Multifactorial Model of Dyspnea in Patients With Cancer

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PROBLEM IDENTIFICATION: Dyspnea is a common and distressing symptom for patients with cancer. Although the risk factors for dyspnea in patients with cancer are likely to be multifactorial, a comprehensive description of these risk factors and associated mechanisms is not available in the extant literature.

LITERATURE SEARCH: A search of all relevant databases, including Cochrane Library, PubMed®, Embase®, Web of Science, and CINAHL®, was done from January 2009 to May 2022. Case-control and cohort studies that had either a cross-sectional or longitudinal design, as well as randomized controlled trials, were included in the review. Peer-reviewed, full-text articles in English were included. Nineteen studies reported on risk factors for dyspnea.

DATA EVALUATION: The methodologic quality of each study was examined using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

SYNTHESIS: A number of factors can influence the occurrence and severity of dyspnea. Using the Mismatch Theory of Dyspnea as the central core of this Multifactorial Model of Dyspnea in Patients With Cancer, the factors included in this conceptual model are person, clinical, and cancer-related factors, as well as respiratory muscle weakness, co-occurring symptoms, and stress.

IMPLICATIONS FOR PRACTICE: The Multifactorial Model of Dyspnea in Patients With Cancer can be used by clinicians to evaluate for multiple factors that contribute to dyspnea and to develop individualized and multilevel interventions for patients experiencing this symptom.

KEYWORDS breathlessness; cancer; conceptual model; dyspnea; risk factors

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Dyspnea is a common and distressing symptom that occurs in about 58% of patients with cancer (Shin et al., 2023). Despite its associated burden, dyspnea is underestimated in clinical practice (Iyer et al., 2014). The American Thoracic Society defined dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (Parshall et al., 2012, p. 436). In addition, the American Thoracic Society noted that "the experience of dyspnea derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses" (Parshall et al., 2012, pp. 436–437). Although the risk factors for the occurrence and/or severity of dyspnea in patients with cancer are likely to be multifactorial (Ban et al., 2016; Booth et al., 2008; McKenzie et al., 2018), a comprehensive description of these factors and associated mechanisms is not available in the extant literature.

A recent review on the mechanisms that underlie dyspnea focused on patients with terminal lung cancer (Fukushi et al., 2021). In this review, the authors suggested that the tumor mass, presence of a malignant pleural effusion, and/or respiratory muscle weakness contributed to a mismatch between afferent (i.e., intended respiratory motor output) and efferent (e.g., ventilatory outputs that were accomplished) signaling (Fukushi et al., 2021). Although many clinicians associate the occurrence of dyspnea exclusively with patients with lung cancer or patients at the end of life, findings from epidemiologic studies noted that patients with other types and stages of cancer report dyspnea (Bausewein et al., 2010; Damani et al., 2018; Dudgeon, Kristjanson, et al., 2001; McKenzie et al., 2018; Reddy et al., 2009; Rowbottom et al., 2017). For example, in a cross-sectional study of dyspnea in 923 patients with cancer (Dudgeon, Kristjanson, et al., 2001), only 9.4% had primary or metastatic lung cancer. The remaining 90.6% of patients with heterogeneous types of cancer

experienced dyspnea from a variety of factors (e.g., cancer treatment, comorbid conditions). Although the 2021 National Comprehensive Cancer Network palliative care guidelines on dyspnea summarized a number of clinical trials of various pharmacologic and nonpharmacologic interventions (Dans et al., 2021), they concluded that evidence of the efficacy of these interventions is limited. In addition, the American Society of Clinical Oncology guideline on management of dyspnea in advanced cancer noted that an inadequate understanding of the pathophysiology of dyspnea makes it challenging to develop novel interventions (Hui et al., 2021). Therefore, the purpose of this article is to describe the factors that contribute to the mechanisms that underlie dyspnea in patients with cancer. This article begins with a summary of the mechanisms that underlie normal breathing in healthy individuals, followed by a description of the mechanisms that underlie dyspnea. In addition, the evidence to support each of the factors that contributes to dyspnea in patients with cancer is summarized and critiqued. The article concludes with recommendations for clinical practice and research.

Physiology of Normal Breathing

Respiratory Muscles

Respiratory muscles, which are used for inspiration and expiration, include the internal and external intercostal muscles, the diaphragm, and the muscles of the abdomen, neck, and upper limbs (Jolley & Moxham, 2006). While the diaphragm and intercostal muscles generate intrathoracic pressures, the abdominal muscles coordinate with the diaphragm to compensate for the increased ventilatory drive that is needed during exercise (Aliverti, 2016).

Mechanoreceptors

Neural innervation and chest wall receptors: Intercostal muscles are innervated by the intercostal nerves that originate in the thoracic spine (Tang & Bordoni, 2022). The diaphragm is innervated by the phrenic nerve, which originates in the third to fifth cervical spine (Burki & Lee, 2010). Various types of receptors are involved in breathing. Muscle spindles and Golgi tendon organs in the diaphragm and intercostal muscles detect muscle tension and contraction (Fukushi et al., 2021). While muscle spindles are abundant in intercostal muscles, Golgi tendon organs dominate in the diaphragm (Motoyama & Finder, 2011). These stretch reflex receptors are innervated by spinal motor neurons that project to the somatosensory cortex (Burki & Lee, 2010).

Lung receptors: The lung contains three main mechanoreceptors that transmit afferent information to the respiratory center in the brain (e.g., slowly adapting pulmonary stretch receptors, irritant receptors, C fibers) (Parshall et al., 2012). Slowly adapting pulmonary stretch receptors, which lie within the smooth muscles of the trachea and central airways, are activated in response to an increase in lung volume and mediate the termination of inspiration (Parshall et al., 2012). Irritant receptors are located superficially within the epithelial cells of the carina and large bronchi (Motoyama & Finder, 2011). Irritant receptors are stimulated by cigarette smoke (Motoyama & Finder, 2011) and various mediators of inflammation (e.g., histamine, bradykinin, serotonin) (Fukushi et al., 2021). In addition, irritant receptors mediate bronchoconstriction, coughing, and mucus secretion (Motoyama & Finder, 2011). Both of these mechanoreceptors transmit information to the respiratory center through the vagus nerve (Brinkman et al., 2022). C fibers located in the alveolar walls, lung interstitium, and pulmonary capillaries (Parshall et al., 2012) are sensitized by an increase in interstitial fluid volume and/or pulmonary arterial and capillary pressures (Fukushi et al., 2021). In particular, juxtacapillary receptors (i.e., J receptors, a type of C fiber), which are located in the alveolar septa (Fukushi et al., 2021), are activated by pulmonary vascular congestion (Banzett et al., 2015).

