COGNITIVE SYMPTOMS AND IMMUNE RESPONSES IN COLORECTAL CANCER

by

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DEDICATION

To my husband, son, mom, and dad

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TABLE OF CONTENTS

DEDICATION …….. ii

ACKNOWLEDGEMENTS ……. iii

LIST OF TABLES ……... viii

ABSTRACT ……. xi

CHAPTER I. INTRODUCTION ……..... **1**

Study Aim and Research Questions ……..... 3

Cognitive Impairment in Cancer survivors …… 4

Patient Characteristics Associated with Cognitive Impairment …….. 14

The Immune Response: Inflammation and the Acute Phase Reaction 20

The Acute Phase Reaction: Cognitive Function ……... 25

Theoretical Framework …….. 31

References …….. 34

CHAPTER II. COGNITIVE SYMPTOMS IN COLORECTAL CANCER SURVIVORS …….. **61**

Introduction …… 61

Methods …….. 64

Measures …… 65

Study Procedures …… 69

Data Analyses …… 70

Results …… 71

Discussion …….. 74

References …….. 79

CHAPTER III. INFLAMMATORY CYTOKINES AND BIOMARKERS IN COLORECTAL CANCER …… 89

Introduction …… 89

Methods …….. 91

Measures …… 92

Study Procedures …… 94

Data Analysis …….. 95

Results …… 96

Discussion …….. 100

References …….. 109

CHAPTER IV. COGNITIVE SYMPTOMS AND INFLAMMATION ….. 122

Introduction …… 122

Methods …….. 125

Measures …… 125

Study Procedures …… 131

Data Analysis …….. 132

Results …… 132

Discussion …….. 138

References …….. 145

CHAPTER V. CONCLUSIONS ……... 162

Improving Colorectal Cancer Survivorship …… 163

Limitations …….. 166

Recommendations for Future Research …….. 168

Implications for Nursing Practice and Research …… 170

References …….. 176

LIST OF TABLES

Table

1.1	Alterations in Attention and Memory Before Cancer Treatment……	49
1.2	Alterations in Attention and Memory Associated with Cancer Treatments: Surgery ……	50
1.3	Alterations in Attention and Memory Associated with Cancer Treatments: Chemotherapy and Radiation Therapy ……	51
1.4	Alterations in Attention and Memory Associated with Cancer Treatments: Immunotherapy……	54
1.5	Patient Characteristics Associated with Alterations in Attention and Memory …….	55
1.6	Circulating Inflammatory Cytokines in Individuals with Cancer Prior to Any Treatment (Serum, Plasma) ……..	56
1.7	Inflammatory Cytokines and Cognitive Function ……..	58
2.1	Medical and Demographic Characteristics of Individuals With and Without Colorectal Cancer …….	83
2.2	Disease and Treatment Characteristics of Individuals with Colorectal Cancer …….	84
2.3	Means and Standard Deviations of Physical and Psychological Symptoms	85
2.4	Means and Standard Deviations of Overall Attention Measures ……	86
2.5	Means and Standard Deviations of Attention and Memory Measures ...	87
2.6	Pearson Correlation Coefficients Between Directed or Controlled Attention and Working Memory and Selected Covariates ……	87
2.7	Predictors of Attention and Working Memory Standardized Total Composite Score ……	88

2.8	Predictors of Attention and Working Memory Attentional Function Index Self-report ……	88
3.1	Sample Characteristics ……..	114
3.2	Medical and Treatment Characteristics of Individuals with Colorectal Cancer …….	115
3.3	Means and Standard Deviations of Inflammatory Cytokines and Biomarkers ……..	116
3.4	Pearson Correlation Coefficients Between Inflammatory Cytokines and Biomarkers and Immune Function Modifiers …….	117
3.5	Predictors of Tumor Necrosis Factor-alpha …….	118
3.6	Predictors of Interleukin-6 ……..	118
3.7	Predictors of C-reactive Protein …….	119
3.8	Predictors of Interleukin-10 ……..	119
3.9	Predictors of Transforming Growth Factor – beta1 ……..	120
3.10	Predictors of TNF-α/IL-10 Ratio ……..	120
3.11	Predictors of IL-10/TNF-α Ratio ……	121
4.1	Sample Characteristics ……	152
4.2	Mean and Standard Deviations of Physical and Psychological Symptoms	153
4.3	Pearson Correlation Coefficients Between Cognitive Function Variables and Inflammatory Cytokines and Biomarkers ……	154
4.4	Pearson Correlation Coefficients Between Cognitive Function Variables and Potential Cognitive Function Modifiers ……	155
4.5	Pearson Correlation Coefficients Between Serum Levels of Inflammatory and Biomarkers and Potential Immune Function Modifiers ……	156
4.6	Predictors of Standardized Total Composite Score with IL-6 …….	157
4.7	Predictors of Standardized Total Composite Score with CRP ……..	157

4.8 Predictors of Standardized Total Composite Score with IL-6 and CRP … 158

4.9 Predictors of Attentional Function Index with CRP ……. 158

4.10 Predictors of Attentional Function Index with TGF-β1 …… 159

4.11 Predictors of Attentional Function Index with CRP and TGFβ1 ……. 159

4.12 Predictors of RAVLT delayed recall with TNF-α …… 160

4.12 Predictors of RAVLT delayed recall with IL-6 ……. 160

4.14 Predictors of RAVLT delayed recall with TNF-α and IL-6 ……. 161

ABSTRACT

Individuals with cancer may experience cognitive symptoms related to the immune system's response to the cancer and cancer treatments. Specifically, inflammatory cytokines can induce clusters of physical symptoms and behavioral responses called 'sickness behaviors'. Cognitive symptoms appear to occur alongside sickness behaviors in individuals with cancer. Little research has examined cognitive symptoms and immune function in individuals with colorectal cancer (CRC). The purpose of this cross-sectional comparative study was to 1) describe cognitive symptoms and inflammatory cytokine and biomarker expression in individuals with CRC, and 2) begin to characterize the relationship between cognitive symptoms and inflammatory cytokines and biomarkers. A biobehavioral model was used to examine cancer-related cognitive symptoms and proposes that symptoms and physiologic changes share a common psychoneuroimmunologic mechanism.

Participants included 50 men and women newly diagnosed with primary or recurrent CRC within the past six months (M = 55 years) and a comparison group of 50 similar individuals without CRC (M = 58 years). Cognitive symptoms were measured using tests of attention (Attention Network Test), directed attention and working memory (Digit Span, Trail Making Test, Attentional Function Index), and long-term memory (Rey Auditory Verbal Learning Test, Everyday Memory Questionnaire). Pro-inflammatory cytokines (interleukin-1beta, interleukin-6, tumor necrosis factor-alpha) and biomarkers

(interleukin-1 receptor antagonist, C - reactive protein, interleukin-10, transforming growth factor-beta1) were measured using standard commercial assays.

As hypothesized, CRC participants performed worse on measures of directed attention and working memory and had higher serum levels of interleukin-6, C-reactive protein, and interleukin-10 compared to healthy controls. Unexpectedly, CRC participants had lower serum levels of transforming growth factor-beta1 compared to controls. Significant relationships were found between cognitive and immune variables using multiple regression analyses. Specifically, 1) higher serum C-reactive protein levels predicted poorer directed attention and working memory performance [$F = (7, 91) = 6.17$, $p < 0.001$], and 2) higher C-reactive protein and lower transforming growth factor-beta1 levels predicted poorer directed attention and working memory on self-report [$F = (8, 90) = 9.92$, $p < 0.001$] after controlling for covariates. These novel findings have important implications for understanding the illness experience in CRC and developing interventions to optimize cognitive function.

CHAPTER I

INTRODUCTION

Currently there are nearly 14 million individuals in the United States with a personal history of cancer (American Cancer Society, 2013). Cancer and cancer treatments can affect the health and normal functioning of cancer survivors (Institue of Medicine, 2006). Cognitive function is one such functional ability altered by cancer and cancer treatments. Cognitive processes consistently altered in this population include attention, working memory, and long-term memory (Wefel, Vardy, Ahles, & Schagen, 2011). These cognitive processes are necessary for planning and carrying out tasks, learning, problem solving, interpersonal behavior, and effective functioning (Mesulam, 2000). As such, they are critical for understanding and coping with cancer and cancer treatments as well as fundamental for everyday functioning. Little is known about the mechanisms that may underlie cognitive symptoms and impaired function in individuals with cancer. One potential mechanism is an increase in inflammatory cytokine expression secondary to the immune system's response to the cancer cells and tissue injury (Cleeland et al., 2003; Kelley et al., 2003). Specifically, pro-inflammatory cytokines (e.g. interleukin-1, interleukin-6, tumor necrosis factor-alpha) produced in the tumor's microenvironment or by immune cells at the site of tissue injury (secondary to cancer treatments) can act on the central nervous system to elicit symptoms and behavioral responses that generally favor the recovery of the individual but can be

detrimental to health if excessive (Balkwill & Mantovani, 2012; Hart, 1988; Kumar, Abbas, Fausto, Robbins, & Cotran, 2005; Murphy, Travers, Walport, & Janeway, 2012).

Cognitive symptoms and impaired function appear to occur alongside cytokine-induced symptoms and behavior and have been associated with pro-inflammatory cytokines in preclinical and clinical studies (Ader, 2007; Smith, Tyrrell, Coyle, & Higgins, 1988; Spath-Schwalbe et al., 1998; Vollmer-Conna et al., 2004). These studies suggest that alterations in attention and memory experienced by some individuals with cancer may be part of an immune response to the cancer and/or cancer-related treatments. The relationship between cytokines and cognitive function in individuals with cancer has been largely unexplored. Individuals with colorectal cancer may be particularly vulnerable to cytokine-induced cognitive changes given that colorectal cancer is characterized by large tumors capable of producing significant amounts of inflammatory cytokines. After an extensive literature search, only a few studies were found that examined cognitive function in individuals with cancer during the initial phase of the illness (Bond, Dietrich, & Murphy, 2012; Cimprich, 1999; Hermelink et al., 2007; Meyers, Albitar, & Estey, 2005; Meyers, Byrne, & Komaki, 1995) and even fewer that examined cognitive function in colorectal cancer survivors (Vardy et al., 2007). Further, only one preliminary study was found that examined the relationship between cognitive function and cytokine expression in individuals with cancer (Meyers et al., 2005). Thus, this dissertation study will begin to address these understudied and important areas of colorectal cancer survivorship.

This dissertation paper consists of five chapters. The introduction chapter will include: the dissertation study's specific aim and three research questions, a brief review

of the literature examining cognitive impairment and systemic inflammation in cancer, and a novel biobehavioral model in which to study cognitive changes in individuals with cancer. The subsequent three chapters will present completed research for each of the three research questions. Finally, chapter five will summarize major research findings, discuss strengths and limitations of the work, and describe directions for future studies.

Study Aim and Research Questions

The specific aim with corresponding hypotheses for this study:

Aim 1. To examine if a relationship exists between deficits in attention and memory and alterations in the expression of pro-inflammatory cytokines and selected biomarkers of inflammation in individuals newly diagnosed with colorectal or recurrent colorectal cancer.

Hypothesis 1a: Compared to participants without colorectal cancer, individuals newly diagnosed with colorectal cancer or recurrent colorectal cancer will show alterations in the cognitive performance on measures of attention, working and long-term memory.

Hypothesis 1b: Compared to participants without colorectal cancer, individuals newly diagnosed with colorectal or recurrent colorectal cancer will show alterations in the expression of pro-inflammatory cytokines interleukin-1beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), and selected biomarkers of inflammation.

Hypothesis 1c: Lower performance on objective measures of attention and memory will be related to elevated levels of pro-inflammatory cytokines interleukin-1beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha

(TNF-α), and selected biomarkers of inflammation in the combined group of individuals with and without colorectal cancer.

Cognitive Impairment in Cancer Survivors

Alterations in attention and memory have been observed in individuals with a variety of tumors including: breast, prostate, lung, colorectal, ovarian, testicular, melanoma, leukemia, and lymphoma (Skaali et al., 2011a; Vardy & Tannock, 2007; Wefel, Vardy, et al., 2011). They have also been observed alongside focal neural deficits in individuals with central nervous system disease (primary and metastatic tumors) suggesting that a ubiquitous physiological response to the cancer may underlie changes in attention and memory (Correa, 2010). The time course of cognitive decline and recovery for an individual cancer survivor is largely unknown. Cross-sectional studies and longitudinal studies assessing treatment-associated effects suggest that cancer survivors can experience cognitive changes after diagnosis and before any treatment, during primary and adjuvant therapy, and up to 20 years post treatment (Koppelmans et al., 2012; Vardy & Tannock, 2007). Not all cancer survivors experience cognitive changes or are equally affected suggesting that there may be additional patient characteristics that contribute to an individual's ability to function (e.g. age, presence of comorbid health problems) (Cimprich, 1998; Wefel, Vardy, et al., 2011). This section will: 1) review alterations in cognitive function in individuals with cancer and 2) describe patient characteristics associated with cognitive symptoms and impaired function in individuals with cancer. The focus of this review will be on non-central nervous system cancers and treatments.

Cancer Associated Changes in Attention and Memory Function

Several research studies have assessed cognitive function in individuals with cancer before *any* treatment (Bond et al., 2012; Cimprich, 1998, 1999; Cimprich & Ronis, 2001; Hermelink et al., 2007; Meyers et al., 2005; Meyers et al., 1995). See Table 1.1. Six of these seven studies found that individuals with leukemia, lung, breast, and head and neck cancers performed or perceived their function to be significantly worse on tasks requiring attention, working memory, and long-term memory (Digit Span, Trail Making Test A & B, Symbol Digit Modalities Test, d2, Regensberg Word Fluency Test, Verbal Selective Reminding test, Rey's Auditory Verbal Learning Test**,** Hopkins Verbal Learning Test, Necker Cube Pattern Control test, Attentional Function Index) (Bond et al., 2012; Cimprich, 1999; Cimprich & Ronis, 2001; Hermelink et al., 2007; Meyers et al., 2005; Meyers et al., 1995). One study by Cimprich (1998) did not observe significant alterations in attention and working memory in women with early stage breast cancer prior to surgery. However, Cimprich (1998) did find that scores on a brief battery of neuropsychological tests were skewed to the lower end of the published normative range suggesting that subtle changes in attention and working memory were present (Digit Span, Digit Symbol Modalities Test, Necker Cube Pattern Control test).

Together, the above studies provide evidence that individuals newly diagnosed with cancer can experience changes in attention, working memory, and long-term memory at diagnosis and before any treatment for the disease. These studies suggest that cognitive changes may be associated with the cancer itself. Further research is needed to explore whether there is a subgroup of individuals that is particularly vulnerable to the effects of

cancer or if cognitive changes are associated with how an individual responds to a new diagnosis of cancer.

Cancer Treatment Associated Changes in Attention and Memory

Surgery. Although research studies have observed deficits in attention, working memory, and long-term memory after surgery and before adjuvant therapy, few studies have assessed the effects of surgery on cognitive function in individuals with cancer using a pre/post or longitudinal design (Cimprich, 1999; Cimprich et al., 2010; Cimprich & Ronis, 2001; Quesnel, Savard, & Ivers, 2009; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004; Wefel et al., 2011). To date, three studies were found that examined cognitive function before and after surgery (Cimprich, 1998; Cimprich & Ronis, 2001; Hedayati, Schedin, Nyman, Alinaghizadeh, & Albertsson, 2011). See Table 1.2. Specifically, Cimprich (1998) assessed cognitive function in 74 women newly diagnosed with early stage breast cancer approximately 12 days before and 15 days after breast conserving surgery or mastectomy. She found that older women (65 - 79 years) as well as middle-aged women (46 – 64 years) undergoing a mastectomy experienced a significant decline in performance on measures of attention and working memory from pre to post surgery (Composite Score: Digit Span, Symbol Digit Modalities Test, & Necker Cube Pattern Control Test) but not for middle aged women undergoing breast conserving surgery or younger women (25 – 45 years). Hedayati and colleagues (2011) assessed cognitive function in 71 women newly diagnosed with breast cancer before diagnosis and 63 women without breast cancer. Participants in the breast cancer group were assessed before diagnosis and one month after breast conserving surgery or mastectomy. Researchers found that individuals

with breast cancer performed worse at baseline on measures of attention and working memory and failed to improve after surgery unlike women in the healthy control group who improved significantly at retest (Cognitive Stability Index). Researchers noted that a failure to find a practice effect in women with breast cancer may suggest a subtle decline in function. Finally, Cimprich and Ronis (2001) assessed cognitive function in 47 older women (55 to 79 years) newly diagnosed with early stage breast cancer (I, II) and 48 women of similar age in a healthy control group. Participants in the breast cancer group were assessed approximately 12 days before and at two time points after breast conserving surgery or mastectomy (two weeks, three months). Researchers found that individuals with breast cancer performed significantly worse on measures of attention and memory at baseline compared to healthy individuals but that after surgery they gradually improved (between two weeks after surgery and three months after surgery) (Composite Score: Digit Span, Symbol Digit Modalities Test, & Necker Cube Pattern Control Test).

These three studies suggest that some individuals with cancer can experience cognitive changes prior to surgery and that cognitive deficits can persist or gradually get better after surgery. Further, these studies suggest that a subgroup of individuals (older age, more extensive surgery) can experience an acute decline in function after surgery (Cimprich, 1998; Cimprich & Ronis, 2001; Hedayati et al., 2011).

From an immune perspective, the pattern of cognitive recovery observed in some individuals may be associated with a dampening down of the immune response secondary to a reduced tumor burden (surgical removal of the primary tumor). Alternatively, the failure for attention and memory to improve to performance levels observed in healthy

controls as well as cognitive decline observed in other individuals may be associated with a continued immune response to the surgical intervention (extensive tissue injury) as well as other factors (e.g. aging immune and central nervous systems).

