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BIOMARKERS: SYMPTOMS, SURVIVORSHIP, AND QUALITY OF LIFE

Christine Miaskowski, RN, PhD, FAAN and
Professor and Associate Dean for Academic Affairs American Cancer Society Clinical Research Professor, Sharon A. Lamb Endowed Chair, Department of Physiological Nursing, University of California, San Francisco, CA

Bradley E. Aouizerat, RN, PhD, MAS
Associate Professor Department of Physiological Nursing and Institute for Human Genetics, University of California, San Francisco, CA

Abstract

Objectives—To review the evidence on a number of biomarkers that show potential clinical utility in the prediction of and treatment responsiveness for the four most common symptoms associated with cancer and its treatment (i.e., pain, fatigue, sleep disturbance, depression).

Data Sources—Review and synthesis of review articles and data-based publications.

Conclusions—A growing body of evidence suggests that sensitive and specific biomarkers will be available to assist clinicians with the assessment and management of symptoms.

Implications for Practice—Nurses will play a critical role in educating patients about their risk for specific symptoms based on an evaluation of specific biomarkers. Nurses will be involved in using biomarker data to titrate medications based on patient's responses to symptom management interventions.

Keywords

biomarkers; genomics; pain; fatigue; depression; sleep disturbance; symptoms; quality of life

INTRODUCTION

As noted in the previous papers in this issue of Seminars in Oncology Nursing, a variety of biomarkers are used in risk appraisal, early detection, diagnosis, and management of cancer. Some of these biomarkers have been available for decades. In contrast, the use of biomarkers to evaluate symptoms and quality of life (QOL) of in patients undergoing cancer treatment and in cancer survivors is a relatively new field of scientific inquiry.[1-3] Delays in the development of biomarkers for the assessment of cancer symptoms and for the evaluation of the impact of cancer and its treatments on various aspects of QOL may be attributed to a number of factors. First, symptoms and QOL outcomes are subjective

Address correspondence to: Christine Miaskowski, RN, PhD, FAAN, Professor, Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, 415-476-9407 (phone), 415-476-8899 (fax), chris.miaskowski@nursing.ucsf.edu.

phenomenon. Initial efforts to assess these phenomena were focused on the development and testing of valid and reliable instruments to evaluate these important patient-reported outcomes. Second, symptom management and QOL researchers, for the most part, worked in a relative vacuum and lacked expertise in the development and testing of biomarkers based on molecular mechanisms. However, as the underlying mechanisms for the most common symptoms experienced by cancer patients and survivors (i.e., pain,[4] fatigue,[5,6] sleep disturbance,[7-9] depression[10-12]) are being elucidated through studies in both animals and humans, the need to identify clinically relevant biomarkers for individual symptoms and symptom clusters,[13-15] as well as QOL outcomes has become a scientific imperative.

The development of sensitive and specific biomarkers, that correlate with subjective reports of symptoms and QOL, could be used to identify patients at greatest risk for more severe symptoms and poorer QOL outcomes. In addition, as with treatments for cancer, sensitive and specific biomarkers could be used to monitor the efficacy of symptom management and QOL of life interventions, as well as the side effects associated with these interventions. This convergence of subjective and objective measures could lead to the development of personalized symptom management strategies prior to the initiation of cancer therapy that might prevent the development of chronic symptoms, as well as decrements in functional status and poorer QOL outcomes particularly in cancer survivors.

The development of specific biomarkers for the most common symptoms associated with cancer and its treatments, as well as biomarkers of treatment efficacy is still in its infancy but initial efforts are promising. The purpose of this paper is to review the evidence on a number of biomarkers that show potential clinical utility in the prediction of and treatment responsiveness for the four most common symptoms associated with cancer and its treatment and that persist in cancer survivors, namely pain, fatigue, sleep disturbance, and depression. When research findings from patients with cancer are not available, data are provided on the sensitivity and specificity of the various biomarkers from other populations. This paper concludes with a discussion of the clinical implications for these biomarkers and recommendations for future research.