Upper airway receptors: The larynx has three primary receptors (i.e., pressure receptors, irritant [or drive] receptors, and flow [or cold] receptors) (Motoyama & Finder, 2011). Irritant receptors rapidly respond to changes in and movement of the laryngeal cartilage (Parshall et al., 2012). Pressure receptors are sensitive to changes in transmural laryngeal pressure (Motoyama & Finder, 2011). Temperature changes stimulate flow receptors (Motoyama & Finder, 2011). In terms of facial receptors, the trigeminal nerves are involved in the sensation of dyspnea (Parshall et al., 2012). Although the exact mechanisms that underlie the effects of airflow and temperature changes on dyspnea are not established, cold airflow on the face decreases the sensation of dyspnea (Fukushi et al., 2021).

Chemoreceptors

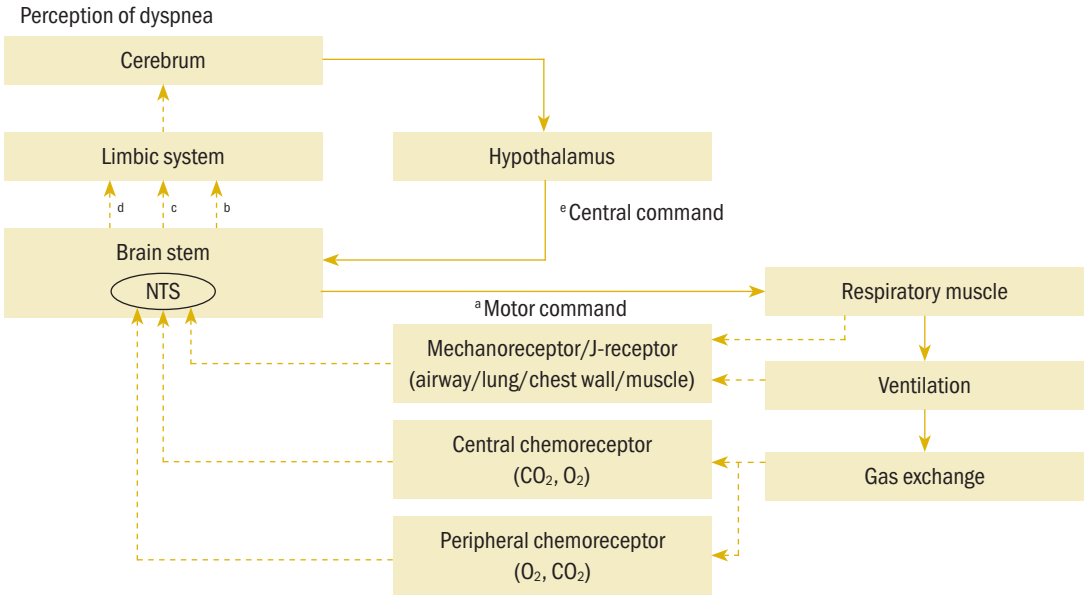
Central chemoreceptors located within the cerebellum and brain stem (e.g., medulla, pons, midbrain) are activated by hypercapnia (Parshall et al., 2012). Peripheral arterial chemoreceptors within the carotid

body are stimulated by hypercapnia, hypoxia, and acidosis (Parshall et al., 2012). The carotid body comprises around 15% of the total driving force of the respiratory system (Brinkman et al., 2022). Increased afferent information is transmitted to the respiratory center in the lower brain stem, which directly and indirectly increases respiratory neural output (Fukushi et al., 2021).

Respiratory Center and Brain Regions

The respiratory center, located in the medulla oblongata and pons of the brain stem, generates and maintains the rhythm of respiration (Pal & Chen, 2014). Three major groups of neurons compose the respiratory center. The ventral respiratory group and the dorsal respiratory group (DRG), located in the medulla, control the basic rhythm of respiration

FIGURE 1. Dyspnea Pathways



[a] Motor command
[b] Motor command corollary discharge
[c] Integrated input from mechanoreceptors
[d] Integrated input from chemoreceptors
[e] Central command
J-receptor—juxtacapillary receptor; NTS—nucleus tractus solitarius

Note. Dashed lines indicate sensory information, and solid lines indicate motor information.

Note. The lower brain stem respiratory neural network produces a motor command[a] that modulates upper airway patency and drives the respiratory pump muscle. Copies of the motor command signal are transmitted to the limbic system and cerebrum as a type of sensation that reflects the amount of respiratory effort (motor command corollary discharge[b]). The ventilatory output, realized by the motor command, is monitored by respiratory mechanoreceptors in the lungs, airways, and muscle spindles in the intercostal muscles. The information is projected to the lower brain stem, limbic system, and cerebral cortex and processed as an integrated mechanical respiratory sensation[c]. The integrated mechanical respiratory sensation and motor command corollary discharge are counter compared in higher brain centers, and the quantitative and/or phasic mismatch causes dyspneic sensation. Further, signals from peripheral and central chemoreceptors are summated as integrated chemical respiratory sensation[d] in higher brain centers. The integrated chemical respiratory sensation modifies respiratory sensation. The threshold and sensitivity for the perception of dyspnea are also influenced by the mental state. Dyspnea perception augments the central command[e] that descends as a respiratory drive signal from the hypothalamus to the lower brain stem, which heightens respiratory lower brain stem neural output. The brain respiratory feedback system maintains ventilation at an appropriate level.

Note. From "Mechanisms Underlying the Sensation of Dyspnea," by I. Fukushi, M. Pokorski, & Y. Okada, 2021, *Respiratory Investigation, 59*(1), p. 74 (https://doi.org/10.1016/j.resinv.2020.10.007). Copyright 2021 by Elsevier. Reprinted with permission.

(Pal & Chen, 2014). In particular, the DRG initiates inspiration and receives pulmonary afferent input from the vagus nerve (Pal & Chen, 2014). The ventral respiratory group consists of four groups of neurons, which are involved in inspiration and expiration (Pal & Chen, 2014).

