An Evaluation of Co-Occurring Cancer-Related Cognitive Impairment and Anxiety in Patients Receiving Chemotherapy Using Latent Variable Modeling and Pathway Impact Analysis

by

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Abstract

An Evaluation of Co-Occurring Cancer-Related Cognitive Impairment and Anxiety in Patients Receiving Chemotherapy Using Latent Variable Modeling and Pathway Impact Analysis

Kate Oppegaard

Cognitive changes associated with cancer and its treatments, known as cancer-related cognitive impairment (CRCI), are reported by up to 75% of patients and 60% of those who have completed treatment. Because a number of cognitive domains are impacted, CRCI results in decrements in multiple domains of quality of life. In addition, because of gaps in knowledge regarding its underlying mechanism(s), progress is slow in the development of prevention or mitigation strategies. Equally important, anxiety is a common symptom that co-occurs with CRCI. Despite high prevalence rates for both symptoms, CRCI and anxiety are often evaluated as individual symptoms. However, because anxiety can impact cognitive function and vice versa, an assessment of the co-occurrence of both symptoms warrants evaluation.

Therefore, the first three aims of this dissertation were to: 1) develop a comprehensive conceptual model of CRCI; 2) test this newly developed conceptual model; and 3) conduct a scoping review of the literature to describe the depth and breadth of available evidence on blood-based biomarkers of CRCI. In addition, using data from a sample of patients with heterogenous types of cancer with distinct joint CRCI AND anxiety profiles (n=1332), the fourth, fifth, and sixth aims of this dissertation were to: evaluate for differences in demographic and clinical characteristics among the three CRCI AND anxiety latent classes; evaluate for differences in levels of global stress, cancer-specific stress, cumulative life stress, and resilience among the three CRCI AND anxiety latent classes; and evaluate for perturbed pathways associated with membership in the No CRCI AND Low Anxiety class compared to the High CRCI AND High Anxiety class.

In terms of Aim 1, an original comprehensive conceptual model of CRCI, named the Multifactorial Model of CRCI (MMCRCI), was developed. The MMCRCI was designed based on a review of the literature that included over 100 review and state of the science papers published between 2017 and 2022. The specific concepts in the conceptual model include social determinants of health, patient-specific factors, co-occurring symptoms, treatment factors, and biologic mechanisms. The model can be used to design pre-clinical and clinical studies of CRCI.

In terms of Aim 2, structural regression methods were used to evaluate the MMCRCI using data from a large sample of outpatients receiving chemotherapy for a variety of cancers. The goals were to determine how well the concepts in the MMCRCI predicted CRCI and to determine the relative contribution of each of these concepts to deficits in perceived cognitive function. Of the four MMCRCI concepts evaluated, while co-occurring symptoms explained the largest amount of variance in CRCI, treatment factors explained the smallest amount of variance. These findings suggest that testing individual components of the MMCRCI may provide useful information on the relationships among various risk factors for CRCI, as well as on refinements of the model.

In terms of Aim 3, a scoping review was done that synthesized the extant literature on associations between subjective and/or objective measures of CRCI and blood-based biomarkers in adults with non-central nervous system cancers. A total of 95 studies were included in this review. Of note, a wide variety of biomarkers were examined. The majority of studies evaluated patients with breast cancer. A variety of cognitive assessment measures were used. The most consistent significant associations were with various subjective and objective measures of CRCI and levels of interleukin-6 and tumor necrosis factor. This review concluded with directions for future research.

In terms of Aims 4 and 5, a latent profile analysis identified subgroups of patients with distinct joint CRCI AND anxiety profiles (i.e., latent classes). In addition, differences in demographic and clinical characteristics, as well as levels of global stress, cancer-specific stress, cumulative life stress, and resilience were reported. In terms of the symptom profiles, three latent classes were identified (i.e., No CRCI AND Low Anxiety (57.3%), Moderate CRCI AND Moderate Anxiety (34.5%), and High CRCI AND High Anxiety (8.2%)). All of the stress measures showed a dose response pattern. Higher levels of co-occurring CRCI AND anxiety were associated with several demographic (e.g., age, marital status) and clinical (e.g., functional status, comorbidity burden) characteristics, as well with as with higher levels of stress and lower levels of resilience. Increased knowledge of modifiable characteristics and sources of stress associated with the co-occurrence of these two symptoms will assist clinicians to identify high risk patients, and with the development and testing of interventions.

In terms of Aim 6, perturbations in neurodegenerative pathways associated with the CRCI AND High anxiety classes were identified. Five neurodegenerative pathways were significantly perturbed, namely: Amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Prion disease, and Pathways of neurodegeneration - multiple diseases. Four common biological processes across these perturbed neurodegenerative pathways were identified (i.e., apoptosis, mitochondrial function, endoplasmic stress, oxidative stress). While these findings warrant confirmation, they suggest that these two symptoms may share common mechanisms across patients with cancer and patients with neurodegenerative diseases.

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List of Abbreviations

APOE = Apolipoprotein E

AFI = Attentional Function Index

BDNF = brain-derived neurotrophic factor

BC = breast cancer

CRCI = cancer-related cognitive impairment

COMT = catechol-O-methyltransferase

CNS = central nervous system

CD-RISC = Connor-Davidson Resilience Scale

CpG = cytosine-phosphate-guanine

DNA = deoxyribonucleic acid

HPA = hypothalamic-pituitary-adrenal

IES-R = Impact of Event Scale-Revised

IL = interleukin

KPS = Karnofsky Performance Status

LSC-R = Life Stressor Checklist-Revised

MMCRCI = Multifactorial Model of Cancer-Related Cognitive Impairment

RNA = ribonucleic acid

PSS = Perceived Stress Scale

SCQ = Self-Administered Comorbidity Questionnaire

SNP = single nucleotide polymorphism

SDOH = social determinants of health

STAI-S = Spielberger State Anxiety Inventory

SRM = structural regression models

TNF = tumor necrosis factor

WBC = white blood cell

Introduction to the Dissertation

Cognitive changes associated with cancer and its treatments, known as cancer-related cognitive impairment (CRCI), are reported by up to 75% of patients and 60% of those who have completed treatment.[1] While treatment (e.g., chemotherapy) is one risk factor,[2] the causes and mechanisms of CRCI are multifactorial.[3-5] Because a number of cognitive domains are impacted,[2] CRCI results in decrements in activities of daily living,[6] personal and work-related responsibilities,[7, 8] financial well-being,[6] and emotional and social well-being.[9] Because of gaps in knowledge of its underlying mechanisms, progress is slow in the development of prevention and mitigation strategies.

The need for a comprehensive conceptual model of CRCI

One important research gap is the absence of a comprehensive conceptual model of CRCI. A conceptual model provides a visualization of the relationships among a set of concepts (i.e., variables that can be empirically observed or measured) that are thought to be related to a phenomenon.[10] As a result, a conceptual model summarizes existing knowledge and provides a way to understand and/or predict causal linkages and generate hypotheses.[10] While previous models were developed that may be useful for select groups of patients (e.g., patients receiving chemotherapy, survivors who completed treatment),[11-13] a more comprehensive conceptual model of CRCI is needed to guide future research across various types of cancer and treatments along the continuum of care.

CRCI and anxiety in patients with cancer

Anxiety is a common symptom that co-occurs with CRCI. Anxiety is reported by 16% to 42% of patients with cancer.[14-17] In patients receiving chemotherapy, higher levels of anxiety are associated with delays in seeking treatment;[18] prolongation of the duration of co-occurring symptoms;[19] and decrements in quality of life.[20] Despite high prevalence rates for these two symptoms,[1, 14-17] CRCI and anxiety are often evaluated as individual symptoms. However,

because anxiety can impact cognitive function and vice versa,[21] an assessment of the co-occurrence of both symptoms warrants evaluation.

Potential roles for stress and resilience in CRCI and anxiety

Associations between CRCI and anxiety may be related to perturbations in shared neuroendocrine mechanisms involved in anxiety and/or stress responses that lead to decrements in cognitive function.[22, 23] In addition, changes in cognitive function may induce emotional responses that contribute to the anxiety and/or stress response.[24, 25] Because a cancer diagnosis and subsequent treatments are known to be stressful experiences, an evaluation of various types of stress (e.g., global stress, cancer-specific stress, cumulative life stress) associated with CRCI and anxiety is warranted.

Psychological resilience can be described as an individual's ability to positively adapt to stress.[26] Levels of resilience vary based on a variety of characteristics (e.g., exposure to different life circumstances[26]). However, resilience is considered a modifiable characteristic and one that may support coping and mitigate symptoms of the stress response.[27] Therefore, levels of resilience warrant consideration when evaluating the relationships among CRCI, anxiety, and stress in patients with cancer.

Rationale for the analytic method used to create the symptom phenotype

Given that many factors may contribute to the co-occurrence of CRCI and anxiety during cancer treatment and that patients may differ in their experience of these symptoms, an evaluation of inter-individual variability in patients' responses is warranted. Using the person-centered analytic approach of latent profile analysis (LPA), one can identify subgroups of patients with distinct joint CRCI and anxiety profiles (i.e., latent classes). For the remainder of this dissertation, the joint CRCI and anxiety profiles that were identified using LPA will be referred to as the CRCI AND anxiety latent classes.

Gene expression and pathway analyses to evaluate the molecular mechanisms that underlie the CRCI AND anxiety latent classes

As noted in one review,[28] while a variety of inter-related factors (e.g., tumor biology, psychological distress, cancer treatments) may underlie the co-occurrence of CRCI and anxiety, little is known about their common underlying mechanism(s). One approach that can be used to identify associations between symptoms and molecular mechanisms is gene expression profiling. Gene expression is the functional product of a gene. A gene expression analysis that evaluates ribonucleic acid (RNA) expression begins with the quantification of RNA. Then, an evaluation of associations between the phenotype of interest and gene expression is performed.[29] Because genes work in concert to perform various biological processes, patterns of gene expression associated with a phenotype can be evaluated in higher orders of biology (e.g., groups of genes or defined biological pathways). Using this approach allows for the identification of perturbated signaling pathways that may serve as targets for therapeutic interventions.[30, 31]

Only one study evaluated for pathway perturbations associated with the occurrence of CRCI. In this study of patients receiving chemotherapy who did and did not self-report CRCI,[32] CRCI was associated with perturbations in five inflammatory pathways (i.e., cytokine-cytokine receptor interaction, mechanistic target of rapamycin, interleukin (IL)-17, mitogen-activated protein kinase, tumor necrosis factor (TNF)). Of note, no studies have evaluated for pathway perturbations associated with anxiety as an individual symptom. In addition, no pre-clinical or clinical studies have evaluated for associations between the co-occurrence of CRCI and anxiety and pathway perturbations.

Focus of the dissertation research

The first three aims of this dissertation were to: 1) develop a comprehensive conceptual model of CRCI; 2) test this newly developed conceptual model; and 3) conduct a scoping review of the literature to describe the depth and breadth of available evidence on blood-based biomarkers of CRCI. In addition, using data from a sample of patients with heterogenous types of cancer with distinct joint CRCI AND anxiety profiles (n=1332), the fourth, fifth, and sixth aims of this dissertation were to: evaluate for differences in demographic and clinical characteristics among the three CRCI AND anxiety latent classes; evaluate for differences in levels of global stress, cancer-specific stress, cumulative life stress, and resilience among the three CRCI AND anxiety latent classes; and evaluate for perturbed pathways associated with membership in the No CRCI AND Low Anxiety class compared to the High CRCI AND High Anxiety class.

This dissertation includes five papers. The first paper describes a conceptual model of CRCI.[33] The second paper reports on an evaluation of this conceptual model using structural regression methods.[34] The third paper describes a scoping review of blood-based biomarkers of CRCI.[35] The fourth paper reports on a LPA the identified distinct joint CRCI AND anxiety latent classes and evaluated for associations with demographic and clinical characteristics as well as with stress and resilience. The final paper reports on a pathway impact analysis that identified perturbations in neurodegenerative pathways associated with the CRCI AND anxiety latent classes.

In the first paper (Chapter 1), an original comprehensive conceptual model of CRCI named the Multifactorial Model of CRCI (MMCRCI) is presented. The MMCRCI was developed based on a review of the literature that included over 100 review and state of the science papers published between 2017 and 2022. The specific concepts in this conceptual model include: social determinants of health, patient-specific factors, co-occurring symptoms, treatment factors, and biologic mechanisms. The model can be used to design pre-clinical and clinical studies of CRCI. Based on the gaps in knowledge identified during the development of the MMCRCI,

recommendations were made for future research. This chapter is a reprint of the paper that was published in the *Oncology Nursing Forum*.[33]

In the second paper (Chapter 2), structural regression methods were used to evaluate the MMCRCI using data from a large sample of outpatients receiving chemotherapy for breast, gynecological, gastrointestinal, or lung cancer. Specifically, the relationships between self-reported CRCI and four of the MMCRCI concepts (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms) were examined. The goals were to determine how well the concepts in the MMCRCI predicted CRCI and to determine the relative contribution of each of these concepts to deficits in perceived cognitive function. Of the four MMCRCI concepts evaluated, co-occurring symptoms explained the largest amount of variance in CRCI, while treatment factors explained the smallest amount of variance. These findings suggest that testing individual components of the MMCRCI may provide useful information on the relationships among various risk factors for CRCI, as well as for refinements of the model. In terms of risk factors for CRCI, the co-occurrence of other common symptoms associated with cancer and its treatments may be more important than treatment factors, patient-specific factors, and/or social determinants of health in patients receiving chemotherapy. This chapter is a reprint of the paper that was published in *Nursing Research*.[34]

The third paper (Chapter 3) reports on the findings from a scoping review that was designed to synthesize the extant literature on associations between subjective and/or objective measures of CRCI and blood-based biomarkers in adults with non-central nervous system cancers. The literature search was done for studies published from the start of each of the six databases through to October 20, 2021. A total of 95 studies were included in this review and a wide variety of biomarkers were examined. The majority of these studies evaluated patients with breast cancer. A variety of cognitive assessment measures were used. The most consistent significant associations were with various subjective and objective measures of CRCI and levels of IL-6 and TNF. One of the conclusions of this review was that biomarker research is in an

exploratory phase. This review synthesized findings and proposed directions for future research. This chapter is a reprint of the paper that was published in *Critical Reviews in Oncology/Hematology*.[35]

The fourth paper (Chapter 4) describes findings from a joint LPA in which subgroups of patients with distinct joint self-reported CRCI AND state anxiety profiles (i.e., latent classes) were identified in patients with breast, gastrointestinal, gynecological, or lung cancer. In addition, differences in demographic and clinical characteristics, as well as levels of global stress, cancer-specific stress, cumulative life stress, and resilience were reported. In terms of the symptom profiles, three latent classes were identified (i.e., No CRCI AND Low Anxiety (57.3%), Moderate CRCI AND Moderate Anxiety (34.5%), and High CRCI AND High Anxiety (8.2%)). All of the stress measures showed a dose response pattern (i.e., as the CRCI AND anxiety profile worsened, scores for all three types of stress increased). The two highest symptom classes reported higher occurrence rates for six specific stressors (e.g., emotional abuse, physical abuse, sexual harassment). Higher levels of CRCI AND anxiety were associated with several demographic (e.g., age, marital status) and clinical (e.g., functional status, comorbidity burden) characteristics, as well as with higher levels of stress and lower levels of resilience. Increased knowledge of modifiable risk factors and sources of stress associated with the co-occurrence of these two symptoms will assist clinicians to identify high risk patients and to develop and test targeted interventions.

In the fifth paper (Chapter 5), an extreme phenotype approach was used to evaluate for perturbations in neurodegenerative pathways associated with CRCI AND anxiety. Of note, cognitive impairment and anxiety commonly co-occur in patients with a variety of neurodegenerative diseases. Five neurodegenerative pathways were significantly perturbed, namely: Amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Prion disease, and Pathways of neurodegeneration - multiple diseases. Four common biological processes across these perturbed neurodegenerative pathways were identified (i.e., apoptosis,

mitochondrial function, endoplasmic stress, oxidative stress). These biological processes are described in the context of emerging research that suggests that each of these processes is associated with cognitive changes and/or anxiety in patients with cancer or in patients with neurogenerative diseases (e.g., Parkinson disease).

The dissertation concludes by highlighting clinical implications of this research. In addition, directions for future research are summarized. Taken together, the research presented in this dissertation increases our knowledge of the phenotypic characteristics and molecular mechanisms associated with CRCI as a single symptom and the co-occurrence of CRCI AND anxiety in patients receiving chemotherapy.

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Chapter 1

The Multifactorial Model of Cancer-Related Cognitive Impairment

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Abstract

Cognitive changes associated with cancer and its treatments, known as cancer-related cognitive impairment (CRCI), are common. While progress is being made, significant gaps exist in our knowledge of CRCI. Evidence suggests that the mechanisms and associated causes of these cognitive changes are multifactorial. One important issue is the absence of a comprehensive conceptual model of CRCI. A conceptual model summarizes existing knowledge and provides a way to understand and/or predict causal linkages and generate hypotheses. Therefore, the purpose of this paper is to present the Multifactorial Model of CRCI (MMCRCI), a conceptual model that is based on established and emerging evidence. This model is inclusive of all cancer types and associated treatment(s). The specific concepts in the model are: social determinants of health, patient-specific factors, co-occurring symptoms, treatment factors, and biologic mechanisms. Based on the MMCRCI, suggestions are made for future research. While it would be ideal to evaluate all of the concepts/components in this model in a comprehensive fashion, we hypothesize that investigators with existing data sets could evaluate portions of the model to determine directionality for some of the proposed relationships. The model can be used to design pre-clinical and clinical studies of CRCI.

Introduction

Cognitive changes associated with cancer and its treatments, known as cancer-related cognitive impairment (CRCI), are reported by up to 75% of patients and 60% of those who have completed treatment.[1] While chemotherapy is one factor,[2] evidence suggests that the causes and mechanisms of the various cognitive changes are multifactorial.[3-5] Because a number of cognitive domains are impacted,[2] CRCI results in decrements in activities of daily living,[6] personal[7] and work-related responsibilities,[8] financial well-being,[6] and emotional and social well-being.[9]

Despite efforts by the International Cognition and Cancer Task Force to harmonize assessment methods,[10] both conceptual and empiric issues in CRCI research remain.[11] From a conceptual perspective, neuropsychological tests may not detect the subtle changes and specific cognitive processes associated with CRCI.[11] Empiric issues include: the absence of a universal definition of CRCI; the lack of consensus on a standard battery of subjective and objective measures to diagnose CRCI and monitor changes overtime; and the lack of correlation between neuropsychological test results and subjective reports of CRCI.[11]

An equally important issue is the absence of a comprehensive conceptual model of CRCI. A conceptual model provides a visualization of the relationships among a set of concepts (i.e., variables that can be empirically observed or measured) that are thought to be related to a phenomenon.[12] As a result, a conceptual model summarizes existing knowledge and provides a way to understand and/or predict causal linkages and generate hypotheses.[12]

In 2007, Hess and Insel published a conceptual model of CRCI that was specific to chemotherapy.[13] These authors proposed that changes in cognitive function may occur along two different but interacting pathways (i.e., psychosocial impact of a cancer diagnosis, direct physiologic effects of the cancer treatment). Both antecedents (e.g., cancer treatment) and consequences (e.g., decreased quality of life) of CRCI were identified, as well as various

mediators and moderators. While informative, a limitation of this model was that it focused only on cognitive changes in individuals who received chemotherapy.

In 2009, this model was updated by Myers to include the integration of the Theory of Unpleasant Symptoms.[14] Because patients with cancer experience multiple co-occurring symptoms.[15] the blending of the initial conceptual model with this middle-range theory allowed for an evaluation of CRCI within the context of its potential impact of other symptoms. However, since these two models were published, research focused on CRCI has expanded exponentially.

More recently, Ahles and Hurria published a conceptual model that focused on predictors of cognitive changes in cancer survivors.[16] A strength of this model was highlighting the need to consider stress as a potential risk factor for CRCI. However, the model's exclusive focus on survivors limits its application to patients receiving active treatments and/or those in the advanced stages of cancer. While these previous models may be useful for select groups of patients, a more comprehensive conceptual model of CRCI is needed to guide future research across the continuum of care. Therefore, the purpose of this paper is to present the Multifactorial Model of Cancer-Related Cognitive Impairment (MMCRCI), a conceptual model that is based on established and emerging evidence.

Development of the MMCRCI

Literature review

The first step in the development of the MMCRCI was a comprehensive review of the literature that identified factors (i.e., risk, protective, mechanistic) associated with CRCI. The search was inclusive of all types of cancer and associated treatment(s). Pediatric studies were excluded because the factors associated with CRCI may differ in this age group. In addition, cognitive changes associated with oncologic emergencies (e.g., hypercalcemia of malignancy) were excluded because effective management of an oncologic emergency generally results in resolution of associated cognitive changes.[17]

The following key words and/or phrases were searched using PubMed and Google Scholar: cancer-related cognitive impairment; chemotherapy-related cognitive impairment; cancer-associated cognitive dysfunction; cancer AND cognition OR cognitive. In PubMed, search terms were mapped to their respective Medical Subject Headings for expanded results when possible. Keyword searches were supplemented by hand-searches of the reference lists of relevant articles. Over 130 state of the science or systematic review articles published between 2017 and 2021 were identified. These reviews were the primary sources of evidence for the development of the MMCRCI. In addition, some of the emerging evidence in the model is supported by studies of other types of cognitive impairment that warrant evaluation in patients with cancer.

Conceptual organization of the MMCRCI

Once the factors associated with CRCI were identified, they were organized into broader concepts. As illustrated in Figure 1.1, the specific concepts in the MMCRCI are: social determinants of health (SDOH), patient-specific factors, co-occurring symptoms, treatment factors, and biologic mechanisms. These concepts are represented by concentric circles. These concentric circles are layered because the directionality of many of the associations between/among the concepts and CRCI are not well established. In addition, the visualization of these concepts is layered within the Figure because of the potential overlaps and/or interactions between/among the various concepts. The adjacent breakout boxes on the Figure list specific factors included in each of the five concepts. Within the breakout boxes, the factors are ordered based on the strength of evidence (i.e., established through to emerging). As illustrated by the oval at the bottom of the model, the model encompasses the entire continuum of cancer care (i.e., prior to cancer diagnosis into survivorship). It should be noted that the timepoint(s) when assessments of CRCI are done is likely to impact the relationships between and among the various concepts in the MMCRCI because these concepts and their inter-relationships are dynamic in nature.

Assumptions of the MMCRCI

The underlying assumptions of the MMCRCI are: 1) the causes and consequences of cognitive changes associated with cancer and its treatments are multifactorial; 2) these cognitive changes need to be evaluated in the context of these multiple contributing factors; and 3) knowledge of the mechanism(s) that underlie CRCI, as well as effective interventions to prevent and treat this symptom will be identified based on research that uses this model. While it is well documented that CRCI has a negative impact on a variety of patient outcomes,[13] because they are distant from the underlying concepts that contribute to this symptom, they are not included in this model.

Operational definition of CRCI

An operational definition is an essential component of any conceptual model because it serves to represent a concept as a variable that can be measured empirically.[18] Challenges exist in the development of a definition of CRCI because multiple cognitive domains are affected and a large amount of inter-individual variability exists.[19, 20] Often included in the definition of CRCI are the cognitive domains that are most affected (e.g., attention, concentration, memory, processing speed, executive function).[2, 21] Alternatively, symptoms associated with various cognitive changes are described (e.g., slow processing speed, inability to concentrate).[22] Based on a synthesis of definitions from several papers,[13, 14, 16, 19, 23] the definition of CRCI for the MMCRCI is as follows: CRCI is a temporary or persistent subjective and/or objective change in higher-order mental processes that occurs with cancer and/or its treatment(s).

Model components

The rationale for and the evidence that supports each of the components of the MMCRCI and specific factors within each component are summarized in the next section of this paper.

Social determinants of health

According to Healthy People 2030,[24] SDOH are defined as "the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks." Studies that evaluated the role of SDOH in the occurrence and/or severity of CRCI are limited. As noted in two systematic reviews,[25, 26] multiple SDOH (e.g., neighborhood disadvantage, lower socioeconomic status, access to healthcare, lower levels of education) contribute to undesired outcomes associated with cancer. Therefore, their inclusion in the MMCRCI is warranted. In addition, associations are documented between multiple SDOH (e.g., food insecurity, neighborhood economic disadvantage) and an increased risk for cognitive decline.[27]

As noted by Ahles and Root,[28] the impact of cultural differences in cognitive styles or socioeconomic status on CRCI are examples of valuable information that is missing from CRCI research to date. Future studies need to include more diverse samples of patients to allow for an increased understanding of the relationships between/among SDOH and CRCI. One innovative approach to evaluate SDOH is the development and use of a "polysocial risk score".[29] This score would allow for the aggregation of multiple SDOH and an evaluation of their impact on CRCI.

Patient-specific factors

The next concept in the MMCRCI is patient-specific factors. These factors can impact the occurrence and/or persistence of CRCI throughout the cancer care continuum. While age is the most common demographic characteristic evaluated, results are inconsistent in terms of its association with CRCI.[30] Given that the majority of CRCI research has focused on women with breast cancer,[5, 30-33] the occurrence and impact of CRCI in other genders warrant evaluation. Other demographic characteristics that are potential risk factors for CRCI include a decreased cognitive reserve and lower level of education.[34] Additional research is needed to assess for associations between/among pre-existing or developing comorbid conditions and CRCI. In

terms of concomitant medications, while the use of medications for pain and depression are associated with CRCI,[13] other types of medications warrant evaluation (e.g., anxiolytics).

Decrements in physical activity may be an important risk factor for CRCI. Exercise increases the expression of neurotrophic and neuroprotective factors that have anti-inflammatory effects and contribute to hippocampal neurogenesis.[35] Of note, the use of exercise as an intervention for CRCI is an area of intense investigation (for reviews see: [36-40]). However, additional information is needed on the mechanism(s) that underlie this association, as well as on the type, dose, and timing of exercise interventions.

Only one study evaluated for associations between personality traits and CRCI. In this study of patients with breast cancer,[41] negative affectivity was associated with an increase in self-reported problems with cognition and attention. While research in oncology is limited, in one review of associations between personality traits and cognitive abilities in older adults,[42] higher levels of openness were associated with better general cognitive ability, fluid ability, episodic memory, and verbal ability. These findings support the inclusion of personality traits in the MMCRCI.

Only one study evaluated the relationship between coping and CRCI in patients with cancer.[43] Findings suggest that avoidant coping styles mediate the relationships between stress and worse performance on neuropsychological tests in the domains of memory and verbal fluency. While research in oncology is limited, previous research in patients with Parkinson's disease found that a decrease in task-oriented coping was associated with cognitive impairment and that those with reduced task-oriented coping were at increased risk for depression, anxiety, and decrements in quality of life.[44] Additional investigations are needed on the effects of different coping styles on CRCI.

In terms of acute stress, a review of the potential role for self-regulation in the development of CRCI highlights pre-clinical research that suggests a bi-directional relationship between self-regulation and executive function.[45] The authors hypothesized that coping with

cancer and its treatments creates demands on self-regulatory capacities. In other words, energy spent on cancer-related stress and coping consumes and diverts mental energy from other cognitive functions and subsequently contributes to CRCI.

In a paper that described potential associations between chronic stress and CRCI,[46] the authors hypothesized that individuals with a history of chronic stress may have an increased allostatic load that results in physiologic changes in the prefrontal brain. These brain changes may lead to hypothalamic-pituitary-adrenal (HPA) axis disruption that impairs one's ability to adaptively cope with stress. In turn, the psychobiological effects of cancer and associated treatment(s) are amplified and place patients at increased risk for CRCI.

While definitions vary, psychological resilience generally refers to an exposure to adversity and a subsequent positive adaptation.[47] However, sociocultural factors may influence how resilience is defined in different populations. [47] Resilience may influence the risk for CRCI because of its association with other contributing factors (e.g., coping style, personality, stress perception[48]) and these factors warrant consideration in future studies.

While research specific to CRCI is limited, in a study of the general population,[49] loneliness and social isolation were associated with decrements in objectively measured cognitive function. In another study of older adults,[50] social isolation was associated with poorer cognitive function and that cognitive reserve moderated this relationship. Equally important, COVID-19 mitigation efforts resulted in increases in social isolation, leaving those with cognitive impairment at increased risk for a higher symptom burden.[51] These findings support the evaluation of loneliness and social isolation in the MMCRCI.

Co-occurring symptoms

Co-occurring symptoms is the next concept in the MMCRCI. Critical components of this concept include the occurrence, severity, duration, frequency, and distress of each symptom. Co-occurring symptoms may pre-exist or develop as a result of the cancer and its treatment(s) or occur as a result of comorbid conditions. A large amount of inter-individual variability exists in

symptom experiences. Equally important, symptoms are dynamic within and across each of the concepts included in the MMCRCI. In a systematic review of longitudinal studies that evaluated self-reported CRCI,[30] the most frequent moderators of CRCI were depressive symptoms and fatigue. Another review aimed to synthesize the research on a number of psychological symptoms associated with CRCI in patients with breast cancer.[5] Depression was the most frequently associated symptom, followed by anxiety, both anxiety and depression, worry, undefined psychological distress, and mental fatigue. Psychological distress stimulates the HPA axis and sympathetic nervous system,[52] which triggers increased production of a number of neuroendocrine substances (e.g., cortisol, dopamine) that may contribute to CRCI. Ongoing research is needed to understand how other co-occurring symptoms may moderate or mediate CRCI.[19]

Treatment factors

The components in the treatment factors concept include: type of treatment, as well as its dose, duration, timing (e.g., chronotherapy), associated toxicities and/or adverse effects, and/or combinations of treatments. Several reviews have highlighted the potential mechanisms that may contribute to CRCI based on types of treatment (for general overview see[21]; for reviews on: chemotherapy,[53, 54] radiation therapy,[55] targeted therapy,[56] hormonal therapy,[33, 57] stem cell transplantation,[58] surgery,[59] see associated references).

Given that many types of cancer require combinations of treatments,[20, 60] the potential additive or synergistic effects of multiple sequential or concurrent treatments warrant consideration in a model of CRCI. In a meta-analysis of patients with colorectal cancer,[60] individuals who received a higher number of treatment modalities were more likely to self-report CRCI. Additional research is needed to understand the mechanisms by which cancer therapies impact cognition.[61]

Biologic mechanisms

As shown in Figure 1.1, the final concept in the model is biologic mechanisms. Given that the etiology of CRCI is multifactorial,[19] numerous mechanisms may contribute to its occurrence, severity, and persistence. On the Figure, the mechanisms are ordered based on the strength of existing evidence. A summary of the findings to support each mechanism is provided in the next section of this paper.

A number of inflammatory mechanisms (e.g., signaling molecules carried by extra cellular vesicles) are implicated as potential causes of pre-treatment CRCI because the cancer itself induces the activation and/or production of cytokines.[3, 62] These inflammatory responses may affect the central nervous system and contribute to neuroinflammation.[62] Throughout the cancer care continuum, one review noted that the most frequently measured biomarkers of CRCI were inflammatory substances in plasma.[63] Overall, findings from these studies suggest that the administration of chemotherapy dysregulates cytokine levels and has a negative impact on brain function that results in CRCI. In addition, higher levels of circulating pro-inflammatory cytokines may cross the blood brain barrier and result in neurotoxic damage and associated behavioral symptoms (e.g., depression, fatigue).[64]

Genetic variations associated with increased susceptibility for CRCI include genetic loci involved in a variety of biological processes (e.g., inflammation, deoxyribonucleic acid (DNA) damage and repair) as well as genes associated with neuronal degeneration, repair, and transmission.[65] As noted in one systematic review,[65] while some evidence suggests that the apolipoprotein e4 allele is associated with an increased risk for CRCI, other studies found no association. Studies that evaluated other candidate genes are limited and yielded inconclusive results (for review see[65]).

Anemia was one of the earliest mechanisms that was evaluated for its associations with CRCI.[13] While in some studies increases in hemoglobin levels were associated with improvements in cognitive function,[66, 67] in other studies no associations were found.[68, 69]

In terms of structural brain changes, findings from one systematic review of longitudinal neuroimaging studies in patients with breast cancer suggest that distinct patterns associated with structural, perfusion, and functional changes may begin shortly after the initiation of chemotherapy and persist beyond treatment.[70] These data suggest specific vulnerability in the frontal lobes. The authors of this review suggested that neuroimaging techniques may be more sensitive than neuropsychological tests to detect CRCI. Another systematic review summarized the findings from both cross-sectional and longitudinal studies that examined structural neuroimaging outcomes in patients with and survivors of non-central nervous system cancers who received various types of treatments.[71] Across the majority of the studies, structural brain changes were identified following cancer treatment(s) that included evidence of reduced global and local gray matter volumes; impairments in white matter microstructural integrity; and brain network alterations.

Oxidative stress occurs because of an imbalance between reactive oxygen species and antioxidants and is implicated as a mechanism for CRCI. One review focused on an examination of the effects of oxidative stress on CRCI in both preclinical and clinical studies of chemotherapy administration.[72] In brief, findings suggest that oxidative stress contributes to CRCI by causing changes in the expression and activity of pro- and antioxidant enzymes; signal transduction pathways; DNA and ribonucleic acid damage; and regulation of gene expression. As noted in another review,[73] chemotherapy can lead to the production of reactive oxygen species in the brain that results in increased in emissions of biophotons, that may contribute to neuronal pathology.

Three studies evaluated for associations between neurofilament proteins (i.e., biomarkers of axonal damage) and CRCI.[74-76] In a study of women with breast cancer receiving chemotherapy,[74] serum high-molecular-weight neurofilament subunit (pNF-H) was evaluated as a predictive marker of CRCI. While pNF-H levels increased in a dose-dependent manner, no associations were found with changes in cognitive measures. In studies of patients with gastric[75]

and breast cancer,[76] no associations were found between neurofilament light chain levels and objective measures of CRCI.

Accelerated brain aging caused by cancer treatments is another potential mechanism for CRCI. In a longitudinal study of women with breast cancer,[77] a neuroimaging-based machine learning algorithm was used to predict brain age. Compared to healthy controls, findings suggest positive correlations between brain aging metrics and cognitive impairment (i.e., verbal memory interference), as well as acute decreases in cortical thickness.

Two studies evaluated for associations between biomarkers that may be reflective of accelerated biological aging and CRCI. In a study of breast cancer survivors,[78] prediction models were created and evaluated to predict objective cognitive performance using measures of amyloid beta (Aβ)-42, Aβ-40, tau, and 13 cytokines. Results suggest that neurodegenerative biomarkers interact with cytokines to influence the persistence of CRCI into survivorship. In another study of survivors of breast cancer,[79] high leukocyte DNA damage and low telomerase activity were associated with worse executive function. In addition, high leukocyte DNA damage was associated with worse memory and low telomerase activity was associated with worse attention and motor speed. Additional research is needed to understand how accelerated biological aging may contribute to CRCI.

An emerging area of research is the evaluation of associations between DNA methylation and CRCI. For example, in a longitudinal study of patients with breast cancer,[80] increased methylation at one CpG site (i.e., cg16936953) was associated with decrements in self-reported cognitive function. In another longitudinal study of patients with early-stage breast cancer,[81] 56 differentially methylated positions were associated with decreases in objectively measured memory.

Gene expression studies provide information about cellular responses to environmental changes.[82] While studies of associations between CRCI and changes in gene expression are limited, they can be used to identify perturbed biological pathways associated with CRCI. For

example, in a study that evaluated differentially expressed genes and perturbed pathways between patients with cancer who did and did not report CRCI,[83] perturbations in cytokine-specific pathways as well as pathways involved in cytokine production and cytokine activation were identified.

In terms of autoimmune responses, one study evaluated neuronal autoantibodies associated with objective reports of CRCI in patients with melanoma.[84] Compared to patients who were antibody-negative, patients who were antibody-positive (i.e., immunoglobulin A/immunoglobulin M anti- N-methyl-D-aspartate receptor antibodies) were at increased risk for CRCI across multiple cognitive domains. While research in oncology is limited, N-methyl-D-aspartate receptor antibodies are associated with other types of cognitive impairment (e.g., encephalitis, dementia).[84]

Another emerging hypothesized mechanism for CRCI is alterations in the neuroprotective effects of a type of extracellular vesicle called exosomes. One review suggested that exosomes play a role in neuronal cell communication; have the ability to cross the blood brain barrier; and have roles in neurodegeneration and neuroprotection.[85] Future research focused on total or cell-type specific exosomes may identify novel mechanisms for CRCI. Equally important, stem cell derived exosomes may be useful as a therapeutic intervention for CRCI.[86]

Disruptions of the microbiota-gut-brain axis may be another mechanism for CRCI.[87-90] The microbiota-gut-brain axis represents a bidirectional communication pathway between the gastrointestinal tract and the brain.[91] Microbiota-brain communication is facilitated through microbial metabolites (e.g., neurotransmitters, short-chain fatty acids).[87] Chemotherapy-induced nausea was associated with memory problems as well as other symptoms (e.g., fatigue, mood swings) that may be linked to alterations in the microbiota-gut-brain axis.[89]

Taken together, many plausible biologic mechanisms of CRCI exist. In addition, as noted in Table 1.1, many important mechanistic-based questions warrant investigation. Importantly,

future studies can use the MMCRCI to ensure that mechanism-focused studies include an evaluation(s) of other important factors.