COMMON MECHANISTIC PATHWAYS MAY UNDERLIE THE MOST COMMON SYMPTOMS ASSOCIATED WITH CANCER AND ITS TREATMENT

A growing body of evidence suggests that pain, fatigue, sleep disturbance, and depression may be associated with immunological processes that include the activation of innate immune inflammatory responses and subsequent regulation by a number of neuroendocrine pathways (i.e., hypothalamic-pituitary-adrenal (HPA) axis, 5-hydroxytryptamine (5HT) neurotransmitter dysregulation, circadian rhythm disruption, alterations in adenosine triphosphate (ATP) metabolism, vagal afferent activation, and glucocorticoid signaling).[6,12,15-19] The “classic” example that is used to illustrate the potential mechanistic associations among pain, fatigue, sleep disturbance, and depression is cytokine-induced sickness behavior.[20-23] Sickness behavior can be observed in sick animals or induced by the administration of lipopolysaccharide (i.e., the pathophysiological components of bacteria). The physiological responses that occur as a result of sickness behavior included fever, pain, and increased activity in the HPA axis and the autonomic nervous system. Additional reactions associated with cytokine-induced sickness behavior include a general decrease in activity, somnolence, cognitive impairment, decreased social interaction, decreased sexual activity, and decreased food intake.[20-23] The similarities between cytokine-induced sickness behaviors and symptoms experienced by cancer patients led to investigations of a number of cytokines and neuroendocrine molecules as potential biomarkers for pain, fatigue, sleep disturbance, and depression.

TYPES OF BIOMARKERS FOR CANCER SYMPTOMS

In an excellent review,[20] Gilbertson-White and colleagues summarized many of the methodological issues associated with the measurement of cytokines as biomarkers of common cancer symptoms. While this review focused on the evaluation of cytokines, many of these issues are similar for all of the molecules involved in the various inflammatory and neuroendocrine pathways cited above. The most common types of molecules that are measured as potential biomarkers of symptoms include proteins, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA). The measurement of specific proteins provides information on the actual levels of a specific molecule or its receptor in serum or a tissue. In these types of biomarker studies, patients with a symptom may be compared to healthy controls; the severity of a symptom may be correlated with increases or decreases in the level of a particular protein; or changes in the levels of a particular protein during and following a symptom management intervention may be assessed. In studies that use DNA, mutations or common variations in DNA are hypothesized to be associated alterations in gene function. In these types of studies, symptom severity levels or responses to a symptom management intervention in individuals with a particular genomic alteration are compared to individuals without that genetic alteration. In studies that use RNA, alterations in gene expression are evaluated in the context of symptom severity or symptom management. These types of RNA studies assume that variation in the expression of a particular biomarker will be associated with variation in symptom perception or response.

STUDIES OF PROTEINS AS BIOMARKERS FOR COMMON CANCER SYMPTOMS

Serum cytokines are the most common proteins that have been investigated as biomarkers for a variety of cancer symptoms.[20,22,24-35] For example, in one of the first case reports of serum cytokine elevations, Meyers and colleagues[36] found that higher symptom severity scores were associated higher levels of tumor necrosis factor alpha (TNF-α).

Serum cytokines and fatigue

A number of studies have found associations between cancer-related fatigue and changes in cytokine concentrations. In one of the earliest studies of patients with metastatic colorectal cancer,[37] higher pretreatment levels of pro-inflammatory cytokines were associated with higher levels of fatigue. In another study of breast cancer survivors with persistent fatigue an average of 5 years after diagnosis,[38] these patients had significantly higher serum levels of interleukin-1 receptor (IL-1ra), soluble tumor necrosis factor receptor type II (sTNF-RII), and neopterin compared to healthy controls. In addition, the fatigued survivors had lower serum cortisol levels than healthy controls. In a more recent study of the association between inflammatory cytokines and symptoms,[39] increases in fatigue severity were associated with higher levels of sTNF-RII in patients who recently completed chemotherapy treatment for breast cancer.

Serum cytokines and pain

In a recent review on the mechanisms of cancer pain,[4] Schmidt and colleagues noted that cytokines are provocative candidates for cancer pain because they are produced at high levels within cancer cells. In animal models of cancer pain,[40,41] increases in levels of TNF-α in the environment around the tumor resulted in increased mechanical and thermal hypersensitivity. In studies of patients with non-small cell lung cancer undergoing chemotherapy[26] and patients at nadir following allogeneic stem cell transplantation,[42] increases in serum IL6 levels were associated with increases in pain severity scores.

Serum cytokines and depression

The role of inflammation in the development of depression was the subject of a several review articles.[10,43-45] In addition, a recent meta-analysis of associations between depression, C-reactive protein (CRP), IL1, and IL6[46] found that each biomarker was positively associated with depressive symptoms. In a recent study of patients with advanced metastatic cancer,[47] higher levels of IL6 were associated with higher levels of depressive symptoms.