The pontine respiratory group, located in the pons, includes the apneustic and pneumotaxic centers, which control the pattern and rate of breathing (Pal & Chen, 2014). Afferent information ascends from the lower brain stem and is integrated in the cerebral cortex, where dyspnea is perceived (Fukushi et al., 2021). During this process, the symptoms of anxiety and depression, which affect the limbic system, can alter the severity of and distress from dyspnea (Fukushi et al., 2021). The medullary respiratory center receives descending signals from the cerebral cortex and hypothalamus (Fukushi et al., 2019). The hypothalamus is involved in the modulation of respiration in hypoxic and hypercapnic conditions and under stress (Fukushi et al., 2019). The descending signals from the medullary respiratory center are transmitted to the somatic motor neurons located in the anterior horn of the spinal cord (Burki & Lee, 2010).

Mechanisms of Normal Breathing

Each rhythmic respiratory cycle begins with inspiration and ends with expiration. The respiratory system consists of three components, namely the central neural respiratory center, the sensory input system, and the muscular effector system (Brinkman et al., 2022). During the first step of respiration, the respiratory neural network (i.e., the DRG) in the lower brain stem generates a motor command that is sent to the respiratory muscles. Once the respiratory muscles receive this signal, they initiate inspiration by contracting the diaphragm and intercostal muscles. This process decreases intrathoracic pressure and increases volumes in the thoracic cavity that allow air to enter the lungs. Expiration occurs passively in response to the elastic recoil of the lungs and thorax. These rhythmic contractions of the respiratory muscles are controlled and monitored by the respiratory centers within the medulla and the pons.

Motor command corollary discharge: Normal breathing results from well-coordinated interactions between the respiratory muscles and the cerebral cortex (Brinkman et al., 2022). When the respiratory neural network in the lower brain stem generates the motor command, copies of the motor command signal (i.e., motor command corollary discharge) are simultaneously transmitted to the cerebral cortex through the limbic system (Fukushi et al., 2021). As a result, the cerebral cortex, a higher brain center, can detect a quantitative and phasic mismatch between afferent and efferent signaling and adjust for any disparities (Fukushi et al., 2021).

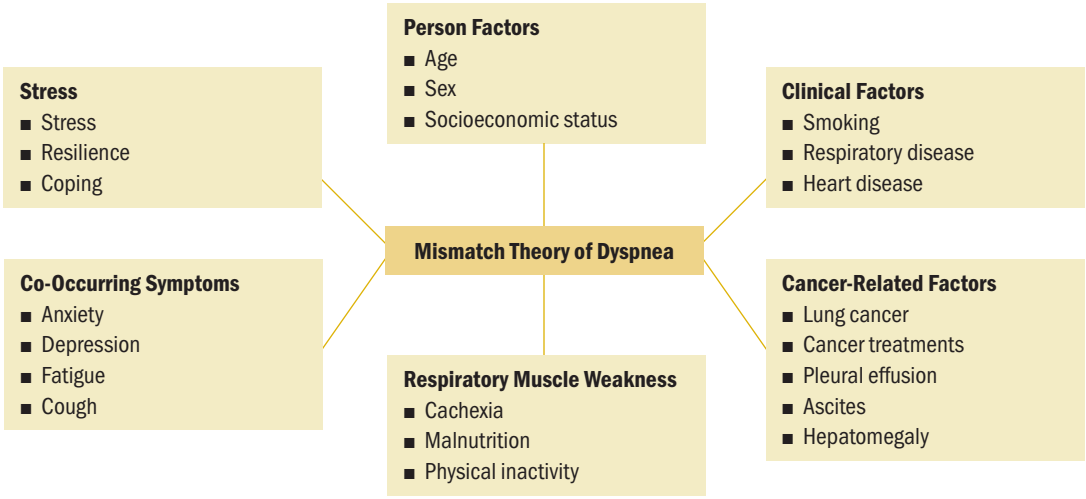
Respiratory homeostasis: Chemoreceptors and mechanoreceptors are involved in the respiratory feedback loop that sends sensory afferent information to the cerebral cortex through the limbic system (Burki & Lee, 2010). In particular, mechanoreceptors in the lungs, chest wall, airways, and spindles of the respiratory muscles monitor the actual ventilatory motor output (Burki & Lee, 2010). This information is transmitted to the cerebral cortex through the lower brain stem and limbic system (Fukushi et al., 2021). Finally, the cerebral cortex compares the integrated chemical and mechanical sensations with the motor command corollary discharges (De Vito, 2021). Within the normal threshold, the sensory cortex eliminates, minimizes, and/or compensates for the differences between afferent and efferent signals to maintain respiratory homeostasis (De Vito, 2021). As a result, breathing under normal conditions is an unconscious process.

Pathophysiology of Dyspnea

Mismatch Theory of Dyspnea

Sensory-perceptual/quality components: According to the Mismatch Theory of Dyspnea (Fukushi et al., 2021), when the threshold between motor command corollary discharge and afferent inputs is exceeded, the cerebral cortex perceives dyspnea (see Figure 1). Increased afferent input from mechanoreceptors and chemoreceptors augments the neural input to the respiratory muscles. This enhanced motor command increases the level of ventilation and facilitates gas exchange. Chemoreceptors are stimulated by hypercapnia, hypoxia, and acidosis (Parshall et al., 2012). Mechanoreceptors are stimulated by increased load and capacity imbalance. For example, on the one hand, increased respiratory load (or pressure) can occur because of lung stiffness, chest wall stiffness, airway flow resistance, and/or an augmented ventilatory demand. On the other hand, reduced capacity of the respiratory muscles results from muscle weakness and hyperinflation (Mioxham & Jolley, 2009). Under these pathologic conditions, augmentation of the respiratory drive cannot occur. An increase in ventilatory load and/or a reduction in muscle capacity results in

FIGURE 2. The Multifactorial Model of Dyspnea in Patients With Cancer



the progressive and continuous mismatch between motor command corollary discharge and integrated afferent information (Fukushi et al., 2021).

Distress components: Anxiety, depression, and anticipatory fear can amplify dyspnea (Fukushi et al., 2021; Scano et al., 2013) by decreasing the threshold and increasing the sensitivity for dyspnea perception (Fukushi et al., 2021). An unpleasant emotional state is associated with neural activation of the limbic system (e.g., amygdala, anterior insula) (Scano et al., 2013). Information from the limbic system is integrated into the cerebral cortex and influences the level of dyspnea (Fukushi et al., 2021) by affecting higher-order neural processing of respiratory sensations (von Leupoldt et al., 2011). Interestingly, anxiety affects the later higher-order neural processing of respiratory sensations instead of the first-order sensory processing (von Leupoldt et al., 2011). This finding suggests that the distress component of dyspnea may have distinct mechanisms from the sensory/perceptual component. On the other hand, the mechanisms that underlie dyspnea under negative emotional states may be associated with an excessive ventilatory drive or a blunted perception of achieved ventilatory output. This hypothesis is supported by the finding that individuals prone to panic disorders tended to experience dyspnea even in the absence of decreased ventilatory capacity (Parshall et al., 2012).