Implications for nursing

The MMCRCI has numerous implications for nursing practice and research. Nurses are the clinicians who interact most with patients throughout the cancer care continuum. Nurses can assess patients for cognitive changes and provide education, support, and referrals. Knowledge of the occurrence of CRCI and factors that contribute to this devastating symptom will allow for better assessments of modifiable and non-modifiable risk factors. Using the MMCRCI, nurses may be able to identify those patients who may want to participate in research studies.

Importantly, the MMCRCI highlights the need for studies that evaluate CRCI in the context of its multiple contributing factors. Nurse scientists can use this model to design future studies that take a more comprehensive approach to understanding CRCI. In doing so, effective interventions to prevent and treat this symptom will be identified.

Conclusions

Based on several decades of research, our knowledge of CRCI has increased substantially. However, in addition to the conceptual and empiric issues described earlier, a comprehensive conceptual model of CRCI is lacking. Therefore, the MMCRCI was developed to summarize existing knowledge and provide a framework to guide future research. As with other symptoms (e.g., fatigue), the National Cancer Institute, in collaboration with professional organizations (e.g., Oncology Nursing Society, American Society of Clinical Oncology, Multinational Association of Supportive Care in Cancer, International Cognition and Cancer Task Force), needs to convene a state-of-the science conference to develop a consensus on the definition of CRCI; preferred methods to assess CRCI; as well as directions for future research.

Based on the MMCRCI, Table 1.1 provides a list of suggestions for future research. Undoubtedly, given the impact of CRCI on patients and survivors, other omics approaches as

well as electroencephalographic measurements of brain activity (e.g., frontal-midline theta) will be explored as potential biomarkers for and/or used to evaluate the efficacy of interventions for this devastating symptom. While it would be ideal to evaluate all the concepts/components of the MMCRCI in a comprehensive fashion, this approach may be cost prohibitive. However, we hypothesize that investigators with existing data sets can evaluate portions of the model to determine directionality for some of the proposed relationships. In addition, the MMCRCI can be used to design pre-clinical and clinical studies of CRCI. As more research is conducted, the MMCRCI will need to be updated and/or refined.

Table 1.1 Directions for Future Research on Cancer-Related Cognitive Impairment (CRCI)

General research questions
• Which subjective and objective measures of CRCI have the highest positive predictive value to diagnosis CRCI; assess for changes in CRCI over time; and determine the efficacy of interventions for CRCI? • What are the normative ranges and clinically meaningful change scores for subjective and objective measures of CRCI? • How can both subjective and objective measures of CRCI be analyzed to allow for a comprehensive understanding of both objective and perceived changes in cognitive function? • What are the best approaches to evaluate the clinical relevance of CRCI? • What are the critical characteristics to include in a comprehensive model to diagnosis CRCI and to evaluate for improvements in or worsening of CRCI?
Social determinants of health
• What roles do social determinants of health (e.g., food insecurity, neighborhood economic disadvantage, sex, gender, race, ethnicity) play in the occurrence, severity, and persistence of, as well as in the mechanisms that underlie CRCI? • What are the relative contributions of individual social determinants of health versus a polysocial risk score to the occurrence, severity, and persistence of, as well as the mechanisms that underlie CRCI?
Patient-specific factors
• Does premature aging and/or frailty associated with cancer and/or its treatments influence the occurrence, severity, and/or distress associated with CRCI? • What types of association(s) exist between/among pretreatment comorbidities and associated treatments and the occurrence, severity, and/or distress of CRCI? • What modifiable patient-specific factors are associated with the occurrence, severity, and/or distress of CRCI? • What types of associations exist between cognitive reserve and CRCI? • Are specific coping behaviors and levels of resilience protective factors that mitigate the occurrence, severity, and/or distress of CRCI? • Do specific personality traits contribute to or mitigate the occurrence, severity, and/or distress of CRCI?
Co-occurring symptoms
• What are the most common symptoms that co-occur with CRCI? • Does the occurrence, severity, duration, frequency, and distress of co-occurring symptoms mediate and/or moderate the experience of CRCI? • Do treatments for common co-occurring symptoms increase or decrease the occurrence, severity, and/or distress associated with CRCI?
Treatment factors
• What are the occurrence rates and severity of CRCI within each type of cancer treatment? • What are the occurrence rates and severity of persistent CRCI within each type of cancer treatment? • Does the addition of cancer treatments result in additive or synergistic effects on the occurrence, severity, and/or distress of CRCI?

Biologic mechanisms
• Does the pretreatment occurrence of CRCI differ based on the type of cancer? • How do cancers impact neuronal functioning? • Do chemicals/signals secreted by tumors contribute to the occurrence, severity, and/or distress associated with CRCI? • Do chemical substances produced in response to the psychological stress of a cancer diagnosis, associated treatments and/or related consequences influence the occurrence, severity, and/or distress of CRCI? • What are genetic variations associated with susceptibility to both early and late CRCI? • Do common and distinct mechanisms underlie the development of CRCI associated with various types of cancer and/or cancer treatments? • Are different mechanisms associated with subjective versus objective measures of CRCI? • Which biomarkers need to be included in a biosignature to predict the occurrence, worsening, and/or improvements in CRCI? • Do the biomarkers for CRCI change over time? • Does a multi-staged data integrated omics analysis identify molecular mechanisms for the occurrence of CRCI?

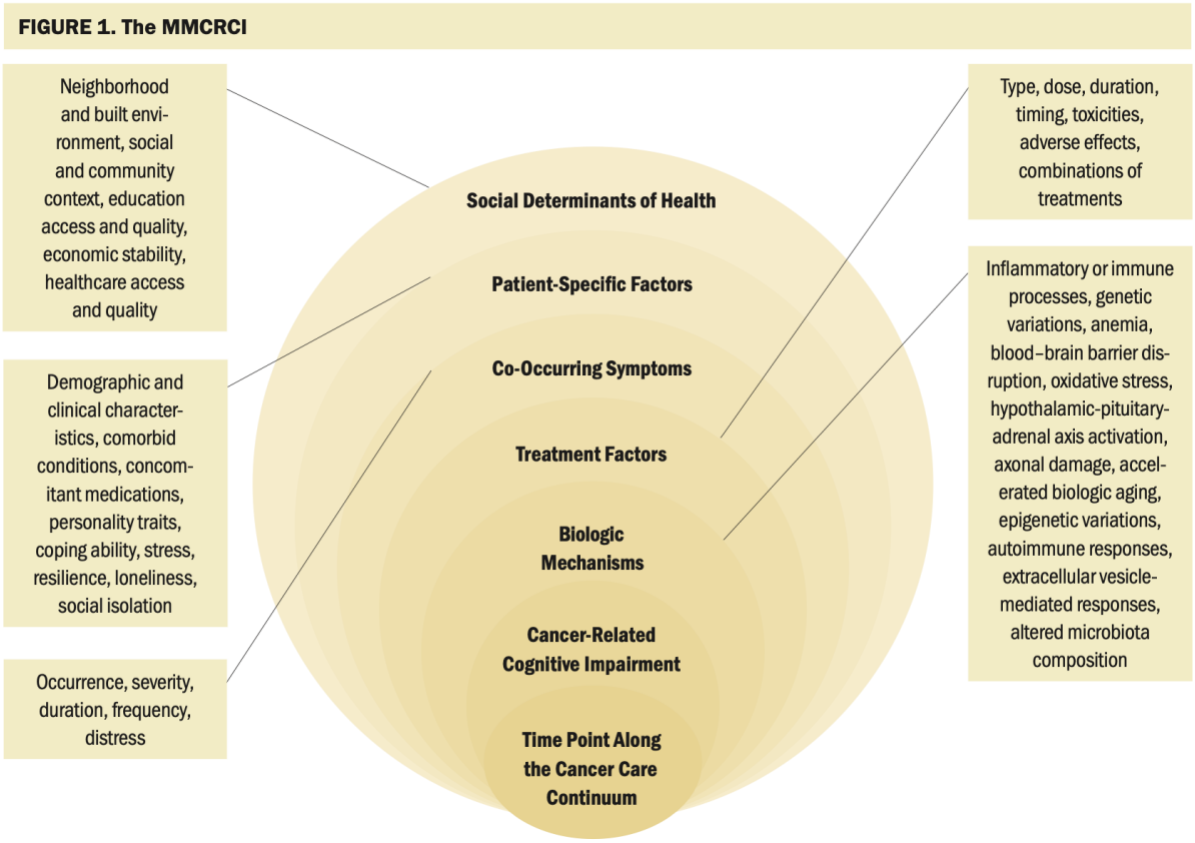

Figure 1.1 The Multifactorial Model of Cancer-Related Cognitive Impairment (MMCRCI)
The MMCRCI is composed of concentric circles that layer to represent the overlapping and interacting concepts that are known or are hypothesized to be associated with cancer-related cognitive impairment. Adjacent breakout boxes list specific factors included in each of these concepts. As illustrated by the oval at the bottom of the model, the model encompasses the entire continuum of cancer care (i.e., prior to cancer diagnosis into survivorship). It should be noted that the timepoint(s) when assessments of cancer-related cognitive impairment are done is likely to impact the relationships between and among the various concepts in the MMCRCI because these concepts are dynamic in nature.

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Chapter 2

An Evaluation of the Multifactorial Model of Cancer-Related Cognitive Impairment

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Abstract

Background: Cancer-related cognitive impairment (CRCI) is reported by up to 75% of patients and 60% of survivors. A variety of characteristics are associated with the occurrence and/or severity of CRCI. However, an important gap in knowledge of risk factors for CRCI is the relative contribution of each factor. The Multifactorial Model of Cancer-Related Cognitive Impairment (MMCRCI) is a conceptual model of CRCI that can be used to evaluate the strength of relationships between a variety of factors and CRCI.

Objectives: The purpose of this study was to use structural regression methods to evaluate the MMCRCI using data from a large sample of outpatients receiving chemotherapy. Specifically, the relationships between self-reported CRCI and four of the MMCRCI concepts (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms) were examined. The goals were to determine how well the concepts of the MMCRCI predicted CRCI and to determine the relative contribution of each of the concepts to deficits in perceived cognitive function.

Methods: This study is part of a larger, longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy. Adult patients had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Self-reported CRCI was assessed using the Attentional Function Index. Available study data were used to define the latent variables.

Results: On average, patients were 57 years of age, college educated, with a mean Karnofsky Performance Status score of 80. Of the four MMCRCI concepts evaluated, while co-occurring symptoms explained the largest amount of variance in CRCI, treatment factors explained the smallest amount of variance. A simultaneous structural regression model that estimated the joint effect of the four exogenous latent variables on the CRCI latent variable was not significant.

Discussion: These findings suggest that testing individual components of the MMCRCI may provide useful information on the relationships among various risk factors for CRCI, as well as refinements of the model. In terms of risk factors for CRCI, co-occurring symptoms may be more important than treatment factors, patient-specific factors, and/or social determinants of health in patients receiving chemotherapy.

Introduction

Cancer-related cognitive impairment (CRCI) is reported by up to 75% of patients and 60% of those who have completed treatment.[1-3] While not fully understood, the causes of CRCI are thought to be multifactorial (e.g., tumor-related effects,[4] treatment-related effects,[5] and/or patient-specific characteristics[6]). A variety of cognitive domains are impacted (e.g., memory, attention, processing speed).[7] Consequently, CRCI negatively impacts the everyday lives of those who experience it.[8] These negative impacts include decrements in work-related responsibilities,[9] financial well-being,[10] and overall well-being.[11] Prevention and mitigation strategies for CRCI remain limited,[12, 13] likely due to the lack of understanding of its underlying mechanism(s) and comprehensive evaluation of associated risk factors.

Treatment factors (e.g., hormonal changes, direct effects of chemotherapy) and co-occurring symptoms (e.g., anxiety, depression, fatigue) are among the most frequently identified risk factors for CRCI.[5, 14] In addition, a variety of demographic and clinical characteristics are associated with the occurrence and/or severity of CRCI.[15, 16] However, an important gap in our knowledge of the various risk factors is the relative contribution of each risk factor to CRCI. In other words, which risk factor makes the most significant contribution to its occurrence, severity, and/or persistence? This knowledge is needed to begin to prioritize modifiable factors that are amenable to interventions.

One analytic approach that can be used to explore the strength of the relationships between/among variables is structural regression modeling (i.e., a type of structural equation modeling). Structural regression methods were developed to evaluate complex patterns of inter-relationships among variables.[17] Therefore, these methods can be used to estimate the strength of the relationships between variables in a conceptual model.[17] While structural regression methods were used to evaluate a number of outcomes in patients with cancer (e.g., resilience,[18] post-traumatic growth,[19] quality of life[20]), this analytic approach has not been used to evaluate risk factors for CRCI.

The Multifactorial Model of Cancer-Related Cognitive Impairment (MMCRCI) is a comprehensive conceptual model of CRCI that includes factors with known or hypothesized associations with CRCI.[21] Within the MMCRCI, these factors are organized into broader concepts, namely, social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms, and biologic mechanisms. While the MMCRCI is based on an extensive review of the literature, it requires testing. Therefore, the purpose of this study was to use structural regression methods to evaluate the MMCRCI using data from a large sample of oncology outpatients receiving chemotherapy. Specifically, the relationships between CRCI and four of the MMCRCI concepts (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms) were examined; the joint effect of the four concepts on CRCI were evaluated; and the unique contribution of co-occurring symptoms on CRCI controlling statistically for the contributions of each of the other three concepts were determined. The overall goal was to determine how well the concepts in the MMCRCI predicted CRCI and to determine the relative contribution of each of the concepts to deficits in cognitive function.

Methods

Study sample and procedures

This study is part of a larger, longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy.[22] In brief, eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 2234 patients were approached and 1343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment. Data from the enrollment

assessment (i.e., prior to receipt of second or third cycle of chemotherapy) were used in this analysis.

Conceptual model

The structural regression models (SRM) evaluated in this study are based on the MMCRCI.[21] Available study data were used to define observed indicators as latent variables[23-25] that mapped to each of the concepts in the MMCRCI (Figure 2.1).

Variables

Demographic questionnaires obtained information on age, gender, ethnicity, education, employment status, and income. Medical records were reviewed for disease and treatment information.

Outcome variable: Self-reported CRCI was assessed using the Attentional Function Index (AFI),[26] a 16-item instrument designed to assesses an individual's perceived effectiveness in performing daily activities that are supported by attention, working memory, and executive functions (e.g., setting goals, planning and carrying out tasks). A higher total mean score on a 0 to 10 numeric rating scale indicates greater capacity to direct attention.[26] Clinically useful cut-points for attentional function are as follows: <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function.[27] Cronbach's alpha for the total AFI score was 0.93.

Latent variables: Estimation of the endogenous latent CRCI variable was carried out with a measurement model that used the individual AFI items as indicators of the latent score. When that measurement model was examined, because numerous correlated residuals were found among the items, the fit of the measurement model to the data was very poor. Therefore, the latent CRCI score was estimated following the recommendations of Jøreskog and Sørbom ([28] as reported in[29]) by estimating the measurement error and residual variance as (1 – reliability)*AFI computed variance. This value was defined as the CRCI "latent variable" residual variance for the subsequent SRM.

Measurement models for each of the exogenous latent variables were created using the concepts in the MMCRCI (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms). The indicator variables for each of the exogenous latent variables were selected from available study data. Specific information about each of the exogenous latent variables is described below (see Figure 2.1).

Social determinants of health: Indicator variables used for this exogenous latent variable included: annual household income, years of education, cumulative lifetime stress, and resilience. Cumulative lifetime stress was assessed using the Life Stressor Checklist-Revised (LSC-R), an index of lifetime trauma exposure (e.g., being mugged, death of a loved one, sexual assault).[30] Resilience was assessed using the Connor-Davidson Resilience Scale (CD-RISC), an instrument that evaluates a patient's personal ability to handle adversity.[31]

Patient-specific factors: Indicator variables for this exogenous latent variable included: age, functional status, comorbidity burden, the personality domain of neuroticism, global perceived stress, and cancer-specific stress. Functional status was assessed using the Karnofsky Performance Status (KPS) scale.[32] Comorbidity burden was assessed using the Self-Administered Comorbidity Questionnaire (SCQ) score.[33] The personality domain of neuroticism was assessed using the NEO-Five Factor Inventory (NEO-FFI).[34] Global perceived stress was assessed using the Perceived Stress Scale (PSS),[35] a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week. Cancer-specific stress was assessed using the Impact of Event Scale-Revised (IES-R).[36, 37]

Treatment factors: Indicator variables for this exogenous latent variable included: hemoglobin level, white blood cell count, toxicity of chemotherapy regimen, antiemetic regimen (i.e., number and type(s) of antiemetic medications), and chemotherapy cycle length. The toxicity of chemotherapy regimen was determined using the MAX2 index.[38] Briefly, the MAX2 score is the average of the most frequent grade four hematologic toxicity and the most frequent grade three

to four nonhematologic toxicity reported in publications of a regimen and correlates well with the average overall risk of severe toxicity for that regimen.

Co-occurring symptoms: Indicator variables for this exogenous latent variable included: severity of morning and evening fatigue, state anxiety, sleep disturbance, depressive symptoms, and severity of worst pain. Morning and evening fatigue were assessed using the Lee Fatigue Scale (LFS).[39] State anxiety was assessed using the Spielberger State Anxiety Inventory (STAI-S).[40] Sleep disturbance was assessed using the General Sleep Disturbance Scale (GSDS).[41, 42] Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression scale (CES-D).[43] Severity of worst pain was assessed using the Brief Pain Inventory.[44]

Statistical Analysis

Statistical analyses were performed with Stata version 16.1 (StataCorp LLC, College Station, TX). Means, standard deviations, and percentages were calculated for demographic and clinical characteristics. All variables were assessed for appropriateness for inclusion in the SRM. Indicator variables that were included in the models were either continuous or ordinal. Given the large sample size, normality of the parameter estimates was assumed based on the Central Limit Theorem.[45] Missing data were accommodated with the use of full information maximum likelihood (FIML) and the Expectation-Maximization (EM) algorithm.[46] In Stata, this method of estimation is called maximum likelihood with missing values (mlmv).

The usual Newton-Raphson (NR) algorithm for likelihood estimation was employed for most of the models. However, for the most complex models when mlmv was used, convergence with NR failed. For these models, the Berndt-Hall-Hall-Hausman (BHHH) algorithm was used for several (e.g., 10) iterations; then estimation switched to NR for several iterations; then back to BHHH until convergence was achieved. Model fit for each of the measurement models and SRM were evaluated using recommended fit indices. Absolute fit was evaluated using the Chi-square test of goodness of fit.[24] Model parsimony was evaluated using the root mean square error of approximation (RMSEA).[47] Comparative fit was evaluated using the comparative fit

index (CFI).[48] A Chi-square close to nonsignificant, RMSEA of <.06, and CFI of >.95 were used as the desirable cutpoints for these fit indices.

Modification indices were examined to improve model fit by incorporating correlated residuals into some measurement models for exogenous latent variables. Standardized parameter estimates for the measurement model coefficients were used to interpret the relative importance of indicators that were measured on incongruent scales. A two-sided p-value of <0.05 was considered statistically significant for hypothesis tests on the unstandardized coefficients. SRM were built in the following order: an individual measurement model for each exogenous latent variable was estimated with significant coefficients; an individual SRM for the CRCI latent variable was regressed on each exogenous latent variable; and a simultaneous SRM was evaluated that regressed the CRCI latent variable on the four exogenous latent variables jointly. Finally, three hierarchical SRMs were built to estimate the unique contribution of co-occurring symptoms on the CRCI latent variable, controlling for either the effect of social determinants of health, patient-specific factors, or treatment factors.

Results

Sample characteristics

Demographic, clinical, symptom, stress, and resilience characteristics of the 1343 patients are summarized in Table 2.1. On average, patients were 57 years of age, college educated, with a mean KPS score of 80. The majority were female, White, receiving only chemotherapy, and receiving chemotherapy on a 21-day cycle. Patients in this study had an average AFI score of 6.4, which suggests a moderate level of CRCI.

Measurement models for each exogenous latent variable

Fit indices for the measurement models for each of the exogenous latent variables are listed in Table 2.2. All of the models fit indices met the established cutpoints (i.e., Chi-square close to nonsignificant, RMSEA of <.06, and CFI of >.95). Details on each of the measurement models for the four exogenous latent variables are provided in Appendix 2.1.

SRM for the CRCI latent variable regressed on each exogenous latent variable

Results of the individual SRM for the CRCI latent variable regressed on each exogenous latent variables are listed in Table 2.3. As indicated by the standardized path coefficients, co-occurring symptoms (-0.762), patient-specific factors (-0.658), and social determinants of health (0.653) had the largest effects on the CRCI latent variable. In contrast, treatment factors (0.092) had the smallest effect. Details on each of the SRM for the CRCI latent variable regressed on each exogenous latent variable are provided in Appendix 2.1.

Simultaneous and hierarchical SRM

A simultaneous SRM that estimated the joint effect of the four exogenous latent variables on the CRCI latent variable was not significant (data not shown). The results of each hierarchical SRM that estimated the effect of co-occurring symptoms on the CRCI latent variable, controlling for each exogenous latent variable, are listed in Table 2.4. For each SRM, pairwise comparisons were done that evaluated the unique contribution of co-occurring symptoms using the difference in R^2 between a model for one of the other three exogenous variables alone, followed by a model with co-occurring symptoms added. The unique variance contributions of co-occurring symptoms on CRCI, after controlling for social determinants of health, patient specific factors, or treatment factors, were 0.203, 0.144, and 0.574, respectively.

Discussion

In a large sample of patients receiving chemotherapy, this study is the first to use structural regression methods to examine the relationships between self-reported CRCI and four of the concepts in the MMCRCI (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms). Specifically, CRCI was operationalized as perceived changes in the domains of attention, working memory, and executive functions as measured by the AFI. This evaluation included an examination of the joint effect of the four concepts on predicting CRCI. In addition, in three separate SRM, the unique contribution of co-occurring symptoms on CRCI, after controlling for the each of the other concepts was estimated.

A strength of this study is the evaluation of the unobservable influence of the broader MMCRCI concepts on CRCI through the creation of exogenous latent variables. Good model fit was achieved for each of the measurement models that represented the MMCRCI concepts (i.e., the exogenous latent variables; Table 2.2). As noted in one review,[49] specific groups of risk factors, rather than individual risk factors, may increase patients' risk for CRCI. Our results support this hypothesis and provide initial information on groups of risk factors that warrant further evaluation.

Each exogenous latent variable was significantly associated with the CRCI latent variable. These findings suggest that these four MMCRCI concepts are valid predictors of CRCI and support the multifactorial nature of CRCI. The majority of the indicator variables selected for each exogenous latent variable were supported by available evidence.[21] However, some of the indicator variables are relatively novel. For example, some personality domains (e.g., neuroticism, openness) are associated with increased risk for other types of cognitive impairment.[50] However, in the only study of patients with cancer,[51] negative affectivity was associated with decrements in self-reported cognition and attention. The specific domain of neuroticism from the NEO-FFI was selected as one of the indicator variables in the patient-specific latent variable because of its association with CRCI in our sample. However, other personality domains warrant evaluation in future studies.

In terms of other novel indicator variables, cumulative life stress and resilience were included as part of the social determinants of health latent variable. Cumulative life stress was included because it is associated with other social determinants of health (e.g., lower income, discrimination).[52] In terms of resilience, as noted in one review,[53] individuals vary considerably in their ability to adapt to various life stressors, as well as in the development of resilience. Therefore, resilience is an important factor to consider as part of a more comprehensive evaluation of cumulative life stress and other social determinants of health. It is worth noting that resilience was included in the patient-specific factors concept in the original MMCRCI. However,

the authors describe potential overlap among the model concepts, which supports the inclusion and evaluation of resilience as part of the social determinants of health latent variable. Annual income and years of education were the other indicator variables included in the social determinants of health latent variable. In a study that evaluated for associations between formal education, income, and cognitive function across 22 countries with varying income levels,[54] findings suggest that education had the dominant effect on cognitive functioning. Of note, this effect was large enough that it may offset the adverse impact of living in poverty on cognitive function. While the current study evaluated one set of factors to represent the concept of "social determinants of health," additional research is warranted to determine which social determinants are the most significant risk factors for CRCI.

In terms of the other types of stress, indicator variables representing global and cancer-specific stress were included in the patient-specific factors latent variable. As noted by Ahles and Hurria,[49] studies are needed that evaluate stress as a risk factor for CRCI. While the aim of this study was not to examine the effect of the individual indicator variables, global stress was the variable within the patient-specific factors latent variable that had the largest association with CRCI (Appendix 2.1). This finding is consistent with previous research that found that higher levels of perceived stress were an independent predictor for self-reported CRCI.[55] In addition, this finding supports the need to evaluate various types of stress as risk factors for CRCI.

Interestingly, the simultaneous SRM that evaluated the joint effect of the latent variables that represented the four MMCRCI concepts on CRCI was not significant. This finding was unexpected for two reasons. First, each of the exogenous latent variables were independently and significantly associated with the CRCI latent variable. Second, based on conservative estimates of observations to predictor ratios for SRM (e.g., 15:1), the large sample size in the current study allowed for evaluation of a complex SRM.[56] However, it is possible that the level of multicollinearity among the variables and/or small effect sizes contributed to this result.[56] Taken

together, the joint effect of the four MMCRCI concepts may be difficult to parse out when evaluated in a complex SRM despite an adequate sample size. Rather than a complex SRM, future studies using the MMCRCI can test smaller and/or individual parts of the model.

Of the four MMCRCI concepts evaluated, treatment factors explained the smallest amount of variance in CRCI. Data on a relatively comprehensive list of treatment-related factors (i.e., white blood cell count, hemoglobin level, a rating of the toxicity of the chemotherapy regimen, number and type(s) of medications in the antiemetic regimen, chemotherapy cycle length) were included in this exogenous latent variable. This finding supports previous research that found that CRCI occurs independent of treatment factors (e.g., it occurs prior to treatment,[5] months to years after completion of treatment,[14] across various cancer types,[57] independent of treatment regimen[3]). While not evaluated routinely, the inclusion of the type of antiemetic regimen was justified because of the potential adverse effects associated with these medications (e.g., mood changes, fatigue) that may impact cognitive function.[58] However, some treatment factors that were not included in this exogenous latent variable but are associated with CRCI (i.e., dose intensity,[5] higher number of chemotherapy cycles[59]) need to be evaluated in future studies of the MMCRCI.

In contrast, co-occurring symptoms explained the largest amount of variance in CRCI (Table 2.4). This exogenous latent variable included some of the most common symptoms associated with cancer and its treatments (i.e., morning and evening fatigue, state anxiety, sleep disturbance, depression, pain).[22] Our findings are consistent with previous research that found that decrements in cognitive function associated with each of these co-occurring symptoms (i.e., fatigue,[60], anxiety,[61] sleep disturbance,[62] depression,[63] pain[64]).

In addition, the hierarchical regression models demonstrated the unique contribution of co-occurring symptoms on CRCI, even after controlling for social determinants of health, patient specific factors, and treatment factors (Table 2.4). Across these three models, co-occurring symptoms accounted for a large amount of variance in CRCI. These findings showcase several

important directions for future research. First, common mechanism(s) may be driving multiple co-occurring symptoms in patients with cancer. Importantly, research that focuses on the identification of common mechanism(s) for co-occurring symptoms is sparse.[65] Second, future studies need to consider an evaluation of other common symptoms that co-occur with CRCI. As noted by Lacourt and colleagues,[66] a need exists to identify different phenotypes of CRCI based on the presence of other co-occurring symptoms. Finally, our findings support previous research that suggests that intervention strategies that can effectively target more than one symptom may result in significant improvements in cognitive function.[67]

While this study has numerous strengths (e.g., first study to evaluate the MMCRCI, use of a large sample of patients receiving chemotherapy, inclusion of a variety of factors known or hypothesized to be associated with CRCI), some limitations are worth noting. First, the operationalization of the concepts and outcome for the evaluation of the MMCRCI were limited to the available data and/or appropriateness for use in SRM. Other indicator variables can be used to define and test this model and may yield different findings. For example, testing this model based on an objective measure of CRCI may provide different insights into the relationships between/among the various concepts in the MMCRCI. In addition, because other potentially important risk factors for CRCI (e.g., gender, type of cancer) were represented by nominal variables in this study, they could not be evaluated as part of a latent variable. Finally, these data represent one timepoint in the treatment trajectory. Longitudinal evaluation of these findings is warranted in future studies.

In conclusion, our findings suggest that testing individual components of the MMCRCI may provide useful information on the relationships among various risk factors for CRCI, as well as refinements of the model. In terms of risk factors for CRCI, co-occurring symptoms may be more important than treatment factors, patient-specific factors, and/or social determinants of health in patients receiving chemotherapy. This knowledge can be used to design future studies as well as prioritize interventions to prevent and/or improve CRCI.

Table 2.1 Demographic, Clinical, Stress, Resilience, and Symptom Characteristics (n=1343)

Abbreviation: SD = standard deviation

[a]Clinically meaningful cutoff scores or range of scores are in parentheses

Demographic and Clinical Characteristics	**Mean (SD)**
Age (years)	57.2 (12.4)
Education (years)	16.2 (3.0)
Neuroticism personality domain	15.1 (8.0)
Karnofsky Performance Status score	80.0 (12.5)
Self-administered Comorbidity Questionnaire score	5.5 (3.2)
MAX2 score	0.17 (0.08)
Hemoglobin	11.5 (1.4)
White blood cell count	7.3 (4.1)
	% (n)
Gender (% female)	77.8 (1044)
Self-reported ethnicity	
American Indian/Alaskan Native	0.46 (6)
Asian	11.8 (155)
Black or African American	7.5 (98)
Native Hawaiian or Other Pacific Islander	1.0 (13)
White	72.9 (956)
Mixed Ethnic Background	5.3 (69)
Other	1.1 (15)
Annual household income	
Less than $30,000[+]	18.4 (221)
$30,000 to $70,000	21.2 (254)
$70,000 to $100,000	16.9 (203)
Greater than $100,000	43.6 (523)
Cancer diagnosis	
Breast cancer	40.2 (540)
Gastrointestinal cancer	30.7 (412)
Gynecological cancer	17.4 (233)
Lung cancer	11.8 (158)
CTX regimen	
Only chemotherapy	70.1 (922)
Only targeted therapy	3.0 (39)
Both chemotherapy and targeted therapy	26.9 (354)
Cycle length	
14-day cycle	42.1 (558)
21-day cycle	50.6 (671)
28-day cycle	7.3 (97)
Antiemetic regimen	
None	7.1 (92)
Steroid alone or serotonin receptor antagonist alone	20.5 (265)
Serotonin receptor antagonist and steroid	47.7 (618)
Neurokinin-1 receptor antagonist and two other antiemetics	24.8 (321)

Stress and Resilience Measures[a]	Mean (SD)
Perceived Stress Scale total score	18.5 (8.2)
Impact of Event Scale-Revised total score (≥24)	18.8 (13.1)
Life Stressor Checklist-Revised total score (range 0–30)	6.1 (3.9)
Connor Davidson Resilience Scale total score (range 0–40)	30.1 (6.4)
Symptoms[a]	
Depressive symptoms (≥16.0)	12.8 (9.7)
State anxiety (≥32.2)	33.9 (12.4)
Morning fatigue (≥3.2)	3.5 (2.9)
Evening fatigue (≥5.6)	5.9 (2.7)
Sleep disturbance (≥43.0)	52.5 (20.2)
Attentional function (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	6.4 (1.8)
Worst pain intensity score (range 0-10)	6.1 (2.5)

Table 2.2 Fit Indices for the Measurement Models for Each Exogenous Latent Variable

Abbreviations: CFI = comparative fit index; df = degrees of freedom; RMSEA = root mean squared error of approximation

Latent variable	Chi-square (df)	p-value	RMSEA	CFI
Social determinants of health	6.35 (2)	0.042	0.040	0.982
Patient-specific factors	21.78 (7)	0.003	0.040	0.992
Treatment factors	6.97 (3)	0.073	0.031	0.986
Co-occurring symptoms	22.61 (7)	0.002	0.041	0.994

Table 2.3 Results of Individual Structural Regression Models for the Cancer-Related Cognitive Impairment Latent Variable Regressed on Each of the Exogenous Latent Variables

Exogenous Latent variable	p-value	Path coefficient	Standardized path coefficient	Model R^2
Social determinants of health	0.001	0.863	0.653	0.427
Patient-specific factors	<0.001	-0.873	-0.658	0.433
Treatment factors	0.028	0.092	0.092	0.008
Co-occurring symptoms	<0.001	-1.177	-0.762	0.581

Table 2.4 Hierarchical Structural Regression Models that Estimate Unique Contribution of Co-occurring Symptoms on the Cancer-Related Cognitive Impairment Latent Variable for Either Social Determinants of Health, Patient Specific Factors, or Treatment Factors

*Change in R^2 between SRM of latent variable and outcome variable versus SRM of latent variable, outcome variable, and co-occurring symptoms

[a]Indicator variables for social determinants of health included: years of education, annual income, cumulative lifetime stress, resilience levels

[b]Indicator variables for co-occurring symptoms included: morning and evening fatigue, state anxiety, depressive symptoms, sleep disturbance, occurrence of pain

[c]Indicator variables for patient-specific factors included: age, functional status, comorbidity burden, the personality domain of neuroticism, perceived stress, cancer-specific stress

[d]Indicator variables for treatment factors included: white blood cell count, hemoglobin level, a rating of the toxicity of the chemotherapy regimen, number and type(s) of medications in the antiemetic regimen, chemotherapy cycle length

Abbreviations: CFI = Comparative fit index; CoOccSym = co-occurring symptoms; PtSpecFx = patient specific factors; RMSEA = root mean squared of approximation; SDOH = social determinants of health; SRM = structural regression model; TxFx = treatment factors

Exogenous Latent Variables	Models	Path coefficient	Z-statistic	p-value	Model R^2	Change in R^{2*}	95% Confidence interval
Pairwise comparison model testing for social determinants of health							
SDOH[a]	Model 1	0.863	8.27	<0.001	0.427	n/a	0.66, 1.07
SDOH CoOccSym[b]	Model 2	0.443 -0.951	3.37 -9.11	0.001 <0.001	0.630	0.203	0.19, 0.70 -1.16, -0.75
Pairwise comparison model testing for patient-specific factors							
PtSpecFx[c]	Model 1	-0.873	-19.50	<0.001	0.433	n/a	-0.96, -0.79
PtSpecFx CoOccSym	Model 2	0.611 -1.729	1.92 -4.92	0.055 <0.001	0.577	0.144	-0.01, 1.23 -2.42, -1.04
Pairwise comparison model testing for treatment factors							
TxFx[d]	Model 1	0.092	2.20	0.028	0.008	n/a	0.01, 0.17
TxFx CoOccSym	Model 2	-0.059 -1.189	-1.18 -18.23	0.237 <0.001	0.582	.574	-0.16, 0.04 -1.32, -1.06

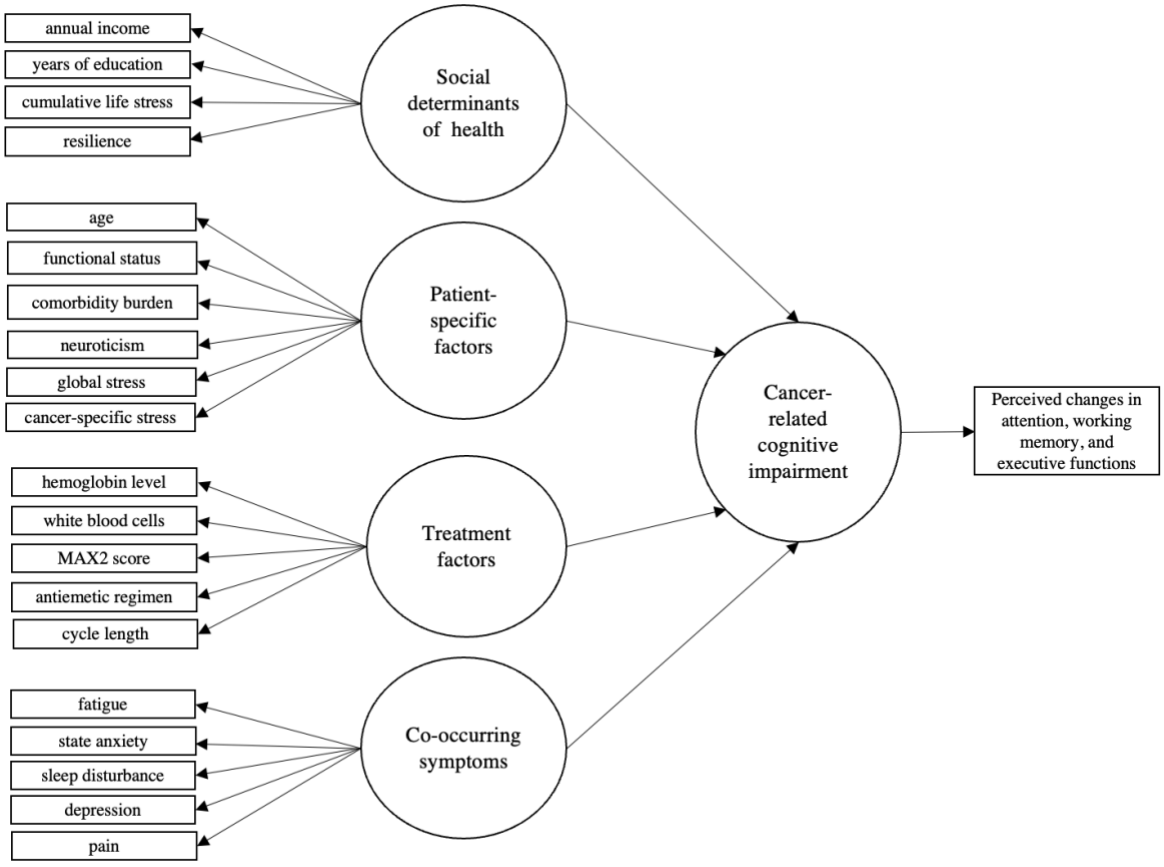

Figure 2.1 The hypothetical model to be evaluated based on the Multifactorial Model of Cancer-Related Cognitive Impairment.