Chemotherapy. Eight studies were found that examined the effects of chemotherapy on cognitive function using a pre/post or longitudinal design (Bender et al., 2006; Hensley et al., 2006; Hermelink et al., 2007; Hess et al., 2010; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Kaasa, Olsnes, & Mastekaasa, 1988; Skaali, Fossa, et al., 2011a; Skaali, Fossa, & Dahl, 2011). See Table 1.3. Excluded from this review were studies that included a population of individuals receiving multiple therapies (i.e. chemotherapy plus hormone therapy or radiation therapy). Two of the eight studies included in this review assessed individuals prior to surgery or any other therapy (neoadjuvant chemotherapy or main treatment) and six studies assessed individuals after surgery and before initiating chemotherapy (adjuvant chemotherapy). The majority of these studies observed cognitive decline in individuals with cancer or a subgroup of individuals with cancer over the course of the chemotherapy. Specifically, Hermelink and colleagues (2007) assessed cognitive function in women before and prior to their final cycle of neoadjuvant chemotherapy (epirubicin, paclitaxel, cyclophosphamide) for breast cancer. They found that individuals with breast cancer before any treatment for their disease performed significantly worse on measures of attention and memory compared to normative data. Additionally, they observed cognitive decline in a subgroup of individuals with breast cancer. Specifically, researchers found that 27 of 101 women newly diagnosed with breast cancer had a significant decline in cognitive function over the course of chemotherapy on a battery of neuropsychological tests that included tests of

attention and memory (Logical Memory I & II, Digit Span, d2, Trail Making A & B, Regensberg Word Fluency Test). Kaasa and colleagues (1988) assessed cognitive function in 62 men and women with inoperable non-small cell lung cancer before main treatment with chemotherapy and five weeks after the last course of chemotherapy (cisplatin, etoposide). In this study researchers observed a decline in attention and memory function (lower scores from baseline) in a subgroup of individuals on a variety of neuropsychological measures including: Trail Making Test A (29), Trail Making Test B (50), Verbal Learning Test – 10 trial (32), Verbal Learning Test - 5 trial (6), Benton Visual Retention Test - correct answers (43), and Benton Visual Retention Test - incorrect answers (50). Hess and colleagues (2010) assessed cognitive function in 27 individuals newly diagnosed with ovarian cancer at three time points: after surgery and before chemotherapy, after three cycles of chemotherapy and after six cycles of chemotherapy (platinum-based therapy). Researchers found that 92 of participants at time two and 86 of participants at time three showed a decline in at least one of three subtests of the Cognitive Stability index (a decrease of one or more standard error of the mean [SEM] from baseline). Jansen and colleagues (2008) assessed cognitive function in 30 individuals with breast cancer at two time points: before the initiation of chemotherapy and after four cycles of chemotherapy (doxorubicin, cyclophosphamide). Researchers found that 33 of participants demonstrated a decline in attention and memory function (a decrease of one or more standard deviation [SD]) (Repeatable Battery of Adult Neuropsychological Status, RBANS). Finally, Skaali and colleagues (2011a) assessed 122 individuals with testicular cancer after orchiectomy and before chemotherapy and 12 months after chemotherapy (bleomycin, etoposide, cisplatin).

Researchers found that 38 of participants receiving one to four cycles of chemotherapy showed a decline of $\geq$ 10 on measures of attention and memory (CANTAB). Additionally, Skaali and colleagues (2011b) found that approximately a quarter of participants reported an increase in attention and memory problems one year after treatment (two questions: How is your attention/memory; four response alternatives).

In contrast to the above, two studies were found that did not observe a decline in attention and memory in individuals with cancer receiving chemotherapy for their disease. The first study by Bender and colleagues (2006) assessed cognitive function in women with early stage breast cancer receiving chemotherapy alone (n = 19), receiving chemotherapy and hormone therapy (n = 15) and not receiving chemotherapy or hormone therapy (n = 15). Participants were assessed at three time points: after surgery and before chemotherapy, within one week of completing chemotherapy or similar time in individuals not receiving chemotherapy, and one year after completing chemotherapy or a similar time in individuals not receiving chemotherapy. Researchers did not observe any difference on cognitive measures at baseline between the groups nor did they observe any significant decline in performance in women receiving chemotherapy only (Rey Auditory Verbal Learning Test, Four Word Short Memory Test, Rey Complex Figure Test). In the second study by Hess and colleagues (2007) cognitive function was assessed in 20 women with ovarian cancer before chemotherapy and after their 2^{nd} and 5^{th} cycles of chemotherapy. Researchers observed a non-significant trend toward improved performance on measures of attention and working memory over the course of chemotherapy (Trail Making A & B, Digit Span Forward). Interestingly, highly educated

participants in this study reported a decline in attention and memory function after two cycles of chemotherapy and a return to baseline after five cycles of chemotherapy.

Together the above studies provide evidence that some individuals with cancer experience a decline in attention and memory function over the course of chemotherapy while other individuals may experience improved or no change in attention and memory function. Given the observation that individuals with cancer may also experience deficits in their attention and memory before chemotherapy, these studies may also suggest that individuals with deficits in attention or memory before chemotherapy can: 1) improve and possibly return to baseline function over the course of chemotherapy, 2) not improve nor decline but remain with deficits over the course of chemotherapy, and 3) decline and experience further losses in attention and memory over the course of the chemotherapy. Further research is needed to examine attention and memory function in individuals with cancer receiving chemotherapy and an individual's pattern of cognitive functioning from pre-treatment to completion of the therapy.

From an immune perspective, cognitive recovery and stability may be associated with reduced tumor burden (effects of chemotherapy on primary tumor or micrometastatic disease). Declines in cognitive function may be associated with a continued inflammatory immune response to the cancer (progression, metastatic disease) and/or tissue injury associated with the chemotherapy as well as other unidentified factors.

Radiation Therapy. Two studies were found that examined the effects of non-CNS radiation therapy on cognitive function. Similar to the review above, studies were excluded if they included a population of individuals receiving a mix of therapies (e.g. radiation therapy plus hormone therapy). One of the two studies was excluded from this

review because of concern that findings may be related to incidental cerebral irradiation (nasopharyngeal carcinoma) (Lam, Leung, & Chan, 2003). The remaining study by Kaasa and colleagues (1988) assessed cognitive function in 34 individuals with inoperable non-small cell lung cancer receiving radiation therapy to the site of the primary tumor. Participants were tested before radiation therapy and 11 weeks after treatment was ended. See Table 1.3. Researchers did not compare pretreatment performance on cognitive measures to normative data or a control group. Researchers found a decline in attention and memory function in a subgroup of participants (lower scores from baseline) (24 on Trail Making Test A, 31 on Trail Making Test B, 41 on the Verbal Learning Test – 10 trials, 41 on the Verbal Learning Test - 5 trials, 38 on the Benton Visual Retention Test- correct answers, and 21 on the Benton Visual Retention Test- incorrect answers). Findings from this study provide preliminary evidence that some individuals newly diagnosed with cancer receiving local radiation therapy for non-CNS tumors can experience changes in cognitive function over the course of radiation therapy.

From an immune perspective, declines in cognitive function may be associated with the cancer, tissue injury associated with the radiation therapy, and/or other unidentified factors. Further research is needed to assess cognitive and immune function individuals receiving local radiation therapy for non-CNS tumors.

Immunotherapy. Three studies were found that examined cognitive function in individuals receiving immunotherapy for cancer using a pre/post or longitudinal study design (Bender et al., 2000; Capuron et al., 2002; Capuron, Ravaud, & Dantzer, 2001). See Table 1.4. Excluded from this review were studies that included individuals

receiving a mix of other therapies (i.e. immunotherapy plus chemotherapy or radiation therapy). Two of the three studies included in this review assessed individuals after surgery and before any other therapy. Specifically, Bender and colleagues (2000) assessed cognitive function in 18 individuals with melanoma receiving postoperative adjuvant interferon-alpha 2b (high dose, low dose) and a control group of individuals with melanoma not receiving adjuvant therapy. The authors observed a non-significant decline in attention and working memory function in individuals receiving high dose interferon-alpha 2b (TMT B). In a second study by Capuron and colleagues (2002), researchers assessed cognitive function of 20 men and women with melanoma receiving postoperative adjuvant interferon-alpha therapy with or without paroxetine for interferon-associated symptoms. Researchers found a significant increase in cognitive symptoms in individuals receiving interferon alone 12 weeks after initiating therapy (Neurotoxicity Scale: memory disturbances & poor concentration). Further, the percentage of individuals experiencing moderate to severe intensity of cognitive symptoms during interferon therapy alone were as follows: 30 loss of concentration, 15 memory disturbances, 15 word-finding problems, 10 episodes of confusion and 10 indecisiveness. Finally, the third study by Capuron and colleagues (2001) assessed cognitive function in 47 individuals with renal cell cancer and melanoma receiving interleukin 2 and/or interferon alpha. Researchers found that individuals receiving IL-2 monotherapy experienced an acute decline in performance on the measures of attention and memory five days after initiating therapy that appeared to persist at one month (Spatial Working Memory test, Stockings of Cambridge test). Individuals receiving high dose interferon-alpha therapy showed an acute decline in performance on a measure of attention

(multiple choice task) five days after initiating therapy that tended to persist at one month as well. Together, these studies provide preliminary evidence that individuals with cancer receiving immunotherapy can experience changes in attention and memory early in the course of therapy that can persist while receiving treatment.

From an immune perspective, declines in cognitive function may be associated with the immunotherapy and/ or stimulation of the immune response. Further research is needed to assess the long-term effects of immunotherapy on cognitive function in cancer survivors and whether attention and memory function improves after cessation of therapy.

Summary

The above studies provide evidence that individuals with cancer can experience changes in attention, working memory, and long-term memory at diagnosis and before any treatment for the disease and during/after treatment for the disease. Alterations in immune function may underlie these changes. Specifically, a robust production of inflammatory cytokines related to the cancer pathogenesis or cancer treatments may induce cognitive changes**.** Continued research is needed to assess cognitive function in cancer survivors with a variety of tumors over the trajectory of the illness. Further, research is needed to describe the subgroup of cancer survivors who experience cognitive changes and whether immune responses to the cancer and cancer treatments contribute to these cognitive changes.

Patient Characteristics Associated with Cognitive Impairment

To date, most studies assessing cognitive function in individuals with cancer have controlled for patient characteristics in the statistical analysis (covariates) but few studies

have assessed the potential effect of patient characteristics on cognitive function in individuals with cancer (possible risk factors). Eight studies were found that assessed the impact of patient characteristics on cognitive functioning in cancer survivors (Ahles et al., 2010; Ahles et al., 2003; Cimprich, 1998; Cimprich, So, Ronis, & Trask, 2005; Merriman et al., 2010; Schilder et al., 2010; Small et al., 2011; Vearncombe et al., 2009). These studies assessed patient characteristics across the disease trajectory from after diagnosis and before any treatment to up to five years after diagnosis. See Table 1.5. Characteristics associated with an increase in vulnerability to cognitive impairment in individuals with cancer include: older age, genotype (APOE ε4 allele, COMT Val allele), presence of other health problems, changes in hormones, and psychological distress. These characteristics will be discussed further below.

Age. Older age has been associated with poorer performance on measures of attention and working memory and is a significant predictor of attention and memory function in individuals newly diagnosed with breast cancer prior to treatment (Cimprich et al., 2005). Older age has also been associated with cognitive decline in women with breast cancer undergoing surgery and adjuvant chemotherapy (with or without radiation therapy, endocrine therapy) (Ahles et al., 2010; Cimprich, 1998). Cognitive changes in older adults may be related to both an aging brain and immune system. An aging brain has been associated with neurobiological decline and more recently functional changes. Recent research from neuroimaging studies suggests that an older brain may be functionally different or reorganized compared to a younger brain (Reuter-Lorenz & Lustig, 2005). Specifically, older adults appear to show more widespread brain activation (recruit more neural circuitry) than younger adults performing similar tasks.

This difference in activation may allow an older individual to compensate for efficiency or functional declines elsewhere in the brain and effectively perform a task (Reuter-Lorenz & Cappell, 2008). However, these functional changes may not always be sufficient to overcome deficits on high demand tasks or conditions requiring sustained use of neural circuitry.

An aging immune system may also contribute to cognitive changes. Specifically, an aging immune system is associated with low-level inflammation characterized by circulating cytokines (TNF-alpha, IL-6) and an increase in white cells (neutrophils, monocytes and natural killer cells) (Bruunsgaard, 2006). Cancer and cancer treatments can further stimulate the immune system resulting in an increased systemic cytokine response and alterations in attention and memory. Older age has also been associated with more reactive immune cells in the CNS (microglia). These immune cells appear to produce an exaggerated CNS inflammatory cytokine response to a peripheral immune challenge. An amplified inflammatory cytokine response in the brain can negatively affect neural plasticity and the neural substrate that supports attention and memory function (Corona, Fenn, & Godbout, 2012).

Interestingly, younger age has been associated with perceptions of poorer functioning on tasks that require attention and working memory in women newly diagnosed with breast cancer as well as women with breast cancer receiving adjuvant radiation therapy (Cimprich et al., 2005; Merriman et al., 2010). These findings suggest that younger women with breast cancer may also experience subtle changes in their attention and memory function (possibly related to inflammation and/or psychological distress) that are not detectable on standard tests of neuropsychological function.

Genotype. The APOE ε4 allele and the COMT-VAL allele have been associated with lower performance on measures of attention and memory in individuals with breast cancer (Ahles et al., 2003; Small et al., 2011). Other genetic factors that may affect cognitive function in individuals with cancer include polymorphisms in genes affecting the expression of inflammatory cytokines. Specifically, TNF-α-308 promoter single nucleotide polymorphism (SNP) has been associated with cognitive complaints in women treated with chemotherapy for breast cancer (Ganz et al., 2013). Further, IL-1β and IL-6 polymorphisms have been associated with cancer-related symptoms (fatigue, pain, sleep disturbances) but not yet explored in relation to cognitive impairment (Miaskowski & Aouizerat, 2012). Continued research is needed to assess the effect of immune-related genetic factors on cognitive function in cancer survivors.

Other Health Problems and Behaviors. Presence and number of health problems has been associated with poorer performance on measures of attention and memory function as well as perception of attention and memory function in women with breast cancer prior to any treatment and after surgery before adjuvant therapy (Cimprich et al., 2005; Schilder et al., 2010; Vearncombe et al., 2009). Further, a decline in hemoglobin coupled with increased anxiety over the course of chemotherapy in women with breast cancer was found to significantly predict impairment in attention and memory function (Vearncombe et al., 2009). Inflammation and systemic cytokine expression can underlie *some* health problems and behaviors. Specifically, systemic inflammatory cytokine expression has been observed in individuals with infection, cardiovascular disease, diabetes, obesity, rheumatoid arthritis and other immune-mediated inflammatory diseases, smoking, alcohol consumption, and sleep disturbances (Calle & Fernandez,

2012; Giamarellos-Bourboulis & Raftogiannis, 2012; O'Connor & Irwin, 2010; Tedgui & Mallat, 2006; Williams & Meyers, 2002; Wisse, 2004). Individuals with cancer and other health problems or behaviors that induce systemic inflammatory cytokine expression may experience increased levels of circulating inflammatory cytokine and be more vulnerable to cognitive changes.

Hormones. Estrogen/androgen deprivation therapy for breast and prostate cancer has been associated with subtle but significant declines in cognitive function (Jamadar, Winters, & Maki, 2012; Walker, Drew, Antoon, Kalueff, & Beckman, 2012). Chemotherapy may also induce menopause in breast cancer survivors and individuals who experience treatment-induced menopause appear to be more vulnerable to cognitive decline than women who were post-menopausal at time of treatment initiation (Jenkins et al., 2006). To date, only one study was found that assessed the impact of hormones as a risk factor for cognitive changes in individuals with cancer. The study by Schilder and colleagues (Schilder et al., 2010) assessed the effect of lifetime estrogen exposure (number of reproductive years) and use of hormone replacement therapy (ever) on cognitive function in post-menopausal women with and without breast cancer. Breast cancer survivors were assessed after surgery and before adjuvant systemic therapy. Researchers found that a higher number of reproductive years in women with breast cancer predicted worse performance on attention and working memory measures. There were no significant findings associated with hormone replacement therapy and the study did not describe time since last menses. Estrogen and testosterone deficiency has been associated with subtle increases in pro-inflammatory cytokines (Maggio et al., 2005; Pfeilschifter, Koditz, Pfohl, & Schatz, 2002). These increases may be limited to the first

few years following age-related hormone changes when symptoms and other related conditions (bone loss) are most prominent. Individuals with cancer who have recently experienced a decline in estrogen or testosterone (natural or treatment-induced) may experience increased systemic inflammatory cytokine expression. Cancer and cancer treatments may further increase systemic cytokine expression leading to alterations in attention and memory.

Psychological Distress. At this time, psychological distress remains a poorly understood risk factor for impaired cognitive function in cancer survivors. However, anxiety and depressed mood have been correlated with poor performance on neuropsychological tests (word list learning, digit symbol, TMT) and perceived attention and memory function in individuals with cancer before any treatment and during/after therapy (Bender et al., 2006; Bond et al., 2012; Cimprich, 1999; Hermelink et al., 2007; Skaali, Fossa, et al., 2011b; Wefel, Vidrine, et al., 2011). Additionally, a study by Musselman and colleagues found that individuals with cancer who were depressed had higher levels of plasma IL-6 compared to individuals with cancer without depression and healthy controls (Musselman et al., 2001). This finding suggests that individuals with cancer experiencing psychological stress **(**a precipitant of mood disorders) can experience greater systemic inflammatory cytokine expression compared to individuals not experiencing psychological stress and thus may be more vulnerable to cognitive changes (Kendler, Karkowski, & Prescott, 1999). Immunologic models of psychological stress propose that persistent activation of the HPA axis and sympathetic nervous system can lead to a decreased ability to restrain the pro-inflammatory response and/or hyperactivity

resulting in the systemic expression of pro-inflammatory cytokines which can affect cognitive function (Elenkov, 2008).

Summary. The above studies provide preliminary evidence that patient characteristics including age, genotype, presence of other health problems, changes in hormones, and psychological stress can increase vulnerability to cognitive impairment in individuals with cancer. Alterations in immune function and an over expression of pro-inflammatory cytokines may be associated with these characteristics. Further research is needed to 1) assess the potential effect of patient characteristics on cognitive function in individuals with cancer (risk factors) and 2) examine whether an increased expression of inflammatory cytokines may underlie *certain* patient characteristics associated with cognitive decline.

The Immune Response: Inflammation and the Acute Phase Reaction

The immune system protects an individual from harmful stimuli and conditions and has a critical role in eradicating malignant cells as well as reducing immunogenicity of tumors (Chow, Moller, & Smyth, 2012). The immune system responds to noxious stimuli (i.e. infection, malignant cells) through inflammation. The goal of the inflammatory response is to destroy and/or remove the inciting stimulus, limit injury to the individual, and initiate the repair of injured tissues (Kumar et al., 2005). The inflammatory response is characterized by both local and systemic responses. The systemic response, also known as the *acute phase reaction* (APR), occurs when there is significant injury or threat to the individual and provides an additional level of defense against noxious stimuli. It consists of metabolic changes (negative nitrogen balance, decreased gluconeogenesis, increased lipolysis), physiologic changes (fever, altered

concentration of plasma constituents; hematopoietic changes, hepatic changes), and behavioral changes (anorexia, fatigue, somnolence) (Gabay & Kushner, 1999). These systemic effects provide additional support by enhancing leukocyte emigration and function, sustaining the immune response, limiting local tissue injury, creating a hostile environment for microbes, and reducing energy demands (Gabay & Kushner, 1999; Hart, 1988). The APR is mediated by inflammatory cytokines originating from immune cells, hematopoietic cells (platelets), stromal cells, and tumor cells in the tumor microenvironment or at sites of tissue injury. Inflammatory cytokines associated with the APR include: interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and Transforming Growth Factor-β1 (TGF-β1). These cytokines can act on one or more target cells locally or at distant sites in the body to induce effects.