Serum cytokines and sleep disturbance

The relationships between inflammation and sleep disturbance and sleep deprivation were described in a number of review articles.[48-57] In a study of patients with metastatic colorectal cancer,[37] high pretreatment levels of pro-inflammatory cytokines were associated with a dampened 24-hour circadian rhythm measured using actigraphy. In addition in the studies of multiple symptoms in patients with NSCLC[26] and allogeneic bone marrow transplant[42] cited above, higher levels of IL6 were associated with higher levels of sleep disturbance.

Taken together, the results of these biomarker studies provide preliminary evidence that changes in a number of serum cytokine levels are associated with fatigue, pain, depression, and sleep disturbance in oncology patients and survivors. The majority of these studies are limited by relatively small sample sizes, heterogenous samples in terms of cancer diagnoses and stages of disease, cross-sectional designs, the use of mean symptom severity scores to characterize the symptom phenotype, and the focus primarily on pro-inflammatory cytokines. Additional research is warranted that attempts a more robust characterization of inter-individual differences in the symptom phenotype; that determines clinically meaningful levels of cytokines that warrant intervention; and that evaluates the contribution of both pro- and anti-inflammatory cytokines to the development of fatigue, pain, depression, and sleep disturbance.

STUDIES OF GENOMIC BIOMARKERS FOR COMMON CANCER SYMPTOMS

The genetic basis for fatigue,[6,58-60] pain,[18,19,61-64] depression,[11,12,65-67] and sleep disturbance[7-9,68] in patients with cancer and other chronic medical condition has been the subject of a number of recent reviews. Again, many of the genetic studies of these symptoms in cancer patients have focused on an evaluation of candidate genes associated with pro- and anti-inflammatory cytokines. Table 1 provides a list of some of the potential candidate genes that may contribute to variation in oncology patients' experiences with fatigue, pain, depression, and sleep disturbance.[6,8,11,18,19,60,62,67,69,70] While some of these candidate genes were evaluated in studies with oncology patients, other candidate genes listed in Table 1 were identified in other patient populations. Due to space constraints, some of the candidate gene studies that were done with oncology patients are summarized below.

In one of the first candidate gene studies of cytokines and cancer-related fatigue,[71] associations were found between polymorphisms in IL1β and fatigue in patients with breast cancer. In addition in studies of patients with breast, prostate, lung, and brain cancers and their family caregivers (FCs), associations were found between polymorphisms in TNF-α[72] and IL6[73] and cancer-related fatigue, as well as sleep disturbance.

In a series of studies,[74-77] Reyes-Gibby and colleagues evaluated the associations between a number of cytokine candidate genes and pain in patients with lung and pancreatic cancer. Of note in patients with lung cancer,[76] select polymorphisms in TNF-α and IL6 were associated

with pain severity and analgesic intake. In addition, in studies of patients with lung[77] and pancreatic[75] cancer, a polymorphism in IL8 was associated with pain severity scores.

While limited in number, findings from these candidate gene studies suggest that genomic biomarkers have the potential to be used to identify patients at highest risk for more severe symptoms and symptom clusters. Additional studies are needed to identify the most common genomic variants that result in functional changes in proteins and are associated with more severe symptoms. Undoubtedly, research will need to evaluate for gene × gene as well as gene × environment interactions to determine the relative contribution of a specific genomic biomarker to the symptom experience of oncology patients.

USE OF BIOMARKERS TO MONITOR THE EFFICACY OF SYMPTOM MANAGEMENT INTERVENTIONS

In addition to the identification of high risk patients, sensitive and specific biomarkers could be used to monitor the efficacy of symptom management interventions and/or the side effects associated with these interventions. An example of this type of biomarker is genetic variation in the liver enzymes CYP2D6 and CYP2C19. These enzymes are involved in the metabolism of numerous medications. Polymorphisms in these genes are associated with inter-individual variability in the metabolism of opioids[62] and antidepressant[78] medications. The CYP2D6 gene is highly polymorphic with over 70 single nucleotide polymorphisms (SNPs) and copy number variations.[79,80] Individuals can be classified, based on their specific gene polymorphisms, into poor (PM), intermediate (IM), extensive/normal (EM), or ultrarapid drug metabolizers (EM).[81] Of clinical importance, the distribution of these classifications varies across ethnic groups. For example, Europeans show the highest frequency of CYP2D6 PMs and African-Americans show the highest frequency of CYP2D6 UMs.[82]