Appendix 2.1 Results for the structural regression models (SRM) evaluated in this study

Legend for variables included in these analyses: age = age at enrollment; antiemetic4grp = antiemetic regimen in four groups; bpi7a3t1 = numeric rating on the pain scale; cdrstott1 = total resilience score at enrollment; cesdtt1 = total depressive symptoms score at enrollment; cyclelen = length of chemotherapy cycle; gstott1 = total sleep disturbance score at enrollment; hgb1 = hemoglobin level at enrollment; iestot = total cancer-specific stress score at enrollment; income4group = annual household income in four groups; kpst1 = functional status at enrollment; leea4t1 = severity of morning fatigue at enrollment; leep4t1 = severity of evening fatigue at enrollment; lscrtot = total cumulative life stressor score at enrollment; max2 = rating of toxicity of the chemotherapy regimen; neosubnt1 = the personality domain of neuroticism subscale score at enrollment; p8 = years of education; psstott1 = total global perceived stress score at enrollment; satott1 = state anxiety score at enrollment; scqtot13t1 = total comorbidity burden score at enrollment; wbc1 = white blood cell count at enrollment

1. Individual SRM for each exogenous latent variable with standardized coefficients

1a. Social determinants of health (SDOH)

Structural equation model Number of obs = 1,342
Estimation method = **mlmv**
Log likelihood = **-12200.284**

(1) **[/]var(SDOH) = 1**

	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Measurement						
cdrstott1						
SDOH	1.266425	.2760341	4.59	0.000	.7254076	1.807441
_cons	30.06297	.1783868	168.53	0.000	29.71334	30.4126
income4grp						
SDOH	1.039868	.1375859	7.56	0.000	.770205	1.309532
_cons	2.84802	.0333882	85.30	0.000	2.782581	2.91346
p8						
SDOH	1.238568	.181102	6.84	0.000	.8836146	1.593521
_cons	16.18374	.0831821	194.56	0.000	16.02071	16.34677
lscrtot						
SDOH	-.698041	.1466779	-4.76	0.000	-.9855244	-.4105576
_cons	6.071066	.1215434	49.95	0.000	5.832845	6.309286
var(e.cdrstott1)	39.16935	1.637251			36.08833	42.51341
var(e.income4grp)	.2771566	.2814008			.0378869	2.027504
var(e.p8)	7.569223	.4998314			6.650319	8.615096
var(e.lscrtot)	15.0566	.6674745			13.8036	16.42334
var(SDOH)	1	(constrained)				

LR test of model vs. saturated: chi2(2) = **6.35**, Prob > chi2 = **0.0418**

1b. Patient-specific factors (PtSpecF)

Structural equation model — Number of obs = 1,343
Estimation method = **mlmv**
Log likelihood = **-26839.362**

(1) **[psstott1]PtSpcF = 1**

Standardized	Coef.	OIM Std. Err.	z	P>|z|	[95% Conf.	Interval]
Measurement						
psstott1						
PtSpcF	.889059	.0130845	67.95	0.000	.8634139	.9147041
_cons	2.261247	.0524008	43.15	0.000	2.158544	2.363951
kpst1						
PtSpcF	-.3402534	.0272068	-12.51	0.000	-.3935778	-.2869291
_cons	6.395511	.1290365	49.56	0.000	6.142604	6.648418
iestot						
PtSpcF	.6686279	.0182707	36.60	0.000	.6328181	.7044377
_cons	1.435579	.0397467	36.12	0.000	1.357677	1.513481
neosubnt1						
PtSpcF	.8138007	.014287	56.96	0.000	.7857986	.8418027
_cons	1.884139	.0466899	40.35	0.000	1.792628	1.975649
age						
PtSpcF	-.2092415	.0286476	-7.30	0.000	-.2653897	-.1530933
_cons	4.629526	.093402	49.57	0.000	4.446461	4.812591
scqtot13t1						
PtSpcF	.2297934	.0283503	8.11	0.000	.1742278	.2853591
_cons	1.710354	.0428414	39.92	0.000	1.626386	1.794321
var(e.psstott1)	.2095741	.0232658			.1685939	.2605153
var(e.kpst1)	.8842276	.0185144			.8486745	.9212701
var(e.iestot)	.5529367	.0244326			.5070648	.6029584
var(e.neosubnt1)	.3377285	.0232535			.2950938	.386523
var(e.age)	.956218	.0119885			.9330073	.9800061
var(e.scqtot13t1)	.947195	.0130294			.9219989	.9730796
var(PtSpcF)	1	.			.	.
cov(e.kpst1,e.scqtot13t1)	-.2488021	.0255193	-9.75	0.000	-.298819	-.1987851
cov(e.age,e.scqtot13t1)	.2740514	.0246694	11.11	0.000	.2257002	.3224026

LR test of model vs. saturated: chi2(7) = **21.78**, Prob > chi2 = **0.0028**

1c. Treatment factors (TxF)

Structural equation model Number of obs = 1,341
Estimation method = **mlmv**
Log likelihood = **-7294.0016**

(1) **[/]var(TxF) = 1**

	Standardized	Coef.	OIM Std. Err.	z	P>|z|	[95% Conf.	Interval]
Measurement							
wbc1							
	TxF	.430954	.045959	9.38	0.000	.340876	.5210321
	_cons	1.764443	.0441976	39.92	0.000	1.677817	1.851069
hgb1							
	TxF	-.2269033	.044471	-5.10	0.000	-.314065	-.1397417
	_cons	8.06331	.1602973	50.30	0.000	7.749133	8.377487
max2							
	TxF	.5836568	.0527868	11.06	0.000	.4801966	.687117
	_cons	2.144184	.0497709	43.08	0.000	2.046635	2.241733
antiemetic4grp							
	TxF	.3824383	.0403019	9.49	0.000	.303448	.4614285
	_cons	2.226806	.0519013	42.90	0.000	2.125081	2.328531
cyclelen							
	TxF	-.1026202	.0414494	-2.48	0.013	-.1838595	-.021381
	_cons	2.705057	.0592755	45.64	0.000	2.588879	2.821235
var(e.wbc1)		.8142786	.0396125			.7402261	.8957395
var(e.hgb1)		.9485149	.0201813			.9097737	.9889057
var(e.max2)		.6593448	.0616187			.5489894	.7918833
var(e.antiemetic4grp)		.853741	.030826			.7954114	.916348
var(e.cyclelen)		.9894691	.0085071			.9729352	1.006284
var(TxF)		1	(constrained)				
cov(e.wbc1,e.hgb1)		.1173286	.0364581	3.22	0.001	.045872	.1887851
cov(e.antiemetic4grp,e.cyclelen)		-.2344487	.0292832	-8.01	0.000	-.2918428	-.1770546

LR test of model vs. saturated: chi2(3) = **6.97**, Prob > chi2 = **0.0728**

1d. Co-occurring symptoms (CoOccSym)

Structural equation model — Number of obs = 1,332
Estimation method = **mlmv**
Log likelihood = **-22455.42**

(1) **[/]var(CoOccSym) = 1**

Standardized	Coef.	OIM Std. Err.	z	P>|z|	[95% Conf.	Interval]
Measurement						
leea4t1						
CoOccSym	.7244978	.0190739	37.98	0.000	.6871136	.7618819
_cons	1.220021	.036463	33.46	0.000	1.148555	1.291488
leep4t1						
CoOccSym	.4828794	.0261378	18.47	0.000	.4316503	.5341085
_cons	2.152524	.0506717	42.48	0.000	2.05321	2.251839
satott1						
CoOccSym	.5265535	.0243953	21.58	0.000	.4787396	.5743674
_cons	2.739825	.0604265	45.34	0.000	2.621391	2.858259
gstott1						
CoOccSym	.8260353	.0172775	47.81	0.000	.7921719	.8598986
_cons	2.591383	.0580637	44.63	0.000	2.47758	2.705186
cesdtt1						
CoOccSym	.6889887	.0192752	35.74	0.000	.6512099	.7267675
_cons	1.323644	.037872	34.95	0.000	1.249416	1.397872
bpi7a3t1						
CoOccSym	.3558161	.0351712	10.12	0.000	.2868818	.4247503
_cons	2.331316	.0705793	33.03	0.000	2.192983	2.469649
var(e.leea4t1)	.475103	.027638			.4239075	.5324813
var(e.leep4t1)	.7668275	.0252428			.7189148	.8179334
var(e.satott1)	.7227414	.0256908			.6741023	.77489
var(e.gstott1)	.3176657	.0285437			.2663704	.3788391
var(e.cesdtt1)	.5252946	.0265608			.4757327	.5800198
var(e.bpi7a3t1)	.8733949	.025029			.8256913	.9238546
var(CoOccSym)	1	(constrained)				
cov(e.leea4t1,e.leep4t1)	.2131637	.0331837	6.42	0.000	.1481248	.2782025
cov(e.satott1,e.cesdtt1)	.6349425	.0190226	33.38	0.000	.5976588	.6722261

LR test of model vs. saturated: chi2(7) = **22.61**, Prob > chi2 = **0.0020**

2. Individual SRM for the CRCI latent variable regressed on each exogenous latent variable with standardized coefficients

2a. Social determinants of health

```
Structural equation model                       Number of obs     =      1,343
Estimation method  = mlmv
Log likelihood     = -14769.201

 ( 1)  [/]var(e.newafitott1) = .2301856
 ( 2)  [/]var(e.AFITot) = 1
 ( 3)  [/]var(SDOH) = 1
```

Standardized	Coef.	OIM Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural						
AFITot						
SDOH	.6533627	.0452777	14.43	0.000	.56462	.7421054
Measurement						
newafitott1						
AFITot	.9643257	.0014273	675.64	0.000	.9615283	.9671231
_cons	3.523938	.0747009	47.17	0.000	3.377527	3.670349
cdrstott1						
SDOH	.5553658	.035484	15.65	0.000	.4858184	.6249132
_cons	4.708892	.0971648	48.46	0.000	4.518452	4.899331
income4grp						
SDOH	.3873964	.0433899	8.93	0.000	.3023538	.472439
_cons	2.452928	.0575088	42.65	0.000	2.340213	2.565643
p8						
SDOH	.2545403	.0435488	5.84	0.000	.1691863	.3398944
_cons	5.364501	.1081509	49.60	0.000	5.152529	5.576473
lscrtot						
SDOH	-.2373849	.0416618	-5.70	0.000	-.3190405	-.1557293
_cons	1.544124	.0455392	33.91	0.000	1.454869	1.633379
var(e.newafitott1)	.0700759	.0027527			.0648831	.0756843
var(e.cdrstott1)	.6915688	.0394132			.6184784	.7732969
var(e.income4grp)	.849924	.0336182			.786523	.9184358
var(e.p8)	.9352092	.0221698			.8927511	.9796866
var(e.lscrtot)	.9436484	.0197798			.9056663	.9832234
var(e.AFITot)	.5731171	.0591655			.4681337	.7016441
var(SDOH)	1	(constrained)				

```
LR test of model vs. saturated: chi2(5)    =    174.77, Prob > chi2 = 0.0000
```

2b. Patient-specific factors

Structural equation model Number of obs = 1,343
Estimation method = mlmv
Log likelihood = -29183.753

(1) [/]var(e.newafitott1) = .2303738
(2) [/]var(e.AFITot) = 1
(3) [/]var(PtSpcF) = 1

	Standardized	Coef.	OIM Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural							
AFITot							
	PtSpcF	-.6577448	.0191338	-34.38	0.000	-.6952464	-.6202433
Measurement							
newafitott1							
	AFITot	.9643218	.0014262	676.15	0.000	.9615265	.9671171
	_cons	3.527347	.0745412	47.32	0.000	3.381249	3.673445
psstott1							
	PtSpcF	.9065456	.0106096	85.45	0.000	.8857512	.9273401
	_cons	2.259139	.0523219	43.18	0.000	2.15659	2.361688
kpst1							
	PtSpcF	-.3681364	.0263939	-13.95	0.000	-.4198675	-.3164053
	_cons	6.395161	.1290265	49.56	0.000	6.142274	6.648049
iestot							
	PtSpcF	.6610044	.0181336	36.45	0.000	.6254632	.6965456
	_cons	1.433888	.0397295	36.09	0.000	1.35602	1.511756
neosubnt1							
	PtSpcF	.7933042	.0133884	59.25	0.000	.7670634	.819545
	_cons	1.881049	.0466563	40.32	0.000	1.789604	1.972493
age							
	PtSpcF	-.2045881	.0282773	-7.24	0.000	-.2600106	-.1491656
	_cons	4.629526	.093402	49.57	0.000	4.446461	4.812591
scqtot13t1							
	PtSpcF	.2420458	.0279008	8.68	0.000	.1873612	.2967304
	_cons	1.710962	.0428423	39.94	0.000	1.626992	1.794931
var(e.newafitott1)		.0700835	.0027506			.0648945	.0756874
var(e.psstott1)		.178175	.0192362			.1441946	.2201631
var(e.kpst1)		.8644756	.0194331			.8272143	.9034154
var(e.iestot)		.5630732	.0239728			.5179944	.6120751
var(e.neosubnt1)		.3706685	.0212422			.3312877	.4147306
var(e.age)		.9581437	.0115704			.9357324	.9810918
var(e.scqtot13t1)		.9414138	.0135066			.9153102	.9682619
var(e.AFITot)		.5673717	.0251703			.5201228	.6189129
var(PtSpcF)		1	(constrained)				
cov(e.kpst1,e.scqtot13t1)		-.2393504	.0256718	-9.32	0.000	-.2896661	-.1890347
cov(e.age,e.scqtot13t1)		.2748485	.0246902	11.13	0.000	.2264567	.3232403

LR test of model vs. saturated: chi2(12) = 116.29, Prob > chi2 = 0.0000

2c. Treatment factors

```
Structural equation model                       Number of obs     =      1,341
Estimation method  = mlmv
Log likelihood     = -9917.0892

 ( 1)  [/]var(e.newafitott1) = .2292613
 ( 2)  [/]var(e.AFITot) = 1
 ( 3)  [/]var(TxF) = 1
```

	Standardized	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural							
AFITot							
	TxF	.0918808	.0414522	2.22	0.027	.010636	.1731256
Measurement							
newafitott1							
	AFITot	.9643664	.0014224	677.97	0.000	.9615785	.9671543
	_cons	3.533927	.0746042	47.37	0.000	3.387705	3.680148
hgb1							
	TxF	.1780899	.0392349	4.54	0.000	.1011909	.2549889
	_cons	8.063676	.1602915	50.31	0.000	7.74951	8.377842
wbc1							
	TxF	-.3913792	.042831	-9.14	0.000	-.4753264	-.3074319
	_cons	1.76444	.044199	39.92	0.000	1.677811	1.851068
max2							
	TxF	-.6263585	.0596751	-10.50	0.000	-.7433196	-.5093974
	_cons	2.144136	.0497717	43.08	0.000	2.046585	2.241686
antiemetic4grp							
	TxF	-.3763142	.044995	-8.36	0.000	-.4645028	-.2881257
	_cons	2.226431	.0519056	42.89	0.000	2.124697	2.328164
cyclelen							
	TxF	.0972163	.0416758	2.33	0.020	.0155333	.1788993
	_cons	2.70504	.0592758	45.63	0.000	2.588862	2.821219
var(e.newafitott1)		.0699974	.0027435			.0648216	.0755865
var(e.hgb1)		.968284	.0139747			.9412779	.9960649
var(e.wbc1)		.8468224	.0335263			.7835967	.9151495
var(e.max2)		.607675	.074756			.4774818	.7733676
var(e.antiemetic4grp)		.8583876	.0338645			.7945156	.9273944
var(e.cyclelen)		.990549	.0081031			.9747938	1.006559
var(e.AFITot)		.9915579	.0076173			.9767401	1.006601
var(TxF)		1	(constrained)				
cov(e.antiemetic4grp,e.cyclelen)		-.2369732	.0291911	-8.12	0.000	-.2941867	-.1797597

```
LR test of model vs. saturated: chi2(8)   =     26.77, Prob > chi2 = 0.0008
```

2d. Co-occurring symptoms

Structural equation model — Number of obs = **1,332**
Estimation method = **mlmv**
Log likelihood = **-24724.035**

(1) **[/]var(e.newafitott1) = .230194**
(2) **[/]var(e.AFITot) = 1**
(3) **[/]var(CoOccSym) = 1**

	Standardized	OIM Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Structural							
AFITot							
	CoOccSym	**-.7620838**	**.0171917**	**-44.33**	**0.000**	**-.7957789**	**-.7283887**
Measurement							
newafitott1							
	AFITot	**.9643762**	**.0014238**	**677.34**	**0.000**	**.9615857**	**.9671668**
	_cons	**3.52725**	**.0745052**	**47.34**	**0.000**	**3.381223**	**3.673278**
leea4t1							
	CoOccSym	**.7025212**	**.0179287**	**39.18**	**0.000**	**.6673816**	**.7376608**
	_cons	**1.220106**	**.0364651**	**33.46**	**0.000**	**1.148635**	**1.291576**
leep4t1							
	CoOccSym	**.4616768**	**.0254677**	**18.13**	**0.000**	**.411761**	**.5115927**
	_cons	**2.152192**	**.0506767**	**42.47**	**0.000**	**2.052868**	**2.251517**
satott1							
	CoOccSym	**.5974612**	**.0219913**	**27.17**	**0.000**	**.554359**	**.6405633**
	_cons	**2.738053**	**.0604228**	**45.31**	**0.000**	**2.619627**	**2.85648**
gstott1							
	CoOccSym	**.7760201**	**.0157845**	**49.16**	**0.000**	**.7450831**	**.8069571**
	_cons	**2.591213**	**.0580672**	**44.62**	**0.000**	**2.477403**	**2.705023**
cesdtt1							
	CoOccSym	**.7606363**	**.0162335**	**46.86**	**0.000**	**.7288192**	**.7924534**
	_cons	**1.321964**	**.0378458**	**34.93**	**0.000**	**1.247787**	**1.39614**
bpi7a3t1							
	CoOccSym	**.3519711**	**.0347167**	**10.14**	**0.000**	**.2839277**	**.4200145**
	_cons	**2.327949**	**.0706689**	**32.94**	**0.000**	**2.18944**	**2.466457**
var(e.newafitott1)		**.0699785**	**.0027461**			**.064798**	**.0755732**
var(e.leea4t1)		**.506464**	**.0251906**			**.4594215**	**.5583233**
var(e.leep4t1)		**.7868545**	**.0235157**			**.7420884**	**.8343211**
var(e.satott1)		**.6430401**	**.0262779**			**.593545**	**.6966626**
var(e.gstott1)		**.3977928**	**.0244981**			**.352562**	**.4488263**
var(e.cesdtt1)		**.4214324**	**.0246956**			**.3757061**	**.472724**
var(e.bpi7a3t1)		**.8761163**	**.0244385**			**.8295035**	**.9253485**
var(e.AFITot)		**.4192283**	**.026203**			**.3708924**	**.4738635**
var(CoOccSym)		**1**	(constrained)				
cov(e.leea4t1,e.leep4t1)		**.2439023**	**.0302705**	**8.06**	**0.000**	**.1845732**	**.3032314**
cov(e.satott1,e.cesdtt1)		**.5767163**	**.0224807**	**25.65**	**0.000**	**.5326549**	**.6207777**

LR test of model vs. saturated: chi2(**12**) = **92.30**, Prob > chi2 = **0.0000**

References

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Chapter 3

Blood-Based Biomarkers of Cancer-Related Cognitive Impairment in Non-Central Nervous System Cancer: A Scoping Review

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Abstract

This scoping review was designed to synthesize the extant literature on associations between subjective and/or objective measures of cancer-related cognitive impairment (CRCI) and blood-based biomarkers in adults with non-central nervous system cancers. The literature search was done for studies published from the start of each database searched (i.e., MEDLINE, Embase, PsycINFO, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, grey literature) through to October 20, 2021. A total of 95 studies are included in this review. Of note, a wide variety of biomarkers were evaluated. Most studies evaluated patients with breast cancer. A variety of cognitive assessment measures were used. The most consistent significant findings were with various subjective and objective measures of CRCI and levels of interleukin-6 and tumor necrosis factor. Overall, biomarker research is in an exploratory phase. However, this review synthesizes findings and proposes directions for future research.

Introduction

Cognitive changes associated with cancer and its treatments, known collectively as cancer-related cognitive impairment (CRCI), are a significant burden for both patients and survivors.[1] While prevalence rates vary across the cancer care continuum and by assessment methods, up to 75% of patients and 60% of those who have completed treatment report CRCI.[2-4] Multiple cognitive domains are impacted (e.g., memory, attention, processing speed, executive function).[5, 6] Consequently, CRCI results in decrements in various aspects of quality of life (e.g., daily functioning,[7, 8] personal relationships,[9] ability to return to work[10]). For some, CRCI can persist for years into survivorship.[11]

A number of phenotypic risk factors are associated with the development and persistence of CRCI (e.g., psychological distress,[12] co-occurring symptoms[13]). Several biological mechanisms are hypothesized to underlie these cognitive changes (e.g., oxidative stress, inflammatory responses, blood brain barrier disruption[14]). However, without a more complete understanding of its underlying mechanism(s), progress will not be made in the development and testing of interventions to prevent and treat CRCI.[15, 16]

The Food and Drug Administration-National Institutes of Health Biomarker Working Group[17] defines a biomarker as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions” (p. 45). Biomarkers can serve a variety of functions (e.g., diagnostic, monitoring, pharmacodynamic/response, predictive, prognostic, susceptibility/risk, safety[18]). In addition, mechanism-based biomarker discovery aims to elucidate the biological processes that underlie a disease or symptom.[19]

In terms of CRCI, the identification of biomarkers is important to be able to: identify patients at increased risk for CRCI; evaluate for changes in CRCI during cancer treatment(s) and into survivorship; identify individuals who may benefit from an intervention; evaluate the

efficacy and/or effectiveness of interventions; and/or determine its underlying mechanisms. It is plausible to hypothesize that different biomarkers will be needed to achieve different goals.

To date, four systematic reviews have summarized associations between CRCI and blood-based biomarkers.[20-23] In the first review that aimed to create an inventory of studies that evaluated biological factors associated with CRCI from blood, saliva, and/or cerebral spinal fluid,[20] 23 studies published between 2005-2015 were summarized. Overall, the authors concluded that potential biomarkers exist (e.g., interleukin (IL)-6, hemoglobin), however, only one database was searched. Bramer et al.[24] aimed to determine the best combination of database searches to produce robust systematic reviews and found at a minimum four databases should be reviewed.

A 2019 review aimed to synthesize available evidence on associations between objective measures of CRCI and germline genetic risk factors across 17 studies published prior to July 2018.[21] Across studies, the findings were inconclusive. Apolipoprotein E (*APOE*) was the most extensively studied genetic marker. Specifically, findings on associations between CRCI and variations in catechol-O-methyltransferase *(COMT*); four deoxyribonucleic acid (DNA) repair genes; five oxidative stress genes; and 22 genes related to breast cancer (BC) were inconclusive. This review did not include an evaluation of associations between subjective measures of CRCI and genetic risk factors.

The third review published in 2019 focused on a synthesis of evidence on the effects of germline genetic polymorphisms on subjective or objective measures of CRCI in both pediatric and adult patients published from 2000 onwards.[22] Findings across 17 studies suggest that CRCI or neuroimaging abnormalities were associated with 38 genetic variations across 15 genes. However, this review was limited to an evaluation of data collected at least six months (i.e., long-term effects) after treatment with chemotherapy, radiotherapy, and corticosteroids.

The final 2019 review focused on an evaluation of associations between subjective and objective measures of CRCI and other common symptoms (i.e., anxiety, depressive symptoms,

fatigue, pain, sleep disturbance) and germline genetic polymorphisms in women with early stage BC during or after treatment.[23] Findings from six studies published through October 2017 suggest that CRCI is associated with variations in *COMT, APOE*, interleukin-one receptor 1 (*IL1R1*), and brain-derived neurotrophic factor (*BDNF*) genes. Limitations of this review include the focus on only patients with BC and inclusion of only those studies that reported statistically significant results.

Given that three reviews focused only on genetic variations[21-23] and the fourth placed restrictions on the included literature,[20] a comprehensive evaluation of biomarkers of CRCI is not available. Over the past two decades, association studies of CRCI and blood-based biomarkers have included a number of traditional biomarkers (e.g., hemoglobin, hormones, blood cell counts, inflammatory markers), as well as more novel ones (e.g., neurofilament proteins, DNA methylation, total ribonucleic acid (RNA) gene expression). Given the paucity of known information about the biomarkers associated with CRCI,[20-23] this scoping review aims to synthesize the extant literature on associations between subjective and/or objective measures of CRCI and blood-based biomarkers in adults with non-central nervous system (CNS) cancers.

Methods

The protocol for this review was published previously.[25] This scoping review follows the six-stage methodology of Arksey and O'Malley.[26] It is guided by the following question: *What blood-based biomarkers have been associated with CRCI in patients with non-CNS cancers?* A comprehensive search strategy was developed by an academic health science librarian with input from the team. The literature search was done for studies published from the start of each database (i.e., MEDLINE, Embase, PsycINFO, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, grey literature) searched through to October 20, 2021. Search strategies are provided in Appendix 3.1. The database searches were supplemented by hand searches of the table of contents of key journals known to publish

studies related to CRCI; review of reference lists of included studies ('snowballing'); and forward citation tracking. Hand searches were done on an ongoing basis through April 1, 2022.

All records retrieved were downloaded into EndNote and duplicates were removed and recorded. Then, citations were uploaded into Covidence (Melbourne, Australia), an internet-based software program designed to facilitate the management of reviews and collaboration among reviewers during the study selection process. Studies were included if they: (1) were clinical studies of patients with a current or former (i.e., survivors) cancer diagnosis; (2) enrolled adults ≥18 years of age; (3) included the measurement of a blood-based biomarker(s); (4) included a subjective and/or objective assessment of cognitive functioning; (5) reported on an association between cognitive function and the biomarker; and (6) were written in English.

Every record was screened by two of three authors (K.O., S.M., C.M.). A third author, who did not screen the article, resolved any conflicts. After confirming strong inter-rater reliability (kappa $\geq$0.80 on a subset of citations), study selection was conducted in two phases, namely, title/abstract screening and full-text review. Data charting was conducted to capture first author, year of publication, country, study design, sample size, type of cancer, timing of the study assessments, objective measure(s) of cognitive function and neuropsychological domains evaluated, subjective measure(s) of cognitive function, blood fraction, biomarker, assay, and associations between cognitive function and biomarker(s).

Results

The search resulted in 25,573 citations (Figure 3.1). Prior to screening, 375 duplicate records were removed. During title and abstract screening, 24,912 records were excluded based on the prespecified inclusion criteria. A total of 286 reports were retrieved for full-text review and 73 studies are included in this review. An additional 22 studies were found using hand-searching methods (e.g., review of reference lists of included studies ('snowballing'), forward citation tracking). For more detailed information on study selection see Figure 3.1.

Cancer types

Across the 95 studies, 61.1% (n=58) evaluated patients with BC; followed by 11.6% (n=11) with heterogenous types of cancer, 5.3% (n=5) with colorectal, and 4.2% (n=4) with testicular cancer. Of the remaining 17 studies, one or two of them evaluated patients with the following cancers: non-Hodgkin's lymphoma, lung, prostate, multiple myeloma, pancreatic, thyroid, acute myelogenous leukemia, gastric, melanoma, head and neck, renal cell, gastrointestinal stromal tumor, and patients receiving hematopoietic cell transplant.

Study designs

Across the 95 studies, 57.9% (n=55) were longitudinal, 36.8% (n=35) were cross-sectional, and 5.3% (n=5) were a randomized control trial (RCT). Sample sizes ranged from 13 to 2,520, with a median sample size of 91. In addition, 31.6% (n=30) included non-cancer controls.

Measures of cognitive function

Across the 95 studies, 33.7% (n=32) included both subjective and objective measures of cognitive function. In the remaining studies, 26.3% (n=25) included only a subjective measure(s) and 40% (n=38) included only an objective measure(s).

A total of 16 different subjective measures were used with the most frequent being: Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog) (n=24),[27] European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (n=11),[28] Attentional Function Index (n=4),[29] Cognitive Failures Questionnaire (n=4),[30] Squire Memory Questionnaire (n=2),[31] Everyday Cognition scale (n=3),[32] Prospective and Retrospective Memory Questionnaire (n=2),[33] and Patient Assessment of Own Functioning Inventory (n=2).[34] The remaining subjective measures were used in a single study: Brief Rating Inventory of Executive Functioning for Adults,[35] MD Anderson Symptom Inventory,[36] Patient Reported Outcomes Measurement System (PROMIS) Cognitive Abilities,[37] Fatigue Symptom Checklist,[38] Profile of Moods States - Confusion Subscale,[39] Multifactorial

Memory Questionnaire,[40] Breast Cancer Prevention Trial Symptom Checklist,[41] and Cognitive Difficulties Scale.[42]

A total of 12 different objective approaches were used to measure cognitive function, with the most frequent being: an investigator-developed battery (i.e., two or more neuropsychological tests) (n=36), Mini Mental State Examination (MMSE) (n=15),[43] Cambridge Neuropsychological Test Automated Battery (n=7),[44] a single neuropsychological test (versus two or more) (n=6), Headminder (n=5),[45] Montreal Cognitive Assessment (MoCA) (n=3),[46] High Sensitivity Cognitive Screen (n=2),[47] and CNS Vital Signs (n=2).[48] The remaining objective measures were used in a single study: National Institute of Health Toolbox Cognition Battery,[49] Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery,[50] Automated Neuropsychological Assessment Metric,[51] and the Cognitive Stability Index.[45]

Biomarkers

The various biomarkers evaluated across the 95 studies were grouped into the following categories: genetic, immune-related, neuroendocrine, common laboratory tests, and other (Table 3.1). A brief summary of the findings for each category is presented below. Because some studies evaluated more than one type of biomarker, they are referenced more than once. Within each category, results are reported for the most common biomarkers followed by the biomarkers that were evaluated in a limited number of studies. Of note, due to the volume of studies and measures of cognitive function included in this review, biomarkers are reported in terms of their association(s) with subjective (i.e., self-reported) or objective measures and cognitive domain (when available). However, the specific measure(s) are not reported. Table 3.2 provides an overview of specific biomarkers reported to have significant associations with CRCI.

Genetic biomarkers (n=27)

Fifteen studies evaluated for associations between various measures of CRCI and *APOE* alleles. Of these, ten found no associations with subjective[52-59] or objective[53-58, 60, 61] measures. In a study of BC survivors that used a subjective measure, compared to individuals who were heterozygous or homozygous for the rare G allele (AG or GG), individuals who were homozygous for the common allele (AA) of *APOE* rs429358 had greater improvements in the visuospatial cognition domain in the 12 weeks after a mindfulness intervention.[62] The remaining four studies reported on associations between objective measures and the *APOE* ε4 allele. In a study of survivors of either BC or lymphoma, compared to individuals who did not have the ε4 allele, individuals with at least one ε4 allele had poorer performance in the domains of visual memory and spatial ability.[63] In another study of patients with BC, no main effect of *APOE* was found.[64] However, an increased risk for declines in the domains of processing speed and working memory was found in patients who did not have a smoking history and had the ε4 allele. In a third study of patients with BC, regardless of type of treatment, associations were found across time between poorer verbal learning, visual learning, and memory performance in patients with one or more ε4 alleles.[65] In terms of specific treatments, patients who received only anastrozole and had one or more ε4 alleles had poorer performance on executive function tasks and had further decreases in attention scores at six and 12 months after the initiation of anastrozole. In contrast, for patients who received chemotherapy in addition to anastrozole and who had one or more of the ε4 alleles, improvements in verbal learning and memory occurred over the 12 months after the initiation of treatment. In another study of patients with testicular cancer who received surgery or surgery and chemotherapy, worse overall cognitive performance was observed in individuals who received both treatments and who had an ε4 allele.[66]

Six studies evaluated for associations between measures of CRCI and variations in *BNDF* genes. In three studies, no associations were found between subjective[56, 62] or objective[56, 67] measures and *BDNF* rs6265. However, in two studies that evaluated *BDNF* rs6265 in patients with BC, individuals with the Met allele had lower odds of developing self-reported CRCI.[68, 69] Another study of patients with BC evaluated *BDNF* rs6265 for its potential contribution to the dysregulation of cytokines that would affect BDNF levels and found that rs6265 did not moderate cytokine levels, which showed inverse relationships with BDNF levels.[70]

Five studies evaluated for associations between various measures of CRCI and variations in cytokine genes. In a study of patients with BC that calculated an additive genetic risk score for three genes (i.e., tumor necrosis factor (*TNF*)-308, *IL6*-174, and *ILβ*-511), increased self-reported memory complaints were reported by patients with a higher number of high-expression alleles.[71] In another study of patients with BC, a two-fold increase in the odds of belonging to a class of patients with worse self-reported CRCI was associated with being heterozygous or homozygous for the rare A allele (GA or AA) of *IL1* receptor 1 rs949963.[72] In a study of patients with heterogenous types of cancer and their family caregivers, a four-fold increase in the odds of belonging to a lower self-reported attentional function class was associated with each additional copy of the rare G allele of *IL6* rs1800795.[73] In a study of patients with BC, no associations were found between subjective or objective measures and *IL6* rs1800795 or *TNF-α* rs1800629.[74] However, in a separate study of patients with BC, worse self-reported CRCI was associated with the G allele in a dominant model of *TNF-α* rs1800629.[75]

Three studies evaluated for associations between various measures of CRCI and variations in the *COMT* gene. In two studies, no associations were found between subjective[62] or objective[67] measures of CRCI and *COMT* rs4860. In a study of patients with BC, compared to patients with the GG genotype of *COMT* rs165599, patients with the GA and AA genotypes had a lower odds of developing cognitive decline.[56] In the dominant model, the GG and GA

genotypes of *COMT* rs165599 were associated with worse scores on both subjective and objective measures.

In a study of BC survivors that evaluated a mindfulness-based stress reduction intervention, improvements in a subjective measure of CRCI were associated with a single nucleotide polymorphism (SNP) in four genes (i.e., *APOE* (results reported above), methylenetetrahydrofolate reductase (*MTHFR*), solute carrier family 6 member 4 (*SLC6A4*), ankyrin repeat and kinase domain containing 1 (*ANKK1*)).[62] Survivors who were homozygous for the common G allele (GG) of *MTHFR* rs1801133 experienced greater improvements in three outcomes (i.e., visuospatial, planning, satisfaction) compared to individuals who were heterozygous or homozygous for the rare A allele. Survivors who were homozygous for the common G allele (GG) of *SLC6A4* rs16965628 had greater improvements in three outcomes (i.e., memory, organization, global cognition) compared to individuals who were heterozygous or homozygous for the rare C allele (GC or CC). Survivors who were heterozygous or homozygous for the rare A allele (GA or AA) of *ANKK1* rs1800497 experienced greater improvements in planning and global cognition than individuals who were homozygous for the common G allele. *ANKK1* rs1800497 was a moderator of the effect of the intervention on cognitive outcomes (i.e., the outcomes of language, visuospatial, planning, and divided attention demonstrated an interaction between the intervention and genotype). All outcomes were in the same direction (i.e., survivors who were homozygous for the common allele of *ANKK1* rs1800497 had greater benefit from the intervention).

In a study of patients with heterogenous types of cancer, patients who were heterozygous or homozygous for the rare G allele of MYD88 innate immune signal transduction adaptor *(MYD88)* rs6853 had better cognitive function based on an objective measure.[67] In the same study, no association was found between an objective measure and C-reactive protein (*CRP*) rs2794521.

In two studies from a cohort of patients with BC, objective measures of CRCI were evaluated for associations with a variety of candidate genes. In brief, in the first study, performance on every cognitive function composite score was associated with one or more oxidative stress and DNA repair gene polymorphisms when main effects of the SNP and/or group x SNP interactions were evaluated.[76] In the second study, associations between genetic risk/protection scores and variability in pretreatment cognitive function performance were associated with polymorphisms across 25 candidate genes.[77] In a sample of patients with BC, oxidative stress and DNA repair gene polymorphisms were evaluated for associations with membership in subgroups of patients based on a subjective measure.[59] Individuals who were heterozygous or homozygous for the rare G allele of excision repair 5, endonuclease (i.e., *ERCC5*) rs873601 had an increased odds of membership in the subgroup described as *more frequent cognitive problems reported through the first year of adjuvant therapy then improving*.

In a study of patients with prostate cancer, the rate of impaired cognitive performance based on objective measures decreased over time in patients who were heterozygous or homozygous for the rare A allele (GA or AA) of G protein subunit beta 3 (*GNB3*) rs1047776.[60] In patients who were homozygous for the common G allele (GG), the rate of impaired cognitive performance doubled over the course of 12 months.