The Acute Phase Reaction in Individuals with Cancer

Individuals with cancer appear to experience an acute phase reaction (APR) to the cancer and cancer treatments. Specifically, research studies have observed cytokine-induced metabolic changes (increased energy expenditure, muscle wasting, and lipolysis), physiologic changes (fever, increased acute phase proteins, hypoalbuminemia, anemia, leukocytosis and thrombocytosis) and behavioral changes (anorexia, fatigue, changes in sleep, depressed mood) in individuals with cancer (Argiles, Busquets, Felipe, & Lopez-Soriano, 2005; Bower, 2008; Buergy, Wenz, Groden, & Brockmann, 2012; Dalal & Zhukovsky, 2006; Spivak, 2005; Wilcox, 2010). Additionally, an over expression of APR-associated inflammatory cytokines has been observed in individuals with cancer both after diagnosis and before any treatment and in response to cancer therapies.

Research studies examining cytokine expression in the systemic circulation of individuals with cancer before any treatment have found interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) to be consistently elevated in a variety of tumors including: breast, prostate, colorectal, gastric, melanoma, leukemia, lymphoma, ovarian, cervical, testicular, kidney, and sarcoma (Chopra, Dinh, & Hannigan, 1998; Dosquet et al., 1994; Duffy et al., 2008; Dymicka-Piekarska, Matowicka-Karna, Gryko, Kemona-Chetnik, & Kemona, 2007; Esfandi, Mohammadzadeh Ghobadloo, & Basati, 2006; Gaiolla, Domingues, Niero-Melo, & de Oliveira, 2011; Ikeguchi et al., 2009; Jablonska et al., 2001; Kabir & Daar, 1995; Kaminska et al., 2005; Lambeck et al., 2007; Maccio et al., 2005; Meyers et al., 2005; Nikiteas et al., 2005; Porter et al., 2001; Rutkowski, Kaminska, Kowalska, Ruka, & Steffen, 2003; Shariat et al., 2001; Yeon et al., 2011). See Table 1.6. Interestingly, elevated IL-6 levels also appear to be related to tumor stage and prognosis with higher levels being associated with advanced disease and poor prognosis. Research studies have also observed an increase in APR-associated cytokines secondary to cancer treatments including surgery, chemotherapy, and radiation (Baker, El-Gaddal, Williams, & Leaper, 2006; Bower et al., 2009; Mettler et al., 2004; Nakazaki, 1992; Sleijfer, Vujaskovic, Limburg, Schraffordt Koops, & Mulder, 1998; Tang et al., 1996; Tsavaris, Kosmas, Vadiaka, Kanelopoulos, & Boulamatsis, 2002). Together these studies suggest that individuals with cancer experience a systemic inflammatory response to the cancer and cancer treatments.

The Acute Phase Reaction: Communication Pathways to the Brain

Peripheral inflammatory cytokines can communicate with the brain through several pathways including: 1) active transport across the blood brain barrier, 2)

activation of blood brain barrier cells to induce the synthesis and release of secondary immune messengers (e.g. prostaglandins), 3) activation of immune cells in the circumventricular organs to induce the synthesis and release of cytokines, 4) activation of peripheral afferent nerves to transmit an immune message to the brain, and 5) infiltration of activated peripheral immune cells into the brain (D'Mello, Le, & Swain, 2009; Dantzer, Konsman, Bluthe, & Kelley, 2000; Konsman, Kelley, & Dantzer, 1999; Quan & Banks, 2007; Quan, Whiteside, & Herkenham, 1998). These pathways are not mutually exclusive but rather appear to complement each other. It has been proposed that the rapid immune to brain cytokine signaling via peripheral afferent nerves may prime the brain for additional immune messages via other pathways (Dantzer et al., 2000; Konsman et al., 1999). Transmission of the immune message to the brain results in locally produced cytokines within the brain (Dantzer et al., 2000). These cytokines can activate local neurons as well as recruit immune cells (microglial cells, perivascular macrophages) in adjacent brain regions to propagate the immune message to distant regions of the brain (Dantzer et al., 2000; Konsman et al., 1999; Vitkovic et al., 2000). Production of inflammatory cytokines in the brain is generally transient, however, if there is no resolution of the peripheral immune challenge, prolonged inflammatory cytokine expression and activated glial cells can contribute to a persistent altered brain environment (Godbout & Johnson, 2006).

The Acute Phase Reaction: Neural Function

The relationship between pro-inflammatory cytokine expression and neural function has been primarily assessed in preclinical studies. These studies suggest that an overexpression of cytokines is associated with impaired function (Ader, 2007; McAfoose

& Baune, 2009). Potential pathways by which increased levels of pro-inflammatory cytokines alter neural processes and the substrate that supports attention and memory include: 1) inhibiting long-term potentiation or the strengthening of synaptic contacts between neurons, 2) activating the HPA axis and altering the production of corticosteroids necessary for memory processes (inverted U-shaped relationship), 3) altering the concentration, metabolism, and/or reuptake of neurotransmitters in the prefrontal cortex, hippocampus, and hypothalamus (dopamine, norepinephrine, acetylcholine, serotonin and glutamate), and 5) impairing neurogenesis (Ader, 2007; Dunn, 1992; Godbout & Johnson, 2006; Hayley, Brebner, Lacosta, Merali, & Anisman, 1999; Ida et al., 2008; Kabiersch, del Rey, Honegger, & Besedovsky, 1988; Lacosta, Merali, & Anisman, 1998; Linthorst, Flachskamm, Muller-Preuss, Holsboer, & Reul, 1995; McAfoose & Baune, 2009; Rada et al., 1991; Zalcman et al., 1994). In humans, preliminary research in neurodegenerative conditions characterized by activated microglia and inflammatory cytokine expression in the brain (Alzheimer's and Parkinson's Disease) suggests that persistent inflammatory cytokine expression can impair neurogenesis and neuronal maturation (Hoglinger et al., 2004; Johnston, Boutin, & Allan, 2011; Li et al., 2008; Panaro & Cianciulli, 2012; Ziabreva et al., 2007). Further research is needed to build on these findings and examine how persistently increased pro-inflammatory cytokine expression in the brain can affect neural functions in humans.

Summary

Individuals with cancer can experience increased systemic inflammatory cytokine expression secondary to the immune system's response to the cancer and cancer treatments. Pro -inflammatory cytokines originating in the periphery can communicate

with the brain resulting in increased brain cytokines. Inflammatory cytokines within the brain can alter neural processes that support attention and memory function including neural plasticity, neuroendocrine function, neurotransmitter function and neurogenesis. If there is no resolution of a peripheral immune challenge (i.e. cancer) prolonged inflammatory cytokine expression within the brain has the potential to alter the brain environment. Continued research is needed to 1) describe the acute phase response in individuals with cancer, and 2) describe the communication pathways and effects of inflammatory cytokines on neural processes in humans.

The Acute Phase Reaction: Cognitive Function

Inflammatory cytokines have been associated with changes in cognitive functioning. Evidence for cytokine-induced changes in cognitive function comes from preclinical and clinical studies. Research studies using animal models have exclusively focused on alterations in learning and memory. Findings from these studies suggest that increased levels of inflammatory cytokines can impair hippocampal dependent memory processes. Importantly, findings from these studies also suggest that older age may be associated with an exaggerated neuroinflammatory response and increased vulnerability to cytokine-induced cognitive changes. For a review, see Huang & Sheng (2010). In humans, studies have assessed the cognitive behavior of individuals with minor illnesses and individuals with experimentally induced inflammation (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008; Capuron, Lamarque, Dantzer, & Goodall, 1999; Exton et al., 2002; Krabbe et al., 2005; Reichenberg et al., 2001; Smith et al., 1988; Smith, 1992; Smith, Tyrrell, Coyle, & Willman, 1987; Spath-Schwalbe et al., 1998; Vollmer-Conna et al., 2004). Additionally, one study was found that assessed the relationship between

cytokine expression and cognitive function in individuals newly diagnosed with leukemia and myelodysplastic syndrome (Meyers et al., 2005). These studies will be reviewed below.

Individuals with Minor Illnesses. Studies of cognitive behavior have been done in both healthy individuals injected with influenza and sick individuals with acute bacterial and viral infections(Capuron et al., 1999; Smith, 1992; Smith et al., 1987; Vollmer-Conna et al., 2004). See Table 1.7. Individuals with experimentally induced minor illnesses (influenza A & B) reported feeling drowsy and were impaired on objective measures of attention two to four days after injection with the virus. Alterations in attention included: a decreased ability to detect and respond to stimuli and an impaired ability to block irrelevant stimuli during an attention-demanding task (Stroop, Variable Fore-Period Simple Reaction Time task, Fives Detection Task) (Smith, 1992; Smith, et al., 1987). Attention and memory have also been found to be impaired in individuals with flu-like symptoms (Capuron et al., 1999). In a study by Capuron and colleagues(Capuron et al., 1999), individuals presenting with flu-like symptoms to a health clinic were assessed for cognitive changes and found to be impaired on three subtests of the Extended Rivermead Behavioral Memory Test (ERBMT) . Specifically, sick individuals were impaired on their ability to remember previously presented pictures and on their ability to recall a short newspaper article that they had just read (immediate and delayed recall). These cognitive tasks were significantly impaired in individuals with and without a fever suggesting that fever is not a necessary condition for cognitive impairment in sick individuals. Finally, the specific relationship between cytokines and cognitive function in individuals with minor illnesses has been relatively unexplored.

Only one research study was found that examined the relationship between cytokines and subjective reports of cognitive symptoms in individuals with acute bacterial and viral illnesses. This study found a strong positive correlation between IL-6 and poor concentration (Vollmer-Conna et al., 2004).

Interestingly, not all individuals with minor illnesses appear to experience cognitive changes. Specifically, Smith (1992) and Smith and colleagues (1987) assessed the cognitive function of healthy individuals injected with a cold virus (corona virus, rhinovirus) and observed that individuals with a cold did not perform significantly worse on measures of attention compared to individuals without (Stroop). These findings, along with the observation of attention and memory deficits in individuals with other minor illnesses, suggest that an individual's cognitive response to an immune challenge may depend on the nature and/or severity of the illness.

Individuals with Inflammation. Attention and memory of individuals with inflammation has been examined in healthy individuals injected with inflammatory cytokines or endotoxins (Brydon et al., 2008; Exton et al., 2002; Krabbe et al., 2005; Reichenberg et al., 2001; Smith et al., 1988; Spath-Schwalbe et al., 1998). See Table 1.7. Findings from these studies have been mixed with some studies finding a significant deterioration in attention, working memory and long-term memory function and other studies finding no change. Four studies were found that suggest a role for inflammatory cytokines in changes in attention and memory experienced by acutely ill individuals. First, Brydon and colleagues (2008) assessed the effects of peripheral inflammation following typhoid vaccination on cognitive function using a double blind crossover design. Researchers found that individuals who experienced a greater inflammatory

response (higher IL-6 levels) to the vaccination had significantly impaired performance on a measure of attention (Stroop). Second, Reichenberg and colleagues (Reichenberg et al., 2001) found that healthy young men injected with low dose *salmonella abortus* in a double blind crossover design experienced an impaired ability to recall story items (immediate & delayed), recall figures (immediate & delayed) and learn a 15 word list. These memory disturbances were significantly and positively correlated with cytokine expression in the first few hours after endotoxin administration. Interestingly, Reichenberg and colleagues (Reichenberg et al., 2001) also found that memory disturbances were evident 10 hours after endotoxin administration when all other behavioral responses to the endotoxin had subsided (fever, anorexia, depressed mood, anxiety). A third study by Smith, Tyrrell, Coyle, & Higgins (1988) examined the effects of varying doses of the cytokine interferon-alpha (IFN-α) on performance of a measure of attention (variable fore-period simple reaction-time task) and a measure of simple reasoning (Baddeley's syntactic reasoning tasks). Researchers found that healthy men and women given a higher dose of IFN-α (1.5 MU) were slower to detect and respond to stimuli but were not impaired on reasoning performance. These findings suggest that IFN-α may selectively alter attentional processes. Additionally, these findings suggest that the dose of cytokine can affect the expression of cognitive deficits. The fourth study by Spath-Schwalbe and colleagues (1998) assessed the effects of IL-6 on subjective feelings of concentration and found that subjects reported greater difficulties with concentration three hours after IL-6 administration compared to controls but that these complaints were transient and resolved 12 hours after IL-6.

In contrast to the above, two studies were found that did not find a significant change in cognitive function after administration of cytokines and cytokine inducers to healthy individuals. Krabbe and colleagues (2005) examined the effects of low dose *Escherichia coli* endotoxin on attention and working memory in healthy young men in a double blind crossover design. They found that low dose endotoxemia did not result in any significant changes in attention and memory function within the first 24 hours after endotoxin administration (Word List, Letter-Number Sequencing, Digit Span, Digit Symbol Coding Test, & Trail Making Test). However, they did report that poorer performance on the word-list learning test was related to higher levels of IL-6 and soluble tumor necrosis factor receptor. The second study by Exton and colleagues (2002) used a cross over design to examine the effects of a single dose of the cytokine interferon-beta-1b (IFN-β-1b) on attention and short-term memory in healthy male medical students and found that subcutaneous administration of IFN-β-1b at a dose which induced responses such as fever (8 MU) was not associated with changes in cognitive performance on objective measures of attention and memory (Trail Making Test, Digit Span, & d2). Unfortunately, the results of this study were limited by the finding that the scores on objective measures were high at all time points suggesting that the measures may have lacked sensitivity to subtle changes over the testing period (ceiling effect). These two studies were limited by a small sample size, a sample consisting of young men only, and an experimental design that examined the acute effects of a single dose of endotoxin or cytokine.

Individuals with Cancer. Only one study was found that assessed the relationship between cognitive function and cytokine expression in individuals with

cancer. The study by Meyers and colleagues (2005) assessed attention and memory function and measured serum levels of pro-inflammatory cytokines in individuals newly diagnosed with acute myelogenous leukemia or myelodysplastic syndrome. Researchers found that higher levels of IL-6 were associated with worse performance on measures of attention and working memory (Trail Making Test B). This finding suggests that cognitive changes in cancer survivors may be related to cytokine expression and systemic immune system activation.

Summary. The above studies provide evidence that immune activation and systemic inflammatory cytokine expression can affect attention, working memory, and long-term memory. The observation that experimentally induced cold viruses as well as experimentally induced low levels of inflammation (low dose cytokine administration) did not affect cognitive performance suggest that the nature of immune challenge as well as severity of the immune response or amount of systemic cytokines are important factors in the expression of cognitive deficits and symptoms. Unfortunately, only one study was found that observed the effects of peripheral immune activation and cytokine expression on cognitive function in individuals with cancer. Continued research is needed to describe: 1) the relationship between types of immune challenges and inflammatory cytokine expression and cognitive deficits, 2) the quantitative relationship between circulating inflammatory cytokine and cognitive deficits, and 3) the relationship between circulating inflammatory cytokines and cognitive deficits in individuals with cancer.

Theoretical Framework

Toward A Biobehavioral Model of Cognitive Symptoms in Individuals in Cancer

This review has described research at the interface of immunology, oncology, and cognitive neuropsychology and neuroscience and directed the conceptualization of a novel biobehavioral model in which to study cognitive changes in individuals with cancer. See Figure 1. This biobehavioral model suggests that individuals with cancer can experience an increase in inflammatory cytokine expression secondary to the cancer, tissue injury associated with cancer treatments, immunotherapy, infection, and from other health problems. Inflammatory cytokines originating from local sites in the body can communicate with the brain and alter neural and cognitive function. Specifically, peripheral inflammation and inflammatory cytokine expression has been associated with changes in attention, working memory and long-term memory. Cognitive symptoms and impaired attention and memory function in individuals with cancer have been observed alongside other cytokine induced physical symptoms and behavioral responses known as *Sickness Behavior* suggesting that alterations in cognitive function may be a part of a cluster of immune mediated physical symptoms and behavioral responses (Bower, 2008; Cleeland et al., 2003; Hart, 1988; Meyers et al., 2005). Sickness behavior refers to fatigue, anorexia, decreased general and social activity, hyperalgesia, and changes in sleep pattern and architecture (Dantzer, 2004; Watkins & Maier, 200; Hart, 1988). Cognitive function modifiers that have been associated with poorer performance on measures of attention and memory function in individuals with cancer include: older age, fewer years of education, anemia, symptom distress, anxiety, depression and menopause (Cimprich, 1999, Cimprich et al., 2005; Vearncombe et al., 2009). Immune function

modifiers that have been associated with alterations in inflammatory cytokine expression include: older age, advanced stage of disease, anxiety, depression, smoking history, and an increase in body mass index (BMI) (Belluco et al., 2000; Bruunsgaard & Pedersen, 2003; Chung & Chang, 2003; Cottam et al., 2004; Cull et al., 1996; Krabbe, Pedersen & Bruunsgaard, 2004; Lutgendorf et al., 2008; Musselman et al., 2001; Thorton, Andersen Crespin, & Carson, 2007).

Definitions of Attention, Working Memory, and Long-term Memory

Directed Attention and Working Memory. Attention, specifically directed or controlled attention, allows an individual to focus attention on important information in the environment while actively inhibiting other stimuli in the environment (James, 1892; Kaplan & Berman, 2010). Directed attention is necessary for goal-oriented behaviors and social functioning, and allows an individual to interact in the world in a purposeful way (Kaplan & Berman, 2010). Working memory shares a close functional connection with directed attention. It is a cognitive process that allows a limited amount of information to be maintained and manipulated so that higher cognitive functions can be achieved (Mesulam, 2000). Working memory is critical for learning, comprehension, verbal fluency, retrieving memories, reasoning, and problem solving (Mesulam, 2000). The neural substrate that supports directed attention and working memory and is responsible for exerting control over stored contents includes the dorsolateral prefrontal cortex and the anterior cingulate cortex (Bush, Luu, & Posner, 2000; Posner, Rothbart, & Sheese, 2007; Smith && Jonides, 1999).