Genetic variation in the CYP2D6 gene has important implications in terms of symptom management. EMs obtain the expected therapeutic effect from a standard dose of a drug. However, patients within the other three groups are at risk for poor efficacy and/or side effects if given a drug that is incompatible with their genetic makeup. For example, prodrugs, like codeine, are less efficacious in PM because they require chemical conversion of codeine to its active product (in this case morphine). It should be noted that approximately 8% to 10% of the Caucasian population and 50% of people of Asian descent have a polymorphism in CYP2D6 that renders the enzyme inactive. These individuals do not obtain any analgesia from codeine.[83] In contrast, patients who are UMs of codeine have a higher risk of opioid-induced side effects.[84,85]

This type of biomarker will be useful in determining the efficacy of pharmacologic interventions for the most common symptoms associated with cancer and its treatment. In addition, each patient's metabolizer status could be evaluated prior to his/her enrollment in a clinical trial and be used as an inclusion/exclusion criteria or taken into account in drug titration studies. This approach is feasible given the fact that CYP2D6 and CYP2C19 diagnostic testing is FDA approved with the Roche AmpliChip®.[81,86]

USE OF BIOMARKERS TO EVALUATE THE QOL OF ONCOLOGY PATIENTS

In an excellent review article,[12] Spranger and colleagues provide evidence primarily from twin studies that the heritability estimates for individuals' ratings of subjective well-being and life satisfaction range between 40% and 50%. For example, Bartels and Boomsma,[87] in a study of 5,024 adolescent twins and their siblings, found that four measures of positive emotional states (i.e., QOL in general, satisfaction with life, quality of life at present, and

subjective happiness) loaded on a similar set of genes. In addition, in a study of over 3,000 twins,[88] the same set of genes was found to be involved in self-ratings of optimism, overall health, and mental health. These investigators suggested that these QOL-related factors may share a common genetic basis that represents the heritable mechanism behind an individual's positive orientation. Undoubtedly, additional studies are warranted to confirm these findings and evaluate the contribution of specific environmental effects (e.g., effects of cancer and its treatment) on patients' evaluations of their QOL in conjunction with their genetic makeup.

IMPLICATIONS FOR CLINICAL PRACTICE

Compared to their use in early detection, diagnosis, and treatment of cancer, the use of biomarkers in the assessment and management of common symptoms and various domains of QOL is still in its infancy. However, based on a growing body of evidence and progress in genomics research, an increased number of sensitive and specific biomarkers will be developed to assist clinicians in the identification of high risk patients and in the evaluation of the efficacy of symptom management interventions. While a number of issues will need to be addressed in the next decade, the era of personalized health care is becoming a clinical reality.[89-91]

Nurses will play a critical role in educating patients about their risk for specific symptoms based on an evaluation of a number of biomarkers. In addition, they will be involved in using biomarker data to titrate symptom management medications based on patient's responses to treatment. As in other aspects of cancer care, symptom management will become more individualized and personalized. Because nurses are educated to care for the whole patient, they are in a unique position to evaluate a particular biomarker within the context of the patient's symptom experience, as well as the impact of a variety of environmental factors (e.g., personality characteristics, level of family support, income), on the selection and evaluation of specific symptom management interventions. Undoubtedly, nurses will need additional education and training to be able to interpret the results of biomarker testing; to be able to use the results to select symptom management interventions; and to use specific biomarkers to determine the efficacy of a variety of pharmacologic and nonpharmacologic interventions to manage symptoms.

IMPLICATIONS FOR RESEARCH

Given the fact that the use of biomarkers in symptom management and QOL is still in its infancy, research is needed in a number of areas. Table 2 lists priority areas of investigation that will enable the integration of biomarkers into symptom management research and clinical care. While substantial progress has been in the development of valid and reliable instruments to assess the most common symptoms associated with cancer and its treatment, additional research is needed to refine the conceptualization of specific symptom phenotypes. For example, as noted by Lyon and colleagues,[60] the adoption of a consistent definition for fatigue is needed in order to realize the benefits of genomic biomarkers. The reconceptualization of each symptom phenotype needs to be done within the context of evaluating the impact of various demographic, clinical, and environmental characteristics on the patient's symptom experience. In addition, careful characterization of acute and chronic symptoms phenotypes is needed because different biomarkers may be associated with different temporal phenotypes. Finally, newer methods of longitudinal data analysis (e.g., hierarchical linear modeling, growth mixture modeling) may be useful tools to characterize inter-individual variability in acute and chronic symptom experiences and the identification of more homogeneous symptom phenotypes (e.g., patients with persistently high levels versus low levels of fatigue).[72,73,92-94]

Equally important for the development of sensitive and specific biomarkers for use in symptom management is the ability to replicate findings across studies and test hypotheses in large samples of patients. Symptom management scientists will need to develop large scale collaborations that include the establishment of phenotypic data repositories. In order to accomplish this goal, researchers will need to agree on a standard set of symptom assessment and QOL measures that can be used across studies. The Patient-Reported Outcomes Measurement Information System (PROMISE) initiative is an example of an effort to develop a standard battery of valid and reliable measures that can be used in symptom management and QOL research.[95] Once these phenotypic data repositories are established, the capacity to validate biomarkers within and across a number of symptoms will be facilitated.