One study evaluated for associations between subjective and objective measures of CRCI and DNA methyltransferase 1 (*DNMT1*) in patients with BC.[78] While no associations with objective measures were found, patients who were heterozygous or homozygous for the rare A allele of *DNMT1* rs2162560 experienced a decrease in the odds of cognitive decline across subjective measures of concentration and functional interference. In a subgroup analysis of patients who were $\leq$51 years of age, patients who were heterozygous or homozygous for the rare A allele of *DNMT1* rs2162560 were protected against decrements in the domains of memory, concentration, and mental acuity.

Immune-related biomarkers (n=43)

Cytokines – Of the 38 studies that evaluated associations between CRCI and levels of circulating cytokines, thirteen studies found no associations between subjective[54, 55, 79-86] or objective[54, 55, 82-90] measures of CRCI and changes in the levels of a variety of circulating cytokines. However, 21 studies did report associations. Nine studies reported associations between decrements in various subjective[74, 91-94] and objective[95-98] measures and higher IL-6 levels. Nine studies reported associations between decrements in various subjective[93, 99, 100] and objective[66, 98, 100, 101] measures and higher levels of various biomarkers of TNF (i.e., TNF-α,[66, 93, 100, 102] soluble TNF-receptor I (TNFR-1),[103] or soluble TNF-receptor II (TNFR-2)[98, 99, 101]). In a study of BC survivors, compared to healthy controls, self-reported CRCI was associated with lower serum carotenoid concentrations, which were in turn associated with higher levels of soluble TNFR-2 and IL-6.[104]

In a study of patients with BC, a worse objective global deficit score was associated with higher levels of IL-8.[57] In contrast, in a study of patients with acute myeloid leukemia or myelodysplastic syndrome, better objective performance in the memory domain was associated with higher levels of IL-8.[95]

In a study of patients with BC, slower objective response speed and more severe self-reported CRCI were associated with higher IL-1β levels.[105] In addition, better objective response speed and less severe self-reported CRCI were associated with higher IL-4 levels. In a study of patients with BC, worse CRCI was associated with higher IL-1β and IL-4 levels based on a subjective measure.[100]

In a study of patients with BC, increased difficulty with self-reported concentration and forgetfulness were associated with reductions in monocyte chemoattractant protein one (MCP-1) levels.[106] In a study of patients with BC, worse scores on an objective measure of CRCI were associated with lower levels of insulin-like growth factor one (IGF-1).[107] In a study of patients

with head and neck cancer, worse self-reported CRCI was associated with higher levels of IL-2.[108]

Three studies of BC survivors evaluated for associations between various subjective or objective measures of CRCI and circulating cytokines. In the first study, neuropsychological test scores were predicted by different cytokine profiles based on machine learning algorithms.[109] In the second study that used machine learning algorithms, interactions were found between amyloid beta and tau and cytokines that influenced cognitive functioning.[110] In the third study, results of an exploratory descriptive network analysis of symptoms and cytokines suggest that self-reported CRCI, stress, loneliness, depressive symptoms, and fatigue co-occur and that IL-2 may contribute to a common mechanistic pathway for these co-occurring symptoms.[111]

Other immune biomarkers – Of the 14 studies that evaluated CRP levels, eight found no associations between various subjective[92, 99, 104, 112, 113] or objective[66, 90, 99, 104, 107, 112] measures of CRCI and CRP levels. In terms subjective measures, three studies reported that worse cognitive function was associated with higher levels of CRP.[81, 82, 114] In terms of objective measures, worse scores on a test of verbal fluency;[94] decrements in the learning and memory domain;[85] and decrements in verbal memory, visual memory, and overall total neuropsychological scores[98] were associated with higher levels of CRP.

In a study of patients with renal cell cancer or gastrointestinal stromal tumors, objective measures were used to assess CRCI.[85] Decrements in the domains of learning and memory were associated with higher neutrophil counts and higher erythrocyte sedimentation rates.

In a study of patients with lung cancer, trends in self-reported confusion were associated with different trends in white blood cell (WBC) and monocyte counts and levels of tartrate-resistant acid phosphatase 5a (TRACP5a; i.e., a marker of chronic inflammation).[81] Namely, as confusion scores increased, WBC and monocytes decreased and TRACP5a increased.

In a study of BC survivors, measures of blood cell counts were used as biomarkers of systemic inflammation (i.e., granulocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio,

systemic immune-inflammation index).[115] Global cognitive performance (i.e., general cognitive factor) was evaluated using scores from five neuropsychological tests. A lower (i.e., worse) general cognitive factor score was associated with higher overall levels of systemic inflammation.

A study of patients and survivors of BC evaluated for associations between objective measures of CRCI and cell counts of cluster of differentiation (CD) positive (+) cells [116]. Compared to BC survivors, poorer neuropsychological test performance was associated with higher levels of CD4+ and CD8+ cells in those patients receiving treatment.

Neuroendocrine biomarkers (n=14)

Seven studies evaluated associations between various subjective or objective measures of CRCI and sex hormones. No associations were found with follicle stimulating hormone,[54, 55, 57, 108] luteinizing hormone,[54, 55, 57, 108] estrogen,[108] or testosterone.[54, 55, 85, 117] Additionally, no association was found with estradiol,[54, 57, 85, 118] with the exception of one study of patients with colorectal cancer in which decrements in global cognitive impairment, as well as reductions in information processing speed and verbal and visual memory, were associated with lower estradiol levels in females.[55]

In the four studies that evaluated thyroid-related markers in patients with non-thyroid cancers, no associations were found between subjective or objective measures of CRCI and thyroid-related markers (i.e., triiodothyronine (T_3),[89, 108] thyroxine (T_4),[89, 108] thyroid stimulating hormone (TSH)[85, 89, 108, 119]). In a study of older patients with differentiated thyroid carcinoma, better performance in the domain of visuospatial function was associated with higher serum levels of free T_4.[120]

In a study of patients with testicular cancer before treatment, poorer neuropsychological performance was associated with higher cortisol levels.[94] In a study of the same cohort after treatment, no associations were found between neuropsychological performance and cortisol levels.[66]

A study of BC survivors used subjective and objective measures to assess CRCI.[112] No associations were found between any of the measures and insulin resistance, as measured by the homeostatic model assessment 2 of insulin resistance (HOMA2-IR).

One study evaluated for associations between subjective and objective measures of CRCI and levels of dehydroepiandrosterone (DHEA) and its sulfated form (i.e., DHEAS) in patients with BC.[121] A lower odds of developing self-reported CRCI was associated with higher pre-chemotherapy DHEAS levels.

Common laboratory tests (n=22)

Twenty-one studies evaluated for associations between various measures of CRCI and hemoglobin levels. Of these, 15 found no associations with subjective[122] or objective[54, 55, 57, 85, 87, 95, 108, 116, 119, 123-127] measures. Across the remaining six studies, only objective measures were used. Results from four studies suggest that in patients receiving treatment for anemia (e.g., epoetin alfa), improvements in cognitive function scores were associated with improvements in hemoglobin levels.[128-131] Two additional studies of patients receiving chemotherapy found associations between decrements in visual memory[132] and poorer performance when following a number and/or letter sequence and in the domain of nonverbal memory[133] and declines in hemoglobin levels.

Four studies found no associations between subjective[85, 127] or objective[85, 116, 119] measures of CRCI and absolute neutrophil,[127] complete blood,[116] WBC,[119] red blood cell,[119] and platelet[85, 119] counts. In five studies, no associations were found between subjective or objective measures of CRCI and liver function tests or creatinine levels.[54, 55, 57, 85, 108] In three studies, no associations were found between subjective or objective measures of CRCI and thrombin-anti-thrombin, pro-thrombin fragment-1 and -2, and D-dimer levels.[54, 55, 57]

No associations were found between subjective[85, 108] or objective[85, 108, 119] measures of CRCI and levels of vitamin B1,[108] vitamin B12,[85, 108, 119] or folate.[108, 119] In two studies of patients with colorectal cancer[54, 55] and one study of patients with BC,[57] no associations were found

between subjective or objective measures of CRCI and the vitamin-related amino acid homocysteine. Finally, in a study of patients with colorectal cancer, no associations were found between subjective measures of CRCI and levels of vitamin D3.[134]

Other biomarkers (n=23)

Of the nine studies that evaluated for associations between various measures of CRCI and circulating BDNF levels, three found no associations with subjective[82, 84, 112] or objective[84, 112] measures. In the remaining six studies, associations were reported between decrements in both subjective[69, 135] and objective[83, 87, 135, 136] measures of CRCI and lower BDNF levels. In addition, in a study of patients with BC, patients with self-reported CRCI had lower BDNF levels that were associated with higher levels of circulating cytokines.[70] Of note, this inverse relationship was strongest in patients with persistent CRCI. In a study of patients with BC, lower levels of the BDNF receptor tropomyosin kinase B were associated with worse performance on an objective measure of cognitive flexibility.[136]

Three studies evaluated for associations between subjective[137] and objective[137-139] measures of CRCI and neurofilament protein levels. Across these three studies, no associations were found.

In two studies of patients with testicular cancer, no associations were found between objective measures of CRCI and human chorionic gonadotropin, alpha fetoprotein, or lactate dehydrogenase.[117, 140] In two studies of patients with colorectal cancer, no associations were found between subjective or objective measures of CRCI and carcinoembryonic antigen.[54, 55]

In a study of patients with melanoma, compared to individuals who were antibody-negative, patients who were antibody-positive (i.e., immunoglobulin A/immunoglobulin M anti-N-methyl-D-aspartate receptor antibody) were at an increased risk for CRCI across multiple objectively measured cognitive domains (e.g., memory, attention, executive function).[141]

In a study of patients with BC, mitochondrial DNA was assessed for associations with subjective and objective measures of CRCI.[142] No associations were found between mitochondrial DNA and any of these measures.

In a study of BC survivors, no associations were found between a subjective measure of CRCI and telomerase activity, leukocyte DNA damage, and telomere length.[86] Lower scores on objective measures of executive function and memory were associated with high DNA damage. In addition, lower scores in standardized attention, executive function, and motor speed were associated with reduced telomerase activity. In a study of patients with BC, seven of the eight objectively measured cognitive domains evaluated (except complex attention) were associated with chromosome-specific telomere length at timepoint two (i.e., mid-point of the chemotherapy cycle).[143]

In a study of patients with heterogeneous types of cancer, patients were grouped based on self-reported cognitive function as having either high or low cognitive function and total RNA gene expression was quantified.[144] A pathway impact analysis identified five biological signaling pathways related to inflammatory mechanisms (e.g., cytokine-cytokine receptor interaction, TNF signaling) that were perturbed between the two groups.

Two studies evaluated for associations between various measures of CRCI and DNA methylation. In a study of patients with BC that aimed to profile the epigenome-wide alterations in leukocyte DNA methylation, four cytosine-phosphate-guanine (CpG) sites (i.e., cg16936953 of vacuole membrane protein-1/microRNA 21 *(VMP1/MIR21)*, cg01252023 of coronin actin binding protein, 1B (*CORO1B)*, cg11859398 of sidekick cell adhesion molecule 1 (*SDK1)*, cg19956914 of sulfatase modifying factor 2 (*SUMF2)*) were significant in a multivariable model.[145] Increased methylation levels at cg16936953 of *VMP1/MIR21* were associated with decrements in self-reported cognitive function. In a second study of patients with BC, no associations were found between objective measures of psychomotor speed, reaction time,

complex attention, or cognitive flexibility and differential methylation.[146] However, 56 differentially methylated positions were associated with the memory domain.

Discussion

This scoping review is the first to synthesize findings from 95 studies that evaluated for associations between subjective and/or objective measures of CRCI and blood-based biomarkers in adults with non-CNS cancers. Across these 95 studies, a wide variety of biomarkers were evaluated. This discussion focuses on the specific rationale for each of the biomarker categories; an evaluation of biomarker utility; and recommendations for future research.

Genetic biomarkers

The *APOE* gene was the earliest biomarker evaluated,[63] likely influenced by the role of the *APOE* ε4 allele as the most significant genetic predictor of Alzheimer's disease.[147] While evidence suggests that *APOE* effects the two hallmark lesions associated with Alzheimer's disease (i.e., amyloid-β peptide plaques, neurofibrillary tangles containing tau),[147] the *APOE* gene may impact cognition through additional mechanisms (e.g., alterations in lipid binding, alterations in oxidative stress and/or inflammation, reductions in turnover of neural progenitor cells, disruptions in the blood brain barrier.[148] In terms of CRCI, results remain inconclusive. The presence of the *APOE* ε4 allele was either not associated with[52-61] or was associated with decrements[63-66] and/or improvements[62, 65] in a wide variety of cognitive domains. With the exception of one study,[62] all of the associations with *APOE* alleles were identified using objective measures of cognitive function. Given the variability in the types and timing of CRCI measures and the fact that the findings from fifteen studies are inconclusive,[52-66] limited evidence exists to support *APOE* as a robust biomarker for CRCI.

Among 17 studies, hundreds of SNPs across a multitude of candidate genes were evaluated.[56, 59-62, 67-78] However, validation studies are needed to be able to draw definitive

conclusions. The reader is referred to three reviews for additional information on genetic variations associated with CRCI.[21-23] Given the complexity of CRCI, future studies need to consider using a multi-staged data-integrated multi-omics analysis.[149] This approach integrates multiple levels of 'omics' data in a stepped approach and may facilitate a more comprehensive evaluation of the mechanisms that underlie CRCI. Conceivably, blood-based biomarkers may provide more rigor and accuracy if captured and analyzed as molecular signatures that encompass multiple analytes using different platforms (e.g., cells, genes, microRNAs, proteins, metabolites).[150]

Immune-related biomarkers

An evaluation of associations between CRCI and changes in plasma or serum cytokines is one of the largest categories of biomarker research. Cytokines are involved in a number of biological processes (e.g., non-specific responses to infection, specific responses to antigens).[151] In terms of patients with cancer, increased production of pro-inflammatory cytokines is associated with a variety of factors (e.g., stress,[152] tumor microenvironment,[153] chemotherapy administration[154]). Across 21 studies, findings suggest that cytokine dysregulation may be an underlying mechanism for CRCI.[57, 66, 74, 91-103, 105-109] Because cytokine levels may differ based on the blood fraction used (e.g., plasma or serum), choice of anticoagulant used, and timing of specimen processing (e.g., immediately after collection, post freeze-thaw cycle(s)), these factors warrant consideration in future studies.[155, 156] Across studies in this review, the most consistent associations were found between CRCI and higher levels of IL-6 and TNF.[66, 74, 91-101]

IL-6 is a proinflammatory cytokine that induces acute-phase protein expression and associated increases in vascular permeability, activation of lymphocytes, and production of antibodies.[157] As noted in one review,[157] higher levels of IL-6 were associated with cognitive impairments in other chronic conditions (i.e., dementia, liver cirrhosis). Several mechanisms are hypothesized to explain how IL-6 impacts cognitive function. For example, IL-6 overexpression

may impair neurotransmission in brain structures that modulate cognitive functions.[157] Equally plausible, changes in IL-6 can result in impairments in adult hippocampal neurogenesis.[157] Findings from this review suggest that higher levels of IL-6 are associated with decrements in various subjective[74, 91-94] and objective[95-98] measures of CRCI.

Microglia (i.e., macrophages that reside in the CNS) are one of the primary synthesizers of TNF-α.[158] The binding of TNF-α to its receptors results in many downstream effects (e.g., immune-stimulation, sleep regulation).[158] In terms of CRCI, one hypothesis is that TNF-α crosses the blood brain barrier and contributes to neuronal death in both the hippocampus and pre-frontal cortex.[154] Findings from this review suggest that higher levels of TNF-α and its receptors are associated with decrements in various subjective[93, 99, 100] and objective[66, 98, 100, 101] measures of CRCI.

While the data on IL-6 and TNF-α suggest that they may be useful biomarkers for CRCI, other cytokines (e.g., IL-1β,[100, 105] IL-8[57, 95]) warrant additional evaluation. Future studies need to evaluate individual or multiple cytokines in combination with other biomarkers,[70, 104, 110] or as parts of networks.[109, 111] In addition, diurnal variation in cytokine levels should be considered.[159] These types of studies may provide a more complete picture of CRCI's underlying mechanism(s) and whether cytokines can be used to monitor the efficacy or effectiveness of interventions for CRCI.

Neuroendocrine biomarkers

While cancer is a stressful experience, an evaluation of stress-related mechanisms for CRCI is limited. As noted in one review,[160] stress influences cognitive function (both positively and negatively) through acute and chronic secretion of cortisol. Across two studies, associations between objective measures of CRCI and cortisol levels showed different results depending on the timing of the assessments (i.e., prior to treatment, poorer neuropsychological performance was associated with higher cortisol levels,[94] after treatment(s) no associations were found[66]). The authors suggested that these differences may be due to the more pronounced effects of

stress at the time of the patient's diagnosis that decrease over time.[66] However, neuroendocrine-immune interactions may contribute to CRCI. For example, short-term increases in cortisol can suppress inflammation by binding to glucocorticoid receptors on cytokine-producing cells.[161] Longer-term increases in cortisol contribute to increased levels of inflammation because glucocorticoid receptors are downregulated.[161] Future research needs to determine if changes in cortisol and one or more inflammatory markers would be useful biomarkers of CRCI.

Thyroid hormone is known to play an important role in the development of the CNS and in neurocognitive function.[120] Thyroid dysfunction is associated with a variety of psychoneurological symptoms (e.g., mood changes, memory impairment).[120] In terms of CRCI, better performance on the Trail Making Test-A (reported to assess the domain of visuospatial function in this study) was associated with higher serum T_4 levels in older patients with differentiated thyroid carcinoma.[120] The authors suggested that the administration of levothyroxine resulted in an excessive amount of thyroid hormone that had a positive impact on some cognitive domains in patients who were deficient in endogenous thyroid hormone or had impairments in their hypothalamic-pituitary-adrenal axis.[120] Of note, in patients without thyroid cancer, no associations were found between various measures of CRCI and a variety of thyroid-related biomarkers.[54, 55, 57, 85, 108, 117] Taken together, additional research on the utility of thyroid-related biomarkers in patients with thyroid cancer is warranted. However, evidence to date does not support a role for this biomarker in patients with other types of cancer.

Common laboratory tests

Hemoglobin is another early and frequently evaluated biomarker. This biomarker was selected because treatment-induced anemia was thought to contribute to the development of CRCI.[133] To date, no evidence exists to suggest that subjective measures of CRCI are associated with hemoglobin levels.[55, 85, 108, 122, 124-127] In the four studies of patients who received erythropoiesis-stimulating treatments for anemia that used the MMSE to assess CRCI, results

suggest that this measure is able to detect improvements in cognitive function associated with increases in hemoglobin levels.[128-131] Two additional studies of patients receiving chemotherapy found associations between decrements in various objective measures of CRCI and declines in hemoglobin levels.[132, 133] However, the majority of studies included in this review suggest that hemoglobin in not a useful biomarker of CRCI.[54, 55, 57, 85, 87, 95, 108, 116, 119, 122-127]

Across most of the studies that evaluated other common laboratory tests, the scientific rationale for the selection of the various biomarkers was not provided or was reported to be exploratory.[54, 55, 57, 85, 108, 115, 119] The exception was for biomarkers associated with nutritional deficiencies (e.g., B vitamins). While research is limited, no evidence exists to support the assertion that common laboratory tests evaluated across the studies included in this review (e.g., creatinine, liver function tests) are associated with CRCI. The exception may be for blood cell counts that are known to be inflammatory/immune markers (e.g., absolute granulocyte, lymphocyte, and platelet counts[115] and CD4+, CD8+, and CD16+ counts[116]). However, these biomarkers require validation.

Other biomarkers

Neurotrophic factors (e.g., BDNF) play important roles in many neurophysiological processes (e.g., neuroprotection, regulation of neurogenesis, control of short- and long-lasting synaptic interactions that influence the mechanisms that underlie memory and cognition).[162] Previous research demonstrated that neurotrophic factors are able to cross the blood brain barrier as well as circulate systemically.[163] In terms of CRCI, decrements in both subjective[69, 135] and objective[83, 87, 135, 136] measures of CRCI were associated with lower levels of BDNF. In terms of *BDNF* genes, in two studies, protective effects were identified in patients with the *BDNF* Met allele in the development of self-reported CRCI.[68, 69] Taken together, additional research is needed to determine if BDNF (levels and/or genes) are a useful biomarker for the prediction of CRCI and/or its associated mechanisms. For a detailed review of the relationships between

various BDNF biomarkers and measures of CRCI in CNS and non-CNS cancers, the reader is referred to.[164]

Neurofilament proteins are neuronal-specific cytoskeletal proteins that play important roles in cell structural stability and are released into the circulation in response to axonal damage.[139] Because these proteins are associated with other neurodegenerative diseases (e.g., neuropathy), they were hypothesized to be a useful biomarker for CRCI.[139] Across three studies, no associations were reported between CRCI and neurofilament proteins.[137-139] However, each of these studies used measures that may not be sensitive to detect CRCI (e.g., a dementia-screening measure). Given that in one study neurofilament protein levels increased in a dose-dependent manner during the administration of chemotherapy,[137] this biomarker warrants additional investigation.

Study characteristics

In terms of study designs, 57.9% of studies were longitudinal, which allowed for evaluation of changes over time in both CRCI and various blood-based biomarkers. However, timing of the assessments was highly variable across these 55 studies. To be clinically useful as a biomarker to detect changes in CRCI over time and/or to elucidate the efficacy/effectiveness of interventions, the biomarker needs to be collected prior to the onset of cognitive changes and assessed at appropriate intervals. Given the patients with cancer may have CRCI prior to treatment,[2] biomarkers need to be collected as soon as possible after diagnosis to have a "baseline" level prior to treatment. In addition, the optimal timing for collection of biomarkers needs to be determined. The timing of the collection of a specimen will depend on the intended purpose of the biomarker. Across studies in this review, timepoints in the treatment trajectory were consistently reported. However, far fewer studies specified the specific time of day that the biomarker was collected. This information may be critical for some biomarkers, as circadian control of immune function (e.g., proinflammatory cytokine release) and hormone release (e.g., cortisol) are well established.[159]

In terms of the characteristics of study participants, 61.1% of studies evaluated patients with BC and the median sample size was 91. Investigations of associations between CRCI and a variety of biomarkers in more diverse samples are needed to determine biological mechanisms that may be tumor-specific and/or treatment(s)-specific (including evaluation of CRCI in people receiving novel treatments), and to identify/confirm demographic and clinical characteristics that may be risk factors for CRCI. It should be noted that because of small sample sizes, some studies were not adequately powered to detect associations.

The FACT-Cog was the most frequently used subjective measure of CRCI. In terms of scoring, a variety of approaches were reported (e.g., use of a minimum clinically important difference;[68-70, 78, 93, 105, 121, 142] use of the Perceived Cognitive Impairment (PCI) subscale as the primary outcome;[53, 86, 111, 118] use of "standard scoring methods";[108] use of a summary score[54, 57]). Various scores on the FACT-Cog correlated with a variety of biomarkers (e.g., circulating cytokines,[93, 105, 111] *DNMT1* genotype,[78] *BDNF* genotype,[68, 69] BDNF levels,[69, 135] dehydroepiandrosterone[121]). Given the lack of consistency across studies, the ideal FACT-Cog scoring method to represent the CRCI phenotype remains unclear. While the authors of the FACT-Cog (version 3) recommended using the PCI subscale as a primary outcome,[86] many studies included in this review did not use this subscale.

The EORTC QLQ-C30 was the second most frequently used subjective measure. However, the EORTC QLQ-C30 cognitive function scale has only two items (i.e., one addressing concentration, one addressing memory). A more robust evaluation of self-reported cognitive function may be more useful to establish the CRCI phenotype. Equally important, the measure selected may depend on the type of biomarker being investigated. For example, mechanism-based biomarker studies may require a more in-depth assessment of cognitive function to be able to elucidate the utility of the biomarker. In contrast, for efficacy or effectiveness biomarker studies, shorter and clinically feasible measures may be more useful. While not used in any study included in this review, the Cancer Neuroscience Initiative Working

Group recommended the PROMIS Cognitive Function Scale in combination with other subjective measures that are appropriate for the study aim(s) (e.g., a domain-specific measure such as the Attentional Function Index).[165]

Investigator-developed batteries of two or more neuropsychological tests were the most common objective measures. However, the specific measures included in these batteries varied widely. In terms of determining the presence of CRCI, methods used to score the various measures were highly variable, including: calculation of a global composite score;[94] transformation of each neuropsychological test's raw score into a standardized score followed by conversion to z scores using age-matched normative data;[99, 108] evaluation of a total neuropsychological performance score;[98] generation of a general cognitive factor score using principal component analysis to assess global cognitive performance;[115] and use of the Reliable Change Index.[132] The International Cognition and Cancer Task Force (ICCTF) recommends a particular battery of neuropsychological tests.[166] In addition, the ICCTF recommends a multi-step approach to the scoring of objective measures that specifies a cut-point for the determination of impairment for each test and the inclusion of a battery-wide scoring method when several measures are used.[166]

Objective measures (e.g., neuropsychological tests) are considered to be the gold standard to establish a diagnosis of cognitive dysfunction.[166] However, limitations exist in terms of cost; need for trained personnel to administer; participant burden; and lack of correlation with patients' reports of cognitive changes.[167] Careful consideration of the sensitivity and specificity of neuropsychological tests to detect CRCI is also necessary. In a meta-analysis that evaluated the sensitivity of several neuropsychological tests to detect impairments in various domains of cognitive function induced by chemotherapy,[168] results suggest that only six tests were sensitive to chemotherapy-induced impairment across four of the eight cognitive domains.

In a review that aimed to critically analyze the available meta-analytic literature on CRCI,[169] inconsistencies among the cognitive domains measured as well as which

neuropsychological tests measure which domains were described. Future research needs to determine which objective measures are sensitive, specific, can detect subtle changes, and are feasible to use in clinic or home settings. The incidence of self-reported CRCI is much higher than objectively measured CRCI,[165] which suggests two distinct aspects of CRCI (i.e., objective cognitive performance and subjective experience of the individual). Therefore, both subjective and objective assessments may be needed to determine the CRCI phenotype.[170] In future studies, harmonization of across measures would facilitate comparison across studies and/or pooling of data for a meta-analysis. Additional research is needed to determine if specific subjective and/or objective measures of CRCI are associated with common and/or distinct biomarkers.

Limitations

While this scoping review provides a synthesis of the extant literature on associations between CRCI and blood-based biomarkers in adults with non-CNS cancers, some limitations are worth noting. First, only studies that evaluated blood-based biomarkers were included. Evaluation of biomarkers from other tissue(s) as well as other types of biomarkers (e.g., microbiome-related[171]) may provide useful information about the underlying mechanism(s) and therapeutic targets for CRCI. Second, only studies published in English were included, which may bias results. Third, a quality appraisal tool was not used to assess studies. Finally, the search strategy may not have captured some potentially relevant articles, however, the use of an academic librarian and hand search methods helped to mitigate this concern.

Conclusions

The purpose of this scoping review was to elucidate current biological correlates of CRCI with the goal to inform future research leading to the identification of clinically relevant biomarkers associated with CRCI. In addition, this review highlights gaps in knowledge. While a wide variety of biomarkers have been evaluated, this research is primarily exploratory. As noted in Table 3.1, given that many biomarkers were evaluated in only a single study, validation

studies are needed. However, findings from this scoping review can be used to guide future CRCI research (see Table 3.3).

Additional biomarkers that have the potential to elucidate the mechanisms that underlie CRCI are emerging in the scientific literature. For example, exosomes may play a role in the development of CRCI because of their activity within the CNS (e.g., neurodegeneration, neuroprotection), as well as their associations with other cancer-related symptoms (e.g., cachexia, fatigue).[172] Others hypothesize that CRCI may be caused by chemotherapy-induced damage to tubulin within microtubules.[173] As new anti-cancer therapies and/or mechanisms emerge, additional biomarkers will warrant investigation. In addition, novel approaches to biomarker discovery will provide new insights. For example, systems biology approaches will allow for combined analysis of several types of molecular data in a single study.[174, 175] A team science approach, that allows for pooling of shared knowledge and resources, will be critical to continue to move the field of CRCI research forward. These efforts are important to reduce the impact of CRCI on patients and survivors.

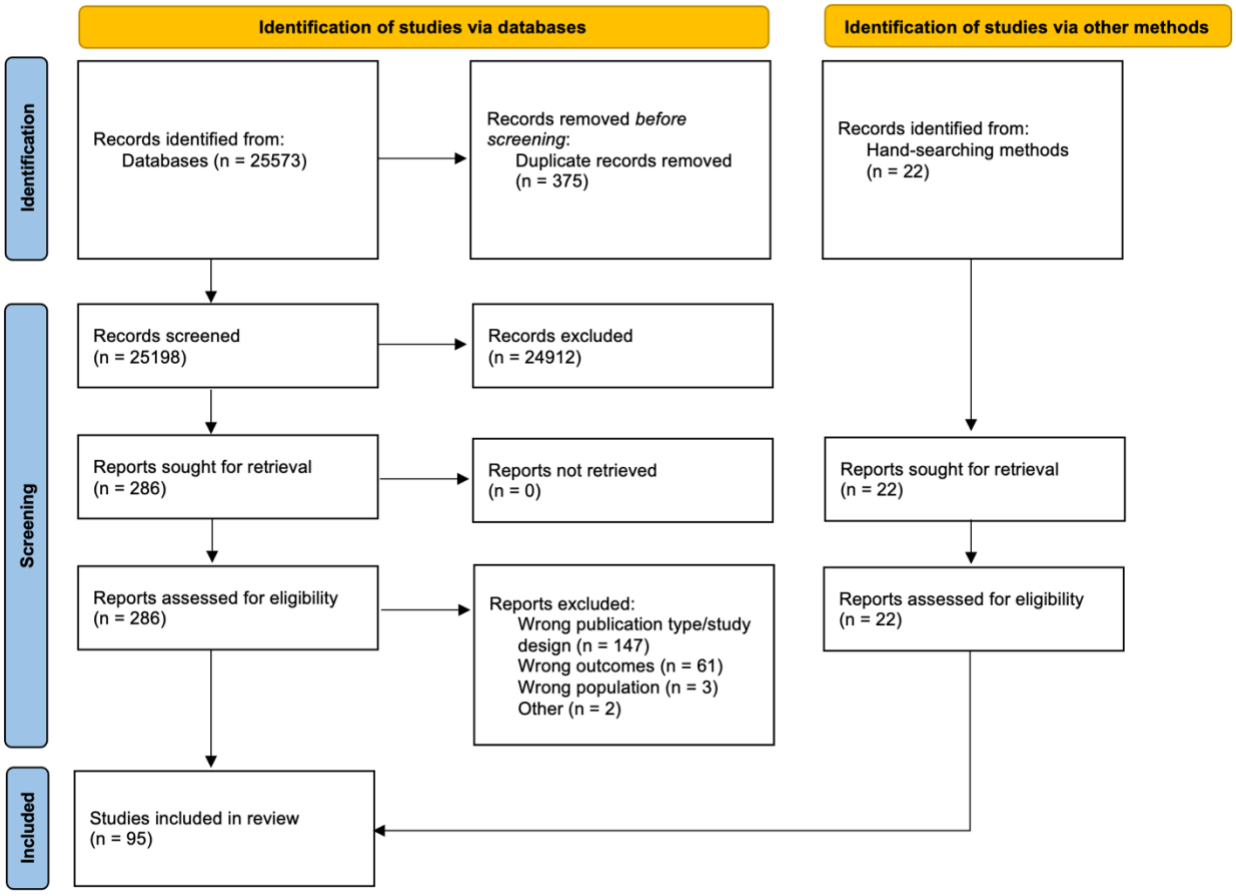


Figure 3.1 PRISMA flowchart of study selection process. Figure adapted from*:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Table 3.1 Summary of Biomarkers by Category, Type of Cognitive Function Measure(s), and Associated Reference(s)

Abbreviations: ANC = absolute neutrophil count; APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; CBC = complete blood count; CD = cluster of differentiation; COMT = catechol-O-methyltransferase; CRP= c-reactive protein; DNA = deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; GM-CSF = granulocyte-macrophage colony stimulating factor; HOMA2-IR = homeostatic model assessment two of insulin resistance; IFN = interferon; IGF = insulin-like growth factor; IL = interleukin; MCP = monocyte chemoattractant protein; mGPS = Glasgow Prognostic Score; MIF = macrophage migration inhibiting factor; R = receptor; RBC = red blood cell; T3= triiodothyronine 3; T4 = thyroxine 4; TNF = tumor necrosis factor; TRACP5A Tartrate-resistant acid phosphatase 5a; TSH = thyroid stimulating hormone; VEGF = vascular endothelial growth factor; WBC = white blood cell

Specific biomarker(s)	Studies that used a subjective measure(s)	Studies that used an objective measure(s)	Studies that used subjective and objective measures
Genetic			
APOE	(Lengacher et al., 2015; McDonald et al., 2013; Merriman et al., 2019)	(Ahles et al., 2014; Ahles et al., 2003; Amidi et al., 2017; Bender et al., 2018; Gonzalez et al., 2015; Koleck et al., 2014)	(Cheng et al., 2016; Dhillon et al., 2019; Mandelblatt et al., 2014; Sales et al., 2019; Vardy et al., 2014; Vardy et al., 2015)
BDNF	(Lengacher et al., 2015; Yap et al., 2021)	(Barratt et al., 2015)	(Cheng et al., 2016; Ng et al., 2016; Yap et al., 2020)
Cytokine genes	(Bower et al., 2013; Cameron et al., 2021; Merriman et al., 2014a; Merriman et al., 2014b)	-	(Chae et al., 2016)
COMT	(Lengacher et al., 2015)	(Barratt et al., 2015)	(Cheng et al., 2016)
Other genes	(Lengacher et al., 2015; Merriman et al., 2019)	(Barratt et al., 2015; Bender et al., 2018; Gonzalez et al., 2015; Koleck et al., 2017; Koleck et al., 2016)	(Chan et al., 2019)
Immune-related			
IL-1	-	(Meyers et al., 2005)	-
IL-1β	(Derry et al., 2015; Ishikawa et al., 2012; Toh et al., 2020; Yap et al., 2021)	(Henneghan et al., 2020; Khan et al., 2016; Tobias et al., 2015)	(Bernstein et al., 2018; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Kesler et al., 2013; Mulder et al., 2014; Vardy et al., 2014;

Specific biomarker(s)	Studies that used a subjective measure(s)	Studies that used an objective measure(s)	Studies that used subjective and objective measures
			Vardy et al., 2015; Zhao et al., 2020)
IL-1ra	(Ishikawa et al., 2012; Pomykala et al., 2013)	(Hoogland et al., 2021; Meyers et al., 2005; Patel et al., 2015)	(Ganz et al., 2013; Hoogland et al., 2019; Zuniga and Moran, 2018)
IL-2	(Ishikawa et al., 2012; Toh et al., 2020; Yap et al., 2021)	(Henneghan et al., 2020)	(Bernstein et al., 2018; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
IL- 4	(Ishikawa et al., 2012; Toh et al., 2020; Yap et al., 2021)	(Henneghan et al., 2020; Tobias et al., 2015)	(Bernstein et al., 2018; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015; Zhao et al., 2020)
IL-5	(Ishikawa et al., 2012)	(Henneghan et al., 2020)	(Henneghan et al., 2021; Henneghan et al., 2018; Mulder et al., 2014)
IL-6	(Boland et al., 2013; Chou et al., 2016; Derry et al., 2015; Ishikawa et al., 2012; Janelsins et al., 2012; Pomykala et al., 2013; Toh et al., 2020; Yap et al., 2021; Zimmer et al., 2018)	(Amidi et al., 2017; Carlson et al., 2018; Henneghan et al., 2020; Hoogland et al., 2021; Jehn et al., 2015; Khan et al., 2016; Meyers et al., 2005; Patel et al., 2015; Shibayama et al., 2014; Shibayama et al., 2019; Tobias et al., 2015; Williams et al., 2018)	(Amidi et al., 2015; Bernstein et al., 2018; Chae et al., 2016; Cheung et al., 2015; Dhillon et al., 2019; Ganz et al., 2013; Henneghan et al., 2021; Henneghan et al., 2018; Hoogland et al., 2019; Jenkins et al., 2016; Kesler et al., 2013; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015; Zimmer et al., 2015; Zuniga and Moran, 2018)
IL-6R	-	(Williams et al., 2018)	-

Specific biomarker(s)	Studies that used a subjective measure(s)	Studies that used an objective measure(s)	Studies that used subjective and objective measures
IL-7	(Ishikawa et al., 2012)	(Henneghan et al., 2020)	(Henneghan et al., 2021; Henneghan et al., 2018)
IL-8	(Chou et al., 2016; Janelsins et al., 2012; Toh et al., 2020) (Ishikawa et al., 2012; Yap et al., 2021)	(Henneghan et al., 2020; Meyers et al., 2005; Williams et al., 2018)	(Bernstein et al., 2018; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Kesler et al., 2013; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
IL-9	(Ishikawa et al., 2012)	-	-
IL-10	(Ishikawa et al., 2012; Toh et al., 2020; Yap et al., 2021)	(Henneghan et al., 2020; Tobias et al., 2015)	(Bernstein et al., 2018; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Jenkins et al., 2016; Kesler et al., 2013; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
IL-12	(Ishikawa et al., 2012)	(Henneghan et al., 2020)	(Bernstein et al., 2018; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Kesler et al., 2013; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
IL-13	(Ishikawa et al., 2012)	(Henneghan et al., 2020)	(Henneghan et al., 2021; Henneghan et al., 2018)
TNF-α	(Boland et al., 2013; Derry et al., 2015; Ishikawa et al., 2012; Toh et al., 2020; Yap et al., 2021; Zimmer et al., 2018)	(Amidi et al., 2017; Carlson et al., 2018; Henneghan et al., 2020; Meyers et al., 2005; Tobias et al., 2015; Williams et al., 2018)	(Amidi et al., 2015; Bernstein et al., 2018; Chae et al., 2016; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Kesler et al., 2013; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015; Zhao et al., 2020)
sTNF-RI	-	(Williams et al., 2018)	-