Long-term Memory. Long-term Memory, specifically declarative memory, is a cognitive process that supports a longer retention of information than working memory,

ranging from minutes to years. Declarative memory includes knowledge about personal experiences and facts about the world (objects, language) (Squire & Alvarez, 1995; Squire, Stark, & Clark, 2004). It is dependent on the hippocampus for the consolidation of memories or the strengthening of associations between new information and previously stored information. The process of consolidation allows for the storage of memories in the neocortex (Squire & Wixted, 2011).

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Table 1.1

Alterations in Attention and Memory Before Cancer Treatment

Reference	Time	Sample				Results
		No.	Patient/ Controls	Gender	Age	
Bond, 2012	After Diagnosis	70	HNC	M & F	*M* = 55 y	Attention & WM: scores significantly lower than expected norms (TMT A & B, SDMT). LTM: scores significantly lower than expected norms (RAVLT).
Cimprich, 1998	After Diagnosis (*M* = 12 days)	74	BC	F	*M* = 56 y	Attention & WM: scores within published norms but skewed to lower range (DS, NCPC, SDMT).
Cimprich, 1999	After Diagnosis (*M* = 11 days)	74	BC	F	*M* = 56 y	Perceived Attention & WM function: 73 reported reduced effectiveness of function (AFI).
Cimprich, 2001	After Diagnosis *M* = 12 days	47 48	BC Healthy	F	*M* = 64 y *M* = 61 y	Attention & WM: scores within published norms for BC & HC groups. Women with BC performed significantly worse than women without breast cancer (DS, NCPC, SDMT).
Hermelink, 2007	After Diagnosis (*M* not reported)	109	BC	F	*M* = 49 y	Attention & WM: scores significantly worse than published norms (D2 test, TMT B, & RWT). One measure significantly better than published norms (Digit Symbol). Individually, 56 had mild cognitive impairment (> 1 test result < 1SD), 32 had moderate cognitive impairment (> 1 test result < 2 SD) on measures of attention and memory.
Meyers, 1995	After Diagnosis (*M* not reported)	21	SCLC	M & F	*M* = 55 y	Attention, WM, & LTM: a significant percentage of participants scored > 1.5 SD below published norms (33 on TMT A, 38 on TMT B, 38 on VSRT-verbal learning & 70 on VSRT-delayed memory)
Meyers, 2005	After Diagnosis (*M* not reported)	54	AML, MDS	M & F	*M* = 60 y	Attention, WM, & LTM: a significant percentage of participants scored > 1.5 SD below the normative mean (28 on TMT A, 29 on TMT B, 44 on HVLT total recall, 41 on HVLT delayed recall).

Note. AFI = Attentional Function Index; AML = Acute Myelogenous Leukemia; BC = Breast Cancer; BVRT = Benton Visual Retention Test; F = Female; HC = Healthy Controls; HCN = head and neck cancer; HVLT = Hopkins Verbal Learning Test; LTM = Long-term Memory; M =Male; *M* = mean; MDS = Myelodysplastic Syndrome; NCPC = the Necker Cube Pattern Control test; RWT = Regensburg Word Fluency Test; SCLC = small cell lung cancer; SDMT = Symbol Digit Modalities Test; TMT A & B = Trail Making Test Part A and Part B; VSRT = Verbal Selective Reminding test; WM = Working Memory; y = year.

Table 1.2

Alterations in Attention and Memory Associated with Cancer Treatment: Surgery

Reference	Study Design	Sample				Results
		No. of Subjects	Patient Group +/- Controls	Gender	Age	
Cimprich, 1998	Pre/Post Test T1: Before Surgery T2: After Surgery, 2 weeks	14 44 16	BC, Younger BC, Middle BC, Older	F	*M* = 37 y *M* = 57 y *M* = 71 y	Before Surgery: Performance on DS, NCPC, & SDMT individuals with BC were within published norms but skewed to lower range. Change Over Time: Older women and middle/older women undergoing mastectomy experienced a significant decline in performance on an attention and WM Composite Score (DS, NCPC, & SDMT).
Cimprich, 2001	Longitudinal T1: Before Surgery T2: After Surgery, 2 weeks T3: After Surgery, 3 months	47 48	BC, Older HC	F	*M* = 64 y *M* = 61 y	Before Surgery: Performance on DS, NCPC & SDMT for individuals in the BC& HC groups were within published norms but skewed to lower range. BC group scored significantly lower on SDMT, NCPC, and an attention and WM Composite Score (DS, NCPC, SDMT) Change Over Time: Significantly improved performance in BC group from T2 - T3 but not HC group (Composite Score: DS, NCPC, & SDMT).
Hedayati, 2011	Pre/Post Test T1: Before Diagnosis T2: After Surgery, 1 month	71 63	BC HC	F	*M* = 59 y *M* = 51 y	Before Surgery: BC group significantly slower on CSI domains response time and processing speed compared to HC group (measures correlate with TMT and SDMT) Change Over Time: BC group did not have any changes in performance on cognitive measures (CSI). Healthy controls performed significantly better on CSI domains attention and processing speed (measures correlate with DS and SDMT).

Note. BC = breast cancer; F = female; CSI = Cognitive Stability Index; DS = the Digit Span test; F = female; HC = healthy controls; *M* = mean; NCPC = the Necker Cube Pattern Control test; SDMT = Symbol Digit Modalities Test; T = time; TMT A & B = the Trail Making Test Part A & B; WM = Working Memory; y = year.

Table 1.3

Alterations in Attention and Memory Associated with Cancer Treatments: Chemotherapy and Radiation Therapy

Reference	Study Design	Sample				Results
		No. Participants		Gender	Age	
Bender, 2006	Pre/Post Test T1: Before CT T2-3: After CT, 1wk & 1 year	19 15 12	BC, CT BC, CT HT BC	F	*M* = 40 y *M* = 44 y *M* = 45 y	Before Chemo: No significant difference between groups on any cognitive measure at baseline. Change Over Time. Performance on 4WSTM (15s and 30 s) declined but was not significant in BC group receiving CT only
Hensley, 2006	Longitudinal T1: Before CT T2-3: After CT, 3 & 6 cycles	20	OC	F	*M* = 54 y	Before Chemo: Cognitive test z scores on all measures were average to high average suggesting no impairment. Change Over Time: Performance on TMT A & B and DS forward improved but was not significant in individuals with OC. No significant change in DS backward in individuals with OC. Highly educated participants with OC reported a decline in attention and memory at T2 and a return to baseline at T3.
Hermelink 2007	Pre/Post Test T1: Before CT T2: Before Final CT	101	BC	F	*M* = 49 y	Before Chemo: Performance on d2 test, TMT B, RWT Lexical Search, RWT Semantic Search, and RWT Lexical Search with Change in Category was significantly poorer in individuals with BC compared to test norms. Change Over Time: Performance on Logical Memory I & II, DS backward, Digit Symbol, d2 test, and RWT Semantic Search significantly improved over time in individuals with BC. Performance on RWT Semantic Search with Change in Category significantly declined over time in individuals with BC. In individual analyses, a decline in cognitive ability was observed in 27 BC participants, improvement in cognitive ability was observed in 28 BC participants, and no change in cognitive ability in 45 BC participants. Self-report on the FEDA and EORTC significantly increased at T2 in BC participants.
Hess, 2010	Longitudinal T1: Before CT T2-3: After CT, 2, 5 cycles	27	OC & PC	F	*M* = 59 y	Before Chemo: Performance on cognitive measures not compared to normative data or healthy controls. Change Over Time: Performance on one of three cognitive domains from a modified battery of the Cognitive Stability index declined in 92 of individuals with cancer at Time 2 and 86 of individuals with cancer at Time 3 ($\geq$ 1 SEM).

(continued)

Table 1.3. Alterations in Attention and Memory Associated with Cancer Treatments: Chemotherapy and Radiation Therapy (continued)

Reference	Study Design	Sample				
		No.	Participants	Gender	Age	
Jansen, 2008	Longitudinal T1: Before CT T2: After CT, 4 cycles	30	BC	F	*M* = 50 y	Before Chemo: Mean test scores for all cognitive measures were within published norms. Four participants did score 1.5 SD below published norms on two or more tests or two SDs on one test suggesting impairment prior to any treatment. Change Over Time: Performance on RBANS visuospatial skills subtest and RBANS total score significantly decreased over time. Performance on Stroop significantly improved over time. In individual analyses, 10 women with BC had a decrease in one or more SDs on two or more cognitive measures after the completion of chemotherapy. In contrast, 5 women with BC had an increase in one or more SDs for two or more cognitive measures after chemotherapy.
Kaasa, 1987	Pre/Post Test T1: Before CT T2: After CT or RT	31 34	NSCLC, CT NSCLC, RT	M, F	*M* = 62 y *M* = 61 y	Before Chemo: Performance on cognitive measures not compared to normative data or control group. No significant differences on any cognitive measure between individuals with NSCLC receiving CT and individual with NSCLC receiving RT. Change Over Time: Performance on Verbal Learning 5 test declined in individuals receiving CT and did not change in individuals with RT (not significant). Performance on Benton error declined in individuals receiving CT and improved in individuals receiving RT (not significant). Performance on Trail Making A & B, Verbal Learning and Benton Correct did not significantly change over time in individuals receiving CT or RT. Individually, performance on the Benton Visual Retention test - error decreased in 14 individuals receiving CT and 6 individuals receiving RT. Performance on the Benton Visual Retention test - correct decreased in 12 individuals receiving CT and 11 individuals receiving RT. Performance on Trail Making A decreased in 8 individuals receiving CT and 7 individuals receiving RT. Performance on Trail Making B decreased in 14 individuals receiving CT and 9 individuals receiving RT. Performance on the Verbal Learning test - 10 word trial decreased in 9 individuals receiving CT and 12 individuals

(continued)

Table 1.3. Alterations in Attention and Memory Associated with Cancer Treatments: Chemotherapy and Radiation Therapy (continued)

Reference	Study Design	Sample				Results
		No.	Participants	Gender	Age	
						receiving RT. Finally, performance on the Verbal Learning test - 5 word trial decreased in 17 individuals receiving CT and 12 individuals receiving RT.
Skaali, 2011	Pre/Post Test T1: Before CT T2: After CT, 1 year	31 38 53	TC +/- RT TC + 1CT TC + >1CT	M M M	*Md* n= 32 y *Mdn* = 35 y *Mdn* = 30 y	Before Chemo: Performance on cognitive measures not compared to normative data. Performance on the CANTAB spatial working memory subtest was significantly better in individuals with TC not receiving CT Change Over Time: Performance on CANTAB, HVLT, GP, TMT A & B, CW, or COWAT did not significantly change over time for any group. No significant group difference were observed in proportions of individuals showing a decline of ≥ 10 on test measures or overall decline. In contrast significantly larger proportions of individuals in the CT groups (+1 CT and > 1 CT) had improvement of ≥ 10 on test measure. Specifically, 38 TC + CT showed a decline of ≥ 10 & 51 TC + CT showed improvement of ≥ 10 (CANTAB, HVLT, GP, TMT A & B, CW and COWAT).
Skaali, 2011	Pre/Post Test T1: Before CT T2: After CT, 1 year	31 38 53	TC +/- RT TC + 1CT TC + >1CT	M M M	*Mdn* = 32 y *Mdn* = 35 y *Mdn* = 30 y	Before Chemo: Not reported. Change Over Time: 29 of individuals with TC receiving 1 CT and 25 of individuals with CT receiving multiple CT had an increase in self-reported cognitive problems (2 questions, 4 responses)

Note. AFI = Attentional Function Index; BC= breast cancer; BVR = Benton Visual Retention test; CANTAB = Cambridge Neuropsychological Test Automated Battery; CT = chemotherapy; F = female; CSI = Cognitive Stability Index; DS = the Digit Span test; EORTC QLQ C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; F = female; FEDA = Fragebogen erlebter Defizite der Aufmerksamkeit [Questionnaire of Experienced Attention Deficits]; HT = hormone therapy; IT = immunotherapy; M = male; NSCLC = non small cell lung cancer; OC = ovarian Cancer; PC = peritoneal cancer; RBANS = Repeatable Battery of Adult Neuropsychological Status; RT = radiation therapy; RWT = Regensburg Word Fluency Test; SD, standard deviation, SEM = standard error of mean; T = time; TC = testicular cancer; TMT A & B = the Trail Making Test Part A & B; VLT = Verbal Learning Test; WM = working memory; WMS-R = Wechsler Memory Scale-Revised; y = year; 4WSTM = Four Word Short Term Memory Test.

Table 1.4

Alterations in Attention and Memory Associated with Cancer Treatments: Immunotherapy

Reference	Study Design	Sample				Results
		No.	Participants	Gender	Age	
Bender, 2000	Longitudinal T1: After Surgery Before IT T2-6: After IT, Every 3 months	6 6 6	Melanoma HD IFN Melanoma LD IFN Melanoma	-	'Adult'	Before immunotherapy: Performance on cognitive measures not compared to normative data or healthy controls. Change Over Time: Performance on TMT A & B, GP, DSS, and DV did not significantly change from among participants for any group. Performance on TMT B declined over the course of therapy in 5 of 6 participants receiving HD IFN.
Capuron, 2001	Longitudinal T1: Before IT T2: After IT, 5 days T3: After 1 month	17 7 7 16	RCC, IL-2 RCC, IL-2+IFN RCC, LD IFN Melanoma, HD IFN	M, F	*M* = 56 y *M* = 51 y *M* = 57 y *M* = 41 y	Before immunotherapy: Performance on cognitive measures not compared to normative data/healthy control group. Performance on the simple choice task, multiple choice task, and spatial working memory was not significantly different between treatment groups at baseline. Performance on the Stockings of Cambridge test was significantly worse in individuals with IL2 + IFN compared to IL2 only at baseline. Change Over Time: Performance on simple-choice task significantly improved on day 5 for individuals in IL-2 group but was no longer present at 1 month. Performance on the multiple-choice task significantly declined in individuals receiving HD IFN and tended to persist at 1 month. Performance on complex trials of the Spatial Working Memory task significantly declined in individuals receiving IL-2 on day 5 and tended to persist at 1 month. Performance on the Stocking of Cambridge test significantly declined on day 5 in individuals receiving IL-2 and persisted at 1 month.
Capuron, 2002	Longitudinal T1: After Surgery Before IT T2: After IT, 2 weeks T3: After IT, 8 weeks T4: After IT, 12 weeks	20	Melanoma, IFN + Paroxetine Melanoma, IFN + Placebo	M, F	*M* = 52 y *M* = 50 y	Before Immunotherapy: Performance on cognitive measures not compared to normative data or healthy controls. Change Over Time: Individuals receiving IFN only reported significantly more memory disturbances and poor concentration at T4 compared to baseline (NRS). Frequency of cognitive symptoms in IFN only group: 30 loss of concentration, 15 memory disturbances, 15 word finding problems, 10 episodes of confusion, & 10 indecisiveness (NRS).

Note. DS = the Digit Span test; DSS = the Digit Symbol Substitution test; GP = the Grooved Pegboard test; HD= high dose; IFN = interferon; IL-2 = interleukin-2; IT = immunotherapy; *M* = mean; RCC = renal cell cancer; T = time; TMT A & B = the Trail Making Test Part A & B; y = year.

Table 1.5

Patient Characteristics Associated with Alterations in Attention and Memory

Reference	Study Design	Sample				
		No.	Patient Group +/- Controls	Gender	Age	Results
Ahles, 2003	Cross-sectional	17	BC /Lymphoma + APOE	M, F	*M* = 58 y	Significantly lower attention and memory function in
	T1: > 5yr after diagnosis	63	ε4		*M* = 55 y	cancer survivors with APOE ε4 compared to without
			BC/ Lymphoma - APOE ε4			(Block Design, Visual Reproduction).
Ahles, 2010	Longitudinal	60	BC+ CT +/- RT +/- HT	F	*M* = 53 y	Older individuals with lower cognitive reserve exposed
	T1-4: Before and 1, 6,	72	BC +/- RT +/- HT		*M* = 52 y	to CT had a significantly lower attention and memory
	&18 months after CT	45	Healthy		*M* = 57 y	function (DSC, TMT A & B, CWI, GP).
Cimprich,	Pre/Post Test	14	BC, Younger	F	*M* = 37 y	Older women and middle/older women undergoing
1998	T1-2: Before and 2	44	BC Middle		*M* = 57 y	mastectomy demonstrated a significant decline in
	weeks after surgery	16	Breast Cancer, Older		*M* = 71 y	attention and WM (DS, NCPC, & SDMT).
Cimprich,	Cross-sectional	184	BC	F	*M* = 55 y	Older age, fewer years of education, chronic health
2005	T1: Before Treatment					problem, and post-menopausal status was associated with worst performance on tests of attention & WM (DS, TMT A & B, TSTW). Younger age was associated with poorer perceived attention & WM (AFI).
Merriman,	Longitudinal	73	BC + RT	F	*M* = 55 y	Younger age, not working, higher number of
2010	T1: Before RT					comorbidities and greater anxiety was significantly associated with worse perceived attention & WM (AFI).
Schilder,	Cross-sectional	205	BC + HT +/- RT – CT	F	*M* = 69 y	Comorbidities, fewer hours on cognitive activities, and
2010	After Surgery	124	Healthy		*M* = 66 y	higher number of reproductive years were significantly associated with poorer performance on measures of attention and memory in BC group (CF, LNS, Stroop CWT, TMT A & B, RAVLT, VAT, WMS).
Small, 2011	Cross-sectional	72	BC CT +/- RT +/- HT	F	*M* = 51 y	Individuals with BC + CT & COMT-Val allele
	After Adjuvant therapy	58	BC RT +/- HT		*M* = 57 y	performed significantly worse on DS, Spatial Span and
		204	Healthy		*M* = 57 y	Color Trails Test.
Vearncombe,	Pre/Post Design	138	BC + CT +/- RT +/- HT	F	*M* = 49 y	A decline in hemoglobin and an increase in anxiety
2009	T1-2: Before and 4 weeks after CT	21	BC +/- RT +/- HT		*M* = 54 y	significantly predicted impairment on in BC + CT

Note. AFI = Attentional Function Index; APOE ε4 = Apolipoprotein E; BC = breast cancer; CT = Chemotherapy; CF = the Category Fluency test; CWI = the Color Word Interference test; CWT, the Color Word test; DS = the Digit Span test; DSC = the Digit Symbol Coding test; GP = the Grooved Pegboard test; HT, Hormone Therapy; F, female; LNS = the Letter Number Sequencing test; M, male; *M*, mean; NCPC = the Necker Cube Pattern Control test; RAVLT = the Rey Auditory Verbal Learning Test; RT = Radiation Therapy; SDMT = the Symbol Digit Modalities Test; TMT A & B = the Trail Making test Part A & B; TSTW = the Three Shapes Three Words test; VAT = the Visual Association Test; WM = Working Memory; y, year.