Methods

To develop this model, a systematic review of the prevalence of and risk factors for dyspnea was performed (Shin et al., 2023). In brief, in collaboration with a medical librarian, literature search strategies were developed using Medical Subject Headings (MeSH) terms and various text words related to dyspnea (i.e., breathlessness, shortness of breath, labored breathing, and difficulty breathing) in adult patients with cancer. The following databases were searched: Cochrane Library, PubMed®, Embase®, Web of Science, and CINAHL®. Case-control and cohort studies that had either a cross-sectional or longitudinal design, as well as randomized controlled trials, were included in the review. Peer-reviewed, full-text articles in English were included. Among the 117 studies that met prespecified inclusion criteria for this systematic review (Shin et al., 2023), only 19 studies reported on risk factors for dyspnea (Ban et al., 2016; Cameron et al., 2012; Currow et al., 2015; Ekström et al., 2016; Feinstein et al., 2010; Ha & Ries, 2020; Hechtner et al., 2019; Hirpara et al., 2020; Krishnan et al., 2021; Larsson et al., 2012; McKenzie et al., 2018, 2020; Mendoza et al., 2019; Murray et al., 2016; Nieder et al., 2018; Reddy et al., 2009; Silvoniemi et al., 2016; Tjong et al., 2021; Weingaertner et al., 2014). Findings from these 19 studies are summarized in this article to justify the various components of the Multifactorial Model of Dyspnea in Patients With Cancer.

Factors Associated With Dyspnea in Patients With Cancer

As illustrated in Figure 2, a number of factors can influence the occurrence and severity of dyspnea in patients with cancer. Using the Mismatch Theory of

Dyspnea (Fukushi et al., 2021) as the central core of the Multifactorial Model of Dyspnea in Patients With Cancer, the factors included in this conceptual model are based on a systematic review of the literature (Shin et al., 2023). Person, clinical, and cancer-related factors, as well as respiratory muscle weakness, co-occurring symptoms, and stress, are included in this model. Select research findings that provide the empirical support for the inclusion of these factors in this model are summarized.

Person Factors

Age: Older patients with cancer are more likely to report higher dyspnea severity scores (Ekström et al., 2016; Hirpara et al., 2020). Vertebral deformities, increased chest wall stiffness, and reductions in lung elasticity increase pressure on respiratory muscles and afferent inputs from pulmonary stretch receptors (Mioxham & Jolley, 2009). In addition, the aging process contributes to a decrease in the number and size of muscle fibers and a reduction in respiratory muscle strength (O'Donnell et al., 2007). A decrease in the capacity of respiratory muscles and an increase in respiratory resistance increase the afferent signals from respiratory muscle spindles. Equally important, as part of the aging process, the amount of alveolar dead space increases (Sharma & Goodwin, 2006), which results in hypoxia and hypercapnia and increases in afferent inputs from chemoreceptors (García-Río et al., 2007). This continuous mismatch between afferent information and motor command corollary discharge augments neural respiratory drive and increases dyspnea (Fukushi et al., 2021). For these reasons, older patients receiving cancer treatments may be more susceptible to dyspnea (De Ruysscher et al., 2009; Ha & Ries, 2020; Larsson et al., 2012; Tjong et al., 2021).

Sex: Findings regarding sex differences in dyspnea in patients with cancer are inconsistent. Although in three studies (Hirpara et al., 2020; Larsson et al., 2012; Tjong et al., 2021), male patients were more likely to experience severe dyspnea, in one study (Mendoza et al., 2019), female patients reported a higher symptom burden. One potential explanation for the higher rates of dyspnea in men is that they have higher rates of smoking (Jamal et al., 2016). Smokers tend to have higher airway resistance, lower peak oxygen uptake, and lower ventilation output, which increase total breathing efforts (Elbehairy et al., 2016). Another plausible hypothesis is that the loss of skeletal muscle mass during chemotherapy differs by sex. As noted in one meta-analysis (Jang et al., 2020), skeletal muscle loss was about 1.6 times higher in men during chemotherapy. Given that respiratory muscles are skeletal muscles, this loss may contribute to a decrease in respiratory muscle strength and result in the mismatch between the motor command corollary discharge and afferent information.

Socioeconomic status: Across several studies (Ekström et al., 2016; Feinstein et al., 2010; Hechtner et al., 2019; Hirpara et al., 2020; Tjong et al., 2021), patients with cancer and a lower socioeconomic status reported more severe dyspnea. However, associations between socioeconomic status and dyspnea cannot be fully explained using the Mismatch Theory of Dyspnea (Fukushi et al., 2021). Instead, this finding may reflect health disparities associated with various demographic (e.g., less education, employment status), clinical (e.g., lower rates of cancer screening, less access to health care), social (e.g., increase in early childhood adversity), and environmental (e.g., poor neighborhoods, air pollutants, occupational hazards) factors that inter-relate with lower socioeconomic status (Booher, 2019).

Clinical Factors

Smoking: Previous or current smoking history in patients with cancer was associated with higher occurrence rates (Ban et al., 2016; Feinstein et al., 2010) and more severe levels of dyspnea (Hechtner et al., 2019). Cigarette smoking is one of the most significant factors for the development of dyspnea in adults (Krzyzanowski et al., 1993; Krzyzanowski & Lebowitz, 1992; Rosi & Scano, 2004). For example, not only do individuals who smoke have three times higher odds of developing dyspnea than those who do not smoke (Krzyzanowski & Lebowitz, 1992), but they also experience dyspnea in the absence of clinical manifestations of chronic airway disease (Elbehairy et al., 2016). The underlying mechanisms for dyspnea may include destruction of small airways, loss of elastic recoil of the lung, lung hyperinflation, and gas trapping because of chronic inflammation (Elbehairy et al., 2016; Regan et al., 2015). These pathologic changes increase the inspiratory resistive work and augment the inspiratory neural drive to the diaphragm. In addition, chronic immune responses change the diaphragm's mechanical properties (Elbehairy et al., 2016), which leads to reductions in the voluntary contribution of the diaphragm to overall pressure generation at vital capacity in the lung (Elbehairy et al., 2016). As a result, the mismatch between the augmented afferent signaling and ventilatory outputs results in dyspnea in individuals with a smoking history.