Specific biomarker(s)	Studies that used a subjective measure(s)	Studies that used an objective measure(s)	Studies that used subjective and objective measures
sTNF-RII	(Pomykala et al., 2013)	(Hoogland et al., 2021; Patel et al., 2015; Williams et al., 2018)	(Carroll et al., 2019; Ganz et al., 2013; Hoogland et al., 2019; Jenkins et al., 2016; Zuniga and Moran, 2018)
IFN- γ	(Ishikawa et al., 2012; Toh et al., 2020; Yap et al., 2021)	(Henneghan et al., 2020)	(Bernstein et al., 2018; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Kesler et al., 2013; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
GM-CSF	(Ishikawa et al., 2012; Toh et al., 2020; Yap et al., 2021)	(Henneghan et al., 2020)	(Bernstein et al., 2018; Cheung et al., 2015; Dhillon et al., 2019; Henneghan et al., 2021; Henneghan et al., 2018; Vardy et al., 2014; Vardy et al., 2015)
IGF-1	(Zimmer et al., 2018)	(Carlson et al., 2018)	-
MCP-1	(Janelsins et al., 2012) (Ishikawa et al., 2012)	(Williams et al., 2018)	(Jenkins et al., 2016)
MIF	(Zimmer et al., 2018)	-	-
VEGF	(Ishikawa et al., 2012)	-	(Jenkins et al., 2016) (Mulder et al., 2014)
Other cytokines	(Ishikawa et al., 2012)	-	-
CRP	(Chou et al., 2016; Oh et al., 2012; Pomykala et al., 2013)	(Amidi et al., 2017; Carlson et al., 2018; Hoogland et al., 2021)	(Amidi et al., 2015; Ganz et al., 2013; Hartman et al., 2019; Hoogland et al., 2019; Mulder et al., 2014; Zuniga and Moran, 2018)
mGPS (CRP + albumin)	(Laird et al., 2016)	-	-
ESR	-	-	(Mulder et al., 2014)
WBC	(Chou et al., 2016)	(Ahles et al., 2008)	-
Monocytes	(Chou et al., 2016)	-	-
Lymphocytes	-	(van der Willik et al., 2018)	-
TRACP5A	(Chou et al., 2016)	-	-
CD cells	-	(Boivin et al., 2020)	-

Specific biomarker(s)	Studies that used a subjective measure(s)	Studies that used an objective measure(s)	Studies that used subjective and objective measures
Neuroendocrine			
Sex hormones	-	(Wefel et al., 2011)	(Bernstein et al., 2018; Dhillon et al., 2019; Klemp et al., 2018; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
TSH	-	(Ahles et al., 2008; Khan et al., 2016; Moon et al., 2014; Mulder et al., 2014)	(Bernstein et al., 2018)
T3	-	(Khan et al., 2016)	(Bernstein et al., 2018)
T4	-	(Khan et al., 2016; Moon et al., 2014)	(Bernstein et al., 2018)
Cortisol	-	(Amidi et al., 2017)	(Amidi et al., 2015)
HOMA2-IR	-	-	(Hartman et al., 2019)
Dehydroepiandrosterone	-	-	(Toh et al., 2019)
Common laboratory tests			
Hemoglobin	(Askren et al., 2014)	(Ahles et al., 2008; Boivin et al., 2020; Castelli et al., 2014; Castelli et al., 2017; Jacobsen et al., 2004; Jehn et al., 2015; Mancuso et al., 2006; Massa et al., 2006; Meyers et al., 2005; Tchen et al., 2003; Vearncombe et al., 2009)	(Bernstein et al., 2018; Cruzado et al., 2014; Dhillon et al., 2019; Hedayati et al., 2012; Iconomou et al., 2008; Kim et al., 2015; Vardy et al., 2014; Vardy et al., 2015)
Creatinine	-	-	(Bernstein et al., 2018; Dhillon et al., 2019; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
Liver function tests	-	-	(Bernstein et al., 2018; Dhillon et al., 2019; Mulder et al., 2014; Vardy et al., 2014; Vardy et al., 2015)
Clotting-related	-	-	(Dhillon et al., 2019; Vardy et al., 2014; Vardy et al., 2015)
ANC	-	(van der Willik et al., 2018)	(Kim et al., 2015)
CBC	-	(Boivin et al., 2020)	(Mulder et al., 2014)

Specific biomarker(s)	Studies that used a subjective measure(s)	Studies that used an objective measure(s)	Studies that used subjective and objective measures
RBC	-	(Ahles et al., 2008)	-
Platelets	-	(Ahles et al., 2008; van der Willik et al., 2018)	-
B1	-	-	(Bernstein et al., 2018)
B12	-	(Ahles et al., 2008)	(Mulder et al., 2014)
Folate	-	(Ahles et al., 2008)	(Bernstein et al., 2018)
Vitamin D3	(Koole et al., 2020)	-	-
Other			
BDNF levels	(Yap et al., 2021; Zimmer et al., 2018)	(Jehn et al., 2015; Palmer et al., 2020)	(Hartman et al., 2019; Jenkins et al., 2016; Tong et al., 2018; Yap et al., 2020; Zimmer et al., 2015)
Neurofilament proteins	-	(Argyriou et al., 2021; Liu et al., 2020)	(Natori et al., 2015)
Carcinoembryonic antigen	-	-	(Vardy et al., 2014; Vardy et al., 2015)
Lactate dehydrogenase	-	(Wefel et al., 2014; Wefel et al., 2011)	(Mulder et al., 2014)
Human chorionic gonadotropin	-	(Wefel et al., 2014; Wefel et al., 2011)	-
Alpha-fetoprotein	-	(Wefel et al., 2014; Wefel et al., 2011)	-
Neuronal antibodies	-	(Bartels et al., 2019)	-
Mitochondrial DNA	-	-	(Chae et al., 2018)
Total RNA gene expression	(Oppegaard et al., 2021)	-	-
Amyloid β-40, amyloid β-42, tau	-	(Henneghan et al., 2020)	-
Tropomyosin kinase B	-	(Palmer et al., 2020)	-
Telomerase	-	-	(Carroll et al., 2019)
Telomere length	-	(Alhareeri et al., 2020)	(Carroll et al., 2019)
DNA damage	-	-	(Carroll et al., 2019)
CpG methylation levels	-	(Yang et al., 2020)	-
CpG probes	(Yao et al., 2019)	-	-
Carotenoids	-	-	(Zuniga and Moran, 2018)

Table 3.2 Reported Associations Between Biomarkers and Better or Worse Cognitive Function*

*This table is not an exhaustive list of significant findings from this review as the complexity of some findings are beyond the scope of this summary.

Abbreviations: Abbreviations: *ANKK1* = ankyrin repeat and kinase domain containing 1; APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; CD = cluster of differentiation; COMT = catechol-O-methyltransferase; CRP= c-reactive protein; DNA = deoxyribonucleic acid; *DNMT1* = DNA methyltransferase 1; ESR = erythrocyte sedimentation rate; *ERCC5* = excision repair 5, endonuclease*; GNB3* = G protein subunit beta 3; IGF = insulin-like growth factor; IL = interleukin; MCP = monocyte chemoattractant protein; mGPS = Glasgow Prognostic Score; *MTHFR* = methylenetetrahydrofolate reductase; *MYD88* = MYD88 innate immune signal transduction adaptor*;* R = receptor; *SLC6A4* = solute carrier family 6 member 4;T_4 = thyroxine 4; TNF = tumor necrosis factor; TRACP5A Tartrate-resistant acid phosphatase 5a; *VMP1/MIR21* = vacuole membrane protein-1/microRNA 21*;* WBC = white blood cell

Associated with Better Cognitive Function	Associated with Worse Cognitive Function
Genetic	
APOE (rs429358, ε4 allele)	*APOE* (ε4 allele)
SNPs in: *COMT, BDNF, ANKK1, MTHFR, SLC6A4, MYD88, GNB3, DNMT1*	SNPs in: *COMT, IL1* R1, *IL6, TNF-α, ERCC5, GNB3*
	↑ Additive genetic risk score across SNPs in three genes *(TNF*-308, *IL6*-174, and *ILβ*-511)
Immune-related	
↑ IL-4, ↑ IL-8	↑ IL-1β, ↑ IL-2, ↑ IL-4, ↑ IL-6, ↑ IL-8, ↑ TNF
	↓ IGF-1, ↓ MCP-1
	↑ CRP
	↑ CRP + ↓ albumin (i.e., mGPS)
	↓ WBC, ↓ Monocytes, ↑ Neutrophils,
	↑ ESR
	↑ TRACP5a
	↑ CD4+ and CD8+
Neuroendocrine	
↑ Free T_4	↑ Cortisol
↑ Dehydroepiandrosterone	↓ Estradiol
Common laboratory tests	
↑ Hemoglobin	
Other	
	↓ BDNF
	↓ Tropomyosin kinase B
	Immunoglobulin antibody positive
	↑ Leukocyte DNA damage
	↓ Telomerase activity
	↑ Methylation levels of cg16936953 *VMP1/MIR21*

Table 3.3 Directions for Future Research on Biomarkers for Cancer-Related Cognitive Impairment (CRCI)

Study design(s)
• Conduct validation studies of biomarkers associated with CRCI • Determine which demographic and clinical characteristics are risk factors for CRCI that may warrant inclusion as covariates in future biomarker studies • Determine if tumor-specific and treatment-specific factors are associated with different biomarkers for CRCI
Measures of cognitive function
• Determine the most valid and reliable subjective and objective measures of CRCI for biomarker discovery • Establish standardized scoring procedures for CRCI measures and associated diagnostic criteria • Identify subjective and objective measures of CRCI, with established diagnostic criteria, that are sensitive to change, feasible for use in clinical and research settings and correlate with biomarkers • Determine if specific subjective and/or objective measures of CRCI are associated with common and/or distinct biomarkers
Selection of biomarkers
• Determine which biomarkers are sensitive and specific for acute versus persistent CRCI • Determine which CRCI biomarkers can be used for risk assessment, diagnosis, prognosis, monitoring, and/or evaluation of the efficacy/effectiveness of interventions
Development of biomarkers
• Evaluate if a single or a combination of biomarkers is more sensitive and/or specific to determine the underlying mechanisms for CRCI • Evaluate if a single or a combination of biomarkers provides more information for risk assessment, diagnosis, prognosis, monitoring, and/or evaluation of the efficacy/effectiveness of interventions for CRCI • Determine the optimal timing for specimen collection depending on intended purpose of the biomarker

Appendix 3.1 Search completed 20 October 2021

Summary:

TOTAL citations retrieved = 10, 858
Duplicates removed (in Endnote) = 449
Citations entered into Covidence = 10 409
Duplicates removed (in Covidence) = 375
Citations for title/abstract screening in Covidence = 10 086

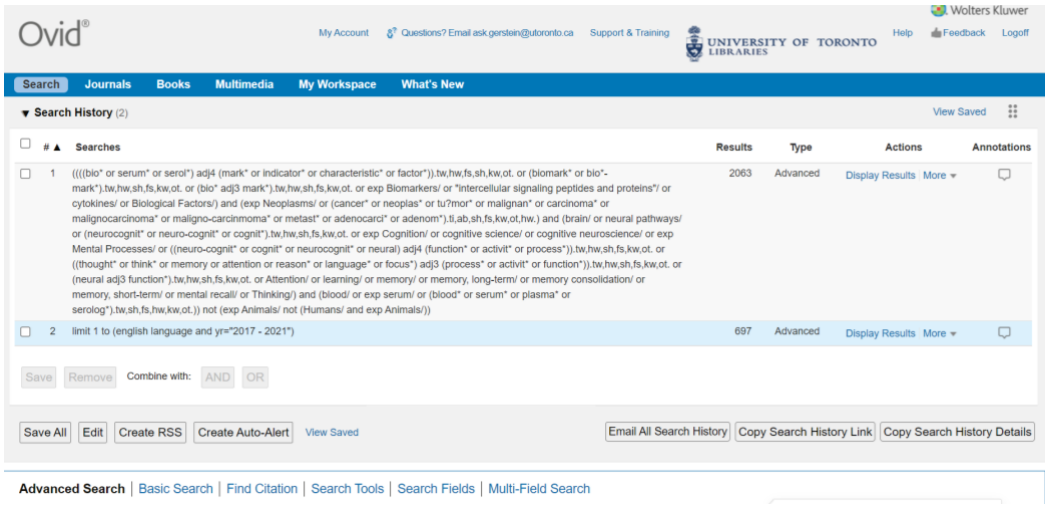
Details by database:

MEDLINE: http://resource.library.utoronto.ca/a-z/more_info.cfm?id=2590&more=1

- Select: **Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present**.

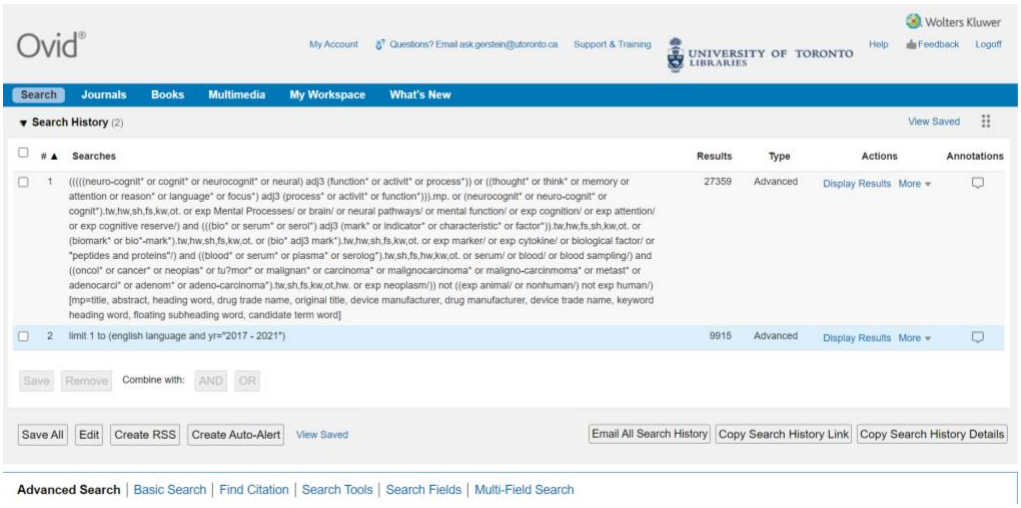
- ((((bio* or serum* OR serol*) adj4 (mark* or indicator* or characteristic* OR factor*)).tw,hw,fs,sh,kw,ot. OR (biomark* OR bio*-mark*).tw,hw,sh,fs,kw,ot OR (bio* adj3 mark*).tw,hw,sh,fs,kw,ot OR exp Biomarkers/ OR "intercellular signaling peptides and proteins"/ or cytokines/ OR Biological Factors/) AND (exp Neoplasms/ OR (cancer* or neoplas* or tu?mor* or malignan* or carcinoma* or malignocarcinoma* or maligno-carcinmoma* or metast* or adenocarci* or adenom*).ti,ab,sh,fs,kw,ot,hw) AND (brain/ or neural pathways/ OR (neurocognit* or neuro-cognit* or cognit*).tw,hw,sh,fs,kw,ot OR exp Cognition/ OR cognitive science/ or cognitive neuroscience/ OR exp Mental Processes/ OR ((neuro-cognit* or cognit* or neurocognit* OR neural) adj4 (function* or activit* or process*)).tw,hw,sh,fs,kw,ot Or ((thought* or think* or memory or attention or reason* or language* or focus*) adj3 (process* or activit* or function*)).tw,hw,sh,fs,kw,ot OR (neural adj3 function*).tw, hw,sh,fs,kw,ot OR Attention/ OR learning/ or memory/ or memory, long-term/ or memory consolidation/ or memory, short-term/ or mental recall/ Or Thinking/) AND (blood/ or exp serum/ OR (blood* or serum* or plasma* or serolog*).tw,sh,fs,hw,kw,ot.)) NOT (exp Animals/ not (Humans/ and exp Animals/))

- *Limit by date 2017- 2021 and English language:* **Results: 697**



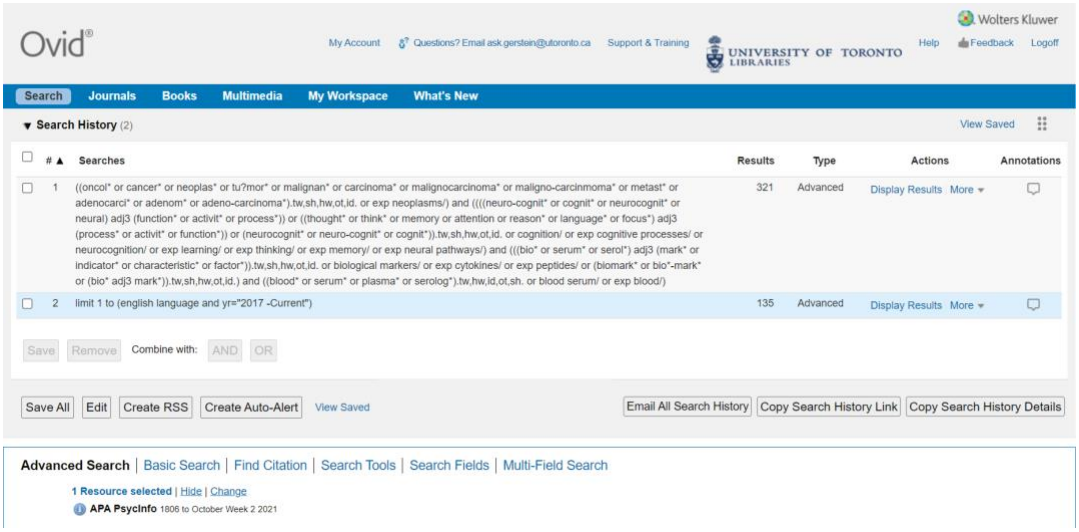
EMBASE: http://simplelink.library.utoronto.ca/url.cfm/189911

- Select: Embase Classic+Embase 1947 to **2021 October 19**
- (((neuro-cognit* or cognit* or neurocognit* or neural) adj3 (function* or activit* or process*)) or ((thought* or think* or memory or attention or reason* or language* or focus*) adj3 (process* or activit* or function*)) or (neurocognit* or neuro-cognit* or cognit*).tw,hw,sh,fs,kw,ot. or exp Mental Processes/ or brain/ or neural pathways/ or mental function/ or exp cognition/ or exp attention/ or exp cognitive reserve/) AND (((bio* or serum* or serol*) adj3 (mark* or indicator* or characteristic* or factor*)).tw,hw,fs,sh,kw,ot. or (biomark* or bio*-mark*).tw,hw,sh,fs,kw,ot. or (bio* adj3 mark*).tw,hw,sh,fs,kw,ot. or exp marker/ or exp cytokine/ or biological factor/ or "peptides and proteins"/) AND ((blood* or serum* or plasma* or serolog*).tw,sh,fs,hw,kw,ot. or serum/ or blood/ or blood sampling/) and ((oncol* or cancer* or neoplas* or tu?mor* or malignan* or carcinoma* or malignocarcinoma* or maligno-carcinmoma* or metast* or adenocarci* or adenom* or adeno-carcinoma*).tw,sh,fs,kw,ot,hw. or exp neoplasm/) not (((exp animal/ or nonhuman/) not exp human/))
- *Limit by date (2017-2021) and English language:* **Results: 9915**



PsycINFO: http://simplelink.library.utoronto.ca/url.cfm/110600

- Select: APA PsycInfo 1806 to **October Week 2 2021**
- ((oncol* or cancer* or neoplas* or tu?mor* or malignan* or carcinoma* or malignocarcinoma* or maligno-carcinmoma* or metast* or adenocarci* or adenom* or adeno-carcinoma*).tw,sh,hw,ot,id. OR exp neoplasms/) AND (((neuro-cognit* or cognit* or neurocognit* or neural) adj3 (function* or activit* or process*)).tw,sh,hw,ot,id OR ((thought* or think* or memory or attention or reason* or language* or focus*) adj3 (process* or activit* or function*)).tw,sh,hw,ot,id OR (neurocognit* or neuro-cognit* or cognit*).tw,sh,hw,ot,id. OR cognition/ or exp cognitive processes/ OR neurocognition/ OR exp learning/ OR exp thinking/ OR exp memory/ OR exp neural pathways/) AND (((bio* or serum* or serol*) adj3 (mark* or indicator* or characteristic* or factor*)).tw,sh,hw,ot,id. OR biological markers/ OR exp cytokines/ OR exp peptides/ OR ((biomark* or bio*-mark*) or (bio* adj3 mark*)).tw,sh,hw,ot,id) AND ((blood* or serum* or plasma* or serolog*).tw,hw,id,ot,sh OR blood serum/ OR exp blood/)
- *Limit by date 2017 - current and English language* **Results: 135**

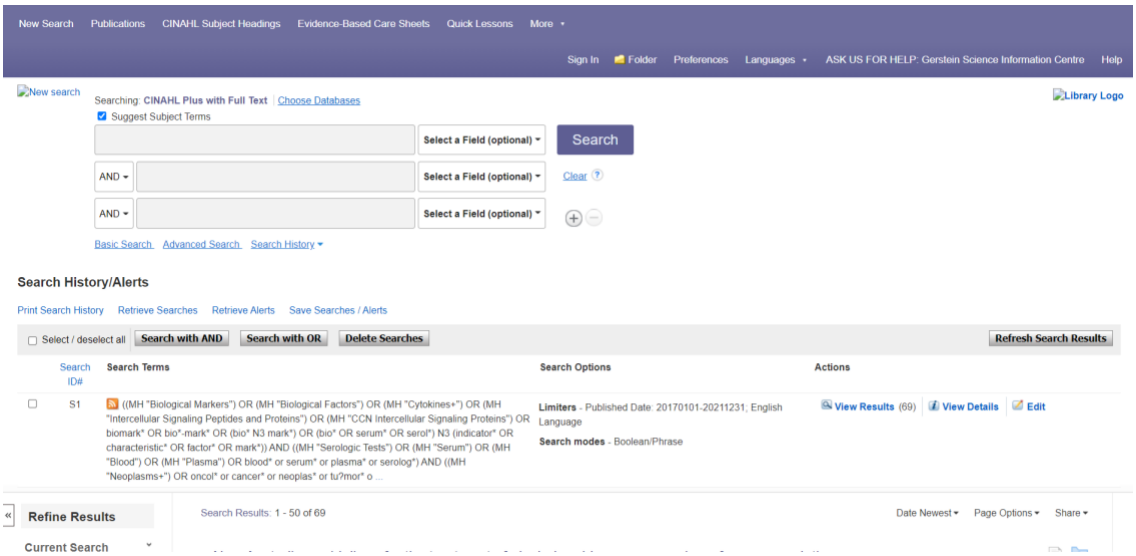


CINAHL: http://simplelink.library.utoronto.ca/url.cfm/54053

- Unclick Suggest Subject Terms at the top of the search bar, then copy and paste the string below:

- ((MH "Biological Markers") OR (MH "Biological Factors") OR (MH "Cytokines+") OR (MH "Intercellular Signaling Peptides and Proteins") OR (MH "CCN Intercellular Signaling Proteins") OR biomark* OR bio*-mark* OR (bio* N3 mark*) OR (bio* OR serum* OR serol*) N3 (indicator* OR characteristic* OR factor* OR mark*)) AND ((MH "Serologic Tests") OR (MH "Serum") OR (MH "Blood") OR (MH "Plasma") OR blood* or serum* or plasma* or serolog*) AND ((MH "Neoplasms+") OR oncol* or cancer* or neoplas* or tu?mor* or malignan* or carcinoma* or malignocarcinoma* or maligno-carcinmoma* or metast* or adenocarci* or adenom* or adeno-carcinoma*) AND ((MH "Cognition+") OR (MH "Mental Processes") OR (thought* or think* or memory or attention or reason* or language* or focus*) N3 (process* or activit* or function*) OR (neuro-cognit* or cognit* or neurocognit* or neural) N3 (function* or activit* or process*) OR neurocognit* or neuro-cognit* or cognit*)

- *Limit by date 2017 - current and English language* **Results = 69**



CENTRAL: http://simplelink.library.utoronto.ca/url.cfm/55558

Copy each line as is, NOT the number.

ID	Search
#1	MeSH descriptor: [Neoplasms] explode all trees
#2	oncol* or cancer* or neoplas* or tu?mor* or malignan* or carcinoma* or malignocarcinoma* or maligno-carcinmoma* or metast* or adenocarci* or adenom* or adeno-carcinoma*
#3	MeSH descriptor: [Biomarkers] explode all trees
#4	MeSH descriptor: [Intercellular Signaling Peptides and Proteins] explode all trees
#5	MeSH descriptor: [Cytokines] explode all trees
#6	biological factors
#7	(bio* or serum* or serol*) near/4 (mark* or indicator* or characteristic* or factor*)
#8	biomark* or bio*-mark*
#9	bio* near/3 mark* biomark* or bio*-mark*
#10	MeSH descriptor: [Brain] explode all trees
#11	MeSH descriptor: [Neural Pathways] explode all trees
#12	MeSH descriptor: [Cognition] explode all trees
#13	MeSH descriptor: [Mental Processes] explode all trees
#14	neurocognit* or neuro-cognit* or cognit*
#15	(neuro-cognit* or cognit* or neurocognit* or neural) near/4 (function* or activit* or process*)
#16	(thought* or think* or memory or attention or reason* or language* or focus*) near/3 (process* or activit* or function*)
#17	neural near/3 function*
#18	MeSH descriptor: [Learning] explode all trees
#19	MeSH descriptor: [Memory] explode all trees
#20	MeSH descriptor: [Mental Recall] explode all trees
#21	MeSH descriptor: [Thinking] explode all trees
#22	MeSH descriptor: [Serum] explode all trees
#23	MeSH descriptor: [Blood] explode all trees
#24	blood* or serum* or plasma* or serolog*
#25	#1 or #2
#26	#3 or #4 or #5 or #6 or #7 or #8 or #9
#27	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#28	#22 or #23 or #24
#29	#25 and #26 and #27 and #28 Publication Year from 2017 to 2021, in Trials

- *Limit by date 2017 - 2021* **Results = 42**

Date Run: *20/10/2021 20:16:07*
Comment:

ID	*Search*	*Hits*
#1	*MeSH descriptor: [Neoplasms] explode all trees*	*84044*
#2	*oncol* or cancer* or neoplas* or tu?mor* or malignan* or carcinoma* or malignocarcinoma* or maligno-carcinmoma* or metast* or adenocarci* or adenom* or adeno-carcinoma**	*254408*
#3	*MeSH descriptor: [Biomarkers] explode all trees*	*21457*
#4	*MeSH descriptor: [Intercellular Signaling Peptides and Proteins] explode all trees*	*28279*
#5	*MeSH descriptor: [Cytokines] explode all trees*	*20874*
#6	*biological factors*	*7326*
#7	*(bio* or serum* or serol*) near/4 (mark* or indicator* or characteristic* or factor*)*	*21939*
#8	*biomark* or bio* mark**	*66382*
#9	*bio* near/3 mark* biomark* or bio* mark**	*38703*
#10	*MeSH descriptor: [Brain] explode all trees*	*12122*
#11	*MeSH descriptor: [Neural Pathways] explode all trees*	*865*
#12	*MeSH descriptor: [Cognition] explode all trees*	*10939*
#13	*MeSH descriptor: [Mental Processes] explode all trees*	*45450*
#14	*neurocognit* or neuro-cognit* or cognit**	*90646*
#15	*(neuro-cognit* or cognit* or neurocognit* or neural) near/4 (function* or activit* or process*)*	*27786*
#16	*(thought* or think* or memory or attention or reason* or language* or focus*) near/3 (process* or activit* or function*)*	*11525*
#17	*neural near/3 function**	*610*
#18	*MeSH descriptor: [Learning] explode all trees*	*17110*
#19	*MeSH descriptor: [Memory] explode all trees*	*7748*
#20	*MeSH descriptor: [Mental Recall] explode all trees*	*2442*
#21	*MeSH descriptor: [Thinking] explode all trees*	*7340*
#22	*MeSH descriptor: [Serum] explode all trees*	*884*
#23	*MeSH descriptor: [Blood] explode all trees*	*16128*
#24	*blood* or serum* or plasma* or serolog**	*462327*
#25	*#1 or #2*	*260631*
#26	*#3 or #4 or #5 or #6 or #7 or #8 or #9*	*104070*
#27	*#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21*	*133910*
#28	*#22 or #23 or #24*	*465224*
#29	*#25 and #26 and #27 and #28 Publication Year from 2017 to 2021, in Trials*	*42*

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Chapter 4

Adverse Childhood Experiences and Higher Levels of Stress Are Associated with the Co-occurrence of Cancer-Related Cognitive Impairment and Anxiety

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Abstract

Purpose: To identify subgroups of patients with distinct co-occurring CRCI AND anxiety profiles and evaluate for differences in demographic and clinical characteristics, levels of global stress, cancer-specific stress, cumulative life stress, and resilience.

Methods: Patients (n=1332) with a diagnosis of breast, gastrointestinal, gynecological, or lung cancer completed the Attentional Function Index and the Spielberger State Anxiety Inventory six times over two cycles of chemotherapy. Global, cancer-specific, lifetime stress, and resilience were evaluated using Perceived Stress Scale, Impact of Event Scale-Revised, Life Stressor Checklist-Revised, and Connor-Davidson Resilience Scale, respectively. Latent profile analysis was used to identify subgroups of patients with distinct CRCI AND anxiety profiles. Differences were evaluated using parametric and non-parametric tests.

Results: Three classes were identified (i.e., No CRCI and Low Anxiety (57.3%), Moderate CRCI and Moderate Anxiety (34.5%), and High CRCI and High Anxiety (8.2%)). Patients in the Moderate and High classes were younger, more likely to be female, had a lower income and a higher comorbidity burden. All of the stress measures showed a dose response effect (i.e., as the CRCI AND anxiety profile worsened, levels of all three types of stress increased). The two higher symptom classes reported higher occurrence rates for six specific stressors (e.g., emotional abuse, physical abuse, sexual harassment).

Conclusion: Findings suggest that higher levels of co-occurring CRCI AND anxiety are associated with some common risk factors, as well as higher levels of stress and lower levels of resilience. Increased knowledge of modifiable risk factors and sources of stress associated with the co-occurrence of these two symptoms will assist clinicians to identify high risk patients and implement individualized interventions.

Introduction

Both cancer-related cognitive impairment (CRCI) and anxiety are reported by up to 75% of patients and 60% of those who have completed treatment.[1] Each of these symptoms contributes to decrements in multiple domains of quality in life.[2, 3] However, despite their high prevalence rates and negative impact, both symptoms are not managed effectively as part of routine cancer care.[4-6] Additional knowledge of common and distinct characteristics associated with the co-occurrence of CRCI AND anxiety will assist with the identification of higher risk patients and provide potential targets for multi-symptom management interventions.

It has been theorized that anxiety can impact cognitive function and vice versa,[7] therefore, an assessment of the co-occurrence of CRCI AND anxiety in is important. This association may be related to perturbations in shared neuroendocrine mechanisms involved in anxiety and/or stress responses that lead to decrements in cognitive function.[8, 9] In addition, the experience of cognitive symptoms may also provoke emotional responses that can further contribute to the stress response.[2, 10] Because a cancer diagnosis and subsequent treatments are known to be stressful experiences, an evaluation of various types of stress (e.g., perceived stress, cancer-specific stress, cumulative life stress) along with CRCI and anxiety is warranted.

Psychological resilience can be described as an individual's ability to positively adapt to stress.[11] Levels of resilience vary based on a variety of characteristics (e.g., exposure to different life circumstances,[11] levels of self-regulation[12]). However, resilience is a modifiable characteristic, which may support coping and mitigate symptoms of the stress response. In a review of resilience-enhancing interventions in patients with cancer,[13] findings from 22 studies suggest that resilience training may be a useful preventive intervention for patients at increased risk for psychological symptoms. Therefore, levels of resilience warrant consideration when evaluating the relationships among CRCI, anxiety, and stress in patients with cancer.

Review of the literature

In a review that aimed to synthesize the findings from studies that evaluated for associations between subjective and/or objective assessments of CRCI and psychological characteristics in patients with breast cancer,[14] only six of the 19 studies included an evaluation of anxiety.[15-20] Across these studies, higher levels of self-reported CRCI and/or poorer performance on neuropsychological tests were associated with higher levels of anxiety. While informative, only a limited number of demographic and clinical characteristics were included and associations between CRCI and anxiety were evaluated using correlation coefficients. This analytic approach does not allow for an examination of inter-individual variability in the co-occurrence of these two symptoms and associated risk factors.

In the same review,[14] only four of the 19 studies included an evaluation of stress. Across these four studies,[21-24] higher levels of self-reported CRCI and/or poorer performance on neuropsychological tests were associated with higher levels of cancer-specific stress and/or the presence of post-traumatic stress disorder (PTSD). However, other types of stress were not evaluated (e.g., perceived stress). In addition, none of the studies included an evaluation of CRCI, anxiety, stress, and resilience in the same sample.

Five additional studies evaluated for associations between anxiety and stress in patients with cancer.[25-29] In the first study,[28] patients with ovarian cancer who reported a history of early life adversity and/or greater danger-related events in the year prior to their diagnosis were more likely to have persistent anxiety during their first year post-diagnosis. In another study of patients with heterogenous types of cancer,[27] higher levels of anxiety were associated with higher levels of stress. In addition, female patients had higher levels of anxiety and higher rates of PTSD symptoms.

In another study of patients with breast cancer,[25] higher levels of anxiety were associated with higher levels of perceived stress, after controlling for age, years of education, and postmenopausal status. In a study of younger (<50 years old) patients with breast cancer

receiving radiotherapy,[26] higher levels of anxiety were associated with higher levels of perceived stress. In addition, higher levels of anxiety were reported by patients who were <39 years of age, married, and non-religious. In the final study of patients with heterogenous types of cancer receiving radiotherapy,[29] higher levels of anxiety and stress were associated with lower levels of resilience. In addition, compared to male patients, women had higher levels of anxiety and stress and lower resilience scores. While these five studies provide important information on associations between higher levels anxiety and higher levels of stress in patients with cancer, only two studies included patients with heterogenous types of cancer; the types of stress evaluated were limited; only one included an evaluation of resilience; and none included an evaluation of CRCI.

In summary, while the literature suggests positive associations between CRCI and anxiety in patients with cancer,[14, 30] no studies have evaluated for inter-individual differences in the co-occurrence of these two symptoms in the same sample. In addition, while various types of stress are associated with both CRCI and anxiety,[14, 25-29] no studies have evaluated for associations between the co-occurrence of these two symptoms and levels of three common types of stress (i.e., global perceived stress, cancer-specific stress, cumulative life stress) and/or resilience. Therefore, the purposes of this study, in a sample of patients with heterogenous types of cancer receiving chemotherapy (n=1332), were to identify subgroups of patients with distinct co-occurring CRCI AND anxiety profiles and evaluate for differences in demographic and clinical characteristics; levels of global, cancer-specific, cumulative life stress, and resilience; and the occurrence and effect of stressful life events (SLEs). We hypothesized that patients who reported higher levels of CRCI AND anxiety would report higher levels of all three types of stress, a higher occurrence of SLEs, and lower levels of resilience.

Methods

Patients and settings

This study is part of a larger, longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy.[31] Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. The major reason for refusal was being overwhelmed with their cancer treatment.

Study procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 consented to participate. These patients completed measures to assess CRCI and anxiety a total of six times over two chemotherapy cycles (i.e., prior to chemotherapy administration, approximately one week after chemotherapy administration, and approximately two weeks after chemotherapy administration). All of the other measures were completed at enrollment (i.e., prior to the second or third cycle of chemotherapy). A total of 1332 patients were included in this analysis.

Measures

Demographic and clinical measures

Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale,[32] Self-Administered Comorbidity Questionnaire (SCQ),[33] Alcohol Use Disorders Identification Test (AUDIT),[34] and a smoking history questionnaire. The toxicity of each patient's chemotherapy regimen was rated using the MAX2 score.[35] Medical records were reviewed for disease and treatment information.

CRCI measure

Self-reported CRCI was assessed using the Attentional Function Index (AFI),[36] a 16-item instrument designed to assesses an individual's perceived effectiveness in performing daily activities that are supported by attention, working memory, and executive functions (e.g., setting goals, planning, carrying out tasks). A higher total mean score on a 0 to 10 numeric rating scale indicates greater capacity to direct attention.[36] Clinically meaningful cutpoints for attentional function are as follows: <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function.[37] Cronbach's alpha for the AFI was 0.93.

Anxiety measure

The 20-items on the Spielberger State Anxiety Inventory (STAI-S) were rated from 1 to 4.[38] The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. A cutoff score of $\geq$32.2 indicates high levels of state anxiety. Cronbach's alpha for the STAI-S was 0.96.

Stress and resilience measures

The 14-item Perceived Stress Scale (PSS) was used as a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week.[39] Cronbach's alpha for the PSS was 0.85.