Table 1.6

Circulating Inflammatory Cytokines in Individuals with Cancer Prior to Any Treatment (Serum, Plasma)

Cancer	Reference	No.	Sample	Results
Breast/Oral	Jablonska, 2001	23/23/12 12	BC/Oral HC	Significantly higher IL-6 & TNF-α levels in stage II BC compared to HC. Significantly higher IL-6 & TNF-α levels late stage compared to early stage BC.
Breast	Chod, 2008	36/20	BC/HC	Significantly higher TGF-β1 levels in BC compared to HC
	Merendino, 1996	20	BC	Significantly higher IL-10 levels compared to controls.
	Yeon, 2011	134/149	BC/HC	Significantly higher IL-1β and IL-6 levels in BC group compared to controls.
Cervical	Chopra, 1998	61/20	CC/HC	Significantly higher TNF-α, and higher TGF-β, & IL-10 compared to early stage/controls.
Colorectal	Bellone, 2001	10/7	CRC/HC	Significantly higher TGF-β1 and TGF-β2 levels compared to HC.
	Dymicka-Piekarska, 2007	42/38	CRC/HC	Significantly higher IL-6 levels in CRC group compared to HC. Significantly higher IL-6 levels in individuals with metastasis than individuals without metastasis.
	Esfandi, 2006	50	CRC	Significantly higher IL-6 levels in individuals with stage IV CRC than early stage.
	Galzia, 2002	50/25	CRC/HC	Significantly higher IL-6 and IL-10 levels compared to controls.
	Kaminska, 2005	157/50	CRC/HC	Significantly higher IL-6, TNF-α, and IL-1RA in CRC group compared to HC. IL-6 and IL-1RA significantly increased with stage and bowel wall invasion.
	Nikiteas, 2005	74/25	CRC/HC	Significantly higher IL-6, TNF-α, and CRP levels in CRC group compared to HC.
Gastric	Kabir, 1995	21/17	GC/HC	Significantly higher IL-1α, IL-1β and IL-6 levels in GC group compared to HC. Significantly lower TNF-α levels in GC group compared to HC.
	Ikeguchi, 2009	90/9	GC/HC	Significantly higher IL-6 levels in GC group compared to HC. IL-6 levels in significantly correlated with advanced disease.
Leukemia	Myers, 2005	54	AML/MDS	Significantly higher IL-1, IL-1RA, IL-6 & TNF-α in individuals with AML/MDS
Lymphoma	Gaiolla, 2011	27/26	HL/HC	Significantly higher IL-6 & IL-10 levels in individuals with cancer
Melanoma	Krasagakis, 1998	25/12	MC/HC	Significantly higher TGF-β1 and TGF-β2 levels compared to HC.
Melanoma	Porter, 2001	218/90	MC/HC	Significantly higher IL-6, & IL-10 levels in melanoma group.
Ovarian	Lambeck, 2007	187/45/50	OC/BD/HC	Significantly higher IL-6 & IL-10 levels compared to HC as well as BD.
	Maccio, 2005	91/95	OC/HC	Significantly higher IL-1β and TNF-α levels in individuals with advanced ovarian cancer (III, IV) compared to controls as well as individuals with local disease (I, II).

(continued)

Table 1.6. Circulating Inflammatory Cytokines in Individuals with Cancer Prior to Any Treatment (Serum, Plasma) (continued)

Cancer	Reference	No.	Sample	Results
Prostate	Shariat, 2001	149/44	PC/HC	Significantly higher IL-6 and IL-6sR in PC + regional lymph node metastasis compared to PC – regional lymph node metastasis and HC.
Renal	Dosquet, 1994	78/56	RCC/HC	Significantly higher levels of TNF- α, IL-6, & IL-10 levels in RCC compared to HC.
Renal	Wunderlich, 1998	20/20	RCC/HC	Significantly higher levels of TGF-β1 in RCC compared to HC
Sarcoma	Rutkowski, 2003	72/22 50	Sarcoma/BD HC	Significantly higher IL-1RA, IL-6, IL-10, TNF RI & TNF RII levels in sarcoma compared to HC. Significantly higher IL-6 & IL-1RA levels in sarcoma group compared to BD.

Note. AML = acute myelogenous leukiemia; BC = breast cancer; BD = benign disease; CC = cervical cancer, CRC = colorectal cancer; CRP = C-reactive protein; GC = gastric cancer, HC = healthy controls; HL = Hodgkin's Lymphoma; HNC = head and neck cancer; IL-1α = interleukin-1 alpha; IL-1β = interleukin-1 beta; IL-1RA = interleukin-1 receptor antagonist; IL-6 = interleukin-6; IL-10 = interleukin-10, MC = melanoma; MDS = myelodysplastic syndrome; OC = ovarian cancer, PC = prostate cancer; RCC = renal cell cancer, TNF-α = tumor necrosis factor-alpha.

Table 1.7
Inflammatory Cytokines and Cognitive Function

Reference	Study Design	Sample No.	Group	Gender	Age	Results
Cognitive Function of Individuals with Minor Illnesses						
Capuron, 1999	Cross-sectional	30	Healthy	M	*M = 23 y*	Significantly lower scores in flu group +/- fever
	T1: Symptoms	29/32	Flu	M	*M = 22 y*	compared to healthy (ERBMT)
Smith, 1992	Pre/Post Design	61	Cold	M, F	-	Significantly more errors individuals with flu. No
	T1-2 Before & 3-4 days after virus	27	Influenza A	M		differences cold group (Stroop).
Smith, 1987	Pre/Post Design	10	Influenza B	M, F	*M = 39 y*	Significantly impairment flu group. No difference
	T1-2: Before & 6-7 days after virus	35	Cold	M, F	*M = 39 y*	cold group (VFRTT & FDT).
Vollmer-Conna,	Cross-sectional	21	Q Fever	M, F	*M = 40 y*	All participants reported impaired concentration.
2004	T1: Symptoms	24	EBV	M, F	*M = 21 y*	IL-6 from PBMC significantly correlated with
		24	RRV	M, F	*M = 39 y*	reports of poor concentration.
Cognitive Function of Individuals with Inflammation						
Brydon, 2008	Cross-over Design	16	*Salmonella*	M	*M* = 25 y	After endotoxin, greater increases in IL-6 from
	T1-2: Before & 2 h after endotoxin					baseline associated impaired attention (Stroop).
Exton, 2002	Cross-over Design	8	Interferon-β	M	*M = 25 y*	After endotoxin, no changes (TMT, DS, d2).
	T1-5: Before & 4, 8, 24 h after cytokine		*1b*			
Krabbe, 2005	Cross-over design	12	*E. coli*	M	*M* = 26 y	After endotoxin, no changes (WLW, LNS, DS,
	T1-5: Before & 1.5, 6, 24 h after endotoxin					DSCT, TMT). Negative correlation IL-6 levels and LTM at T3 (WLL)
Reichenberg,	Cross-over Design	20	S*almonella*	M	*M* = 24 y	After endotoxin, significant decline attention &
2001	T1-3: 1-2, 3-4, & 9-10h after endotoxin		or saline			memory (SR, FR, WLL). Impaired performance was correlated with IL-1RA, TNF-alpha, & IL-6 .
Smith, 1988	Pre/Post Design	18	Interferon-α	M, F	*M* = 44 y	Significant decrease in attention and memory
	T1-12: Before & q3h after cytokine					function (VFPT) in high dose interferon alpha group. No differences on reasoning task (BSR).
Spath-Schwalbe,	Cross-over Design	16	Interleukin-6	M	-	Subjects reported difficulty concentrating at T1.
2006	T1-2: 3 & 9 h after cytokine					

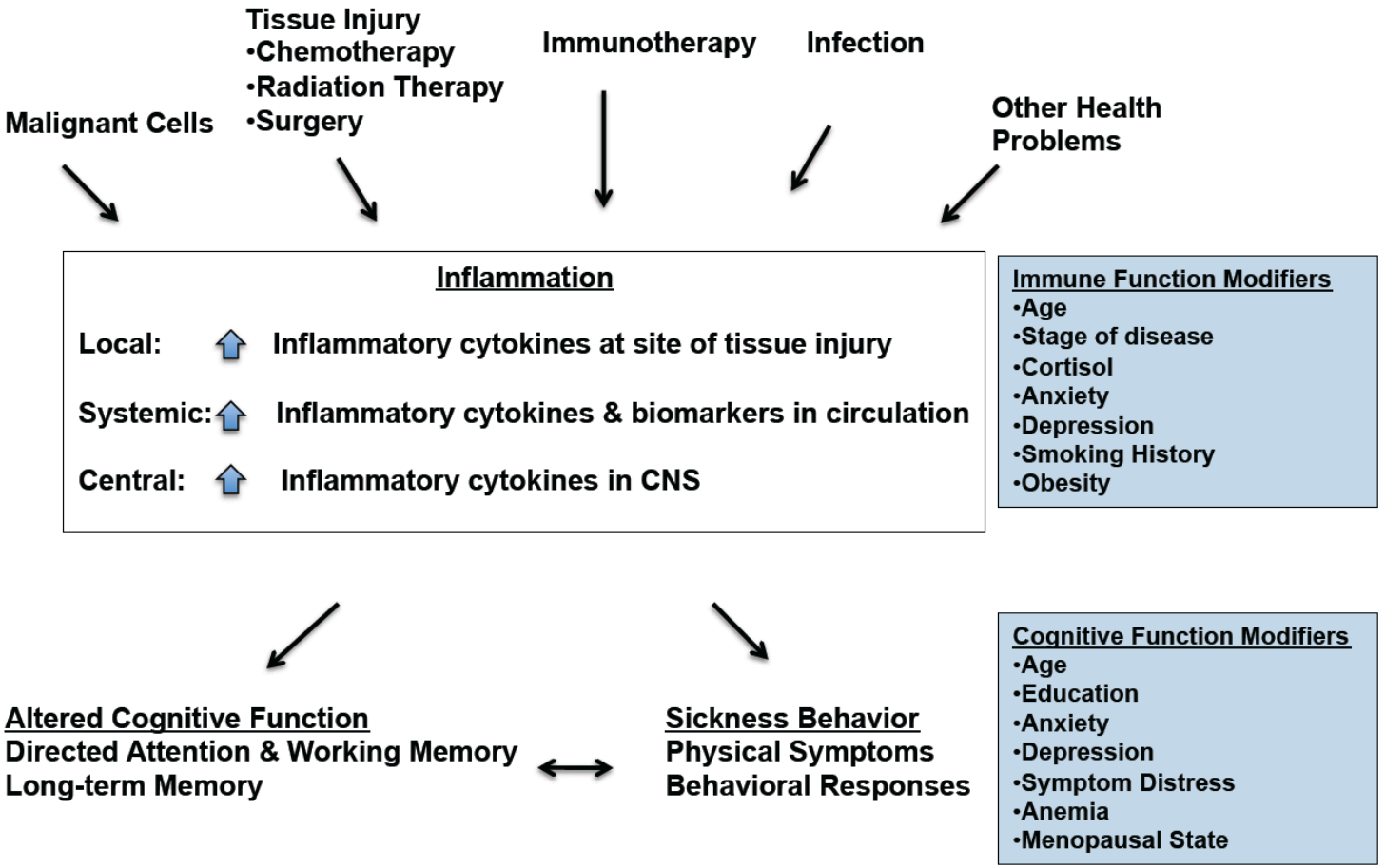
(continued)

Table 1.7. Inflammatory Cytokines and Cognitive Function (continued)

Reference	Study Design	Sample No.	Group	Gender	Age	Results
Cognitive Function of Individuals with Cancer						
	Pre/Post Design T1: Before treatment	54	AML or MDS	M, F	*M* = 60 y	Higher IL-6 levels associated with worse attention & working memory performance (TMT B). Significant attrition T2 not included.

Note. AML = Acute Myelogenous Leukemia, BSR = the Baddley Syntactical Reasoning Task; DS = the Digit Span test; DSCT = the Digit Symbol Coding Test; EBV = Epstein Barr Virus, ERBMT = the Extended Rivermead Behavioral Memory Test; F = female, FDT = the Fives Detection test; FR = the Figure Recall test; LNS = the Letter-Number Sequencing test; M = male; *M* = mean; MDS = myelodysplastic syndrome; PBMC = peripheral blood mononuclear cell; RRV = Ross River Virus, SPTT = the Square Pursuit Tracking Task; SR = Story Recall; T = time; TMT A & B = the Trail Making Test Part A and B; VFRTT = the Variable Fore-period Reaction Time Task; WLL = the Word List Learning test.

Figure 1. Cognitive and Immune Function Biobehavioral Framework



CHAPTER II

COGNITIVE SYMPTOMS IN COLORECTAL CANCER SURVIVORS

Introduction

Colorectal cancer is the third most common cancer in the United States with an estimated 142, 820 new cases in 2013 (American Cancer Society, 2013). Surgery is the main treatment for colorectal cancer, although chemotherapy or radiation therapy may also be used. Cancer and cancer treatments can negatively affect daily functioning of an individual. Cognitive function is a key functional ability that can be altered.

Altered cognitive function is a distressing experience reported by some individuals with cancer. A growing body of research has observed cognitive deficits in cancer survivors early in the disease trajectory - at diagnosis and before any treatment and during main and adjuvant therapies (Cimprich, 1998; Cimprich & Ronis, 2001; Hedayati, Schedin, Nyman, Alinaghizadeh, & Albertsson, 2011; Kaasa, Olsnes, & Mastekaasa, 1988; Wefel, Vardy, Ahles, & Schagen, 2011). These cognitive deficits can alter an individual's ability to work, achieve personal goals, and maintain interpersonal relationships (Boykoff, Moieni, & Subramanian, 2009). As such, cognitive changes can have a significant impact on not only the cancer survivor but also his/her family and community.

Changes in cognitive function in individuals with colorectal cancer have been largely unexplored. After an extensive literature search, only a few studies were found that

assessed cognitive function in individuals with colorectal cancer (Patti, Saitta, Cusumano, Termine, & Di Vita, 2011; Vardy, 2007; Walker et al., 1996). The first study, by Vardy and colleagues (2007), assessed cognitive function in individuals with localized cancer receiving surgery alone or surgery plus chemotherapy. The longitudinal study assessed participants at three time points: at baseline after surgery and/or before chemotherapy (n = 182), at 6 months (n = 71) and at 12 months (n = 39). Researchers found that at baseline 30% of participants were cognitively impaired on traditional neuropsychological tests. Additionally, at 12 months participants receiving chemotherapy tended to have worse performance on traditional neuropsychological measures and reported more cognitive problems. Researchers did not describe neuropsychological measures or how they defined cognitive impairment. The second study by Walker and colleagues (1996) assessed cognitive function in 17 individuals with advanced colorectal cancer receiving chemotherapy alone or chemotherapy plus immunotherapy (interleukin-2) during the first 12 weeks of therapy. Researchers found that participants in both groups experienced cognitive decline from baseline on measures of attention and memory from the Cognitive Drug Research System (Walker et al., 1996). Additionally, two patients receiving chemotherapy plus immunotherapy developed severe neuropsychological problems (hallucinations, persistent confusion) that were attributed to the interleukin-2 therapy and resolved with discontinuation of therapy. Finally, a third study by Patti and colleagues (2011) assessed postoperative delirium in 100 individuals undergoing colorectal surgery for carcinoma. Researchers found that 18% of participants developed postoperative delirium using the established Confusion Assessment Method. Postoperative delirium was associated with a history of postoperative delirium, older age, alcohol abuse, low

albumin, intra-operative hypotension, intra-operative blood loss, and elevated intra-operative infusion volume.

Together these studies suggest that cognitive impairment may be an important symptom experienced by some individuals with colorectal cancer. Interpretation of findings, however, is difficult because of heterogeneous measures and definitions of cognitive impairment that were used as well as the diversity among cancer-treatments (standard and experimental therapies). Additionally, two of the three studies were limited by a small sample size or significant attrition over time. As such, further research is needed to investigate cognitive function and to precisely describe affected cognitive domains by using: 1) current cognitive neuroscience theory to guide the investigation and interpretation of findings, 2) a sample size that has sufficient power to detect deficits in cognitive function, 3) neuropsychological and self-report measures that are sensitive to subtle cognitive impairment in individuals with cancer, and 4) a healthy comparison group to determine whether cognitive deficits are present.

Cognitive domains that appear to be most vulnerable to the effects of cancer and cancer treatments include attention, working memory, and long-term memory (Wefel, Vardy, et al., 2011). Selective attention is a basic cognitive process that allows an individual to focus on certain stimuli in the environment. Directed or controlled attention is a form of selective attention that allows an individual's personal intention to determine what important information is actively focused on in the environment while inhibiting other distracting information (Kaplan & Berman, 2010). It is characterized by mental effort and an ability to actively inhibit stimuli that may be of interest to the individual but are irrelevant to completing a task or achieving a goal. Working memory shares a close

functional connection with directed or controlled attention and is a cognitive process that allows an individual to hold online a limited amount of information and to perform cognitive operations on it (Smith & Jonides, 1999). Long-term memory, specifically declarative memory, is a cognitive process that allows an individual to acquire and use information about personal experiences or knowledge about the world (Squire & Wixted, 2011). Together, directed or controlled attention and memory are necessary for planning and carrying out tasks, problem solving, and effective social functioning. As such, they are critical for everyday functioning as well as coping with a new diagnosis of cancer and making informed decisions about treatment.

The objective of this study was to assess attention and memory function in individuals newly diagnosed with colorectal cancer or recurrent colorectal cancer. This study tested the hypothesis that when that compared to individuals without colorectal cancer, individuals with colorectal cancer would show alterations in performance on measures of directed or controlled attention, working memory, and long-term memory.

Methods

Study Design, Sample, and Setting

This study used a cross-sectional comparative design to describe differences in cognitive function in individuals newly diagnosed with primary or recurrent colorectal cancer and individuals without colorectal cancer. Participants were recruited from a university medical center in the Midwest and included 50 men and women newly diagnosed with stage I-IV colorectal cancer and 50 men and women without colorectal cancer. The sample included approximately equal numbers of men and women in each group. Patients were assessed at one time point within six months after a new diagnosis

of primary or recurrent colorectal cancer. Participants in the healthy comparison group were assessed at one time point within twelve months after a negative screening colonoscopy.