The main goal for the development of sensitive and specific biomarkers is the identification of patients who are at greatest and at minimal risk for specific symptoms during and after cancer treatment. The use of biomarkers to identify the “extreme phenotypes” for any symptom will allow clinicians to focus resources on patients who are most in need of pre-emptive and ongoing symptom management interventions and may provide insights into protective factors in patients who experience low levels of symptoms. Finally, specific biomarkers need to be developed that can be used to tailor interventions for individual patients as well as judge the efficacy of pharmacologic and nonpharmacologic interventions.

CONCLUSIONS

While patient-reported outcomes, like symptoms and QOL, are view by some clinicians and researchers as “soft” outcomes, a growing body of evidence has demonstrated that these subjective measures are strong predictors of patients’ responses to treatment and survival.[1,96,97] Linking objective biomarkers with subjective assessments will enable clinicians and researchers to improve their diagnostic acumen and provide patients with more effective and evidenced-based symptom management and QOL interventions. Nurses will play a critical role in linking patient-reported outcomes with these sensitive and specific biomarkers.

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Table 1

Candidate Genes As Potential Biomarkers for Common Symptoms in Oncology Patients*

Candidate Gene Categories	Fatigue	Pain	Depression	Sleep Disturbance
Inflammatory pathways	Pro- and anti-inflammatory cytokine genes (e.g., IL1β, IL2, IL4, IL6, IL8, TNF)-α, interferon gamma)	Pro- and anti-inflammatory cytokine genes (e.g., IL1β, IL2, IL4, IL6, IL8, TNF)-α, interferon gamma)	Pro- and anti-inflammatory cytokine genes (e.g., IL1β, IL2, IL4, IL6, IL8, TNF)-α, interferon gamma)	Pro- and anti-inflammatory cytokine genes (e.g., IL1β, IL2, IL4, IL6, IL8, TNF)-α, interferon gamma)
Neuroendocrine pathways – can include genes associated with the following mechanistic pathways: hypothalamic-pituitary-adrenal (HPA) axis, five hydroxtryptamine (5HT) neurotransmitter dysregulation, circadian rhythm disruption, alterations in adenosine triphosphate (ATP) metabolism, vagal afferent activation, and glucocorticoid signaling	Genes associated with variations in serotonin, dopamine, and norepinephrine Clock genes and genes associated with circadian rhythm	COMT 5-HTT OPMR1	5HTT Clock genes and genes associated with circadian rhythm Genes associated with variations in serotonin, norepinephrine, and brain derived neurotrophic factor	Clock genes and genes associated with circadian rhythm Genes associated with variations in serotonin, norepinephrine, and dopamine

* For reviews see - (Taheri 2004; McClung 2007; Turek 2007; Reyes-Gibby, Wu et al. 2008; Miaskowski 2009; Barsevick, Frost et al. 2010; Lau and Eley 2010; Shi, Cleeland et al. 2010; Lyon, McCain et al. 2011; Winkelmann and Kimura 2011)

Table 2

Priority Areas of Investigation to Enable the Integration of Biomarkers into Symptom Management Research and Clinical Practice

- Refine the conceptualization of the symptom phenotype
  - Evaluate the impact of demographic factors on the symptom phenotype
  - Evaluate the impact of clinical factors on the symptom phenotype
  - Evaluate how the symptom phenotype changes over time
  - Differentiate between acute and chronic manifestations of the symptom phenotype
- Develop valid and reliable measures of the symptom phenotype for use in research and clinical practice
  - Determine that symptom phenotype measures are sensitive to changes over time
  - Standardize the use of symptom phenotype measures in research
  - Develop technological approaches to measure the symptom phenotype in a variety of health care settings
  - Establish repositories of phenotypic data on common symptoms
- Develop sensitive and specific biomarkers (i.e., protein and molecular) for use in research and clinical practice
  - Develop and test biomarkers that can be used to identify low and high risk patients for common symptoms and quality of life outcomes
  - Develop and test biomarkers that can be used to guide the prescription of specific pharmacologic and nonpharmacologic interventions
  - Develop and test biomarkers that can be used to guide an evaluation of the efficacy of specific pharmacologic and nonpharmacologic interventions