The 22-item Impact of Event Scale – Revised (IES-R) was used to measure cancer-specific stress.[40] Patients rated each item based on how distressing each potential difficulty was for them during the past week "with respect to their cancer and its treatment". Three subscales evaluate levels of intrusion, avoidance, and hyperarousal perceived by the patient. Sum scores of $\geq$24 indicate clinically meaningful post traumatic symptomatology and scores of $\geq$33 indicate probable PTSD.[41] Cronbach's alpha for the IES-R total score was 0.92.

The 30-item Life Stressor Checklist-Revised (LSC-R) is an index of lifetime trauma exposure (e.g., being mugged, the death of a loved one, a sexual assault).[42] The total LSC–R score is obtained by summing the total number of events endorsed. If patients endorsed an

event, they were asked to indicate how much that stressor effected their life in the past year. These responses were summed to yield a total “Affected” sum score. In addition, a PTSD sum score was created based on the number of positively endorsed items (out of 21) that reflect the DSM-IV PTSD Criteria A for having experienced a traumatic event.

The 10-item Connor-Davidson Resilience Scale (CDRS) evaluates a patient's personal ability to handle adversity (e.g., "I am able to adapt when changes occur"; "I tend to bounce back after illness, injury, or other hardships").[43] Total scores range from 0 to 40, with higher scores indicative of higher self-perceived resilience. The normative adult mean score in the United States is 31.8 ($\pm$5.4).[44] Cronbach's alpha for the CDRS was 0.90.

Data analysis

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using the Statistical Package for the Social Sciences (SPSS) version 28.[45] Latent profile analysis (LPA) was used to identify unobserved subgroups of patients (i.e., latent classes) with distinct CRCI AND anxiety profiles over the six assessments, using the patients’ scores on the AFI and STAI-S. The LPA was performed using MPlus™ Version 8.4.[46]

Estimation was carried out with full information maximum likelihood with standard error and a Chi-square test that are robust to non-normality and non-independence of observations (“estimator=MLR”). Model fit was evaluated to identify the solution that best characterized the unobserved latent class structure with the Bayesian Information Criterion (BIC),[47] Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR), entropy, and latent class percentages that were large enough to be reliable.[48] Missing data were accommodated for with the use of the Expectation-Maximization algorithm.[49]

Differences among the latent classes in demographic and clinical characteristics and stress and resilience measures at enrollment were evaluated using analysis of variance, Kruskal-Wallis, or Chi-square tests. A p-value of $<.05$ was considered statistically significant.

Post hoc contrasts were evaluated using a Bonferroni corrected p-value of <.017 (.05/3 class pairwise comparisons).

Results

Latent profile analysis

Table 4.1 displays the fit indices for the one- through four-class solutions. The 3-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. Although the BIC was smaller for the 4-class than for the 3-class solution, the VLMR was not significant for the 4-class solution, indicating that too many classes were extracted.

As shown in Figure 4.1, of the 1332 patients, 57.3% were classified as No CRCI and Low Anxiety (None), 34.5% as Moderate CRCI and Moderate Anxiety (Both Moderate), and 8.2% as High CRCI and High Anxiety (Both High). Classes were named based on clinically meaningful cutpoints for the AFI[37] and STAI-S.[38] Of note, the No CRCI class reflects a higher AFI score while the High CRCI class reflects a lower AFI score.

Demographic and clinical characteristics

As shown in Table 4.2, compared to the None class, the other two classes were younger; more likely to self-report Hispanic, Mixed, or other ethnicity; less likely to be married or partnered; less likely to be employed; and reported a lower annual household income. Compared to the None class, the Both Moderate class was more likely to be female; live alone; have childcare and eldercare responsibilities; and had a higher MAX2 score. Compared to the None class, the Both High class was less likely to exercise on a regular basis and more likely to self-report a diagnosis of ulcer or stomach disease or kidney disease. Significant differences among the latent classes for KPS scores (i.e., None > Both Moderate > Both High); number of comorbidities; SCQ scores; and a self-reported diagnosis of depression and back pain (i.e., None < Both Moderate < Both High) followed similar patterns.

Stress and resilience

Significant differences among the latent classes in PSS total, IES-R total, IES-R subscale (i.e., intrusion, avoidance, hyperarousal), LSC-R total, and LSC-R affected sum and PTSD sum scores followed the same pattern (i.e., None < Both Moderate < Both High; Table 4.3). Significant differences among the latent classes in CDRS scores were as follows: None > Both Moderate > Both High.

Occurrence of stressors

As shown in Table 4.3, compared to the None class, the other two classes were more likely to report the occurrence of emotional abuse; sexual harassment; physical abuse at ≥16 years; forced to touch at <16 years; and serious physical or mental illness (not cancer). Compared to the None class, the Both Moderate class was more likely to report forced sex at <16 years; having been in jail; and having seen a robbery/mugging. Compared to the None class, the Both High class was more likely to report family violence in childhood; physical neglect; physical abuse at <16 years; forced to touch at <16 years; forced sex at ≥16 years; and having a family member in jail. Differences among the latent classes in the occurrence of serious money problems were as follows: None < Both Moderate < Both High.

Effect of the stressors

As shown in Table 4.5, compared to the None class, the other two classes reported higher effect scores for having been in a serious disaster; having been separated or divorced; having serious money problems; and having an abortion or miscarriage. Compared to the None class, Both Moderate class reported higher effect scores for physical abuse at <16 years; forced to touch at <16 years; having separated or divorced parents; and having had a serious physical or mental illness (not cancer). Compared to the None class, the Both High class reported higher effect scores for family violence in childhood; having seen a serious accident; having a serious accident or injury; having a family member jailed; and having cared for someone with a severe physical or mental handicap. Significant differences among the latent classes for the effects of

emotional abuse; having been in a serious disaster; and the not sudden death of someone close followed a similar pattern (i.e., None < Both Moderate < Both High).

Discussion

This study is the first evaluate for inter-individual differences in the co-occurrence of CRCI AND anxiety in a large sample of patients receiving chemotherapy for four common types of cancer. Based on clinically meeting cutoff scores for the AFI and STAI-S,[37, 38] 42.7% of the patients had moderate or high levels of both of these symptoms. While our study is the first to report prevalence rates for the co-occurrence of distinct CRCI AND anxiety profiles, the combined rate is consistent with previous reports of prevalence rates for the individual symptoms.[50, 51]

In terms of trajectories, regardless of the class, the severity of both CRCI AND anxiety remained relatively stable across the six assessments (Figure 4.1). This finding is consistent with a previous study that found no significant changes in levels of CRCI or anxiety in patients with breast cancer from before to one month after chemotherapy.[20] In contrast, in another study of patients with breast cancer,[18] while CRCI increased from pre-treatment to six months after the receipt of chemotherapy, the severity of anxiety decreased over time. These inconsistent findings may be related to differences in timepoints in the cancer continuum. However, longitudinal studies that evaluate the co-occurrence of these two symptoms across the continuum of cancer care will help to clarify differences in trajectories.

Differences between the independent and joint symptom LPAs

It is worth noting differences in the symptom profiles that emerged when CRCI and anxiety were evaluated as single symptoms compared to the combined analysis. In our LPA of CRCI as a single symptom,[52] a three-class solution was identified (i.e., High (n=495), Moderate (n=368), and Low (n=466)). As shown in Table 4.6, of the 495 patients in the High cognitive function class, 87.1% remained in this class while 12.9% moved into a worse cognitive function class in the joint LPA. Of the 368 patients in the Moderate cognitive function class, 35.1%

remained in this class; 60.1% moved into a better and 4.9% moved into a worse cognitive function class in the joint LPA. Of the 466 patients in the Low cognitive function class, 18.2% remained in this class while 81.8% moved into a better cognitive function class in the joint LPA. Taken together, patients who were identified with a higher level of cognitive function in the single symptom LPA remained in a similar class in the joint LPA. In addition, the majority of patients who were classified as having low or moderate cognitive function in the single symptom LPA were classified as a higher level of cognitive function in the joint LPA.

In our LPA of anxiety as a single symptom,[53] a four-class solution was identified (i.e., Low (n=633), Moderate (n=375), High (n=258), Very High (n=60)). As shown in Table 4.7, of the 633 patients in the Low anxiety class, 99.5% remained in this class in the joint LPA. Of the 375 patients in the Moderate anxiety class, 64.8% remained in this class while 35.2% moved into a no anxiety class in the joint LPA. Of the 258 patients in the High anxiety class, 19% remained in this class while 81% moved into the moderate anxiety class in the joint LPA. Finally, of the 60 patients in the Very High anxiety class, all of them assigned to the High anxiety class in the joint LPA. Taken together, only patients with low and very high levels of anxiety were more likely to be categorized in similar classes in the joint LPA.

Given that this study is the first to do a joint LPA of CRCI AND anxiety, a number of hypotheses for the shifts in profiles of CRCI and anxiety warrant investigation in future studies. First, both measures were done on approximately a weekly basis due to the cycles of chemotherapy. Given that STAI-S assesses “state” anxiety and may be more sensitive to change than the AFI, additional research is warranted that evaluates both symptoms at different intervals over a course of chemotherapy. Equally important, assessments of both symptoms prior to the initiation of chemotherapy may have assisted with interpretation of the LPAs.

Differences in types of stress

While this study is the first to evaluate for differences among three distinct CRCI AND anxiety profiles and three types of stress in the same sample, our findings are consistent with previous reports that higher levels of CRCI[21-24] and anxiety[25-29] are associated with higher levels of various types of stress when these two symptoms were evaluated individually. Of note, for all three of the stress measures (i.e., PSS, IES-R, LSC-R) a dose response effect was observed (i.e., as CRCI AND anxiety profiles worsened, stress scores increased). This finding suggests that these three types of stress may have additive or synergistic effects on patients' levels of CRCI AND anxiety. This hypothesis warrants evaluation with longitudinal assessments of both symptoms and all three measures. These types of studies will provide information on the causal relationships among these variables.

In terms of global stress, while in a study of patients with advanced gastrointestinal cancer, their mean PSS score was 21.8 ($\pm$7.8),[54] our two highest classes score exceeded this value. No clinically meaningful cutoff score for the PSS exists. However, in a study of community dwelling adults,[55] normative mean scores ranged from 20.9 to 25.6. While no studies in patients with cancer were identified, findings from a meta-analysis suggest that higher levels of perceived stress were associated with increased risk for mild cognitive impairment and all-cause dementia.[56] In terms of anxiety, our findings are consistent with previous studies of patients with breast cancer that reported that higher levels of anxiety were associated with higher levels of perceived stress.[25, 26]

In terms of cancer-specific stress, the mean IES-R total score for the Both Moderate class was just below the cutoff for post traumatic symptomatology (23.4 $\pm$12.3) and the mean score for the Both High class indicates probable PTSD (37.4 $\pm$16.7). Of note, across both classes, 28.8% of the patients met the cutoff for PTSD. Our findings are consistent with four studies that reported worse CRCI was associated with higher levels of cancer-specific stress and/or the presence of PTSD.[21-24] In addition, our findings are consistent with a study of patients

with heterogenous types of cancer that reported higher levels of anxiety were associated with higher rates of PTSD symptoms.[27] One potential explanation for these findings is that cognitive impairment, anxiety, and PTSD share common neurobiological mechanisms (e.g., neuroinflammation).[57, 58]

Occurrence and effects of SLEs

Patients in the two worst profiles reported an average of 6.5 and 7.8 SLEs. These rates are similar to a community-based samples of 576 women living in the United States, Colombia, and Hong Kong, whose mean score was 7.0.[59] The occurrence of serious money problems was the only SLE that demonstrated a dose response effect.

Compared to the None class, the occurrence of six SLEs were common to the Both Moderate and Both High classes (Table 5). In addition, compared to the other two classes, the occurrence rates for six SLEs were distinct to the Both High class (i.e., family violence in childhood; physical neglect; physical abuse at <16 years; forced to touch at <16 years; forced sex at ≥16 years; and having had a family member in jail). Of note, emotional abuse, physical abuse ≥16 years, and forced touching <16 years are categorized as adverse childhood experiences (ACEs). No studies were identified that evaluated for associations between CRCI and a history of SLEs. However, in a study of a representative sample of the United States (n = 82,688, ≥45 years),[60] self-reported cognitive decline was associated higher ACE scores, after adjusting for age, gender, race/ethnicity, income, education, employment, diabetes, hypertension, and depression. In addition, a dose response effect was demonstrated for cognitive decline and ACE scores. In terms of anxiety, in a study of patients with ovarian cancer, [28] persistently high anxiety trajectories were found in women who reported exposure to early life adversity.

In terms of the effect of the SLEs, three of them demonstrated a dose response effect (i.e., emotional abuse; been in a serious disaster; the not sudden death of someone close). While previous research focused on the summation of SLEs, a growing body of evidence

suggests that many stressors are multidimensional and that associations exist among traumatic events (e.g., children who are maltreated may experience more than one type of abuse).[61] In addition, ACEs are associated with structural and functional changes in neural stress-regulatory circuits that lead to alterations in self-regulatory abilities and/or stress responses throughout an individual's lifespan.[62, 63]

Differences in resilience

Consistent with our a priori hypothesis, worse CRCI AND anxiety profiles were associated with lower levels of resilience. In fact, resilience scores demonstrated a dose response effect in our sample (i.e., as the symptom profile worsened, resilience scores decreased). The Both Moderate and Both High classes had resilience scores below the normative mean score for adults in the United States.[44] For the Both Moderate class, mean resilience scores are similar to those reported by patients receiving inpatient treatment for gastric cancer.[64] While no studies evaluated for associations between CRCI and resilience in patients receiving chemotherapy, in a study of breast cancer survivors, better performance in the domains of attention, processing speed, and executive function were associated with higher levels of resilience 4 to 9 years after surgery.[65] In terms of anxiety, our findings are similar to a study of patients receiving radiotherapy that reported higher levels of anxiety and stress were associated with lower levels of resilience.[29] Resilience is a dynamic concept because it can be part of an individual's personality (i.e., a trait); a learned behavior; and/or response to stress (i.e., a state).[66] However, resilience is considered a characteristic that can be modified to promote a more successful adaptation to cancer.[67] As noted previously, results from a review that focused on resilience-enhancing interventions suggest that resilience training may be a useful preventive intervention for patients with cancer at increased risk for psychological symptoms.[13]

Demographic and clinical characteristics

As the CRCI and anxiety profiles worsened, five characteristics demonstrated a dose response effect: decreasing functional status score; increasing number of comorbidities; increasing comorbidity burden; and a higher percentage of patients who self-reported diagnoses of depression or back pain. In a study of patients prior to breast cancer surgery,[68] a higher comorbidity burden, a lower functional status score, and a self-reported diagnosis of depression were associated with higher levels of self-reported CRCI. In terms of anxiety, in a study of patients with breast cancer,[69] more comorbidities were a predictor of anxiety. Of note, in a study that evaluated the association between multimorbidity (defined as $\geq$2 physical diseases) and self-reported cognition (i.e., concertation and memory) in a nationally represented, community-based sample of 7,399 individuals in the United Kingdom,[70] multimorbidity was associated with higher rates of concentration and memory complaints. In addition, the regression model demonstrated that stressful life events and any anxiety disorder explained up to 22% and 15% of these associations, respectively.

Compared to the None class, being female was associated with membership in only the Both Moderate class. Our findings are similar to two studies that evaluated either CRCI or anxiety. In a study of 3,108 survivors of types of heterogenous cancer,[51] female gender was a significant predictor of self-reported CRCI. In another study of 10,153 patients with heterogenous types of cancer,[71] females were nearly two times more likely to report clinical levels of anxiety.

Membership in the Both Moderate and Both High classes was associated with an unmarried/unpartnered status, unemployment, and a lower household income. These findings are consistent with a large study of survivors of heterogenous types of cancer that reported that each of these characteristics was associated with the occurrence of self-reported CRCI.[51] In terms of anxiety, in a study of patients with breast cancer,[72] compared to affluent women,

socioeconomically deprived women had higher levels of anxiety. Of note, these characteristics represent some of the most common social determinants of health.

Compared to the None class, the Both High class was less likely to exercise on a regular basis. Exercise is an important intervention to promote cognitive and emotional health.[73] According to a consensus statement from an expert panel,[74] sufficient evidence exists to conclude that aerobic exercise, combined aerobic exercise plus resistance training, and/or resistance training decreases cancer-related anxiety. However, the panel noted that benefits of exercise for CRCI warrant further investigation.

Limitations

Some limitations are worth noting. While CRCI and anxiety were assessed six times over two cycles of chemotherapy, stress, and resilience measures were completed only at enrollment. Therefore, causal relationships between CRCI AND anxiety and various types of stress and/or resilience cannot be determined. Next, CRCI was assessed using a self-report measure. Studies that include objective measures of cognition may elucidate different CRCI AND anxiety profiles. In addition, other factors that may be associated with the co-occurrence of CRCI AND anxiety warrant evaluation. For example, self-regulation is a concept that encompasses a range of emotional, behavioral, and cognitive functions across the lifespan.[75] As noted by Arndt and colleagues,[76] self-regulation is an understudied but potentially important factor in terms of elucidating inter-individual differences in CRCI. Finally, studies that include concurrent evaluation of biomarkers and/or brain activity are needed to identify underlying mechanisms for one and both symptoms.

Conclusions and implications for research

Findings from this study provide novel information about distinct CRCI AND anxiety profiles in patients receiving chemotherapy. A variety of demographic and clinical characteristics were identified that were associated with the co-occurrence of these two symptoms, some of which are modifiable (e.g., optimal treatment of comorbid conditions, exercise). Studies that

evaluate which co-morbid conditions contribute most significantly to the co-occurrence of CRCI AND anxiety, as well as those that investigate the underlying mechanisms for these associations, will provide information that can be used to inform intervention studies. In addition, worse CRCI AND anxiety profiles were associated with higher levels of three common types of stress, exposure to SLEs, and lower levels of resilience. These findings suggest that patients with a significant history of adverse life events and/or trauma may be at an increased risk of a higher symptom burden. Studies are needed that investigate if levels of stress can be modified to reduce the severity of CRCI AND anxiety.

In conclusion, findings from this study provide preliminary evidence for the relationship between CRCI AND anxiety in patients receiving chemotherapy. Further replication of this work will help clinicians identify patients at increased risk for CRCI AND anxiety and initiate timely supportive care referrals. In addition, our findings provide new insights into common risk factors for both CRCI and anxiety that can be targeted in future studies that evaluate multi-symptom management interventions.

Table 4.1 Latent Profile Solutions and Fit Indices for One through Four Classes for the Attentional Function Index and Spielberger State Anxiety Scores Over Six Assessments

Baseline entropy and VLMR are not applicable for the one-class solution

†p< .01; ‡p < .00005

[a]The 3-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. Although the BIC was smaller for the 4-class than for the 3-class solution, the VLMR was not significant for the 4-class solution, indicating that too many classes were extracted.

Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; LL = log-likelihood; n/a = not applicable; ns = not significant, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-36099.12	72314.24	72615.52	n/a	n/a
2 Class	-35102.39	70346.79	70715.59	0.86	1993.46‡
3 Class[a]	-34807.04	69782.09	70218.42	0.87	590.70†
4 Class	-34623.18	69440.35	69944.21	0.81	ns

Table 4.2 Differences in Demographic and Clinical Characteristics at Enrollment Among the CRCI and Anxiety Latent Classes

Abbreviations: CRCI = cancer-related cognitive impairment, CTX = chemotherapy, kg = kilograms, KW = Kruskal Wallis, m^2 = meters squared, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation
[a]Total number of metastatic sites evaluated was 9.

Characteristic	No CRCI and Low Anxiety (1) 57.3% (n=763)	Moderate CRCI and Moderate Anxiety (2) 34.5% (n=460)	High CRCI and High Anxiety (3) 8.2% (n=109)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	58.8 (11.7)	55.0 (13.1)	54.6 (11.8)	F = 16.74, p <.001 1 > 2 and 3
Education (years)	16.3 (3.0)	16.0 (3.0)	16.2 (3.2)	F = 1.65, p = .193
Body mass index (kg/m^2)	26.1 (5.3)	26.2 (6.1)	26.6 (6.1)	F = .463, p = .630
Alcohol Use Disorders Identification Test score	2.9 (2.1)	3.2 (3.0)	2.7 (2.6)	F = 2.68, p = .069
Karnofsky Performance Status score	83.6 (11.5)	76.1 (12.1)	71.1 (11.6)	F = 87.38, p <.001 1 > 2 > 3
Number of comorbid conditions	2.2 (1.3)	2.6 (1.5)	3.2 (1.6)	F = 27.79, p <.001 1 < 2 < 3
Self-administered Comorbidity Questionnaire score	4.9 (2.8)	6.0 (3.4)	7.5 (3.8)	F = 43.56, p <.001 1 < 2 < 3
Time since diagnosis (years)	2.0 (3.7)	2.2 (4.4)	1.4 (3.0)	KW = 1.95, p = .377
Time since diagnosis (years, median)	0.42	0.42	0.42	
Number of prior cancer treatments	1.6 (1.5)	1.7 (1.5)	1.6 (1.5)	F = 0.54, p = .582
Number of metastatic sites including lymph node involvement[a]	1.2 (1.2)	1.3 (1.3)	1.2 (1.2)	F = 1.15, p = .317
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.1)	0.7 (1.0)	F = 1.00, p = .367
MAX2 score	0.17 (0.08)	0.18 (0.08)	0.17 (0.09)	F = 3.27, p = .038 1 < 2
	% (n)	% (n)	% (n)	
Gender (% female)	74.0 (564)	83.5 (384)	81.7 (89)	X^2 = 15.89, p <.001 1 < 2
Self-reported ethnicity				X^2 =13.69, p = .033
Asian or Pacific Islander	12.9 (7)	12.1 (55)	12.0 (13)	NS
Black	7.8 (59)	5.9 (27)	8.3 (9)	NS
Hispanic, Mixed, or Other	8.4 (63)	13.0 (59)	17.6 (19)	1 < 2 and 3
White	70.9 (534)	69.0 (314)	62.0 (67	NS
Married or partnered (% yes)	69.3 (521)	60.0 (271)	50.5 (55)	X^2 = 20.97, p < .001 1 > 2 and 3
Lives alone (% yes)	18.5 (139)	25.3 (115)	27.5 (30)	X^2 =10.22, p = 0.006 1 < 2
Currently employed (% yes)	40.8 (307)	27.4 (125)	28.4 (31)	X^2 = 24.75, p <.001 1 > 2 and 3
Annual household income				KW = 37.75, p <.001 1 > 2 and 3
Less than $30,000	12.4 (83)	23.0 (97)	39.4 (39)	
$30,000 to $70,000	19.9 (134)	24.2 (102)	16.2 (16)	
$70,000 to $100,000	19.2 (129)	15.0 (63)	10.1 (10)	
Greater than $100,000	48.5 (326)	37.8 (159)	34.3 (34)	
Childcare responsibilities (% yes)	19.1 (143)	26.0 (116)	27.8 (30)	X^2 =9.71, p = .008 1 < 2
Elder care responsibilities (% yes)	6.2 (43)	11.1 (46)	7.0 (7)	X^2 = 8.85, p = .012 1 < 2
Past or current history of smoking (% yes)	33.5 (252)	36.4 (164)	43.0 (46)	X^2 = 4.05, p =.132

Characteristic	No CRCI and Low Anxiety (1) 57.3% (n=763)	Moderate CRCI and Moderate Anxiety (2) 34.5% (n=460)	High CRCI and High Anxiety (3) 8.2% (n=109)	Statistics
Exercise on a regular basis (% yes)	73.0 (549)	69.5 (310)	61.5 (64)	$X^2 = 6.45$, p = .040 1 > 3
Specific comorbid conditions				
Heart disease	5.6 (43)	6.3 (29)	3.7 (4)	$X^2 = 1.15$, p = .562
High blood pressure	31.5 (240)	26.7 (123)	34.9 (38)	$X^2 = 4.31$, p = .116
Lung disease	9.8 (75)	12.4 (57)	16.5 (18)	$X^2 = 5.16$, p =.076
Diabetes	8.7 (66)	8.3 (38)	13.8 (15)	$X^2 = 3.45$, p =.178
Ulcer or stomach disease	3.9 (30)	5.2 (24)	10.1 (11)	$X^2 = 7.97$, p = .019 1 < 3
Kidney disease	0.8 (6)	2.0 (9)	3.7 (4)	$X^2 = 7.04$, p = .030 1 < 3
Liver disease	6.7 (51)	6.7 (31)	2.8 (3)	$X^2 = 2.62$, p = .270
Anemia or blood disease	10.6 (81)	13.7 (63)	18.3 (20)	$X^2 = 6.53$, p = .038 No significant pairwise contrasts
Depression	8.9 (68)	28.9 (133)	51.4 (56)	$X^2 = 152.19$, p < .001 1 < 2 < 3
Osteoarthritis	11.7 (89)	12.8 (59)	11.9 (13)	$X^2 = 0.37$, p = .832
Back pain	18.9 (144)	32.0 (147)	47.7 (52)	$X^2 = 55.63$, p<.001 1 < 2 < 3
Rheumatoid arthritis	3.1 (24)	3.0 (14)	3.7 (4)	$X^2 = 0.11$, p = .945
Cancer diagnosis Breast cancer Gastrointestinal cancer Gynecological cancer Lung cancer	 40.0 (305) 32.4 (247) 16.4 (125) 11.3 (86)	 40.4 (186) 28.3 (130) 20.2 (93) 11.1 (51)	 43.1 (47) 26.6 (29) 12.8 (14) 17.4 (19)	$X^2 = 9.58$, p = .143
Prior cancer treatment No prior treatment Only surgery, CTX, or RT Surgery and CTX, or surgery and RT, or CTX and RT Surgery and CTX and RT	 26.2 (194) 40.9 (303) 21.3 (158) 11.6 (86)	 23.0 (103) 43.5 (195) 18.5 (83) 15.0 (67)	 25.0 (27) 42.6 (46) 15.7 (17) 16.7 (18)	$X^2 = 7.19$, p = .304
Metastatic sites No metastasis Only lymph node metastasis Only metastatic disease in other sites Metastatic disease in lymph nodes and other sites	 32.9 (248) 21.0 (158) 22.4 (169) 23.7 (179)	 31.3 (142) 22.3 (101) 19.4 (88) 26.9 (122)	 34.3 (37) 26.9 (29) 18.5 (20) 20.4 (22)	$X^2 = 5.45$, p = .488
Receipt of targeted therapy (% yes)	31.4 (235)	28.0 (126)	23.8 (30)	$X^2 = 1.68$, p = .432
Cycle length 14-day cycle 21-day cycle 28-day cycle	 43.9 (333) 48.4 (367) 7.8 (59)	 39.2 (178) 54.2 (246) 6.6 (30)	 39.3 (42) 54.2 (58) 6.5 (7)	KW = 1.61, p = .448
Emetogenicity of the CTX regimen Minimal/low Moderate High	 18.8 (143) 63.0 (478) 18.2 (138)	 20.2 (92) 58.0 (264) 21.8 (99)	 21.5 (23) 59.8 (64) 18.7 (20)	KW = 0.57, p = .751
Antiemetic regimen None Steroid alone or serotonin receptor antagonist alone Serotonin receptor antagonist and steroid NK-1 receptor antagonist and two other antiemetics	 7.7 (57) 20.4 (152) 49.7 (370) 22.2 (165)	 6.6 (29) 21.8 (96) 45.2 (199) 26.4 (116)	 5.7 (6) 16.0 (17) 43.4 (46) 34.9 (37)	$X^2 = 10.71$, p = .098

Table 4.3 Differences in Stress and Resilience Measures at Enrollment Among the CRCI and Anxiety Latent Classes

Abbreviations: CDRS = Connor Davidson Resilience Scale; CRCI = cancer-related cognitive impairment; IES-R = Impact of Event Scale - Revised; LSC-R = Life Stressor Checklist -Revised; PSS = Perceived Stress Scale; PTSD = post-traumatic stress disorder; SD = standard deviation

[a]Clinically meaningful cutoff scores or range of scores

Measures[a]	**No CRCI and Low Anxiety (1) 57.3% (n=763)**	**Moderate CRCI and Moderate Anxiety (2) 34.5% (n=460)**	**High CRCI and High Anxiety (3) 8.2% (n=109)**	**Statistics**
	Mean (SD)	Mean (SD)	Mean (SD)	
PSS total score (0 to 56)	14.3 (6.1)	22.8 (6.3)	30.2 (7.3)	F= 451.64, p<.001 1 < 2 < 3
IES-R total sum score (≥24)	13.4 (8.9)	23.4 (12.3)	37.4 (16.7)	F= 278.55, p<.001 1 < 2 < 3
IES-R intrusion	0.6 (0.5)	1.2 (0.7)	1.9 (0.8)	F= 244.73, p<.001 1 < 2 < 3
IES-R avoidance	0.8 (0.6)	1.1 (0.7)	1.5 (0.9)	F= 85.07, p<.001 1 < 2 < 3
IES-R hyperarousal	0.4 (0.4)	0.9 (0.6)	1.7 (0.9)	F= 333.84, p<.001 1 < 2 < 3
LSC-R total score (range 0-30)	5.6 (3.5)	6.5 (4.4)	7.8 (4.5)	F= 14.34, p<.001 1 < 2 < 3
LSC-R affected sum (range 0-150)	9.8 (8.5)	13.9 (12.6)	19.4 (14.2)	F= 40.09, p<.001 1 < 2 < 3
LSC-R PTSD sum (range 0-21)	2.7 (2.7)	3.5 (3.3)	4.8 (3.7)	F= 23.07, p<.001 1 < 2 < 3
CDRS total score (range 0-40)	32.5 (5.1)	27.4 (6.4)	24.4 (6.7)	F= 163.95, p<.001 1 > 2 > 3

Table 4.4 Differences Among the Cancer-Related Cognitive Impairment (CRCI) AND Anxiety Latent Classes in in the Percentage of Patients Exposed to Specific Stressors

Stressful Life Event	No CRCI and Low Anxiety (1) 57.3% (n=763)	Moderate CRCI and Moderate Anxiety (2) 34.5% (n=460)	High CRCI and High Anxiety and (3) 8.2% (n=109)	Statistics
	% (n)	% (n)	% (n)	
Interpersonal Violence, Abuse, and Neglect Stressors				
Family violence in childhood	20.9 (129)	26.5 (87)	34.2 (27)	X^2= 8.90, p= .012 1 < 3
Emotional abuse	17.1 (106)	26.2 (87)	38.8 (31)	X^2= 25.50, p <.001 1 < 2 and 3
Physical neglect	3.2 (20)	6.4 (21)	11.3 (9)	X^2= 12.42, p= .002 1 < 3
Sexual harassment	15.3 (94)	21.6 (71)	26.9 (21)	X^2= 10.10, p= .006 1 < 2 and 3
Physical abuse – <16 years	12.5 (77)	15.5 (51)	23.8 (19)	X^2= 7.85, p= .020 1 < 3
Physical abuse – ≥16 years	10.5 (65)	17.3 (57)	20.8 (16)	X^2= 12.34, p= .002 1 < 2 and 3
Forced to touch – <16 years	9.1 (56)	14.7 (48)	18.8 (15)	X^2= 10.71, p= .005 1 < 2 and 3
Forced to touch – ≥16 years	4.4 (27)	7.3 (24)	13.9 (11)	X^2= 12.47, p= .002 1 < 3
Forced sex – <16 years	3.1 (19)	6.7 (22)	4.9 (4)	X^2= 6.70, p= .035 1 < 2
Forced sex – ≥16 years	5.4 (33)	7.0 (23)	12.3 (10)	X^2= 6.03, p= .049 1 < 3
Other Stressors				
Been in a serious disaster	42.1 (260)	38.4 (127)	41.5 (34)	X^2= 1.28, p= .527
Seen serious accident	34.5 (213)	28.4 (95)	36.6 (30)	X^2= 4.24, p= .120
Had serious accident or injury	23.1 (142)	25.0 (82)	29.6 (24)	X^2= 1.80, p= .407
Jail (family member)	18.9 (117)	20.9 (69)	32.1 (26)	X^2= 7.66, p= .022 1 < 3
Jail (self)	4.5 (28)	10.2 (34)	9.9 (8)	X^2= 12.47, p= .002 1 < 2
Foster care or put up for adoption	2.2 (14)	2.4 (8)	3.7 (3)	X^2= .645, p= .724
Separated/divorced (parents)	20.0 (124)	24.6 (82)	23.5 (19)	X^2= 2.92, p= .233
Separated/divorced (self)	35.4 (220)	35.3 (118)	45.0 (36)	X^2= 2.98, p= .226
Serious money problems	15.2 (94)	23.4 (78)	42.0 (34)	X^2= 35.86, p <.001 1 < 2 < 3
Had serious physical or mental illness (not cancer)	15.3 (95)	23.6 (79)	28.0 (23)	X^2= 14.57, p <.001 1 < 2 and 3
Abortion or miscarriage	44.7 (209)	43.0 (120)	46.3 (31)	X^2= .316, p= .854
Separated from child	1.8 (11)	2.2 (7)	3.9 (3)	X^2= 1.45, p= .484

Stressful Life Event	No CRCI and Low Anxiety (1) 57.3% (n=763)	Moderate CRCI and Moderate Anxiety (2) 34.5% (n=460)	High CRCI and High Anxiety and (3) 8.2% (n=109)	Statistics
	% (n)	% (n)	% (n)	
Care for child with handicap	3.8 (23)	4.0 (13)	3.8 (3)	X^2= 0.02, p= .988
Care for someone with severe physical or mental handicap	22.3 (136)	26.7 (87)	31.3 (25)	X^2= 4.42, p= .110
Death of someone close (sudden)	50.2 (310)	46.7 (151)	53.2 (42)	X^2= 1.53, p= .465
Death of someone close (not sudden)	79.4 (483)	80.2 (259)	71.3 (57)	X^2= 3.24, p= .197
Seen robbery/mugging	18.9 (117)	27.8 (92)	22.5 (18)	X^2= 10.02, p= .007 1 < 2
Been robbed/mugged	25.7 (159)	27.9 (91)	28.4 (23)	X^2= 0.66, p= .718

Table 4.5 Differences Among the CRCI and Anxiety Latent Classes in the Effect of Stressor On Life In The Past Year[a]

Abbreviation: CRCI = cancer-related cognitive impairment, KW = Kruskal Wallis, SD = standard deviation
*Range = 1 "not at all" to 5 "extremely"
[a]These data are reported for those patients who reported the occurrence of the stressor (see Table 4.4)

Stressful Life Event*	No CRCI and Low Anxiety (1)	Moderate CRCI and Moderate Anxiety (2)	High CRCI and High Anxiety (3)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Interpersonal violence, abuse, and neglect stressors				
Family violence in childhood	1.7 (1.0)	2.1 (1.3)	2.3 (1.2)	KW= 10.42, p= .005 1 < 3
Emotional abuse	2.2 (1.3)	2.8 (1.3)	3.4 (1.1)	KW= 23.52, p<.001 1 < 2 < 3
Physical neglect	2.4 (1.5)	3.0 (1.2)	3.1 (1.4)	KW= 2.17, p= .337
Sexual harassment	1.4 (0.9)	1.6 (1.0)	1.6 (1.0)	KW= 3.24, p= .197
Physical abuse – <16 years	1.7 (1.1)	2.3 (1.4)	2.0 (1.1)	KW= 8.69, p= .013 1 < 2
Physical abuse – ≥16 years	1.7 (1.1)	2.0 (1.2)	2.3 (1.4)	KW= 4.22, p= .121
Forced to touch – <16 years	1.6 (1.1)	2.4 (1.4)	2.6 (1.7)	KW= 10.69, p= .005 1 < 2
Forced to touch – ≥16 years	1.6 (.8)	2.3 (1.5)	1.8 (1.1)	KW= 2.26, p= .323
Forced sex – <16 years	1.7 (1.2)	2.2 (1.3)	2.3 (1.5)	KW= 1.86, p= .395
Forced sex – ≥16 years	1.6 (1.0)	2.0 (1.4)	1.7 (1.3)	KW= 1.32, p= .517
Other stressors				
Been in a serious disaster	1.2 (0.7)	1.5 (0.9)	1.8 (0.9)	KW= 28.19, p<.001 1 < 2 < 3
Seen serious accident	1.4 (0.8)	1.5 (0.8)	2.0 (1.1)	KW= 15.47, p<.001 1 and 2 < 3
Had serious accident or injury	1.5 (0.9)	1.6 (1.1)	2.1 (1.2)	KW= 10.64, p= .005 1 < 3
Jail (family member)	1.7 (1.2)	2.0 (1.4)	2.5 (1.6)	KW= 8.22, p= .016 1 < 3
Jail (self)	1.6 (1.1)	2.1 (1.4)	1.0 (0.0)	KW= 6.04, p= .049 no significant pairwise contrasts
Foster care or put up for adoption	2.2 (1.4)	2.9 (1.7)	1.7 (1.2)	KW= 1.63, p= .443
Separated/divorced (parents)	1.6 (1.0)	2.0 (1.2)	2.0 (1.5)	KW= 6.73, p= .035 1 < 2
Separated/divorced (self)	1.8 (1.2)	2.4 (1.5)	2.7 (1.4)	KW= 20.37, p< .001 1 < 2 and 3
Serious money problems	2.1 (1.5)	3.1 (1.7)	3.5 (1.5)	KW= 22.50, p< .001 1 < 2 and 3
Had serious physical or mental illness (not cancer)	2.1 (1.3)	2.8 (1.4)	2.5 (1.2)	KW= 10.37, p= .006 1 < 2

Stressful Life Event*	No CRCI and Low Anxiety (1)	Moderate CRCI and Moderate Anxiety (2)	High CRCI and High Anxiety (3)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Abortion or miscarriage	1.4 (0.9)	1.6 (1.0)	2.0 (1.3)	KW= 14.07, p< .001 1 < 2 and 3
Separated from child	2.3 (1.6)	3.3 (1.4)	4.0 (1.7)	KW= 3.94, p= .139
Care for child with handicap	3.3 (1.5)	3.2 (1.1)	3.3 (2.1)	KW= 0.22, p= .898
Care for someone with severe physical or mental handicap	2.4 (1.4)	2.6 (1.5)	3.5 (1.4)	KW= 12.50, p= .002 1 and 2 < 3
Death of someone close (sudden)	2.0 (1.3)	2.3 (1.4)	2.9 (1.6)	KW= 16.14, p< .001 1 < 3
Death of someone close (not sudden)	1.9 (1.2)	2.4 (1.4)	3.0 (1.5)	KW= 45.61, p< .001 1 < 2 < 3
Seen robbery/mugging	1.4 (.9)	1.7 (1.2)	1.9 (1.3)	KW= 5.78, p= .056
Been robbed/mugged	1.5 (1.0)	1.8 (1.2)	2.0 (1.4)	KW= 5.20, p= .074

Table 4.6 Differences in Class Membership Between the CRCI Versus CRCI AND Anxiety LPA

Abbreviations: CRCI = cancer-related cognitive impairment; LPA = latent profile analysis

[1]Atallah M, Cooper B, Muñoz RF, Paul SM, Anguera J, Levine JD, Hammer M, Wright F, Chen LM, Melisko M, Conley YP, Miaskowski C, Dunn LB. Psychological Symptoms and Stress Are Associated With Decrements in Attentional Function in Cancer Patients Undergoing Chemotherapy. Cancer Nurs. 2020;43(5):402-10. doi: 10.1097/ncc.0000000000000713. PubMed PMID: 30998605.