Eligible participants were at least 30 years old and were able to read and write English. All participants were excluded for a history of conditions that could influence cognitive function including: untreated or unstable mental disorder, head injury, alcohol or drug abuse, learning disability, and central nervous system disease. Finally, patients were excluded for a diagnosis of malignancy other than colorectal cancer or skin cancer. Participants in the healthy comparison group were excluded for a diagnosis of malignancy other than skin cancer.

Measures

Cognitive Function Screen

The *Mini-Mental State Exam (MMSE)* is a standardized test that includes 11 questions measuring orientation, memory, attention, and language. A score of greater than 24 was used to indicate no serious cognitive impairment (Folstein, Folstein, & McHugh, 1975; Folstein, Folstein, & Fanjiang, 2000). The measure has been used as a screening measure for dementia (Lezak, Howieson, & Loring, 2004)

Attention

The Attention Network Test (ANT) is a computerized test measuring the three networks of attention including alerting, orienting, and executive control. The executive control network is closely aligned with the theoretical definition of directed attention (Fan, McCandliss, Sommer, Raz, & Posner, 2002; Kaplan & Berman, 2010). The ANT asks participants to determine if an arrow in the center of the screen points to the left or

right. The arrows are accompanied by flankers that point in the same direction and/or cues that provide information on when or where the arrow will occur in random sequence. The three networks are assessed by measuring accuracy and response times, and how responses are influenced by flankers, alerting cues and spatial cues. Scores include an overall mean accuracy and mean response time for correct answers as well as mean response times for correct answers on the three networks. Specifically, the alerting network was calculated by subtracting the double-cue condition scores from the no-cue condition scores, the orienting network was calculated by subtracting the spatial cue condition scores from the center cue scores, and the executive control network was calculated by subtracting the congruent flanker scores from the incongruent flanker scores. For a detailed description of the measure and how it is scored see Fan and colleagues (2002). The instrument has established reliability and validity (Fan et al., 2002; Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010).

Directed Attention and Working Memory

Digit Span (DS) is a standardized test that asks participants to repeat a series of numbers in the order they were given (Digit Span Forward, DSF) or in reverse order (Digit Span Backward, DSB). The score is the number of sequenced numbers repeated before two failed attempts. Digit Span is a valid and reliable measure that has been used in individuals with cancer to detect deficits in directed attention and working memory (Cimprich, 1998; Cimprich & Ronis, 2001; Lezak et al., 2004; Small et al., 2011)

The Trail Making Test (TMT) asks participants to draw a line to connect consecutively numbered circles (TMT A) or consecutively lettered and numbered circles alternating between the two (TMT B). The score is the time taken to complete the task.

The trail making test is a valid and reliable measure that has been shown to be sensitive in detecting directed attention and memory deficits in individuals with cancer (Bond, Dietrich, & Murphy, 2012; Hermelink et al., 2007; Meyers, Byrne, & Komaki, 1995; Reitan, 1979).

The Attentional Function Index (AFI) is a self-rating scale consisting of 13 items on which respondents rate their function on common tasks requiring directed attention and working memory from 0 (not at all) to 10 (extremely well or a great deal). Scores include: a single overall score computed by taking the average of all 13 items as well as mean scores for each of the three subscales namely effective action, attentional lapses, and interpersonal effectiveness. The AFI has correlated positively with objective measures of directed attention and working memory. It is a valid and reliable measure with an internal consistency coefficient ranging from 0.76 to 0.94 in cancer patients and healthy individuals (Cimprich, Visovatti, & Ronis, 2011). In this study, the internal consistency coefficient was 0.91, indicating good reliability.

Long-term Memory

The Rey Auditory Verbal Learning Test (RAVLT) asks participants to recall 15 words from a list. There are five presentations of one list of words (list A) followed by a sixth presentation of a second list of words (list B). Participants are asked to recall the words on the list after each presentation. After recalling the presentation of list B, participants are asked to recall list A immediately and after a 30 minute delay. The score used for long-term memory was the number of words recalled on the 30 minute delayed recall trial. The RAVLT is a valid and reliable measure (Schmidt, 1996). Word list measures

have been shown to be sensitive measures in individuals with cancer (Wefel, Vardy, et al., 2011).

The Everyday Memory Questionnaire (EMQ) is a self-rating scale consisting of 28 items on which respondents rate their frequency of memory lapses for a specific activity of a 7-point scale scored from 1 (not at all in the last month) to 7 (several times a day). The single overall score is computed by taking the average of the 28 items. The EMQ has correlated positively with objective measures of long-term memory in older adults and has an internal coefficient of 0.90 in healthy young adults (Cornish, 2000; Sunderland, Watts, Baddeley, & Harris, 1986). In this study, the internal consistency coefficient was 0.90, indicating good reliability

Adjunct Measures

The Profile of Mood States-Brief Form, a demographic questionnaire, and a medical chart audit form were used to describe the sample population and measure participant characteristics that might affect cognitive function. Characteristics that have been associated with poorer performance on cognitive measures include: age, fewer years of education, presence of other health problems, changes in hormones, and psychological distress (anxiety and depressed mood) (Ahles et al., 2010; Bender et al., 2006; Bond et al., 2012; Cimprich, 1998, 1999; Cimprich, So, Ronis, & Trask, 2005; Hermelink et al., 2007; Merriman et al., 2010; Schilder et al., 2010; Skaali, Fossa, & Dahl, 2011; Vearncombe et al., 2009).

The Profiles of Mood States- Brief Form (POMS-BF) is a self-rating scale consisting of 30 items on which respondents read a list of words (i.e. tense) and rate how they have been feeling in the past week on a scale from 0 (i.e. not at all tense) to 4 (i.e. extremely

tense). The instrument has six subscales, each with 5 items. The subscales include: anxiety, depression, anger, vigor, fatigue, and confusion (McNair, 2012). Scores on each of the subscales are computed by calculating the sum of each subscale. Scores on the total scale (total mood disturbance) are computed by summing the scores on the anxiety, depression, anger, fatigue, and confusion subscales and subtracting the score on the subscale vigor. The internal consistency coefficient for the total POMS-BF has been reported at 0.87 and 0.86 to 0.93 for the anxiety and depression subscales in individuals with cancer suggesting satisfactory reliability (Cimprich, 1999; Cimprich et al., 2005; Lehto & Cimprich, 1999). In the current study, the internal consistency coefficient for the total POMS-BF was 0.80 and for the anxiety and depressed mood subscales were 0.76 and 0.81 respectively.

Selected demographic and medical characteristics were obtained from participants using a demographic questionnaire and from the medical records using a medical chart audit form. Demographic characteristics included age, race, ethnicity, marital status, educational level, occupation, and employment status. Medical characteristics included type and stage of colorectal cancer, current medical conditions, current medications, past history of estrogen replacement therapy, and menopausal state.

Study Procedures

The institutional review board of the university and health system approved the study. Written informed consent was obtained from all study participants. Following consent, participants underwent neuropsychological testing and completed self-report questionnaires in a private room in the ambulatory care area. A trained investigator administered the tests. Testing procedures were as follows: 1) the immediate recall trials

of the RAVLT were administered first; 2) objective measures of directed attention and working memory in random order (ANT, DS, TMT); 3) self-report measures and adjunct measures in random order (AFI, EMQ, POMS-BF, and Demographic Characteristics); and 4) the delayed recall and recognition trail of the RAVLT. Time to complete testing was about 60 minutes.

Data Analysis

Descriptive analyses and independent t-tests were used to describe the sample and determine if there were any significant differences between individuals with and without colorectal cancer on cognitive variables and potential covariates. Multiple regression analyses were used to assess the relationship between cognitive variables and group controlling for covariates which differed between the two groups and which may be related to cognitive function (i.e. age, education, menopause, anxiety). For some analyses, a standardized composite score of directed attention and working memory was computed. This composite score was computed by transforming raw scores on DS and TMT to Z scores based on the sample mean and standard deviation of the measures and summing the Z scores. Given that higher scores on DS and lower scores on TMT indicated better functioning, scores on the TMT were reversed.

Results

Sample Characteristics

On the cognitive function screen, the MMSE, individuals with colorectal cancer (M = 29.28, SD = 0.83) and individuals without colorectal cancer (M = 29.60, SD = 0.73) scored $\geq$ 24 indicating intact cognitive function. The demographic and medical characteristics of participants with and without colorectal cancer can be found in Table

2.1. No significant differences were found in age (t (98) = - 1.63, p = 0.11), years of education (t (98) = - 1.28, p = 0.20), or presence of health problems (χ^2 (1, 100) = 2.34, p = 0.13) between these two groups. For female participants, there was no significant difference in menopausal status (χ^2 (1, 51) = 0.60, p = 0.44) or hormone replacement therapy (χ^2 (1, 51) = 0.18, p = 0.67) between the two groups. There was a significant group difference on the variable *taking medication that could affect cognitive function* with more individuals in the cancer group (n = 26) compared to the healthy group (n = 12) taking medication that could affect cognitive function (χ^2 (1, 100) = 9.38 p = 0.00). Medications that could affect cognitive function included narcotics, antidepressants, and sedatives for insomnia.

The disease and treatment characteristics of participants with colorectal cancer can be found in Table 2.2. Participants with colorectal cancer were assessed anywhere from 6 days to six months after diagnosis ($M \pm$ SD: 67 $\pm$ 49 days). All participants were diagnosed with invasive adenocarcinoma, 48 with a new diagnosis of colorectal cancer and 2 with a new diagnosis of recurrent colorectal cancer. Most colorectal cancer participants were assessed after diagnosis and before any treatment (n = 20), some participants were assessed after surgery only (n = 13), and the remaining participants were receiving chemotherapy or radiation therapy (n = 17) at the time of the research visit.

Group Comparisons in Psychological and Symptom Distress

Scores on the POMS-BF total mood disturbance scale and subscales are presented in Table 2.3. Individuals with colorectal cancer reported greater total mood disturbance, anxiety, confusion and fatigue, and less vigor than the healthy comparison group.

Group Comparisons on Attention and Memory Measures

Scores on neuropsychological and self-report measures of directed attention, working memory, and long-term memory are presented in Tables 2.4 and 2.5. Group mean scores on the standard neuropsychological measures (DS, TMT, RAVLT) were within normal limits (Folstein et al., 1975; Lezak et al., 2004; Reitan, 1979; Schmidt, 1996). No normative data were available for older adults on the ANT, however, mean scores for individuals with and without cancer were similar to findings reported by other researchers (Mahoney et al., 2010).

On the measure of attention, ANT, there were no significant differences between the groups on overall accuracy ($p = 0.14$) or response times ($p = 0.06$). There were also no significant differences on the attentional networks including alerting ($p = 0.61$), orienting ($p = 0.58$) or executive control ($p = 0.63$). Additional analyses, however, found that mean response times for the neutral flanker condition (overall mean RT and mean RT for each cue condition) were significantly longer in individuals with colorectal cancer compared to controls. This finding suggests that individuals with colorectal cancer had more difficulty discriminating the direction of an arrow when flanked by two straight lines on either side, a task that requires directed attention (Eriksen, 1974; Fan et al., 2002). See Table 2.4.

On measures of directed attention and working memory, individuals with colorectal cancer performed significantly worse on DS Forward ($p = 0.01$), TMT part A ($p = 0.03$), and the Standardized Total Composite Score ($p = 0.047$) compared to individuals without. There were no significant differences between the groups on DS Backward ($p = 0.26$) or TMT part B ($p = 0.06$). Additionally, compared to individuals

without colorectal cancer, individuals with colorectal cancer had significantly lower scores on the AFI total score ($p < 0.001$) and two of the three subscales. Specifically, mean scores for individuals with colorectal cancer ($M = 6.94$, $SD = 2.29$) were significantly lower than individuals without colorectal cancer ($M = 8.18$, $SD = 1.25$) on the effective action subscale (t (98) = - 3.37, $P < 0.001$). Likewise, mean scores for individuals with colorectal rectal cancer ($M = 7.02$, $SD = 2.27$) were significantly lower than individuals without colorectal cancer ($M = 7.95$, $SD = 1.81$) on the effective interpersonal relations (t (98) = - 2.26, $p = 0.03$). As such, individuals with cancer reported having significantly more problems carrying out basic tasks that require focused attention (i.e. keeping your mind on what you are doing) and interacting in a deliberate manner that depends on attentional or inhibitory effort (i.e. being patient with others). See Table 2.5.

On the measures of long-term memory, there were no significant differences between groups on the RAVLT delayed word recall trial ($p = 0.86$) or perceived function on the EMQ ($p = 0.47$). See Table 2.5.

Predictors of Directed Attention and Working Memory

Multiple regression analyses were performed to further assess the relationship between the cognitive variables (the standardized total composite score, AFI) and group controlling for possible covariates. These covariates included taking medication that could affect cognitive function, age, gender, education, anxiety, depressed mood, and fatigue. Correlations between the directed attention and working memory variables and selected covariates are presented in Table 2.6. Regression analyses are found in Table 2.7 and 2.8.

The Standardized Total Composite Score. Having colorectal cancer was found to be a significant predictor of directed attention and working memory after controlling for possible covariates. Specifically, having colorectal cancer ($t = 2.18$, $p = 0.03$), older age ($t = -2.85$, $p = 0.01$), and fewer years of education ($t = 3.53$, $p < 0.001$) predicted poorer actual performance, accounting for 27% of the variance in the standardized total composite score, multiple $R = 0.52$, $F(8, 91) = 4.29$, $p < 0.001$. See Table 2.7.

Attentional Function Index (AFI). Fatigue severity was found to be a significant predictor and the only predictor of lower scores on the self-report AFI regardless of colorectal cancer diagnosis. Specifically, greater fatigue ($t = -4.26$, $p < 0.001$) predicted lower perceived effectiveness on common tasks requiring directed attention and working memory, accounting for 38% of the variance in the self-report AFI, multiple $R = 0.62$, $F(8.91) = 6.91$, $p < 0.001$. See Table 2.8.

Discussion

This study examined differences in cognitive function between individuals newly diagnosed with primary or recurrent colorectal cancer receiving standard treatment for the disease and individuals without colorectal cancer. In the first six months after diagnosis, individuals with colorectal cancer performed and perceived their function to be worse on tests of directed or controlled attention and working memory but not long-term memory. When controlling for possible covariates, having colorectal cancer remained an independent predictor of worse cognitive function. In contrast, fatigue significantly predicted perceptions of effectiveness on tasks requiring directed attention and working memory regardless of whether or not the individual had colorectal cancer.

Participants in this sample were similar on most demographic and medical characteristics except for *taking medication that can affect cognitive function*. Compared to the healthy comparison group, significantly more individuals with colorectal cancer were taking narcotics, antidepressants, and sedatives for insomnia. Because of this difference, the variable *taking medication that could affect cognitive function* was included in multiple regression models. Interestingly, taking psychoactive medication was not a significant predictor of performance or perceived effectiveness on measures of directed attention and working memory. Nevertheless, this variable warrants further investigation in future studies examining cognitive function in individuals with colorectal cancer. Specifically, the influence of the medication as well as symptom distress (i.e. pain, depressed mood, insomnia) on cognitive function needs to be further examined.

Participants with colorectal cancer also reported significantly greater psychological and symptom distress than healthy controls as measured by the POMS-BF including anxiety, fatigue/less vigor, and confusion. Psychological distress has been associated with poor performance and perception of effectiveness on tasks requiring attention and memory in other cancer populations (Bender et al., 2006; Bond et al., 2012; Cimprich, 1999; Hermelink et al., 2007; Skaali et al., 2011; Wefel et al., 2011)**.** However, in this study, anxiety and depressed mood did not predict performance or perceptions of effectiveness on objective or subjective measures. Scores on the anxiety and depressed mood subscales were in the low to moderate range and it may have been possible that these low levels of distress were not sufficient to affect attention and memory function or may have even improved performance (Lezak et al., 2004). As

such, continued research is needed to investigate the effect of psychological distress on cognitive function in individuals with cancer.

Symptom distress, specifically fatigue, was also assessed as a potential modifier of cognitive performance in this study. Unexpectedly, fatigue alone independently predicted lower scores on the subjective measure of directed attention and working memory. One possible explanation for this finding is that participants reporting fatigue may be experiencing a common physiologic immune response to the cancer or another health condition and/or behavior (such as rheumatoid arthritis, obesity, smoking) that can the brain and cause subtle declines in function as well as feelings of fatigue. In this regard, individuals with fatigue may be experiencing a cluster of cytokine-induced symptoms and changes in behavior (Cleeland et al., 2003; Kent, Bluthe, Kelley, & Dantzer, 1992). Another perspective, proposed by Cimprich and colleagues (2002), is that individuals with cancer can experience mental or attentional fatigue secondary to the multiple cognitive demands associated with adapting to a new diagnosis of cancer, living with uncertainty about cancer control, and making treatment decisions. Attentional fatigue may manifest as difficulties in completing tasks of daily living and contribute to overall distress. The finding that fatigue was not a significant predictor of objective performance on neuropsychological measures suggests that objective measures may have been less sensitive to subtle deficits in directed attention and working memory perceived by the individual. Continued research is needed to examine the relationship between symptom distress and cognitive function in individuals with colorectal cancer.

The finding of cognitive deficits in individuals with colorectal cancer is consistent with the three previous studies examining cognitive function in individuals with

colorectal cancer (Patti et al., 2011; Vardy et al., 2007; Walker et al., 1996). Unfortunately, these disparate studies are not easily compared. However, this study used cognitive neuroscience theory and previous research findings in individuals with other cancers to guide the assessment of cognitive function in individuals with colorectal cancer. This approach, begins to more clearly define affected cognitive domains and potential patient characteristics that may contribute to an individual's ability to function. Continued research is warranted to describe cognitive deficits and the effects of diagnosis and treatment on cognitive function in individuals with colorectal cancer.

The finding of directed attention and working memory deficits in individuals with colorectal cancer early in the disease trajectory is consistent with studies examining cognitive impairment in other cancer survivors (Wefel, Vardy, et al., 2011). In contrast, individuals with colorectal cancer in this study did not experience deficits in long-term memory compared to individuals in the healthy comparison group. This may have occurred in part because age, education and gender are known to affect performance on the RAVLT and the colorectal cancer group had a cluster of high performing younger women ($\leq$ 45 years) who had a minimum of 16 years education (n = 7). Further, the colorectal cancer group (n = 12) had more young adults (< 50 years) than the healthy comparison group (n = 1). For a comprehensive understanding of long-term memory function in individuals with colorectal cancer, subsequent analyses of memory should consider including a variety of memory tasks that may be more robust with regards to gender differences for example the Complex Figure test (Lezak et al., 2004).