Respiratory disease: The co-occurrence of respiratory disease contributes to the occurrence and severity of dyspnea in patients with cancer (Hechtner et al., 2019; McKenzie et al., 2018; Nieder et al., 2018). Although chronic obstructive pulmonary disease (COPD) is often underdiagnosed in patients with cancer (Parrón Collar et al., 2017), patients with advanced cancer and COPD reported more severe dyspnea (Ekström et al., 2016). The pathophysiology of COPD is characterized by airflow limitations and loss of elastic recoil, which increase respiratory resistance and augment afferent signals from respiratory muscle spindles (Fukushi et al., 2021). In addition, a rise in partial pressure of carbon dioxide increases afferent signals from peripheral chemoreceptors and augments the integrated chemical respiratory sensation (Fukushi et al., 2021). Respiratory muscle weakness, common in patients with advanced cancer and COPD (Jaitovich & Barreiro, 2018; Pin et al., 2018), may hinder changing respiratory motor neural output to ventilation. This discordance between motor command corollary discharge and integrated afferent information increases the perception of dyspnea (Fukushi et al., 2021).

Heart disease: The presence of congestive heart failure is associated with more severe dyspnea in patients with cancer (Ha & Ries, 2020). Patients with congestive heart failure tend to have reduced lung compliance because of pulmonary edema (Dubé et al., 2016). These restrictive ventilatory effects magnify the mechanical effort of ventilation (Fukushi et al., 2021). In addition, interstitial tissue edema activates juxtacapillary receptors (Fukushi et al., 2021), amplifies afferent signals, and increases motor commands and ventilation (Dubé et al., 2016). In addition, cardiopulmonary interactions in patients with chronic heart disease contribute to the development and maintenance of dyspnea (Dubé et al., 2016). The lungs of patients with heart failure undergo a progressive remodeling process in the alveolar-capillary membrane that may result in lung fibrosis (Dubé et al., 2016). This process increases respiratory resistance and creates imbalances in gas exchange (Dubé et al., 2016). Chronic heart failure worsens the deoxygenation of respiratory muscles and decreases inspiratory muscle strength (Mancini et al., 1992). This respiratory muscle weakness prevents the fulfillment of ventilatory requirements and maintains dyspnea (Fukushi et al., 2021).

Cancer-Related Factors

Primary or metastatic lung cancer: Although the occurrence and severity of dyspnea may vary widely depending on the tumor's location, size, and histology, the presence of advanced lung cancer (Ekström et al., 2016; Hechtner et al., 2019; Hirpara et al., 2020; Larsson et al., 2012; Mendoza et al., 2019; Nieder et al., 2018) is associated with severe dyspnea. In patients with primary lung cancer or lung metastases, the tumor can activate single or multiple receptors (Fukushi et al., 2021), namely pulmonary stretch receptors, irritant receptors, and/or pulmonary C fibers (i.e., juxtacapillary receptors) (Burki & Lee, 2010), and augment respiratory neural drive (Fukushi et al., 2021). In addition, lung lesions can hamper gas exchange, which increases arterial partial pressure of carbon dioxide and decreases partial pressure of oxygen. This disturbance in gas exchange leads to increases in afferent discharges from peripheral chemoreceptors and central respiratory drive (Fukushi et al., 2021). However, tumors restrict lung expansion and increase afferent inputs from mechanoreceptors (Fukushi et al., 2021). The increased mismatch between motor command corollary discharge and integrated mechanochemical respiratory sensations augments dyspnea perception (Fukushi et al., 2021).

Malignant pleural effusion: Of a sample of patients with dyspnea, 15% had a malignant pleural effusion (Nieder et al., 2018). Pleural effusions reduce the efficiency of chest wall expansion and decrease total lung capacity (Fukushi et al., 2021). This restrictive ventilatory effect increases sensory information from mechanoreceptors, which augments the motor command, inducing dyspnea (Fukushi et al., 2021). Of note, a large amount of inter-individual variability exists in the effects of malignant pleural effusions on the elasticity and resistance of the lung and chest wall (Thomas et al., 2015) and may differ based on the volume of pleural fluid (Mitrouska et al., 2004).

Hepatomegaly and malignant ascites: Patients with liver metastases are more likely to report dyspnea because of hepatomegaly and/or malignant ascites (Dudgeon, Kristjanson, et al., 2001). Enlarged liver

KNOWLEDGE TRANSLATION

- The Multifactorial Model of Dyspnea in Patients With Cancer can guide oncology clinicians to assess patients with dyspnea more comprehensively by considering multiple contributing factors.
- The model enables clinicians to provide multimodal interventions to alleviate this symptom.
- Oncology nurse scientists can use the model to design more robust observational and/or interventional studies of dyspnea.

and/or ascites elevate the diaphragm, decrease lung volumes, and hamper thoracic expansion (Wittmer et al., 2020). These pressures and restrictions stimulate pulmonary stretch receptors and increase afferent inputs to the cerebral cortex. Although the mismatch between motor command corollary discharge and sensory information increases neural ventilatory drive (Fukushi et al., 2021), enlarged liver and/or ascites hamper the diaphragm from accomplishing the ventilatory outputs intended. As a result, the disassociation between afferent and efferent signaling increases a sense of respiratory effort and causes hyperventilation.

Cancer Treatments

Thoracic surgery: Thoracic surgery is associated with dyspnea in patients with lung cancer (Ha & Ries, 2020). In three longitudinal studies that evaluated trajectories of dyspnea (Ambrogi et al., 2009; Gralla et al., 2009; Raz et al., 2016), dyspnea worsened following surgery and persisted for 24 months (Schulte et al., 2010). Dyspnea occurs because of an increase in respiratory muscle work that is required to maintain a normal workload from local damage or lung resection (Ha & Ries, 2020). In addition, thoracic surgery changes the biophysical and biochemical characteristics of pulmonary surfactants that facilitate alveolar expansion on inspiration and prevent alveolar collapse at the end of expiration (Autilio & Pérez-Gil, 2019; Yamakova et al., 2014). In several longitudinal studies (Kim et al., 2015, 2016; Seok et al., 2014), a significant increase in respiratory resistance and gas exchange imbalance was found after thoracic surgery. Taken together, these changes increase the load on the respiratory muscles and augment afferent information from mechano- and chemoreceptors, which amplifies the motor command and induces dyspnea.