Joint CRCI AND anxiety classes	**Only CRCI classes[1]**			
	High cognitive function (No CRCI) % (n)	**Moderate cognitive function (Moderate CRCI) % (n)**	**Low cognitive function (High CRCI) % (n)**	**CRCI AND anxiety totals**
None	87.1 (431)	60.1 (221)	23.4 (109)	761
Both Moderate	11.7 (58)	35.1 (129)	58.4 (272)	459
Both High	1.2 (6)	4.9 (18)	18.2 (85)	109
Only CRCI totals	495	368	466	

Table 4.7 Differences in Class Membership Between the Anxiety Versus CRCI AND Anxiety LPA

Abbreviations: CRCI = cancer-related cognitive impairment; LPA = latent profile analysis

[1]Oppegaard K, Harris CS, Shin J, Paul SM, Cooper BA, Levine JD, Conley YP, Hammer M, Cartwright F, Wright F, Dunn L, Kober KM, Miaskowski C. Anxiety profiles are associated with stress, resilience and symptom severity in outpatients receiving chemotherapy. Support Care Cancer. 2021. Epub 2021/06/28. doi: 10.1007/s00520-021-06372-w. PubMed PMID: 34176016.

Joint CRCI AND anxiety classes	**Only anxiety classes[1]**				
	Low anxiety % (n)	**Moderate anxiety % (n)**	**High anxiety % (n)**	**Very High anxiety % (n)**	**CRCI AND anxiety totals**
None	99.5 (630)	35.2 (132)	0.0 (0)	0.0 (0)	762
Both Moderate	0.5 (3)	64.8 (243)	81.0 (209)	0.0 (0)	455
Both High	0.0 (0)	0.0 (0)	19.0 (49)	100.0 (60)	109
Only anxiety totals	633	375	258	60	

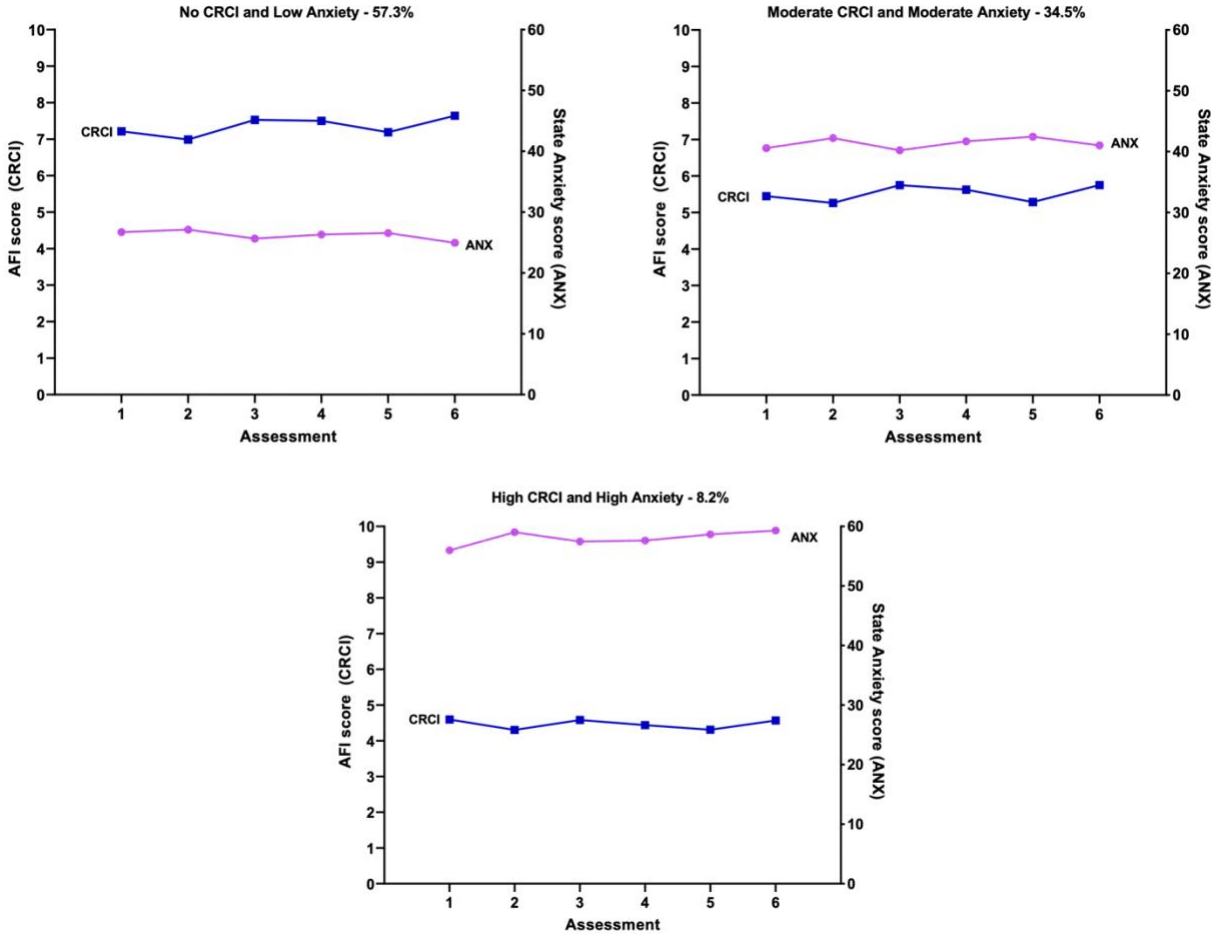

Figure 4.1 Trajectories of cancer-related cognitive impairment AND anxiety for the three latent classes.

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Chapter 5

The Co-occurrence of Cancer-Related Cognitive Impairment and Anxiety is Associated with Perturbations in Neurodegenerative Disease Pathways

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Abstract

Background: Cancer-related cognitive impairment (CRCI) and anxiety co-occur in patients with cancer. Little is known about mechanisms for the co-occurrence of these two symptoms. The purpose of this study was to evaluate for perturbations in neurodegenerative disease pathways associated with the co-occurrence of CRCI AND anxiety.

Methods: Patients completed the Attentional Function Index and the Spielberger State Anxiety Inventory six times over two cycles of chemotherapy. Using latent profile analysis, three distinct joint CRCI AND anxiety profiles were identified: None (57.3%), Both Moderate (34.5%), Both High (8.2%). Gene expression and pathway impact analyses (PIA) between the None and Both High classes were performed in two independent samples using RNA-sequencing (RNA-seq, n=226) and microarray technologies (n=225). Signaling pathways for evaluation were defined using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Results: In the RNA-seq sample, 85.0% of patients were in the None and 15.0% were in the Both High classes. In the microarray sample, 86.0% of patients were in the None and 14.0% were in the Both High classes. Combined PIA identified five perturbed signaling pathways related to neurodegenerative diseases (i.e., Amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Prion disease, and Pathways of neurodegeneration – multiple diseases).

Conclusions: This study is the first to describe perturbations in neurodegenerative disease pathways associated with CRCI AND anxiety in patients receiving chemotherapy. These findings provide new insights into potential targets for the development of mechanistically-based interventions.

Introduction

Cancer-related cognitive impairment (CRCI) and anxiety are common symptoms reported by patients with cancer.[1, 2] However, studies exploring the co-occurrence of these two symptoms are limited and potential mechanism(s) remain unknown. The majority of the research has focused on separate evaluations of each symptom and inflammatory markers.[3-5] While this line of inquiry is reasonable given the known pro-inflammatory effects of cancer and its treatments,[6] emerging evidence suggests that biomarkers of neurodegeneration are associated with CRCI and anxiety.[7]

Of note, cognitive impairment and anxiety are common symptoms in a number of neurodegenerative diseases. For example, in Parkinson's disease, up to 55% of patients report anxiety[8] and up to 75% report decrements in cognitive function that range from mild (e.g., mild cognitive impairment) to severe (e.g., dementia).[9, 10] In Huntington's disease, up to 70% of patients report anxiety[11] and up to 40% report mild cognitive impairment.[12] Given the known neurodegenerative effects of chemotherapy,[7, 13] it is plausible that shared mechanisms contribute to cognitive impairment and anxiety in patients with neurodegenerative diseases and in patients receiving chemotherapy.

In terms of biomarkers of neurodegeneration, two studies evaluated for associations with CRCI, anxiety, and serum neurofilament protein levels (i.e., neuronal-specific cytoskeletal proteins released into the circulation in response to axonal damage) in patients receiving chemotherapy.[14, 15] In both studies, no significant associations were reported. However, in one of these studies,[14] serum neurofilament protein levels increased in a dose-dependent manner, which suggests that a biomarker of neural damage associated with higher doses of chemotherapy can be measured in peripheral circulation.

In another study of breast cancer survivors who completed chemotherapy,[16] associations between CRCI and a number of psychosomatic symptoms (including anxiety) and peripheral levels of amyloid beta and tau (i.e., biomarkers of neurodegeneration), as well as with

cytokines were evaluated. Using machine learning algorithms, interactions were found among amyloid beta, tau, and cytokines that influenced cognitive functioning. In addition, findings suggested that complex, nonlinear associations and/or interactions exist among amyloid beta, tau, and cytokines, that influence the severity of these psychosomatic symptoms. The authors suggested that these neurodegenerative-related proteins may move bidirectionally across the blood-brain barrier to influence psychological and mood-related processes in the brain. Taken together, these findings provide support for additional research on associations between CRCI, anxiety, and biomarkers of neurodegeneration. While research that targets specific neurodegenerative biomarkers is informative, pathway analysis is alternative approach that can be used to identify underlying biological processes. However, no studies have used this approach to evaluate for neurodegenerative pathways associated with the co-occurrence of CRCI and anxiety in patients with cancer.

While prevalence data on the co-occurrence of CRCI and anxiety are limited, recent work from our group using latent profile analysis (LPA) identified three distinct CRCI AND anxiety latent classes in patients receiving chemotherapy (n=1332); namely, No CRCI and Low Anxiety (None; 57.3%), Moderate CRCI and Moderate Anxiety (Both Moderate; 34.5%), and High CRCI and High Anxiety (Both High; 8.2%).[17] Building on the emerging evidence in patients with cancer[7, 14, 16] and patients with other neurodegenerative diseases,[7] using a data-driven approach, we evaluated for perturbed neurodegenerative disease pathways associated with CRCI AND anxiety profiles. Therefore, using an extreme phenotype approach, the purpose of this study was to evaluate for perturbations in neurodegenerative disease pathways between the previously identified None and Both High classes.

Methods

Patients and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy. Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment. Eligible patients were approached in the infusion unit during their first or second cycle of chemotherapy by a member of the research team to discuss study participation and obtain written informed consent.

Patients completed the measures of CRCI and anxiety a total of six times over two cycles of chemotherapy (i.e., prior to chemotherapy administration, approximately one week after chemotherapy administration, approximately two weeks after chemotherapy administration). All of the other measures and collection of blood for ribonucleic acid (RNA) isolation were done at the enrollment assessment. For this study, a total of 717 patients provided a blood sample for the analyses. Of these 717 patients, 357 had their samples processed using RNA sequencing (i.e., RNA-seq sample) and 360 had their samples processed using microarray (i.e., microarray sample) technologies.

Instruments

Demographic and clinical characteristics

Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale,[18] Self-Administered Comorbidity Questionnaire (SCQ),[19] and Alcohol Use Disorders Identification test (AUDIT).[20] The toxicity of each chemotherapy regimen was rated using the MAX2 index.[21] Medical records were reviewed for disease and treatment information.

CRCI measure

Self-reported CRCI was assessed using the Attentional Function Index (AFI),[22] a 16-item instrument designed to assesses an individual's perceived effectiveness in performing daily activities that are supported by attention, working memory, and executive functions (e.g., setting goals, planning, carrying out tasks). Higher total mean score (range 0 to 10) indicates greater capacity to direct attention. Clinically meaningful cutpoints for attentional function are as follows: <5.0 low function, 5.0 to 7.5 moderate function, and >7.5 high function.[23] Its Cronbach's alpha was 0.93.

Anxiety measure

The 20-items on the Spielberger State Anxiety Inventory (STAI-S) were rated from 1 to 4.[24] The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. A cut off score of $\geq$32.2 indicates high levels state anxiety. Its Cronbach's alpha was 0.96.

Data Analysis

Latent profile analysis

In our previous study,[17] LPA was used to identify unobserved subgroups of patients (i.e., latent classes) with distinct CRCI AND anxiety profiles over the six assessments using the patients' scores on the AFI and STAI-S. For the current analysis, using an extreme phenotype approach, an evaluation of perturbations in neurodegenerative disease pathways between the None and Both High classes was performed.

Imputation process

Missing data for demographic and clinical characteristics were imputed by the k-nearest-neighbors method, with k=9. For continuous variables, the Euclidean distance was used to find the nearest neighbors. The imputed value was the weighted average of the nearest neighbors, with each weight originally exp(-dist(x,j)), after which the weights were scaled to one. For categorical variables, distance was 0 if the target and the neighbor had the same value and 1 if they did not. The imputed value was the mode of the nearest neighbors.

Demographic and clinical data

Demographic and clinical data from the two patient samples (i.e., RNA-seq, microarray) were analyzed separately. Differences in demographic and clinical characteristics between the patients in the None and Both High classes were evaluated using parametric and non-parametric tests. Significance was assessed at a p-value of <.05.

In order to not overfit the regression models, the number of demographic and clinical characteristics selected for inclusion was based on the sample size for the smaller of the two latent classes. The variables were chosen based on their previous association with CRCI and/or anxiety (i.e., lives alone, married or partnered, functional status score, and self-reported diagnosis of depression[2, 25, 26]). Characteristics included in the final model were selected using a backwards stepwise logistic regression approach based on the likelihood ratio test. Area under the curve of the receiver operating characteristic curves was used to gauge the overall adequacy of the logistic regression model for each sample.[27] All of these analyses were performed using R version 4.0.5. [28]

Differential expression and pathway impact analyses (PIA)

Details on the gene expression methods and PIA are described elsewhere.[29] In brief, differential expression was quantified using empirical Bayes models that were implemented using edgeR[30] for the RNA-seq sample and limma[31] for the microarray sample. These analyses were adjusted for select demographic and clinical characteristics that were significantly different

between the None and Both High classes. In addition, the models included surrogate variables to adjust for variations due to unmeasured sources.[32] Expression loci were annotated with Entrez gene identifiers. Gene symbols were derived and matched using the HUGO Gene Nomenclature Committee resource database.[33] The differential expression results were summarized as the log fold-change and p-value for each gene. Only genes that had a common direction of expression across the two samples were retained for subsequent analyses.

The PIA included potentially important biological factors (e.g., gene-gene interactions, flow signals in a pathway, pathway topologies), as well as the magnitude (i.e., log fold-change) and p-values from the differential expression analysis for each sample.[34] The PIA included the results of the differential expression analyses for all of the genes (i.e., cutoff free) that had a common direction of differential expression to determine probability of pathway perturbations (pPERT) using Pathway Express (version 2.18.0).[35] A total of 225 signaling pathways were defined using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.[36] For each sample, a separate test was performed for each pathway. Next, Fisher's Combined Probability method was used to combine these test results to obtain a single test (global) of the null hypothesis.[37] The significance of the combined transcriptome-wide PIA was assessed using a false discovery rate (FDR) of 0.01 under the Benjamini-Hochberg procedure.[38] To identify common biological processes involved in the co-occurrence of CRCI AND anxiety, pathway maps for each of the KEGG neurodegenerative disease pathways were reviewed.[36]

Results

RNA-seq performance

A total of 226 patients were included in the RNA-seq sample (Supplemental Figure 5.1). Of these, 85.0% were in the None class and 15.0% were in the Both High class. Median library threshold size was 9,198,950 reads. Following the application of quality control filters, 16,130 genes were included in the final analysis. The common dispersion was estimated as 0.237

yielding a biological coefficient of variation of 0.487, well within the expected value for clinical samples.[39]

Microarray performance

A total of 225 patients were included in the microarray sample (Supplemental Figure 5.1). Of these, 86.0% were in the None class and 14.0% were in the Both High class. All of these samples demonstrated good hybridization performance for biotin, background negative, and positive control assays on the arrays. Following quality control filters, 43,651 loci were included in the final analysis.

Demographic and clinical characteristics

Of 226 patients in the RNA-seq sample (Table 5.1), compared to None class, Both High class was younger; more likely to report Hispanic, mixed, or other ethnicity; and more likely to live alone. In addition, Both High class had a lower performance status; a higher number of comorbidities; a higher comorbidity burden; and were more likely to self-report diagnoses of lung disease, depression, or back pain.

Of the 225 patients in the microarray sample (Table 5.2), compared to None class, Both High class was more likely to report Black, or Hispanic, mixed or other ethnicity and less likely to report White ethnicity; were less likely to be married or partnered; less likely to be employed; had a lower annual income; and less likely to exercise on a regular basis. In addition, Both High class had a higher body mass index; a lower performance status; a higher number of comorbidities; a higher comorbidity burden; were more likely to self-report a diagnosis of depression or back pain; and were more likely to receive an antiemetic regimen that included a neurokinin-1 receptor antagonist and two other antiemetics.

Logistic regression analyses

In the logistic regression analysis for the RNA-seq sample (Table 5.3), three variables were included in the initial model and all of them were retained in the final model (i.e., lives alone, KPS score, self-reported diagnosis of depression) and used as covariates in the gene

expression analysis. In the logistic regression analysis for the microarray sample, three variables were included in the initial model and all of them were retained in the final model (i.e., married or partnered, KPS score, self-reported diagnosis of depression) and used as covariates in the gene expression analysis.

Perturbed signaling pathways associated with CRCI AND anxiety

For the RNA-seq sample, two surrogate variables were identified and included in the final differential expression model. For the microarray sample, zero surrogate variables were identified. For both samples, a total of 4,824 genes were included in the PIA analyses. Using Fisher's Combined Probability method, across the two samples, 25 KEGG signaling pathways were significantly perturbed at an FDR of <0.01 (Supplemental Table 5.1). Of these, five were pathways related to neurodegenerative diseases (Table 5.4).

Discussion

This study is the first to evaluate for perturbed neurodegenerative disease pathways associated with the co-occurrence of CRCI AND anxiety in patients receiving chemotherapy. Five neurodegenerative disease pathways were identified, namely: Amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Prion disease, and Pathways of neurodegeneration - multiple diseases. Using the KEGG pathway maps for each of these neurodegenerative disease pathways, some of the common biological processes across these pathways were identified (see Table 5.5). This discussion focuses on four of these processes as potential mechanisms for the co-occurrence of CRCI AND anxiety, namely: apoptosis, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum (ER) stress.

Apoptosis

Apoptosis (i.e., cell death) is mediated by both intrinsic (e.g., mitochondrial) and extrinsic (e.g., death receptor ligation) cellular processes.[40] Neuronal apoptosis is thought to be involved in cognitive impairment and anxiety in patients with a variety of neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease).[41] In this study, the

Apoptosis pathway was nominally perturbed (FDR = 0.041). Additional support for the involvement of apoptosis comes from a longitudinal study of patients with breast cancer that reported decrements in cognitive function over the course of treatment were associated with upregulation of Bcl-1 homologous antagonist/killer (i.e., a protein involved in apoptosis).[42] However, in another study of patients with gastric cancer,[43] no associations were found between anxiety and variations in apoptosis-related genes (i.e., Bcl-2/adenovirus E1B 19 kDa-interacting protein 3, death-associated protein kinase).

Mitochondrial dysfunction

Mitochondria are organelles that meditate a range of functions (e.g., energy production, apoptosis, ferroptosis, activation of the inflammasome).[44] In this study, the Mitophagy pathway was nominally perturbed (FDR = 0.030). Of note, an emerging body of evidence suggests that a number of symptoms reported by patients receiving chemotherapy, including CRCI and anxiety, are associated with mitochondrial dysfunction.[45, 46] In three preclinical studies,[47-49] nasal administration of mitochondria isolated from healthy human mesenchymal stem cells restored cisplatin-induced decrements in cognitive function. In addition, in a mouse model of Parkinson's disease,[50] the occurrence of anxiety-like behaviors and cognitive dysfunction were associated with mitochondrial dysfunction. The authors hypothesized that mitochondrial dysfunction in dopaminergic cells led to oxidative stress and subsequent behavioral changes.

Oxidative stress

Oxidative stress regulates multiple intrinsic and extrinsic apoptotic pathways across a variety of cell types.[51] In addition, oxidative stress results in deoxyribonucleic acid (DNA) damage within the central nervous system and associated neuronal cell death.[52] As noted in one review,[53] the brain is vulnerable to damage from oxidative stress because it is a lipid-rich environment that consumes high amounts of oxygen. Therefore, oxidative stress-induced damage in the central nervous system is increasingly recognized as a potential mechanism that disrupts neurocircuitry and leads to cognitive deficits.[53]

In terms of CRCI, poorer performance on neuropsychological tests was associated with polymorphisms of oxidative stress- and DNA repair-related genes in survivors of breast cancer.[54] In terms of anxiety, in a pre-clinical study,[55] cyclophosphamide-induced anxiety-like behaviors improved following treatment with an enzymatically hydrolyzed bioactive peptide mixture that decreased oxidative stress, neuroinflammation, neuron apoptosis, and neurogenesis in the mouse hippocampus.

Endoplasmic reticulum stress

The ER is an organelle that performs a variety of functions (e.g., protein synthesis and transport, protein folding, lipid and steroid synthesis). While in this study, an additional pathway related to ER stress was not significant (i.e., Protein processing in the endoplasmic reticulum pathway), in pre-clinical models improvements in cognitive function were associated with or occurred as a result of attenuation of ER stress. For example, in a mouse model of postoperative cognitive dysfunction,[56] administration of resveratrol decreased impairments in learning and memory in aged mice through decreased expression of ER stress pathway proteins and inflammatory mediators (e.g., nuclear factor-κB) in the hippocampus. In a rat model of vascular dementia induced by chronic cerebral hypoperfusion,[57] administration of dl-3-*n*-butylphthalide alleviated spatial learning and memory impairment and inhibited the loss of neurons in the hippocampus. The authors suggested that these neuroprotective effects were, in part, related to downregulation of the ER stress pathways.[58] In terms of anxiety, ER stress-associated inflammation appears to contribute to doxorubicin-induced behavioral changes (e.g., anxiety, depressive symptoms).[59] In a pre-clinical study,[59] treatment with dl-3-*n*-butylphthalide was neuroprotective against doxorubicin-induced anxiety- and depression-like behaviors in rats through attenuation of ER stress-associated neuroinflammation.

Limitations

Some limitations warrant consideration. First, because our patients had diagnoses of breast, gastrointestinal, gynecological, or lung cancer, findings may not generalize to other types of cancer. Because KEGG is an evolving database,[60] future analyses using KEGG or other pathway databases may identify additional mechanisms. While our CRCI AND anxiety phenotypes were created based on longitudinal assessments, blood was collected only once. Future studies need to collect both phenotypic and molecular data to determine if pathway perturbations change over time. Because this study used RNA from peripheral blood, future studies should evaluate for pathway perturbations in other tissues (e.g., cerebral spinal fluid) and/or from a variety of biomarkers (e.g., protein levels, epigenetic markers).

Conclusions and implications for future research

Taken together, our findings suggest that common biological processes may be associated with cognitive impairment and anxiety in patients with neurodegenerative diseases and in patients receiving chemotherapy. An important consideration in the interpretation of our findings is how quickly can the peripheral administration of chemotherapy exert its effects within the central nervous system. Of note, in a pre-clinical study,[61] increased expression of pro-inflammatory cytokine genes in the hypothalamus and/or hippocampus of mice was observed within six hours following the administration of a clinically relevant dose of paclitaxel. In patients with cancer, decrements in cognitive function and associated increases in pro-inflammatory biomarkers were found eight days after the initiation of chemotherapy.[62] Given that patients, in the current study, were assessed prior to their second or third cycle of chemotherapy is supportive of the hypothesis that these common biological processes may contribute to the occurrence of these two symptoms.

In conclusion, this study provides new information on associations between the co-occurrence of CRCI AND anxiety and perturbations in neurodegenerative disease pathways. While these findings warrant confirmation, they add to an emerging body of evidence that

suggests that biological processes associated with neurodegeneration are associated with CRCI and anxiety in patients with cancer.[7] Studies that elucidate if these same pathways are perturbed when CRCI and anxiety are evaluated as individual symptoms will provide important information on common and distinct mechanisms for the single versus the two co-occurring symptoms.

Table 5.1 Differences in Demographic and Clinical Characteristics at Enrollment Between Patients in the RNA-seq Sample with Low CRCI and Low Anxiety (None) and High CRCI and High Anxiety (Both High)

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test; CRCI = cancer-related cognitive impairment; CTX = chemotherapy; FE = Fisher's exact test; kg = kilograms; g/dL = grams per deciliter; KPS = Karnofsky Performance Status; m^2 = meter squared; NK-1 = neurokinin-1; n/a = not applicable; NS = not significant; RNA-seq = ribonucleic acid sequencing; RT = radiation therapy; SCQ = Self-administered Comorbidity Questionnaire; SD = standard deviation; U = Mann-Whitney U test

Characteristic	**None (1) 85% (n=192)**	**Both High (2) 15% (n=34)**	**Statistics**
	Mean (SD)	Mean (SD)	
Age (years)	58.6 (11.9)	53.4 (12.4)	t = 2.34, p = 0.020
Education (years)	16.2 (3.0)	16.1 (3.2)	t = 0.15, p = 0.880
Body mass index (kg/m^2)	25.9 (4.7)	25.4 (4.3)	t = 0.51, p = 0.612
KPS score	80.9 (12.1)	69.6 (10.5)	t = 5.17, p < 0.001
Number of comorbidities	2.2 (1.4)	3.1 (1.7)	t = -3.40, p < 0.001
SCQ score	5.0 (3.0)	7.4 (3.5)	t = -4.02, p < 0.001
AUDIT score	2.8 (2.0)	2.4 (1.6)	t = 1.22, p = 0.225
Time since diagnosis (years)	1.7 (3.2)	1.0 (1.4)	U, p = 0.418
Time since diagnosis (years, median)	0.44	0.44	
Number of prior cancer treatments	1.5 (1.4)	1.3 (1.4)	t = 0.57, p = 0.571
Number of metastatic sites including lymph node involvement	1.2 (1.1)	1.1 (1.1)	t = 0.47, p = 0.637
Number of metastatic sites excluding lymph node involvement	0.7 (1.0)	0.7 (1.1)	t = 0.16, p = 0.875
MAX2 score	0.17 (0.08)	0.19 (0.08)	t = -1.45, p = 0.148
Hemoglobin (g/dL)	11.5 (1.4)	11.4 (1.3)	t = 0.42, p = 0.673
Hematocrit (%)	34.6 (4.0)	34.3 (4.0)	t = 0.44, p = 0.662
	% (n)	% (n)	
Gender			
Female	72.4 (139)	88.2 (30)	FE, p = 0.055
Male	27.6 (53)	11.8 (4)	
Ethnicity			X^2 = 14.92, p = 0.002
Asian or Pacific Islander	18.2 (35)	17.6 (6)	NS
Black	9.4 (18)	0.0 (0)	n/a
Hispanic, Mixed, or Other	8.3 (16)	29.4 (10)	1 < 2
White	64.1 (123)	52.9 (18)	NS
Married or partnered (% yes)	65.1 (125)	52.9 (18)	FE, p = 0.182
Lives alone (% yes)	18.8 (36)	35.3 (12)	FE, p = 0.040
Childcare responsibilities (% yes)	20.3 (39)	35.3 (12)	FE, p = 0.073
Care of adult responsibilities (% yes)	6.3 (12)	8.8 (3)	FE, p = 0.478
Currently employed (% yes)	37.0 (71)	23.5 (8)	FE, p = 0.172
Income			
<$30,000	14.1 (27)	35.3 (12)	
$30,000 to <$70,000	21.9 (42)	14.7 (5)	U, p = 0.101
$70,000 to <$100,000	24.5 (47)	14.7 (5)	
≥$100,000	39.6 (76)	35.3 (12)	
Specific comorbidities (% yes)			
Heart disease	6.3 (12)	0.0 (0)	n/a
High blood pressure	33.9 (65)	35.3 (12)	FE, p = 0.847
Lung disease	6.3 (12)	17.6 (6)	FE, p = 0.036
Diabetes	10.9 (21)	14.7 (5)	FE, p = 0.559

Characteristic	None (1) 85% (n=192)	Both High (2) 15% (n=34)	Statistics
Ulcer or stomach disease	4.2 (8)	0.0 (0)	n/a
Kidney disease	0.5 (1)	2.9 (1)	FE, p = 0.279
Liver disease	5.7 (11)	5.9 (2)	FE, p = 1.000
Anemia or blood disease	7.8 (15)	11.8 (4)	FE, p = 0.499
Depression	9.9 (19)	47.1 (16)	FE, p < 0.001
Osteoarthritis	13.0 (25)	14.7 (5)	FE, p = 0.785
Back pain	22.4 (43)	58.8 (20)	FE, p < 0.001
Rheumatoid arthritis	4.7 (9)	5.9 (2)	FE, p = 0.673
Exercise on a regular basis (% yes)	69.3 (133)	58.8 (20)	FE, p = 0.238
Smoking current or history of (% yes)	32.3 (62)	38.2 (13)	FE, p = 0.555
Cancer diagnosis			
Breast	39.1 (75)	38.2 (13)	
Gastrointestinal	41.7 (80)	29.4 (10)	$X^2 = 5.87$, p = 0.118
Gynecological	13.0 (25)	14.7 (5)	
Lung	6.3 (12)	17.6 (6)	
Type of prior cancer treatment			
No prior treatment	29.2 (56)	32.4 (11)	
Only surgery, CTX, or RT	39.1 (75)	41.2 (14)	$X^2 = 0.60$, p = 0.896
Surgery & CTX, or surgery & RT, or CTX & RT	20.3 (39)	14.7 (5)	
Surgery & CTX & RT	11.5 (22)	11.8 (4)	
CTX cycle length			
14 day cycle	54.2 (104)	32.4 (11)	U, p = 0.050
21 day cycle	37.5 (72)	61.8 (21)	
28 day cycle	8.3 (16)	5.9 (2)	
Emetogenicity of CTX			
Minimal/low	15.1 (29)	14.7 (5)	U, p = 0.698
Moderate	68.8 (132)	73.5 (25)	
High	16.1 (31)	11.8 (4)	
Antiemetic regimens			
None	5.2 (10)	2.9 (1)	
Steroid alone or serotonin receptor antagonist alone	17.2 (33)	17.6 (6)	$X^2 = 0.33$, p = 0.954
Serotonin receptor antagonist and steroid	52.6 (101)	52.9 (18)	
NK-1 receptor antagonist and two other antiemetics	25.0 (48)	26.5 (9)	

Table 5.2 Differences in Demographic and Clinical Characteristics at Enrollment Between Patients in the Microarray Sample with Low CRCI and Low Anxiety (None) and High CRCI and High Anxiety (Both High)

Abbreviations: AUDIT = Alcohol Use Disorders Identification Test; CRCI = cancer-related cognitive impairment; CTX = chemotherapy; FE = Fisher's exact test; g/dL = grams per deciliter; kg = kilograms; KPS = Karnofsky Performance Status; m^2 = meter squared; NK-1 = neurokinin-1; NS = not significant; RT = radiation therapy; SCQ = Self-administered Comorbidity Questionnaire; SD = standard deviation; U = Mann-Whitney U test

Characteristic	**None (1) 86% (n=193)**	**Both High (2) 14% (n=32)**	**Statistics**
	Mean (SD)	Mean (SD)	
Age (years)	57.9 (11.0)	57.2 (11.9)	t = 0.35, p = 0.729
Education (years)	16.9 (2.9)	15.8 (3.1)	t = 1.97, p = 0.051
Body mass index (kg/m^2)	25.8 (5.3)	29.0 (8.1)	t = -2.93, p = 0.004
KPS score	82.6 (10.7)	75.6 (11.9)	t = 3.36, p < 0.001
Number of comorbidities	2.2 (1.2)	3.4 (1.4)	t = -5.30, p < 0.001
SCQ score	4.8 (2.4)	7.7 (2.9)	t = -6.04, p < 0.001
AUDIT score	2.9 (2.0)	2.7 (2.6)	t = 0.64, p = 0.525
Time since diagnosis (years)	2.2 (3.9)	1.4 (2.2)	U, p = 0.693
Time since diagnosis (median)	0.42	0.45	
Number of prior cancer treatments	1.6 (1.6)	1.8 (1.6)	t = -0.67, p = 0.503
Number of metastatic sites including lymph node involvement	1.2 (1.3)	1.0 (1.0)	t = 1.04, p = 0.301
Number of metastatic sites excluding lymph node involvement	0.8 (1.1)	0.5 (1.0)	t = 1.54, p = 0.126
MAX2 score	0.17 (0.08)	0.16 (0.08)	t = 0.66, p = 0.510
Hemoglobin (g/dL)	11.7 (1.4)	12.0 (1.1)	t = -1.15, p = 0.250
Hematocrit (%)	34.9 (4.0)	35.8 (3.0)	t = -1.29, p = 0.200
	% (n)	% (n)	
Gender			
Female	76.7 (148)	78.1 (25)	FE, p = 1.000
Male	23.3 (45)	21.9 (7)	
Ethnicity			
Asian or Pacific Islander	12.4 (24)	6.2 (2)	X^2 = 19.13, p< 0.001
	4.7 (9)	18.8 (6)	NS
Black	6.2 (12)	21.9 (7)	1 < 2
Hispanic, Mixed, or Other	76.7 (148)	53.1 (17)	1 < 2
			1 > 2
White			
Married or partnered (% yes)	75.6 (146)	40.6 (13)	FE, p < 0.001
Lives alone (% yes)	17.6 (34)	21.9 (7)	FE, p = 0.621
Childcare responsibilities (% yes)	20.2 (39)	25.0 (8)	FE, p = 0.638
Care of adult responsibilities (% yes)	5.7 (11)	3.1 (1)	FE, p = 1.000
Currently employed (% yes)	46.6 (90)	21.9 (7)	FE, p = 0.011
Income			
<$30,000	9.8 (19)	43.8 (14)	U, p < 0.001
$30,000 to <$70,000	18.7 (36)	15.6 (5)	1 > 2
$70,000 to <$100,000	20.7 (40)	9.4 (3)	
≥$100,000	50.8 (98)	31.3 (10)	
Specific comorbidities (% yes)			
Heart disease	5.7 (11)	9.4 (3)	FE, p = 0.428
High blood pressure	25.4 (49)	43.8 (14)	FE, p = 0.054

Characteristic	None (1) 86% (n=193)	Both High (2) 14% (n=32)	Statistics
Lung disease	11.4 (22)	9.4 (3)	FE, p = 1.000
Diabetes	7.3 (14)	15.6 (5)	FE, p = 0.160
Ulcer or stomach disease	3.6 (7)	12.5 (4)	FE, p = 0.054
Kidney disease	0.5 (1)	3.1 (1)	FE, p = 0.265
Liver disease	5.7 (11)	3.1 (1)	FE, p = 1.000
Anemia or blood disease	11.9 (23)	18.8 (6)	FE, p = 0.266
Depression	9.3 (18)	65.6 (21)	FE, p < 0.001
Osteoarthritis	11.9 (23)	15.6 (5)	FE, p = 0.565
Back pain	19.7 (38)	40.6 (13)	FE, p = 0.013
Rheumatoid arthritis	3.1 (6)	3.1 (1)	FE, p = 1.000
Exercise on a regular basis (% yes)	76.2 (147)	56.3 (18)	FE, p = 0.029
Smoking current or history of (% yes)	37.8 (73)	50.0 (16)	FE, p = 0.242
Cancer diagnosis			
Breast	36.3 (70)	53.1 (17)	
Gastrointestinal	25.4 (49)	21.9 (7)	$X^2 = 3.63$, p = 0.304
Gynecological	22.3 (43)	12.5 (4)	
Lung	16.1 (31)	12.5 (4)	
Type of prior cancer treatment			
No prior treatment	23.8 (46)	15.6 (5)	
Only surgery, CTX, or RT	40.9 (79)	50.0 (16)	$X^2 = 4.49$, p = 0.213
Surgery & CTX, or surgery & RT, or CTX & RT	22.8 (44)	12.5 (4)	
Surgery & CTX & RT	12.4 (24)	21.9 (7)	
CTX cycle length			
14 day cycle	34.7 (67)	40.6 (13)	U, p = 0.506
21 day cycle	57.5 (111)	53.1 (17)	
28 day cycle	7.8 (15)	6.3 (2)	
Emetogenicity of CTX			
Minimal/low	21.2 (41)	25.0 (8)	U, p = 0.989
Moderate	60.6 (117)	53.1 (17)	
High	18.1 (35)	21.9 (7)	
Antiemetic regimens			$X^2 = 14.88$, p= 0.002
None	10.4 (20)	9.4 (3)	NS
Steroid alone or serotonin receptor antagonist alone	24.9 (48)	12.5 (4)	NS
Serotonin receptor antagonist and steroid	47.7 (92)	31.3 (10)	NS
NK-1 receptor antagonist and two other antiemetics	17.1 (33)	46.9 (15)	1 < 2

Table 5.3 Multiple Logistic Regression Analyses Predicting Membership in the High CRCI AND High Anxiety Class

Abbreviations: AUC = area under curve; CI = confidence interval; CRCI = cancer-related cognitive impairment; RNA-seq = ribonucleic acid sequencing; ROC = receiver operating characteristic

RNA-seq sample (n = 226)			
Predictors	Odds Ratio	95% CI	p-value
Lives alone	1.98	0.78, 4.89	0.140
Karnofsky Performance Status score	0.93	0.90, 0.97	<0.001
Self-reported diagnosis of depression	5.93	2.46, 14.47	<0.001
Overall model fit: AUC of the ROC = 0.822			
Microarray sample (n = 225)			
Predictors	Odds Ratio	95% CI	p-value
Married or partnered	0.23	0.09, 0.58	0.002
Karnofsky Performance Status score	0.95	0.91, 0.99	0.016
Self-reported diagnosis of depression	15.40	6.20, 40.89	<0.001
Overall model fit: AUC of the ROC = 0.882			

Table 5.4 Significantly Perturbed Neurodegenerative Disease Pathways for CRCI AND Anxiety

Note: p = global perturbation p-value adjusted using the Benjamini-Hochberg procedure
Abbreviations: CRCI = cancer-related cognitive impairment; hsa = homo sapiens; ID = identifier

Pathway ID	**Pathway name**	**Combined analysis statistics**
hsa05014	Amyotrophic lateral sclerosis	$X^2 = 25.13$, p = 0.002
hsa05016	Huntington disease	$X^2 = 24.86$, p = 0.002
hsa05012	Parkinson disease	$X^2 = 22.12$, p = 0.004
hsa05020	Prion disease	$X^2 = 19.66$, p = 0.006
hsa05022	Pathways of neurodegeneration - multiple diseases	$X^2 = 18.47$, p = 0.008

Table 5.5 Comparison of the Biological Processes Involved in Each of the Perturbed Neurodegenerative Disease Pathways in the KEGG Database

Note: In order to be able to identify potential biological processes involved in the co-occurrence of cancer-related cognitive impairment AND anxiety, pathway maps within the KEGG database were reviewed. This table provides a summary of some of the biological processes described for each of these pathway maps.