Limitations of the study include a cross-sectional design, use of a convenience sample, and inclusion of participants receiving multiple types of cancer therapies

(surgery, chemotherapy, and/or radiation therapies). Also, while the study examined differences in attention and memory between individuals with and without cancer, it could not answer questions related to potential differences in responses related to stage of cancer because it was not sufficiently powered to do so.

Despite the above limitations this study provides preliminary evidence that some individuals with colorectal cancer may be vulnerable to deficits in directed attention and working memory. Future longitudinal studies are warranted to assess the effects of cancer and cancer treatments on cognitive function in individuals with varying stages of colorectal cancer across the disease trajectory.

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Table 2.1

Medical and Demographic Characteristics of Individuals With and Without Colorectal Cancer (N = 100)

Measures	Colorectal Cancer Group (n = 50)		Healthy Comparison Group (n = 50)	
	M ± SD	N (%)	*M* ± SD	N (%)
Age	55 ± 12		58 ± 7	
Education	16 ± 3		16 ± 3	
Gender				
Male		24 (48)		25 (50)
Female		26 (52)		25 (50)
Race[a]				
Caucasian		38 (76)		42 (84)
Other		10 (20)		7 (14)
Current Marital Status				
Single		16 (32)		10 (20)
Married/Committed		34 (68)		40 (80)
Employment				
Unemployed outside home		25 (50)		34 (68)
Unemployed		25 (50)		16 (32)
Annual household income[b]				
< $31,000		8 (16)		4 (8)
$31,000 - $75,000		16 (32)		21 (42)
> $ 75,000		21 (42)		24 (48)
Other Health Problems				
Yes		37 (74)		44 (88)
No		13 (26)		6 (12)
Medication: Cognitive Function*				
Yes		28 (56)		12 (24)
No		22 (44)		38 (76)

[a]Two colorectal cancer and one healthy participant declined. [b]Five colorectal cancer and one healthy participant declined.

*$p < 0.05$.

Table 2.2

Disease and Treatment Characteristics of Individuals with Colorectal Cancer (n = 50)

Measures	Colorectal Cancer Group (n = 50)	
	M ± SD	N (%)
Time from Diagnosis (day)	67 ± 49	
Tumor Location		
Colon		27 (54)
Rectum		15 (30)
Rectosigmoid Junction		8 (16)
Stage of Cancer		
Stage I & II		16 (32)
Stage III		19 (38)
Stage IV & Recurrent		15 (30)
Treatment		
Before Any Treatment		20 (40)
After Surgery Only		13 (26)
Receiving Chemotherapy and/or radiation therapy		17 (34)

Table 2.3

Means and Standard Deviations of Physical and Psychological Symptoms (N = 100)

	Colorectal Cancer Group (n = 50)		Healthy Comparison Group (n = 50)	
	Mean ± SD	Range	Mean ± SD	Range
Total Score				
Total Mood Disturbance [a]	13.30 ± 16.14*	-10 - 51	0.14 ± 9.60	- 19 - 37
Subscale Scores				
Anxiety	4.76 ± 3.24*	0 - 14	2.58 ± 1.94	0 - 8
Depression	3.00 ± 3.30	0 - 14	1.90 ± 2.30	0 - 10
Anger	2.98 ± 3.53	0 - 17	2.38 ± 1.98	0 - 9
Vigor	8.20 ± 4.92*	0 -20	12.94 ± 3.59	6 - 20
Confusion	4.56 ± 2.93*	1 - 13	2.64 ± 1.65	0 - 8
Fatigue	6.20 ± 4.24*	0 - 17	3.58 ± 2.48	0 - 10

[a]Scores on the Total Mood Disturbance Scale computed by summing the anxiety, depressed mood, anger, confusion and fatigue subscales and subtracting the vigor subscale. Range of scores for this scale is between – 20 and 100.

*$p < 0.05$.

Table 2.4

Means and Standard Deviations of Overall Attention Measures (N = 100)

	Colorectal Cancer Group (n = 50)		Healthy Comparison Group (n = 50)	
	Mean ± SD	Range	Mean ± SD	Range
Cognitive Screen				
Mini Mental State Exam	29.28 ± 0.83*	27 - 30	29.60	27 - 30
Overall Attention[a]				
Attention Network Test: Overall				
Overall Accuracy[b]	0.98 ± 0.06	0.64 – 1.00	0.99 ± 0.01	0.95 – 1.00
Overall Response Time[c]	673.08 ± 113.13	501.08 – 1003.16	635.97 ± 74.98	510.11 – 872.53
Attention Network Test: Networks[c]				
Alerting Network	35.77± 22.70	-2.51 – 88.61	33.42 ± 22.51	- 5.20 – 89.47
Orienting Network	44.59 ± 29.20	- 3.55 – 113.68	47.70 ± 26.87	- 15.46 – 113.39
Executive Control Network	119.08 ± 45.19	48.26 – 311.92	114.85 ± 43.59	44.26 – 270.42
Neutral Flanker Condition[c]				
No Cue	661.38 ± 113.35*	481.33 – 930.91	619.22 ± 74.49	480.92 – 847.13
Center Cue	639.74 ± 121.28*	472.46 – 1024.96	598.11 ± 69.49	472.39 – 776.83
Double Cue	619.03 ± 110.22*	460.13 – 935.00	579.60 + 64.62	461.78 – 792.17
Up/Down Cue	605.01 ± 110.74*	435.16 – 930.63	565.64 ± 76.47	441.38 – 871.13
Mean	631.12 ± 111.40*	464.50 – 950.90	590.54 ± 68.55	466.61 – 821.81

[a] Two male colorectal cancer cases completed practice and session 1 of the Attention Network Test only secondary to insufficient time or decline. [b]Scores are in percentage. [c]Scores are in milliseconds.

*$p < 0.05$.

Table 2.5

Means and Standard Deviations of Attention and Memory Measures (N = 100)

	Colorectal Cancer Group (n = 50)		Healthy Comparison Group (n = 50)	
	Mean ± SD	Range	Mean ± SD	Range
Directed or Controlled Attention and Working Memory				
Digit Span Forward[a]	6.28 ± 1.29*	3.00 - 9.00	7.00 ± 1.47	4.00 – 9.00
Digit Span Backward[a]	4.68 ± 1.27	3.00 – 8.00	4.98 ± 1.36	3.00 – 8.00
Trail Making A[b]	33.37 ± 12.03*	15.00 – 68.60	28.84 ± 8.20	16.30 – 46.90
Trail Making B[b]	75.49 ± 37.57	30.30 – 224.40	63.88 ± 21.95	31.00 – 162.00
Standardized Total Composite Score[c]	- 0.51 ± 2.71*	- 7.57 – 5.27	0.51 ± 2.31	- 7.60 -5.85
Attentional Function Index Total Score	7.07 ± 1.83*	3.23 – 10.00	8.09 ± 1.16	4.15 – 9.85
Long-term Memory				
RAVLT Delayed Word Recall[d, e]	8.49 ± 3.51	0.00 – 14.00	8.38 ± 2.81	2.00 – 15.00
Everyday Memory Questionnaire	49.64 ± 20.88	28.00 – 136.00	46.32 ± 10.23	30.00 – 74.00

[a]Score are the number of digits recalled before two failed attempts. [b]Scores are time to complete task in seconds. [c]Standardized Total Composite Scores = zDSF + zDSB – zTMT A – z TMT B. [d]Scores are number of words recalled. [e]One male colorectal cancer case did not complete task.

*$p < 0.05$

Table 2.6

Pearson Correlation Coefficients Between Directed or Controlled Attention and Working Memory and Selected Covariates (N = 100)

	Age	Education	Gender[a]	Anxiety [b]	Depressed Mood [b]	Fatigue [b]
Standardized Total Composite Score	- 0.25 *	0.38 *	0.07	- 0.08	-0.21 *	- 0.09
Attentional Function Index Total Score	0.07	0.22 *	-0.17	- 0.37 *	- 0.35 *	- 0.57 *

[a] Gender: male = 1, female = 2. [b]Profile of Mood States – Brief Form subscales.

*$p < 0.05$.

Table 2.7

Predictors of Attention and Working Memory Standardized Total Composite Score (N = 100)

Variable	B	SE B	β	p
Group	1.17	0.54	0.23	0.03
Age	- 0.07	0.03	- 0.27	0.01
Gender	0.21	0.49	0.04	0.67
Education	0.31	0.09	0.33	0.00
Medication: affecting cognitive function	0.16	0.52	0.03	0.76
Anxiety	0.09	0.11	0.10	0.43
Depressed mood	- 0.21	0.11	- 0.24	0.06
Fatigue	0.05	0.08	0.08	0.52

$R = 0.52$, $R^2 = 0.27$, $F = 4.29$, $p < 0.001$.

Table 2.8

Predictors of Attention and Working Memory Attentional Function Index Self-report

Variable	B	SE B	β	p
Group	0.29	0.31	0.09	0.36
Age	- 0.01	0.02	- 0.03	0.76
Gender	- 0.30	- 0.29	- 0.09	0.30
Education	0.70	0.05	0.12	0.18
Medication: affecting cognitive function	- 0.26	0.31	- 0.08	0.39
Anxiety	- 0.04	0.07	- 0.07	0.54
Depressed mood	- 0.01	0.06	- 0.01	0.94
Fatigue	- 0.20	0.05	- 0.46	0.00

$R = 0.62$, $R^2 = 0.38$, $F = 6.91$, $p < 0.001$.

CHAPTER III

INFLAMMATORY CYTOKINES AND BIOMARKERS IN COLORECTAL CANCER

Introduction

Currently, it is estimated that there are 1,140,000 men and women in the United States living with a colorectal cancer diagnosis (American Cancer Society, 2011). Both the cancer and treatments for the disease are associated with many distressing symptoms that can affect an individual's ability to function and negatively influence his/her quality of life (Institute of Medicine, 2006). Preventing and/or treating symptoms without compromising cancer control, requires an understanding of potential mechanisms that underlie symptoms. One potential mechanism underlying colorectal cancer-related symptoms is the immune system's response to the cancer and/or cancer treatments (Kelley et al., 2003). Specifically, a growing body of research suggests that inflammation-related cytokines are associated with fatigue and other non-specific symptoms in individuals with cancer (Cleeland et al., 2003). These cytokine-induced symptoms and behaviors have been named 'sickness behavior' (Hart, 1988).

Studies examining sickness behaviors suggest that interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are the primary pro-inflammatory cytokines that communicate with the brain to induce symptoms and behavioral changes (Dantzer, Meagher, & Cleeland, 2012; Hart, 1988; Kelley et al., 2003). Studies examining sickness behaviors in individuals with cancer have observed a relationship

between IL-6 and TNF-α and fatigue (Inagaki et al., 2008; Meyers, Albitar, & Estey, 2005; Wang et al., 2010). Additionally, indirect markers of inflammation have been associated with sickness behavior in individuals with cancer including pro-inflammatory target molecules (C-reactive protein, CRP), molecules related to pro-inflammatory cytokine pathways (interleukin-1 receptor antagonist, IL-1RA), and other immunosuppressive cytokines involved in the regulation of the immune response (transforming growth factor-α, TGF-α) (Bower, Ganz, Aziz, & Fahey, 2002; Bower et al., 2011; Bower et al., 2009; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006; Inagaki et al., 2008; Meyers et al., 2005; Orre et al., 2009; Wang et al., 2010).

At this time, few research studies have assessed circulating inflammatory cytokines and biomarkers in individuals with colorectal cancer. Identification of alterations in pro-inflammatory cytokines, indirect biomarkers of inflammation, and immunosuppressive cytokines in colorectal cancer is the first step in examining sickness behavior in individuals with cancer. The purpose of this study is to determine if selected inflammatory cytokines and biomarkers are over expressed in individuals with colorectal cancer compared to individuals without. Specifically, the study tested the hypothesis that compared to individuals without colorectal cancer, individuals with colorectal cancer will show alterations in the expression of pro-inflammatory cytokines (IL-1, IL-6, TNF-α), indirect pro-inflammatory biomarkers (CRP, IL-1RA) and immunosuppressive cytokines (interleukin-10, IL-10; transforming growth factor-β1, TGF-β1). Further, the study hypothesized that having colorectal cancer would independently predict inflammatory cytokine and biomarker expression controlling for pertinent covariates.

Methods

Study Design, Sample, and Setting

The study design was a cross-sectional comparative design and assessed participants with and without colorectal cancer at one time point. Participants were recruited from a Midwest university hospital between May 2011 and September 2012. Participants included 50 men and women newly diagnosed with primary or recurrent colorectal cancer and 50 men and women without colorectal cancer. Each group had approximately equal numbers of men and women. Participants in the colorectal cancer group were tested within six months of diagnosis and participants in the healthy comparison group were tested within twelve months of a negative colonoscopy. Eligible participants were at least 30 years of age and had sufficient command of the English language to provide informed consent and permit testing. Individuals were excluded if they had a secondary diagnosis of a debilitating medical disorder (i.e. advanced cardiac or respiratory disease), unstable mental or psychiatric disorder, CNS disease, or substance abuse. Patients with colorectal cancer were also excluded for a diagnosis of cancer other than colorectal or skin cancer and those without colorectal cancer were excluded for a previous history of cancer other than skin cancer. To enable recruitment and accrual in an ill population, participants were not excluded for medications that might affect cognitive and immune function such as psychoactive medications including narcotics and antidepressants and anti-inflammatory medications including steroids.

Measures

Inflammatory Cytokines and Biomarkers

Serum inflammatory cytokines and biomarkers measured in this study included interleukin (IL)-1β, IL-6, IL-10, IL-1 receptor antagonist (IL-1RA), tumor necrosis factor – alpha (TNF-α), transforming growth factor-β1 (TGF-β1) and C-reactive protein (CRP). This panel, which includes pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and indirect biomarkers of pro-inflammatory cytokine activity (IL-1RA, CRP), was chosen based on previous research on inflammation and cancer-related symptoms (Lee et al., 2004; Meyers et al., 2005; Orre et al., 2009; Rich et al., 2005; Wang et al., 2012)**.** Further, immunosuppressive cytokines (IL-10, TGF-β1) appear to be important in the cancer pathogenesis of colorectal cancer so were included to gain a greater understanding of the systemic inflammatory response in colorectal cancer (Bellone et al., 2001; Berghella, Pellegrini, Del Beato, Adorno, & Casciani, 1997; Narai et al., 2002; Shim, Kim, Han, & Park, 1999).

Blood samples for inflammatory cytokine and biomarker assays were obtained from each participant in the morning or early afternoon and with routine blood draws for individuals with colorectal cancer. Five milliliters of blood for serum were collected in corvac tubes. Collected blood was allowed to clot for at least 30 minutes and no more than 2 hours before processing. Processing included centrifuging at 1000 g for 15 minutes at room temperature, removing serum, and storing serum at $\leq$ - 70 °C for batch analyses after all participants were enrolled.

Inflammatory cytokines and biomarkers were assayed in duplicate using commercially available cytometric bead array assays and enzyme-linked immunosorbent

assays (ELISA). Specifically, IL-1β, IL-6, TNF-α, and IL-10 were analyzed with Millipore's High Sensitivity Human Cytokine Magnetic Bead panel (HSCYTMAG-60SK), IL-1RA was analyzed with Millipore's Human Cytokine/Chemokine Magnetic Bead panel (HCYTOMAG-60K), TGF-β1 was analyzed with R & D System's DuoSet ELISA development kit (DY240) and C-reactive protein was analyzed with R & D System's DuoSet ELISA development kit (DY 1707). All inflammatory cytokines and biomarker results are the mean of the two measurements.

Adjunct Measures

The Profile of Mood States-Brief Form (POMS-BF), the Inventory of Functional Status Cancer (IFS-CA), a demographic questionnaire and a medical chart audit form were used to measure participant characteristics that might affect immune function. Characteristics that have been associated with higher circulating levels of inflammatory cytokines and biomarkers include: older age, fewer years of education, advanced colorectal cancer, psychological distress, current tobacco use, a higher body mass index, and reduced exercise (Belluco et al., 2000; Chung & Chang, 2003; Galizia et al., 2002; Musselman et al., 2001; Narai et al., 2002; O'Connor et al., 2009).

The POMS-BF is a 30 item self-rating scale with an overall total mood disturbance score and six subscale scores (McNair, 2012). The depression and anxiety subscales were used in this study. Individuals rate themselves on how they have been feeling in the past week on a 4-point scale from 0 (not at all) to 4 (extremely). The POMS-BF has an internal consistency of 0.87 for total mood disturbance and 0.86 to 0.93 for the anxiety and depression subscales in individuals with cancer (Cimprich, 1999; Cimprich, So, Ronis, & Trask, 2005; Lehto & Cimprich, 1999). In this study, the internal

consistency coefficient was 0.80 for the total score and 0.76 and 0.81 for the anxiety and depression subscales respectively.

The IFS-CA is a self-rating scale consisting of 39 questions which assess an individual's ability to perform everyday activities (Tulman, Fawcett, & McEvoy, 1991). The exercise item in the personal care activities subscale was used to assess the extent to which usual exercise had been carried out in the last few weeks. Responses were made on a 4-point scale from 1 (not at all/never exercise as much as usual) to 4 (all the time/fully exercise as much as usual). This instrument has been previously used to examine cytokine-induced changes in behavior in individuals with cancer (Visovatti, Cimprich, & Metzger, 2009).

The demographic questionnaire and medical chart audit form were used to assess the following patient characteristics: age, education level, sex, marital status, race, body mass index, current tobacco use, type and stage of colorectal cancer, current medical conditions, and current medications.

Study Procedures

The study was approved by the institutional review board of the university and health system. Following consent, participants completed self-report measures in a quiet private room in the outpatient area and had blood specimens collected. For most participants all research testing was completed on the same day but for a few participants it was more convenient to collect blood specimens on a separate day. All blood specimens were collected within 14 days of the self-report measures. The principal investigator obtained informed consent and administered the self-report measures. Trained phlebotomy staff collected the blood specimens.