Thoracic radiation therapy: Worsening dyspnea following radiation therapy (De Ruysscher et al., 2009; Nieder et al., 2018; Tjong et al., 2021) may be the sentinel symptom that represents the development of radiation-induced lung injury (Arroyo-Hernández et al., 2021). Factors associated with higher levels of dyspnea in patients undergoing radiation therapy included older age (De Ruysscher et al., 2009), the total lung radiation dose (Cella et al., 2021; Sardaro et al., 2020), heart volume (Cella et al., 2021), and the presence of cardiopulmonary comorbidities (Cella et al., 2021; Nalbantov et al., 2013). In addition, postoperative radiation therapy is associated with a decreased capacity for gas exchange (Dudgeon, Lertzman, & Askew, 2001). A higher total dose of radiation was associated with an increase in airway flow resistance at 12 months (Sardaro et al., 2020). This finding suggests that thoracic radiation therapy causes progressive lung damage, inducing scar tissue (Arroyo-Hernández et al., 2021; Jarzebska et al., 2021). These changes result in insufficient ventilation and gas exchange, as well as increased respiratory efforts to expand the stiffened lung, which increases motor command and augments dyspnea.

Drug-induced lung disease: Certain chemotherapeutic agents (e.g., bleomycin, taxanes, methotrexate, platinum-based drugs, gemcitabine), targeted therapies (i.e., tyrosine kinase inhibitors), and immunotherapies can result in drug-induced lung disease (DILD) (i.e., interstitial pneumonitis and pulmonary fibrosis) and associated dyspnea (Long & Suresh, 2020). As shown in four longitudinal studies (Bahador et al., 2022; Dimopoulou et al., 2002; Rivera et al., 2009; Yumuk et al., 2010), chemotherapy may cause unexpected lung tissue injuries (Dhamija et al., 2020) and deterioration in pulmonary function (Bahador et al., 2022). Multiple factors may contribute to the development of drug-induced pulmonary toxicities, including older age, male gender, preexisting lung disease, higher cumulative dose, and previous or concurrent radiation therapy (Bahador et al., 2022; Rivera et al., 2009; Yumuk et al., 2010). Decreased lung compliance because of DILD prevents sufficient lung expansion and ventilatory output. An increase in ventilatory efforts to inflate the stiffened lung enhances the tension of the intercostal muscles and afferent discharges from muscle spindles during inspiration. This discordance between integrated mechanical respiratory sensation and motor command corollary discharge may result in dyspnea (Fukushi et al., 2021).

DILD is characterized by an increase in diffusion distance (Shao et al., 2021). This injury occurs as a result of progressive damage in the pulmonary capillary bed, which causes a reduction in the diffusion area (Bagnato & Harari, 2015). As a result, decreases in arterial partial pressure of oxygen increase the afferent discharges from peripheral chemoreceptors and integrated chemical respiratory sensations, which may magnify the motor command and increase dyspnea (Fukushi et al., 2021). However, in two studies (Ding et al., 2020; Rivera et al., 2009), although pulmonary toxicity was identified using objective measures, patients did not report increases in dyspnea severity.

Anemia: Anemia occurs in 30%–90% of patients with cancer and is characterized by a reduction in

hemoglobin and hypoxemia (Knight et al., 2004). A decrease in oxygen content in peripheral blood activates chemoreceptors. These augmented afferent signals from chemoreceptors are transmitted to the respiratory center in the brain and increase ventilatory drive (Fukushi et al., 2021). Increased ventilatory requirements augment the work of breathing and induce dyspnea (Fukushi et al., 2021).

Respiratory Muscle Weakness

Respiratory muscle weakness associated with malnutrition, cachexia, and generalized weakness (Ripamonti & Bruera, 1997), as well as physical inactivity (Barğı et al., 2021), contributes to the occurrence and severity of dyspnea. For example, in one cross-sectional study of patients with advanced cancer (Bruera et al., 2000), the strength of inspiratory muscles was negatively correlated with the intensity of dyspnea.

Cachexia and malnutrition: Cachexia is reported in 50%–80% of patients with advanced cancer (Hadzibegovic et al., 2020). In particular, cytotoxic chemotherapy and targeted therapy accelerate the loss of skeletal muscle mass (Jang et al., 2020; Kakinuma et al., 2018), inducing muscle atrophy and muscle weakness (Travers et al., 2008). In addition, malnutrition decreases respiratory muscle strength and maximal voluntary ventilation (Ripamonti & Bruera, 1997). The reduced capacity of the respiratory muscles and augmented neural ventilatory drive increase the mismatch between the motor command corollary discharge and afferent inputs, inducing dyspnea (Mioxham & Jolley, 2009). In addition, respiratory muscle weakness reduces the lung's ability to transfer gas from the alveoli to the blood (Dudgeon, Lertzman, & Askew, 2001), which exaggerates chemoreflex responses, increasing the perception of dyspnea (Fukushi et al., 2021).

Physical inactivity: An increase in dyspnea occurrence (Feinstein et al., 2010) and intensity (Hechtner et al., 2019; Krishnan et al., 2021) is associated with physical inactivity in patients with cancer. One possible explanation for this finding is that cancer and its treatments contribute to a vicious cycle of physical deconditioning, physical inactivity, and respiratory muscle weakness (Ramon et al., 2018), which increases the ventilatory neural drive and worsens dyspnea. For example, among recipients of allogeneic hematopoietic stem cell transplantation, a two-week isolation during engraftment limited patients' physical activity and resulted in impairments in skeletal muscle oxygenation that were associated with muscle weakness and worsening dyspnea during daily activities (Boşnak Güçlü et al., 2021). Although future studies are warranted to examine the direct role of physical inactivity in respiratory muscle weakness and dyspnea severity, in one cross-sectional study of sedentary community-dwelling older adults (Fragoso et al., 2014), physical inactivity was associated with respiratory weakness, which reduced ventilatory capacity and increased dyspnea.

Co-Occurring Symptoms

Anxiety and depression: Anxiety and depression increase dyspnea intensity in patients with cancer (Degens et al., 2020; Ekström et al., 2016; Hechtner et al., 2019; Reddy et al., 2009; Rodríguez Torres et al., 2020). Some evidence suggests that dyspnea catastrophizing in patients with anxiety and depression may increase their emotional responses to respiratory sensations (Jelinčić & von Leupoldt, 2021). This overperception of breathing causes higher activation of the limbic systems and increases the neural ventilatory drive, with a resultant worsening of dyspnea (Finnegan et al., 2021; Fukushi et al., 2021). In addition, a higher symptom burden and decreased physical conditioning in patients with anxiety and/or depression appear to play a role in increasing dyspnea (Alexopoulos et al., 2018; Finnegan et al., 2021).