Abbreviations: KEGG = Kyoto Encyclopedia of Genes and Genomes

KEGG neurodegenerative pathway name	Biological processes							
	Apoptosis	Mitochondrial dysfunction	Oxidative stress	Endoplasmic reticulum stress	Axonal transport defects	Impairment of autophagy	Ubiquitin proteasome disruption	Unfolded protein response
Amyotrophic lateral sclerosis	x	x	x	x	x	x	x	x
Huntington disease	x	x	x	x		x		x
Parkinson disease	x	x	x	x	x		x	
Prion disease	x	x	x	x	x	x		
Pathways of neurodegeneration - Multiple diseases	x	x	x	x	x	x	x	x

Supplemental Table 5.1 Pathway Impact Analysis Results for the Low CRCI and Low Anxiety (None) Versus High CRCI and High Anxiety (Both High) Classes

Abbreviations: CRCI = cancer-related cognitive impairment; FDR = false discovery rate; has = homo sapiens; ID = identifier; KEGG = Kyoto Encyclopedia of Genes and Genomes; microa = microarray sample; pPert = probability of pathway perturbations; RNA-seq = ribonucleic acid sequencing sample

Note: Global FDR adjusted using the Benjamini-Hochberg procedure

Pathway ID	KEGG pathway names	pPert RNA-seq	pPert micora	Global X^2	Global FDR
hsa04060	Cytokine-cytokine receptor interaction	<0.001	<0.001	30.41	0.001
hsa05171	Coronavirus disease - COVID-19	0.003	<0.001	26.51	0.002
hsa05014	Amyotrophic lateral sclerosis	0.007	<0.001	25.13	0.002
hsa05202	Transcriptional misregulation in cancer	0.002	0.001	24.99	0.002
hsa05016	Huntington disease	0.008	<0.001	24.86	0.002
hsa05323	Rheumatoid arthritis	0.009	<0.001	24.52	0.002
hsa05168	Herpes simplex virus 1 infection	0.001	0.009	22.43	0.004
hsa05418	Fluid shear stress and atherosclerosis	0.009	0.001	22.43	0.004
hsa05012	Parkinson disease	0.010	0.001	22.12	0.004
hsa04621	NOD-like receptor signaling pathway	0.007	0.002	21.91	0.004
hsa04144	Endocytosis	0.006	0.003	21.69	0.004
hsa04623	Cytosolic DNA-sensing pathway	0.013	0.001	21.62	0.004
hsa04071	Sphingolipid signaling pathway	0.005	0.005	21.00	0.005
hsa05166	Human T-cell leukemia virus 1 infection	0.030	0.001	20.80	0.005
hsa04061	Viral protein interaction with cytokine and cytokine receptor	0.063	<0.001	20.72	0.005
hsa04064	NF-kappa B signaling pathway	0.003	0.013	20.31	0.006
hsa04260	Cardiac muscle contraction	0.012	0.003	20.08	0.006
hsa05200	Pathways in cancer	0.002	0.022	20.06	0.006
hsa05332	Graft-versus-host disease	0.001	0.032	19.86	0.006
hsa05020	Prion disease	0.012	0.004	19.66	0.006
hsa05162	Measles	0.001	0.040	19.44	0.007
hsa05164	Influenza A	0.003	0.018	19.29	0.007
hsa04380	Osteoclast differentiation	0.006	0.010	19.19	0.007
hsa05161	Hepatitis B	0.004	0.020	18.87	0.008
hsa05022	Pathways of neurodegeneration - multiple diseases	0.008	0.011	18.47	0.009
hsa05165	Human papillomavirus infection	0.003	0.034	18.05	0.010
hsa04151	PI3K-Akt signaling pathway	0.001	0.135	17.82	0.011
hsa05415	Diabetic cardiomyopathy	0.137	0.001	17.79	0.011
hsa04145	Phagosome	0.056	0.002	17.75	0.011
hsa04940	Type I diabetes mellitus	0.003	0.047	17.41	0.012
hsa04810	Regulation of actin cytoskeleton	0.002	0.085	17.35	0.012
hsa04630	JAK-STAT signaling pathway	0.004	0.049	17.08	0.013

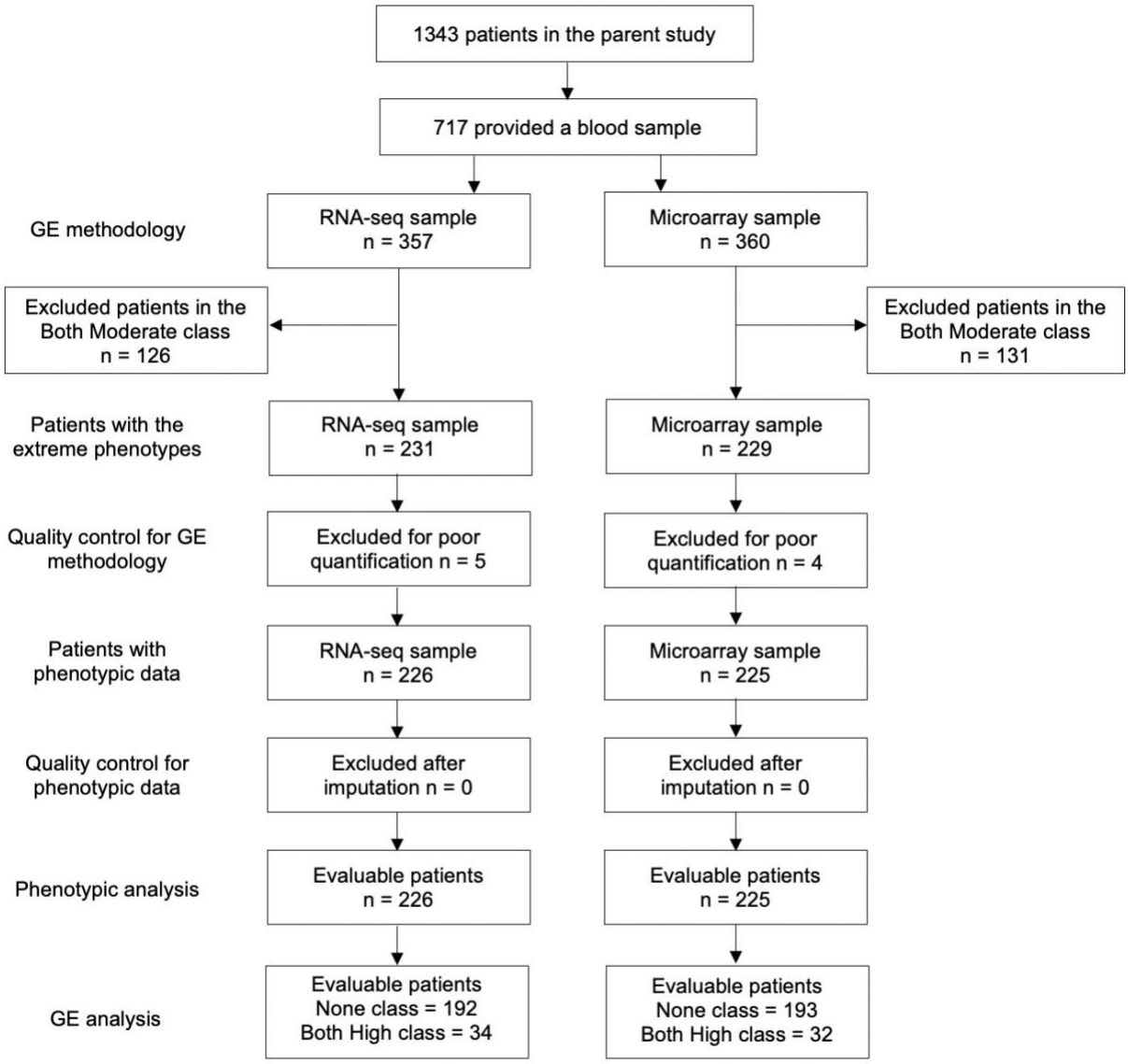
Pathway ID	KEGG pathway names	pPert RNA-seq	pPert micora	Global X^2	Global FDR
hsa04721	Synaptic vesicle cycle	0.026	0.008	16.96	0.013
hsa04510	Focal adhesion	0.009	0.025	16.80	0.014
hsa05320	Autoimmune thyroid disease	0.006	0.038	16.75	0.014
hsa05144	Malaria	0.055	0.004	16.59	0.014
hsa04612	Antigen processing and presentation	0.007	0.033	16.58	0.014
hsa05330	Allograft rejection	0.004	0.062	16.35	0.015
hsa05152	Tuberculosis	0.033	0.011	15.76	0.019
hsa04080	Neuroactive ligand-receptor interaction	<0.001	0.858	15.51	0.021
hsa04216	Ferroptosis	0.008	0.052	15.45	0.021
hsa05169	Epstein-Barr virus infection	0.003	0.129	15.41	0.021
hsa04978	Mineral absorption	0.005	0.087	15.28	0.021
hsa05143	African trypanosomiasis	0.023	0.021	15.23	0.021
hsa04662	B cell receptor signaling pathway	0.054	0.009	15.13	0.022
hsa03320	PPAR signaling pathway	0.024	0.027	14.69	0.026
hsa04723	Retrograde endocannabinoid signaling	0.019	0.037	14.52	0.027
hsa04979	Cholesterol metabolism	0.019	0.037	14.50	0.027
hsa05010	Alzheimer disease	0.090	0.008	14.35	0.028
hsa04137	Mitophagy	0.284	0.003	14.13	0.030
hsa05321	Inflammatory bowel disease	0.575	0.001	14.11	0.030
hsa03440	Homologous recombination	0.081	0.011	14.04	0.031
hsa04010	MAPK signaling pathway	0.001	0.607	14.00	0.031
hsa04350	TGF-beta signaling pathway	0.001	0.847	13.34	0.039
hsa05131	Shigellosis	0.207	0.006	13.38	0.039
hsa03015	mRNA surveillance pathway	0.391	0.003	13.19	0.039
hsa04217	Necroptosis	0.012	0.114	13.18	0.039
hsa04512	ECM-receptor interaction	0.015	0.092	13.17	0.039
hsa04976	Bile secretion	0.003	0.433	13.29	0.039
hsa04210	Apoptosis	0.048	0.031	13.02	0.041
hsa04622	RIG-I-like receptor signaling pathway	0.011	0.139	12.87	0.041
hsa04650	Natural killer cell mediated cytotoxicity	0.008	0.195	12.81	0.041
hsa04913	Ovarian steroidogenesis	0.004	0.38	12.98	0.041
hsa05132	Salmonella infection	0.104	0.015	12.93	0.041
hsa05140	Leishmaniasis	0.013	0.118	12.88	0.041
hsa05417	Lipid and atherosclerosis	0.156	0.010	12.82	0.041
hsa05160	Hepatitis C	0.004	0.452	12.63	0.044
hsa04020	Calcium signaling pathway	0.002	0.747	12.57	0.044
hsa04115	p53 signaling pathway	0.139	0.013	12.56	0.044
hsa04726	Serotonergic synapse	0.032	0.059	12.52	0.044

Pathway ID	KEGG pathway names	pPert RNA-seq	pPert micora	Global X^2	Global FDR
hsa04620	Toll-like receptor signaling pathway	0.029	0.068	12.43	0.045
hsa03018	RNA degradation	0.640	0.003	12.20	0.045
hsa03250	Viral life cycle - HIV-1	0.002	0.853	12.30	0.045
hsa04072	Phospholipase D signaling pathway	0.004	0.454	12.39	0.045
hsa04540	Gap junction	0.005	0.404	12.22	0.045
hsa04613	Neutrophil extracellular trap formation	0.149	0.014	12.34	0.045
hsa04932	Non-alcoholic fatty liver disease	0.034	0.064	12.26	0.045
hsa04950	Maturity onset diabetes of the young	0.005	0.397	12.26	0.045
hsa05206	MicroRNAs in cancer	0.003	0.672	12.11	0.047
hsa05416	Viral myocarditis	0.064	0.039	11.99	0.048
hsa01521	EGFR tyrosine kinase inhibitor resistance	0.004	0.662	11.63	0.055
hsa04668	TNF signaling pathway	0.238	0.012	11.64	0.055
hsa04062	Chemokine signaling pathway	0.049	0.061	11.59	0.055
hsa05412	Arrhythmogenic right ventricular cardiomyopathy	0.019	0.158	11.57	0.055
hsa04015	Rap1 signaling pathway	0.004	0.813	11.46	0.056
hsa05134	Legionellosis	0.816	0.004	11.45	0.056
hsa05231	Choline metabolism in cancer	0.004	0.811	11.46	0.056
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	0.768	0.004	11.34	0.058
hsa01524	Platinum drug resistance	0.023	0.156	11.26	0.059
hsa05146	Amoebiasis	0.091	0.042	11.13	0.062
hsa04014	Ras signaling pathway	0.005	0.880	10.85	0.069
hsa05218	Melanoma	0.009	0.468	10.83	0.069
hsa05215	Prostate cancer	0.005	0.929	10.75	0.071
hsa04972	Pancreatic secretion	0.005	0.955	10.69	0.072
hsa05410	Hypertrophic cardiomyopathy	0.021	0.242	10.56	0.075
hsa05142	Chagas disease	0.025	0.223	10.34	0.081
hsa05167	Kaposi sarcoma-associated herpesvirus infection	0.026	0.229	10.25	0.083
hsa04914	Progesterone-mediated oocyte maturation	0.026	0.232	10.19	0.085
hsa05205	Proteoglycans in cancer	0.012	0.508	10.12	0.086
hsa05230	Central carbon metabolism in cancer	0.009	0.745	10.01	0.089
hsa04140	Autophagy - animal	1.000	0.007	9.93	0.090
hsa04360	Axon guidance	0.014	0.490	9.89	0.090
hsa04928	Parathyroid hormone synthesis, secretion and action	0.075	0.093	9.91	0.090
hsa05163	Human cytomegalovirus infection	0.091	0.077	9.91	0.090
hsa05017	Spinocerebellar ataxia	0.252	0.029	9.81	0.093
hsa01523	Antifolate resistance	0.012	0.621	9.72	0.095
hsa04971	Gastric acid secretion	0.013	0.582	9.69	0.095
hsa04610	Complement and coagulation cascades	0.012	0.741	9.45	0.103

Pathway ID	KEGG pathway names	pPert RNA-seq	pPert micora	Global X^2	Global FDR
hsa05145	Toxoplasmosis	0.034	0.255	9.46	0.103
hsa05222	Small cell lung cancer	0.203	0.044	9.44	0.103
hsa05135	Yersinia infection	0.121	0.076	9.36	0.105
hsa05207	Chemical carcinogenesis - receptor activation	0.030	0.311	9.35	0.105
hsa04141	Protein processing in endoplasmic reticulum	0.448	0.021	9.29	0.106
hsa04150	mTOR signaling pathway	0.561	0.017	9.31	0.106
hsa04625	C-type lectin receptor signaling pathway	0.045	0.221	9.20	0.109
hsa04022	cGMP-PKG signaling pathway	0.031	0.350	9.02	0.116
hsa04666	Fc gamma R-mediated phagocytosis	0.145	0.079	8.92	0.120
hsa04024	cAMP signaling pathway	0.025	0.478	8.81	0.124
hsa05203	Viral carcinogenesis	0.069	0.177	8.79	0.124
hsa04659	Th17 cell differentiation	0.192	0.067	8.70	0.127
hsa05032	Morphine addiction	0.027	0.478	8.70	0.127
hsa05212	Pancreatic cancer	0.187	0.073	8.59	0.131
hsa04921	Oxytocin signaling pathway	0.016	0.891	8.50	0.135
hsa04936	Alcoholic liver disease	0.015	0.940	8.46	0.136
hsa05214	Glioma	0.063	0.261	8.20	0.149
hsa05414	Dilated cardiomyopathy	0.024	0.686	8.22	0.149
hsa05100	Bacterial invasion of epithelial cells	0.034	0.528	8.01	0.158
hsa05130	Pathogenic Escherichia coli infection	0.450	0.040	8.01	0.158
hsa04923	Regulation of lipolysis in adipocytes	0.028	0.659	7.95	0.161
hsa04672	Intestinal immune network for IgA production	0.038	0.534	7.80	0.168
hsa05170	Human immunodeficiency virus 1 infection	0.041	0.492	7.81	0.168
hsa04933	AGE-RAGE signaling pathway in diabetic complications	0.042	0.496	7.72	0.172
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	0.031	0.685	7.67	0.174
hsa05221	Acute myeloid leukemia	0.374	0.063	7.50	0.185
hsa04215	Apoptosis - multiple species	0.745	0.033	7.38	0.191
hsa05219	Bladder cancer	0.033	0.752	7.39	0.191
hsa04066	HIF-1 signaling pathway	0.032	0.806	7.32	0.194
hsa04146	Peroxisome	0.071	0.369	7.29	0.194
hsa05217	Basal cell carcinoma	0.118	0.220	7.30	0.194
hsa04152	AMPK signaling pathway	0.102	0.263	7.23	0.197
hsa04370	VEGF signaling pathway	0.028	0.989	7.17	0.200
hsa04724	Glutamatergic synapse	0.032	0.898	7.10	0.204
hsa04910	Insulin signaling pathway	0.053	0.549	7.08	0.205
hsa04261	Adrenergic signaling in cardiomyocytes	0.040	0.832	6.81	0.223
hsa04530	Tight junction	0.040	0.825	6.80	0.223
hsa04657	IL-17 signaling pathway	0.067	0.493	6.82	0.223

Pathway ID	KEGG pathway names	pPert RNA-seq	pPert micora	Global X^2	Global FDR
hsa04068	FoxO signaling pathway	0.062	0.563	6.70	0.231
hsa04917	Prolactin signaling pathway	0.046	0.787	6.64	0.234
hsa05310	Asthma	0.887	0.041	6.60	0.236
hsa04611	Platelet activation	0.621	0.061	6.55	0.240
hsa04728	Dopaminergic synapse	0.048	0.971	6.11	0.281
hsa04340	Hedgehog signaling pathway	0.067	0.723	6.04	0.285
hsa04664	Fc epsilon RI signaling pathway	0.762	0.064	6.04	0.285
hsa04960	Aldosterone-regulated sodium reabsorption	0.067	0.759	5.96	0.292
hsa04660	T cell receptor signaling pathway	0.991	0.052	5.93	0.293
hsa04713	Circadian entrainment	0.108	0.482	5.91	0.293
hsa04962	Vasopressin-regulated water reabsorption	0.066	0.809	5.86	0.297
hsa04970	Salivary secretion	0.055	0.983	5.82	0.299
hsa04740	Olfactory transduction	0.071	0.777	5.80	0.300
hsa05225	Hepatocellular carcinoma	0.088	0.646	5.74	0.305
hsa04670	Leukocyte transendothelial migration	0.723	0.080	5.69	0.308
hsa04213	Longevity regulating pathway - multiple species	0.156	0.378	5.65	0.310
hsa04714	Thermogenesis	0.590	0.101	5.63	0.311
hsa04270	Vascular smooth muscle contraction	0.069	0.972	5.41	0.336
hsa04744	Phototransduction	0.577	0.122	5.31	0.346
hsa04136	Autophagy - other	0.834	0.088	5.21	0.354
hsa04392	Hippo signaling pathway - multiple species	0.091	0.817	5.20	0.354
hsa04919	Thyroid hormone signaling pathway	0.145	0.512	5.19	0.354
hsa04935	Growth hormone synthesis, secretion and action	0.127	0.606	5.12	0.361
hsa05226	Gastric cancer	0.378	0.219	4.98	0.378
hsa04658	Th1 and Th2 cell differentiation	0.980	0.085	4.96	0.378
hsa05110	Vibrio cholerae infection	0.933	0.094	4.87	0.389
hsa05030	Cocaine addiction	0.255	0.355	4.80	0.396
hsa04114	Oocyte meiosis	0.197	0.481	4.71	0.407
hsa04211	Longevity regulating pathway	0.238	0.407	4.67	0.407
hsa04310	Wnt signaling pathway	0.145	0.663	4.68	0.407
hsa04725	Cholinergic synapse	0.556	0.179	4.61	0.414
hsa05213	Endometrial cancer	0.173	0.593	4.55	0.419
hsa04390	Hippo signaling pathway	0.146	0.729	4.48	0.428
hsa04916	Melanogenesis	0.951	0.114	4.44	0.431
hsa04973	Carbohydrate digestion and absorption	0.386	0.297	4.33	0.445
hsa04722	Neurotrophin signaling pathway	0.129	0.937	4.22	0.460
hsa04918	Thyroid hormone synthesis	0.274	0.453	4.17	0.465
hsa04730	Long-term depression	0.243	0.522	4.13	0.470

Pathway ID	KEGG pathway names	pPert RNA-seq	pPert micora	Global X^2	Global FDR
hsa04727	GABAergic synapse	0.655	0.204	4.03	0.480
hsa05223	Non-small cell lung cancer	0.136	0.975	4.03	0.480
hsa04931	Insulin resistance	0.182	0.742	4.00	0.482
hsa05211	Renal cell carcinoma	0.158	0.880	3.95	0.488
hsa05224	Breast cancer	0.680	0.245	3.58	0.546
hsa04934	Cushing syndrome	0.834	0.221	3.38	0.579
hsa04961	Endocrine and other factor-regulated calcium reabsorption	0.370	0.509	3.34	0.584
hsa04922	Glucagon signaling pathway	0.349	0.572	3.22	0.602
hsa04925	Aldosterone synthesis and secretion	0.392	0.512	3.21	0.602
hsa05034	Alcoholism	0.469	0.470	3.03	0.633
hsa05133	Pertussis	0.469	0.482	2.97	0.639
hsa05216	Thyroid cancer	0.546	0.417	2.96	0.639
hsa04924	Renin secretion	0.327	0.816	2.64	0.698
hsa04122	Sulfur relay system	0.473	0.574	2.61	0.701
hsa04012	ErbB signaling pathway	0.397	0.693	2.58	0.702
hsa04930	Type II diabetes mellitus	0.556	0.497	2.57	0.702
hsa05031	Amphetamine addiction	0.369	0.767	2.53	0.707
hsa04218	Cellular senescence	0.605	0.472	2.51	0.707
hsa03460	Fanconi anemia pathway	0.573	0.547	2.32	0.737
hsa04110	Cell cycle	0.552	0.567	2.32	0.737
hsa05322	Systemic lupus erythematosus	0.585	0.546	2.28	0.741
hsa04912	GnRH signaling pathway	0.584	0.592	2.12	0.768
hsa04915	Estrogen signaling pathway	0.733	0.490	2.05	0.779
hsa04927	Cortisol synthesis and secretion	0.711	0.515	2.01	0.783
hsa05210	Colorectal cancer	0.993	0.385	1.92	0.797
hsa04911	Insulin secretion	0.599	0.691	1.76	0.823
hsa01522	Endocrine resistance	0.999	0.460	1.55	0.860
hsa04330	Notch signaling pathway	0.613	0.787	1.46	0.874
hsa04720	Long-term potentiation	0.569	0.88	1.38	0.883
hsa05220	Chronic myeloid leukemia	0.658	0.821	1.23	0.905
hsa04710	Circadian rhythm	0.763	0.760	1.09	0.925
hsa05150	Staphylococcus aureus infection	0.687	0.861	1.05	0.927
hsa04371	Apelin signaling pathway	0.770	0.810	0.94	0.935
hsa04742	Taste transduction	0.982	0.635	0.94	0.935
hsa04920	Adipocytokine signaling pathway	0.685	0.981	0.80	0.948
hsa04926	Relaxin signaling pathway	0.948	0.700	0.82	0.948
hsa04130	SNARE interactions in vesicular transport	0.900	0.768	0.74	0.951
hsa04929	GnRH secretion	0.923	0.973	0.22	0.995



Supplementary Figure 5.1: Flow diagram of the number of patients available for the gene expression analyses that evaluated for perturbations between the Low cancer-related cognitive impairment (CRCI) AND Low anxiety (None) and the High CRCI AND High anxiety (Both High) latent classes.

Abbreviations: GE = gene expression; RNA-seq = ribonucleic acid sequencing

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Conclusions, Implications for Practice, and Directions for Future Research

The first three aims of this dissertation were to: 1) develop a comprehensive conceptual model of cancer-related cognitive impairment (CRCI); 2) test this newly developed conceptual model; and 3) conduct a scoping review of the literature to describe the depth and breadth of available evidence on blood-based biomarkers of CRCI. In addition, using data from a sample of patients with heterogenous types of cancer with distinct joint CRCI AND anxiety profiles (n=1332), the fourth, fifth, and sixth aims of this dissertation were to: evaluate for differences in demographic and clinical characteristics among the three CRCI AND anxiety latent classes; evaluate for differences in levels of global stress, cancer-specific stress, cumulative life stress, and resilience among the three CRCI AND anxiety latent classes; and evaluate for perturbed pathways associated with membership in the lowest versus the highest CRCI AND anxiety latent classes.

In the Introduction to the Dissertation, the need for a comprehensive conceptual model of CRCI was described. In addition, while anxiety was identified as a symptom that commonly co-occurs with CRCI, few studies have examined the associations between these two symptoms. Subsequently, the rationale for using latent profile analysis to evaluate these two symptoms jointly was provided. Next, the potential roles of various types of stress and resilience were highlighted as factors that warrant consideration along with CRCI and anxiety. Finally, pathway impact analysis was introduced as a way to evaluate for molecular mechanisms that underlie CRCI and anxiety.

In Chapter 1, an original comprehensive conceptual model of CRCI (i.e., the Multifactorial Model of Cancer-Related Cognitive Impairment; MMCRCI) was described. The rationale for each of the five concepts in the conceptual model (i.e., social determinants of health, patient-specific factors, co-occurring symptoms, treatment factors, and biologic mechanisms) were provided. In addition, examples of the specific factors included in each of these concepts were provided. Finally, recommendations were made for future research.

In Chapter 2, structural regression methods were used to evaluate the MMCRCI. The goals of this analysis were to determine how well four of the model concepts (i.e., social determinants of health, patient-specific factors, treatment factors, co-occurring symptoms) predicted CRCI and determine the relative contribution of each of these concepts to deficits in perceived cognitive function. Of note, the co-occurrence of other common symptoms explained the largest amount of variance in CRCI and treatment factors explained the smallest amount of variance. These findings suggest that, in terms of risk factors for CRCI, the co-occurrence of other common symptoms associated with cancer and its treatments may be more important than treatment factors, patient-specific factors, and/or social determinants of health in patients receiving chemotherapy for breast, gynecological, gastrointestinal, or lung cancer. Finally, this study demonstrated that testing individual components of the MMCRCI may provide useful information on the relationships among various risk factors for CRCI, as well as refinements of the model.

In Chapter 3, the findings from a scoping review that aimed to synthesize the extant literature on associations between subjective and/or objective measures of CRCI and blood-based biomarkers in adults with non-central nervous system cancers were reported. Findings from a total of 95 studies were synthesized in this review. A wide variety of biomarkers were examined and the majority of studies evaluated patients with breast cancer. In terms of measures to assess CRCI, a variety of cognitive assessment measures were used and inconsistencies in scoring made comparisons across studies difficult. Overall, the most consistent associations were with various subjective and objective measures of CRCI and levels of interleukin-6 and tumor necrosis factor. This review concluded with directions for future research.

In Chapter 4, findings from a latent profile analysis that identified subgroups of patients with distinct joint self-reported CRCI AND state anxiety profiles were presented. Three latent classes were identified (i.e., No CRCI AND Low Anxiety (57.3%), Moderate CRCI AND

Moderate Anxiety (34.5%), and High CRCI AND High Anxiety (8.2%)). Differences in demographic and clinical characteristics, as well as levels of global stress, cancer-specific stress, cumulative life stress, and resilience among the latent classes were reported. In general, higher levels of co-occurring CRCI AND anxiety were associated with several demographic and clinical characteristics (e.g., female gender, lower functional status), as well as higher levels of stress and lower levels of resilience. Of note, all of the stress measures showed a dose response pattern (i.e., as the joint CRCI AND anxiety profile worsened, scores for all three types of stress increased). The two highest symptom classes reported higher occurrence rates for six specific stressors (e.g., emotional abuse, physical abuse, sexual harassment). Of note, this study is the first to report on associations between CRCI AND anxiety and a history of lifetime trauma.

In Chapter 5, perturbed neurodegenerative pathways associated with membership in lowest compared to the highest CRCI AND anxiety latent classes were evaluated based on the hypothesis that both cognitive impairment and anxiety are common symptoms in patients with neurodegenerative diseases. Five neurodegenerative disease pathways were significantly perturbed, namely: Amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Prion disease, and Pathways of neurodegeneration - multiple diseases. Common biological processes across these perturbed neurodegenerative disease pathways were identified (i.e., apoptosis, mitochondrial function, endoplasmic reticulum stress, oxidative stress). These biological processes were described in the context of emerging evidence that suggests that each of these processes may underlie cognitive changes and/or anxiety in patients with cancer or in patients with neurodegenerative diseases (e.g., Parkinson’s disease).

Implications for practice

Overall, the research presented in this dissertation increases clinicians' knowledge of CRCI as a single symptom and the co-occurrence of CRCI AND anxiety in patients receiving chemotherapy for breast, gynecological, gastrointestinal, or lung cancer. In terms of the MMCRCI, this conceptual model provides information on a variety of factors that are known or hypothesized to contribute to CRCI. This information will allow for better assessments of modifiable and non-modifiable characteristics associated with CRCI. In addition, clinicians can use the visualization of the model as a tool to provide patients with education on CRCI.

The findings from our structural regression model that tested the MMCRCI reinforces the importance of assessing for multiple common symptoms in patients with CRCI. Equally important, these findings provide initial insights about groups of characteristics (e.g., annual household income, years of education, cumulative lifetime stress, levels of psychological resilience), rather than individual characteristics, that may be important predictors of CRCI.

In terms of the joint CRCI AND anxiety latent classes identified in this research, a variety of demographic and clinical characteristics were identified that were associated with the co-occurrence of these two symptoms, some of which are modifiable (e.g., optimal treatment of comorbid conditions, exercise). These findings can be used to assist clinicians to identify patients at increased risk for CRCI AND anxiety and initiate appropriate supportive care referrals.

Directions for future research

The MMCRCI can be used to design pre-clinical and clinical studies of CRCI. As more research is conducted, the MMCRCI will need to be updated and/or refined. Although it would be ideal to evaluate all of the various concepts and components in this model in a comprehensive fashion, investigators with existing datasets could evaluate portions of the model to determine directionality for some of the proposed relationships. Based on the MMCRCI, Table 1.1 provides a list of suggestions for future research. Examples include

investigations of which measures of CRCI have the highest predictive value to diagnosis CRCI and determination of normative ranges and clinically meaningful change scores for various measures of CRCI.

In terms of findings from the testing of the MMCRCI, several important directions for future research were identified. First, because the co-occurrence of other common symptoms accounted for the largest amount of variance in CRCI, one hypothesis is that common mechanism(s) may underlie these symptoms. Therefore, studies that investigate this hypothesis are warranted. Second, a need exists to identify different phenotypes of CRCI based on the presence of other co-occurring symptoms. Future studies that evaluate multiple common symptoms along with CRCI will help to elucidate different CRCI phenotypes. Finally, studies are needed that evaluate if intervention strategies that can effectively target more than one symptom may result in significant improvements in cognitive function.

In terms of the scoping review, Table 3.3 provides several directions for future research. Examples include the need for studies that evaluate if tumor-specific factors are associated with different biomarkers for CRCI. In addition, studies that evaluate if a single or a combination of biomarkers is more sensitive and/or specific to determine the underlying mechanisms for CRCI would be useful. Finally, novel approaches to biomarker discovery will provide new insights. For example, multistage data-integrated omics analyses will allow for combined analysis of several types of molecular data in a single study. This approach may help elucidate the relative contribution of various types of biomarkers (e.g., genetic, epigenetic) to the occurrence and/or severity of CRCI.

In terms of the joint CRCI AND anxiety latent classes that were identified in a large sample of patients receiving chemotherapy, a variety of demographic and clinical characteristics were associated with the co-occurrence of these two symptoms, some of which are modifiable (e.g., optimal treatment of comorbid conditions, exercise). Studies that evaluate which co-morbid conditions contribute most to the co-occurrence of CRCI AND anxiety and those that

investigate the underlying mechanisms will provide information that can be used to inform intervention studies. In addition, worse CRCI AND anxiety profiles were associated with higher levels of three common types of stress, exposure to a higher number of stressful life events, and lower levels of resilience. These findings suggest that patients with a significant history of adverse life events and/or trauma may be at an increased risk of a higher symptom burden. Longitudinal studies will help elucidate the directionality of these relationships.

In terms of associations between membership in the lowest versus highest CRCI AND anxiety latent classes and perturbations in neurodegenerative pathways, findings suggest that common mechanisms may exist for the co-occurrence of cognitive impairment and anxiety in patients receiving chemotherapy and in patients with other neurodegenerative diseases. While these findings warrant confirmation, they support additional investigations focused on these two common cancer-associated symptoms and neurodegenerative mechanisms (e.g., oxidative stress, apoptosis). In addition, studies that evaluate these two symptoms individually will provide important information on common and distinct mechanisms.

In conclusion, this dissertation presented a newly developed comprehensive conceptual model of CRCI. This new model was tested using structural regression methods. Next, the findings from a scoping review of the literature described the depth and breadth of available evidence on blood-based biomarkers of CRCI. In addition, using data from a sample of patients with heterogenous types of cancer with distinct joint CRCI AND anxiety profiles, differences in demographic and clinical characteristics and in levels of global stress, cancer-specific stress, cumulative life stress, and resilience were described. Finally, associations between the CRCI AND anxiety latent classes and perturbed neurodegenerative pathways were reported. Taken together, the research presented in this dissertation increases knowledge of CRCI as a single symptom and the co-occurrence of CRCI AND anxiety in patients receiving chemotherapy and provides substantive directions for future research.

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