an additional 42 articles were excluded because they did not explore a symptom cluster (n = 21), did not include a biomarker in relation to a symptom cluster (n = 19), or were previously unidentified duplicates (n = 2). The process for article selection is described in Figure 1.

Results

There were a total of 14 articles (see Table 2) that explored biological mechanisms related to clustering of cancer-related symptoms.[20-33] Of these 14