Fatigue: Fatigue is another symptom that demonstrated a positive relationship with dyspnea (Brown et al., 2011; Cameron et al., 2012; Chan et al., 2011; Hui et al., 2013; Javadzadeh et al., 2016; Reddy et al., 2009; Rowbottom et al., 2017). For example, in patients with advanced cancer without lung involvement (Barton et al., 2010; Ding et al., 2020), fatigue was described as a plausible cause for their dyspnea. Although the mechanisms that underlie the association between fatigue and dyspnea are not well understood, several hypotheses exist. First, cancer and cancer treatment increase serotonin levels in the central nervous system, which leads to the upregulation of serotonergic receptors (Ryan et al., 2007). These changes reduce somatic motor drive, which contributes to an increase in a sense of effort in respiratory muscles (Ryan et al., 2007). The second hypothesis is that chemotherapy, directly and indirectly, causes damage to skeletal muscles and skeletal muscle weakness (Ding et al., 2020), impairing lung expansion and inhibiting slowly adapting pulmonary stretch receptors (Fukushi et al., 2021). Dyspnea in patients with cancer and fatigue may result from an increase in the mismatch between motor command corollary

TABLE 1. Recommendations for Future Research on Dyspnea in Patients With Cancer

Topic	Recommendation
Pathophysiologic mechanisms	Systemic inflammation ■ Determine the relationships between the occurrence and severity of dyspnea and blood-based markers of inflammation (e.g., serum markers, genotype, gene expression, DNA methylation). Peripheral lung inflammation ■ Evaluate the relationship between the occurrence and severity of dyspnea and healthy and cancerous lung tissue markers of inflammation (e.g., genotype, gene expression, DNA methylation). Comparison studies ■ Compare the findings from the blood-based and lung tissue markers of inflammation.
Distress-related mechanism	■ Determine the relationship between the affective dimension of dyspnea and blood-based markers of inflammation. ■ Use functional magnetic imagery to evaluate changes in brain activity associated with the distress dimension of dyspnea.
Person factors	
Age	■ Evaluate for age differences in the occurrence, severity, and distress of dyspnea using measures of chronologic and biologic aging.
Sex	■ Determine sex differences in the occurrence, severity, and distress of dyspnea. ■ Identify the relative contribution of sex steroid hormones to the occurrence, severity, and distress of dyspnea.
Socioeconomic status	■ Determine the impact of a variety of social determinants of health on the occurrence, severity, and distress of dyspnea. ■ Examine the relationships between financial toxicity and the occurrence, severity, and distress of dyspnea. ■ Examine the relationships between the occurrence of adverse childhood experiences and the occurrence, severity, and distress of dyspnea in adulthood. ■ Examine the relationship between air pollution and the occurrence and severity of dyspnea. ■ Evaluate the mechanisms by which various social determinants of health influence the occurrence, severity, and distress of dyspnea.
Clinical factors	
Smoking	■ Identify lung tissue– and blood-based markers of inflammation associated with dyspnea in smokers with cancer.
Respiratory disease	■ Evaluate the impact of co-occurring respiratory disease on the occurrence, severity, and distress of dyspnea. ■ Evaluate the differences in inflammatory markers between patients with cancer with and without co-occurring respiratory disease. ■ Evaluate for changes in inflammatory markers between patients with cancer with and without co-occurring respiratory disease during cancer treatments.
Heart disease	■ Evaluate the impact of co-occurring heart disease on the occurrence, severity, and distress of dyspnea. ■ Evaluate the differences in inflammatory markers between patients with cancer with and without co-occurring heart disease. ■ Evaluate for changes in inflammatory markers between patients with cancer with and without co-occurring heart disease during cancer treatments.
Cancer-related factors	
Primary or metastatic lung cancer	■ Compare the occurrence, severity, and distress of dyspnea in patients with and without lung cancer. ■ Compare the occurrence, severity, and distress of dyspnea in patients with and without pulmonary metastasis.
Malignant pleural effusion	■ Compare the occurrence, severity, and distress of dyspnea in patients with and without a malignant pleural effusion.

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TABLE 1. Recommendations for Future Research on Dyspnea in Patients With Cancer *(Continued)*

Topic	Recommendation
Cancer-related factors *(continued)*	
Hepatomegaly and malignant ascites	■ Compare the occurrence, severity, and distress of dyspnea in patients with and without hepatomegaly. ■ Compare the occurrence, severity, and distress of dyspnea in patients with and without malignant ascites.
Cancer treatments	
Thoracic surgery	■ Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients following thoracic surgery.
Thoracic radiation therapy	■ Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients during and following thoracic radiation therapy.
Drug-induced lung disease	■ Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients during and following chemotherapy. ■ Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients during and following targeted therapy.
Anemia	■ Evaluate the relationship between the occurrence, severity, and distress of dyspnea and hypoxemia. ■ Evaluate the relationship between the occurrence, severity, and distress of dyspnea and anemia.
Respiratory muscle weakness	
Cachexia and malnutrition	■ Determine the relationship between cachexia and respiratory muscle weakness in patients with cancer. ■ Determine the relationship between malnutrition and respiratory muscle weakness in patients with cancer. ■ Evaluate the relationships between the occurrence, severity, and distress of dyspnea and cachexia. ■ Evaluate the relationships between the occurrence, severity, and distress of dyspnea and malnutrition.
Physical inactivity	■ Evaluate the relationships between the occurrence, severity, and distress of dyspnea and physical inactivity. ■ Evaluate the relationships between the occurrence, severity, and distress of dyspnea and exercise training. ■ Evaluate the relationships between changes in the strength of respiratory muscles following exercise training and biomarkers of inflammation.
Co-occurring symptoms	
Anxiety and depression	■ Determine the relationship between the occurrence, severity, and distress of dyspnea and the co-occurrence of anxiety and depression. ■ Determine the impact of dyspnea in patients with anxiety and/or depression. ■ Evaluate for common and distinct biomarkers associated with the co-occurrence of dyspnea, anxiety, and depression.
Fatigue	■ Determine the differences between physical fatigue, muscle fatigue, and dyspnea (i.e., sense of effort). ■ Determine the relationship between the occurrence, severity, and distress of dyspnea and the co-occurrence of fatigue. ■ Evaluate for common and distinct biomarkers associated with the co-occurrence of dyspnea and fatigue.
Cough	■ Determine the relationship between the occurrence, severity, and distress of dyspnea and the co-occurrence of cough. ■ Evaluate for common and distinct biomarkers associated with the co-occurrence of dyspnea and cough.
Stress	
Stress	■ Determine the relationship between the occurrence, severity, and distress of dyspnea and various types of stress (e.g., global, cancer specific, cumulative life stress). ■ Determine the impact of dyspnea in patients with higher stress levels. ■ Evaluate for neuroendocrine and immune mechanisms that underlie the relationship between stress and dyspnea.

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TABLE 1. Recommendations for Future Research on Dyspnea in Patients With Cancer *(Continued)*

Topic	Recommendation
Stress *(continued)*	
Resilience	■ Determine the relationship between the occurrence, severity, and distress of dyspnea and resilience. ■ Evaluate the relationship between levels of resilience and the impact of dyspnea on patient-reported outcomes (e.g., functional exercise capacity, quality of life).
Coping	■ Determine the relationship between the occurrence, severity, and distress of dyspnea and the use of various engagement and disengagement coping strategies. ■ Evaluate how the use of different coping strategies influences the impact of dyspnea on patient-reported outcomes (e.g., functional exercise capacity, quality of life).

discharge and integrated mechanical respiratory sensation (Fukushi et al., 2021). Another potential mechanism for the co-occurrence of fatigue and dyspnea is through the activation of vagal afferents associated with cancer and its treatment (Ryan et al., 2007). These activated vagal afferent nerves send signals to the lungs that induce bronchoconstriction and mucus secretion. These effects increase ventilatory neural drive and augment dyspnea (Undem & Kollarik, 2005).

Cough: Cough was another symptom that was associated (Chowienczyk et al., 2020; Tanaka et al., 2002) and clustered with dyspnea in patients with cancer (Wong et al., 2017). One hypothesis for this association is that activation of bronchopulmonary C-fiber receptors results in the occurrence of both symptoms (Gracely et al., 2007).

Stress

Stress: Although not studied in patients with cancer, in a study of the general population (Spitzer et al., 2011), exposure to a higher number of traumatic events and the occurrence of post-traumatic stress disorder were associated with increases in airflow limitation. In addition, activation of the hypothalamic–pituitary–adrenal (HPA) axis, in response to stress, can increase inspiratory drive by transmitting descending signals to the medullary respiratory center (Abelson et al., 2010; Fukushi et al., 2019). However, the relationship between dyspnea and HPA axis activation appears to be bidirectional. For example, episodic, excessive, or chronic dyspnea can act as a stressor and activate the HPA axis (Niérat et al., 2017). In contrast, in a study of patients with chronic dyspnea (Ryan et al., 2017), moderate to severe dyspnea was associated with higher levels of perceived stress and flatter diurnal cortisol slopes. Given that patients with cancer experience a wide variety of stressors (Langford et al., 2020), an evaluation of the relationships between dyspnea and stress is warranted.

Resilience and coping: The use of various coping strategies appears to influence an individual's level of resilience in response to stress (Franklin et al., 2012). Although not completely understood, some coping strategies may buffer HPA axis activation and corticolimbic interactions in response to stress (Baratta & Maier, 2019; Franklin et al., 2012). Although no studies have examined associations between dyspnea, stress, resilience, and the use of engagement and disengagement coping strategies, higher levels of dyspnea in patients with COPD were associated with lower levels of resilience (Cannon et al., 2018). Associations between dyspnea, resilience, and coping warrant evaluation in patients with cancer.

Implications for Future Research

Although this article provides a summary of the evidence on the mechanisms and factors associated with dyspnea in patients with cancer, the large amount of inter-individual variability in this symptom across heterogeneous types of cancer and the paucity of research on this symptom suggest numerous areas for investigation. Progress will not be made in the effective management of this symptom without increased knowledge of its underlying mechanisms and associated risk factors. Several areas for future research based on each of the factors in the conceptual model are summarized in Table 1. Although this list of potential research topics is not all-inclusive, it may stimulate research on this common symptom that has significant negative effects on all aspects of the lives of patients with cancer.

Implications for Clinical Practice

This article provides an overview of normal breathing, the pathophysiology of dyspnea, and factors that contribute to dyspnea in patients with cancer. Although the fundamental mechanisms that underlie this symptom are not well understood, clinicians can use the information on various risk factors to guide their assessments and management of patients with cancer. First and foremost, regardless of the type of cancer, clinicians need to perform a comprehensive assessment of dyspnea that includes an evaluation of its severity, distress, and impact. In addition, they need to assess for common co-occurring symptoms. This type of assessment will guide the prescription of appropriate interventions.

For example, if the patient currently smokes, clinicians need to provide education about smoking cessation programs. For patients with co-occurring pulmonary and/or heart diseases, oncology clinicians need to work with patients' primary care physicians to optimize the management of these comorbidities. In addition, patients with dyspnea may benefit from pulmonary rehabilitation programs (Hui et al., 2021) and psychological interventions (e.g., psychoeducation, stress management, relaxation therapy) (Dans et al., 2021). In addition, oncology clinicians can recommend nonpharmacologic interventions (e.g., fan therapy, breathing techniques, supplemental oxygen therapy) to improve dyspnea (Dans et al., 2021; Hui et al., 2021). If patients require pharmacologic interventions, opioids can be used to treat acute dyspnea, bronchodilators may be indicated for bronchospasm, and/or corticosteroids may be used to decrease inflammation (Dans et al., 2021; Hui et al., 2021; Shelton et al., 2019). Management of psychological distress is a crucial component of effective management of dyspnea. If patients have moderate to severe anxiety and/or depression, the prescription of anxiolytics (Dans et al., 2021; Hui et al., 2021) or antidepressants (Pu et al., 2022) may decrease dyspnea. Once these interventions are initiated, ongoing assessments are warranted to evaluate their efficacy and to make adjustments as warranted to optimize the management of dyspnea.

Conclusion

The Multifactorial Model of Dyspnea in Patients With Cancer was presented in this article. This conceptual model was adapted to patients with cancer based on the Mismatch Theory of Dyspnea. The specific factors in the model included person (i.e., older age, male, and lower socioeconomic status), clinical (i.e., smoking and cardiopulmonary disease), and cancer-related factors (e.g., lung cancer, cancer treatment), as well as respiratory muscle weakness (e.g., physical inactivity), co-occurring symptoms (e.g., anxiety, depression, fatigue, cough), stress, resilience, and coping. The large amount of inter-individual variability in this symptom across heterogeneous types of cancer suggests numerous areas for investigation. The authors presented several recommendations for research by individual factors.

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