Data Analysis

Initial analyses used independent t-tests and Chi-square tests to describe 1) participant characteristics that may differ between individuals with and without cancer, and might affect inflammatory cytokine and biomarker expression, and 2) any differences between individuals with and without cancer on inflammatory cytokine and biomarker expression. Pearson correlation coefficients were used to assess the relationship between inflammatory cytokines and biomarkers and selected covariates. Finally, separate multiple linear regression models were constructed to explore whether having cancer independently predicted serum levels of inflammatory cytokines and biomarkers after controlling for covariates which may differ between individuals with and without cancer and which may be related to immune function (i.e. age, education, psychological distress, BMI current tobacco use, exercise). Because inflammatory cytokines and biomarkers had a skewed distribution, data were log transformed using a natural log transformation. Transformation procedures were consistent with other studies assessing inflammatory cytokines and biomarkers in individuals with cancer to permit comparison across studies (Bower et al., 2011; Bower et al., 2009; Wang et al., 2010). Data are presented using log transformed values rather than raw data. For some analyses, an inflammatory ratio was computed. The pro-inflammatory cytokine ratio was calculated by dividing TNF-α levels by IL-10 levels. The anti-inflammatory cytokine ratio was calculated by dividing IL-10 levels by TNF-α levels.

Results

Sample Characteristics

Participant demographic and medical characteristics are presented in Table 3.1. Participants (N = 100) were middle aged (M $\pm$ SD: 56 $\pm$ 10 years), highly educated (M $\pm$ SD: 16 $\pm$ 2.7 years) and predominantly Caucasian (80%). There were no significant differences found on age ($t(98) = -1.63$, $p = 0.11$), education ($t(98) = -1.28$, $p = 0.20$), gender ($\chi^2(1, 100) = 0.00$, $p = 1.00$), marital status ($\chi^2(1, 100) = 1.30$, $p = 0.25$), race ($\chi^2(1, 98) = 0.13$, $p = 0.72$), other health problems ($\chi^2(1, 100) = 2.34$, $p = 0.13$), body mass index ($t(98) = -0.51$, $p = 0.61$), or current tobacco use ($\chi 2(1, 100) = 0.10$, $p = 0.76$) between these two groups.

Participant's reports of psychological and symptom distress as well as frequency of usual exercise are presented in Table 3.1. Compared to individuals without colorectal cancer, individuals with colorectal cancer reported significantly greater total mood disturbance ($t(98) = 4.95$, $p < 0.001$). Further analysis of distress indicated that individuals with colorectal cancer reported significantly more anxiety ($t(98) = 4.09$, $p < 0.001$), fatigue ($t(98) = 3.77$, $p < 0.001$), and confusion ($t(98) = 4.04$, $p < 0.001$) as well as significantly less vigor ($t(98) = -5.50$, $p < 0.001$). The two groups did not significantly differ on feelings of depressed mood ($t(98) = 1.93$, $p = 0.06$) or anger ($t(98) = 1.05$, $p = 0.30$). Finally, individuals with colorectal cancer reported participating in usual exercise significantly less frequently than individuals without colorectal cancer ($t(97) = -6.05$, $p < 0.001$).

Medical and treatment characteristics of individuals in the colorectal cancer group are presented in Table 3.2. The mean number of days from diagnosis to assessment was

67 days (SD = 49 days). Most individuals with colorectal cancer had localized disease (stage I, II, & III) (70%) and were assessed before any chemotherapy or radiation therapy (66%).

Group Differences in Inflammatory Cytokines and Biomarkers

Scores on inflammatory cytokines and biomarkers are presented in Table 3.3. As hypothesized, individuals with colorectal cancer had significantly higher levels of pro-inflammatory cytokines (IL-6), indirect pro-inflammatory biomarkers (CRP), and immunosuppressive cytokines (IL-10) providing evidence of a systemic inflammatory response in individuals with colorectal cancer. Unexpectedly, individuals with colorectal cancer had significantly lower levels of the immunosuppressive cytokine, TGF-β1. To address this, a within group analysis of variance (ANOVA) was conducted to explore the impact of treatment on levels of TGF- β1 in individuals with colorectal cancer. Patients were divided into three groups: before any treatment (group 1), after surgery only (group 2), and receiving chemotherapy and/or radiation therapy (group 3). A statistically significant difference at the $p < 0.05$ level in the levels of TGF-β1 was found for the three treatment groups; $F(2, 47) = 5.00$, $p = 0.01$. Post hoc comparisons using the Tukey HSD test indicated that the mean score for group 1 ($M = 3.41$, SD = 0.24) was significantly higher than group 3 ($M = 3.11$, SD = 0.35). Group 2 fell in between group 1 and 3 and did not significantly differ from either ($M = 3.22$, SD = 0.32). The actual difference between groups was quite large with an effect size of 0.18 using eta squared. This finding suggests that treatment did have an impact on TGF-β1 levels with individuals receiving chemotherapy and/or radiation therapy having significantly lower TGF-β1 levels than individuals before any treatment. Finally, no group differences were found on

IL-1β, IL-1RA or TNF-α. However, it should be noted that serum levels of IL-1β and IL-1RA were very low and fell outside the detectable range in 23% and 45% of participants respectively. Detection of group differences on these assays was limited by assay sensitivity.

Scores on inflammatory cytokine ratios are presented in Table 3.3. Interestingly, individuals with colorectal cancer had significantly lower pro-inflammatory cytokine ratio (TNF-α/IL-10) and a significantly higher anti-inflammatory ratio (IL-10/TNF-α) suggesting a shift toward a more immunosuppressive phenotype of systemic cytokines in colorectal cancer.

Predictors of Inflammatory Cytokine and Biomarker levels

Multiple linear regression analyses were performed to further assess the relationship between the immune variables (TNF-α, IL-6, CRP, IL-10, TGF-β1, TNF-α/IL-10, IL-10/TNF-α) and group controlling for possible covariates. These covariates included: age, education, body mass index, current tobacco use, anxiety, depressed mood, and exercise as much as usual. Because of very low detection, IL-1 and IL-1RA were not included in regression analyses. Correlation between immune variables and selected covariates are presented in Table 3.4.

Pro-inflammatory Cytokines. To determine possible predictors of TNF-α and IL-6 levels, separate multiple linear regression models were constructed using these pro-inflammatory cytokines as the dependent variable. Group and selected covariates were entered as independent variables. Interestingly when controlling for covariates, having colorectal cancer ($t = 2.12$, $p = 0.01$) was a significant independent predictor for TNF-α. In addition, greater anxiety ($t = 3.01$, $p < 0.001$), less depressed mood ($t = -2.29$, $p =$

0.02) and not exercising as much as usual (t = - 2.77, p = 0.01) were also significant. These variables together accounted for 19% of the variance in TNF-α, multiple R = 0.44, F (8, 90) = 2.69, p = 0.01. For IL-6, not exercising as much as usual (t = -3.42, p < 0.01) alone predicted higher levels accounting for 22% of the variance in IL-6 levels, multiple R = 0.47, F (8,90) = 3.11, p < 0.01). Findings from correlation analyses are presented in Table 3.4 and findings from regression analyses are presented in Tables 3.5 and 3.6.

Indirect Pro-inflammatory Biomarkers. To determine possible predictors of CRP levels, multiple linear regression was performed using this indirect pro-inflammatory biomarker as the dependent variable. Group and selected covariates were entered as independent variables. For CRP, having colorectal cancer (t = - 2.85, p = 0.01) and not exercising as much as usual (t = - 2.44, p = 0.02) predicted higher levels accounting for 30% of the variance, multiple R = 0.55, F (8, 90) = 4.79, p < 0.001). Findings from correlation and regression analyses are presented in Tables 3.4 and 3.7 respectively.

Immunosuppressive Cytokines. To determine possible predictors of IL-10, and TGF-β1 levels, separate multiple linear regressions were performed using these immunosuppressive cytokines as the dependent variable. Group and selected covariates were entered as independent variables. The IL-10 and TGF-β1 models did not reach significance. Findings from correlation analyses are presented in Table 3.4 and findings from regression analyses are presented in Tables 3.8 and 3.9.

Inflammatory Cytokine Ratios. Finally, to determine possible predictors of TNF-α/IL-10 and IL-10/TNF-α ratios, separate multiple linear regressions were performed using these inflammatory cytokine ratios as the dependent variables. Group and selected covariates were entered as independent variables. Neither of the models reached

significance. Findings from correlation analyses are presented in Table 3.4 and findings from regression analyses are presented in Tables 3.10 and 3.11.

Discussion

Activation of the immune system and inflammatory cytokine expression has been associated with some cancer and cancer treatment related symptoms. This study assessed inflammatory cytokines and biomarkers in individuals with colorectal cancer as a first step toward examining cytokine-induced symptoms and behaviors or *sickness behavior* in individuals with colorectal cancer. The study found significantly higher levels of interleukin-6 (IL-6), C-reactive protein (CRP) and interleukin-10 (IL-10) in individuals with colorectal cancer compared to healthy controls. Unexpectedly, this study also found significantly lower transforming growth factor – beta1 (TGF-β1) in individuals with colorectal cancer compared to healthy controls, possibly related to cancer treatments. When controlling for possible covariates, having colorectal cancer was an independent predictor of higher circulating levels of TNF-α and CRP. These findings will be discussed further below.

Serum Levels of Inflammatory Cytokines and Biomarkers

Higher inflammatory cytokines and biomarkers in colorectal cancer: IL-6, CRP, and IL-10. Consistent with studies examining the diagnostic and prognostic role of cytokines in colorectal cancer, this study found significantly elevated levels of IL-6, CRP, and IL-10 in individuals with colorectal cancer compared to individuals without (Chung & Chang, 2003; Dymicka-Piekarska, Matowicka-Karna, Gryko, Kemona-Chetnik, & Kemona, 2007; Galizia et al., 2002; Ito & Miki, 1999; Kaminska et al., 2005; Kantola et al., 2012; Kinoshita, Ito, & Miki, 1999; Nikiteas et al., 2005; Ueda, Shimada,

& Urakawa, 1994). However, after controlling for covariates, having colorectal cancer remained a significant predictor of higher CRP levels but not IL-6 or IL-10 levels. This finding suggests that human biobehavioral factors can have an effect on the measurement of circulating cytokines and influence the reliability and interpretation of findings. Interestingly, only a few of the above studies assessed and controlled for potential covariates (exclusion criteria, statistical control) that may affect inflammatory cytokine and biomarker levels (Chung & Chang, 2003; Kantola, et al., 2012; Ueda, et al., 1994). As such, further research is needed to elucidate patterns of inflammatory cytokine and biomarker expression in individuals with colorectal cancer.

Lower inflammatory cytokines and biomarkers in colorectal cancer: TGF-β1. In contrast to other studies assessing the role of TGF-β1 in individuals with colorectal cancer, this study found significantly lower levels of TGF-β1 in individuals with colorectal cancer compared to healthy controls (Bellone et al., 2001; Narai et al., 2002; Shim et al., 1999). Studies examining TGF-β1 in patients with colorectal cancer measured this immunosuppressive cytokine before any treatment unlike this study that measured TBF-β1 levels in patients before and during treatment for the disease. A within group analysis of variance was conducted to explore the impact of treatment on levels of TGF-β1 and found an actual difference in levels between patients who had not yet been treated and those who were receiving chemotherapy and radiation therapy. Specifically, patients receiving chemotherapy and radiation therapy had significantly lower TGF-β1 levels compared to patients who had not yet been treated. Levels of TGF-β1 in patients after primary surgery fell in between the other two treatment groups and was not significantly different. This novel finding suggests that cancer treatments may influence

TGF-β1 levels. Further research is needed to assess the effects of cancer treatments on TGF-β1 in individuals with colorectal cancer.

When controlling for possible covariates, the regression model for TGF-β1 did not reach significance. Similar to the above studies assessing IL-6, IL-10 and CRP in colorectal cancer, studies examining TGF-β1 in colorectal cancer did not control for potential covariates that may influence levels of TGF-β1 (Bellone et al., 2001; Narai et al., 2002; Shim et al., 1999). As such further research is needed to assess TGF-β1 expression in individuals undergoing varying forms of treatments for colorectal cancer.

No group differences were observed in this sample: TNF-α, IL-1β, and IL-1RA. No group differences were observed on levels of TNF-α between individuals with and without colorectal cancer. However, when controlling for possible covariates, having colorectal cancer independently predicted higher levels of TNF-α along with greater anxiety and less depressed mood. Some studies examining TNF-α have found significantly higher levels of circulating TNF-α in individuals with colorectal cancer compared to healthy controls and other studies have excluded this cytokine from analyses because of poor detection (Chung & Chang, 2003; Kaminska et al., 2005; Kantola et al., 2012; Nikiteas et al., 2005; Ueda et al., 1994). One of the strengths of this study was the detection of TNF-α within the assay's working range in all participants. This may have been in part due to the use of a newly available high sensitivity human cytokine magnetic bead panel (see methods section for details) as well as careful sample collection and handling methods. The finding that having colorectal cancer predicted levels of TNF-α after controlling for potential covariates provides evidence for a role for this cytokine in the pathogenesis of the disease and/or treatment for the disease. It also exemplifies why

it is important to assess and control potential covariates. Further research to replicate the above finding is needed.

No group differences were observed in levels of IL-1β and IL-1RA in individuals with and without colorectal cancer. However, serum levels of both these cytokines were very low and fell outside the detectable range in 23% of participants for IL-1β and 45% of participants for IL-1RA. Thus, detection of differences on these cytokines may have been limited by assay sensitivity. Future research with a larger sample size is recommended.

Inflammatory cytokine ratios: TNF-α/IL-10 and IL-10/TNF-α. In this study, individuals with colorectal cancer had significantly lower pro-inflammatory cytokine ratios (TNF-α/IL-10) and significantly higher anti-inflammatory cytokine ratios (IL-10/TNF-α) compared to individuals without. These findings suggest that in addition to alterations in the levels of cytokines in colorectal cancer there also appears to be a shift in the balance of the inflammatory cytokines toward a more suppressive phenotype. To date, no research studies were found that have examined TNF-α/IL-10 or IL-10/TNF-α ratios in individuals with cancer. This novel finding may provide preliminary evidence of the systemic effects of tumor-induced dysfunction of the innate and adaptive immune systems in colorectal cancer (Whiteside, 2010).

Demographic and Biobehavioral Predictors of Inflammatory Cytokines and Biomarker Levels

Separate multiple linear regression models were constructed to assess the relationship between inflammatory cytokines and biomarkers (TNF-α, IL-6, CRP, IL-10, TGF-β1, TNF-α/IL-10, IL-10/TNF-α) and having colorectal cancer controlling for

potential covariates. Participants with and without cancer were similar on most demographic and medical characteristics except for *anxiety* and *not exercising as much as usual*. *Anxiety* and *not exercising as much as usual* were also found to be correlated with certain cytokines and thus were included in regression models. Additionally, a review of the literature found that age, education, body mass index, current tobacco use, and depressed mood may also be potential covariates so these variables were also included as independent variables in the regression models. When controlling for covariates having colorectal cancer, higher anxiety, lower depressed mood, and not exercising as much as usual were significant predictors of greater pro-inflammatory cytokine activity (higher TNF-α Levels, higher CRP levels). Age, education, body mass index, and current tobacco use did not predict inflammatory cytokine and biomarker levels. These results will be discussed below.

Having colorectal cancer. After controlling for possible covariates, having colorectal cancer was a significant predictor of higher levels of TNF-α and CRP. Having colorectal cancer also predicted higher levels of the anti-inflammatory cytokine ratio IL-10/TNF-α as well as lower levels of TGF-β1 and the pro-inflammatory cytokine ratio TNF-α/IL-10 although these regression models did not reach significance. Finally, having colorectal cancer did not predict IL- 6 or IL-10 levels.

This study hypothesized that having colorectal cancer would be a significant predictor of inflammatory cytokine and biomarker levels as cancer and cancer treatments have been associated with the activation of the immune system and inflammatory cytokine expression (Cleeland et al., 2003). Having colorectal cancer was a significant predictor of higher levels of the pro-inflammatory cytokine TNF-α and the indirect pro-

inflammatory biomarker CRP. These findings are important. TNF-α is produced early in the response to an immune challenge and is responsible for the production of other pro-inflammatory cytokines including IL-1β and IL-6 and amplification and maintenance of the inflammatory response (Cavaillon, Adib-Conquy, Fitting, Adrie, & Payen, 2003; Mant et al., 2008). Further, TNF-α along with IL-1β and IL-6 are thought to have a primary role in inducing the expression of sickness behaviors (Konsman, Parnet, & Dantzer, 2002). Indirect markers of TNF-α activity have been associated with fatigue in individuals with cancer (Bower al., 2002; Bower et al., 2011).

CRP is an acute phase protein produced by hepatocytes in the liver and is under the transcription control of cytokines originating at sites of pathology- mainly IL-6 (Gabay & Kuscher, 1999). CRP binds with a variety of ligands including components of bacteria, fungi and parasites as well as damaged cell membranes and apoptotic cells and activates the complement system (Pepys & Hirschfield, 2003). It has been described as an exquisitely sensitive biomarker of systemic inflammation and has been used in cardiovascular disease alongside other clinical and pathologic results to evaluate disease (Pepys & Hirschfield, 2003). Increased levels of circulating CRP have been associated with fatigue in individuals with cancer and may be a sensitive biomarker of sickness behavior. (Bower et al., 2009; Orre et al., 2009; Wratten et al., 2004)

The finding that having colorectal cancer significantly predicted CRP and not IL-6 is an interesting finding and may reflect the complex role of IL-6 in cancer pathogenesis as well as aging, health behaviors, psychological distress, and other health problems. Similarly, the finding that having colorectal cancer did not predict levels of immunosuppressive cytokines (IL-10, TGF-β1) or inflammatory cytokine ratios may

reflect the complex role of these cytokines in cancer pathogenesis as well as aging and other health problems and behaviors. Further research is needed to assess inflammatory cytokine and biomarker expression as well as biobehavioral factors that might affect their expression in colorectal cancer to gain a better understanding of the systemic inflammatory response and sickness behavior in individuals with colorectal cancer.

Psychological distress. In this study, individuals with colorectal cancer reported significantly more anxiety but not depressed mood compared to individuals without colorectal cancer. Additionally, higher anxiety and lower depressed mood were significant predictors of higher TNF-α levels across groups. These finding are consistent with that of other researchers assessing psychological distress in healthy individuals as well as individuals with cancer (Arranz, Guayerbas, & De la Fuente, 2007; Kim et al., 2012; Maes et al., 1998; Pitsavos et al., 2006). Both anxiety and depressed mood have been associated with activation of the inflammatory response and may be part of the immune system's response to the cancer and threat to survival (Miller, 2009). Specifically, anxiety is associated with arousal and increased activity and is important for protection against future threats while depressed mood allows for the shutting down of behavioral activity and conservation of resources. It has been proposed that cytokine expression associated with the source or nature of the threat as well as genetics and past experiences determine the individual's response to a threat (Miller, 2009). In this regard, anxiety in colorectal cancer survivors may be part of sickness behavior responses that support an individual's survival and adaptation to a life threatening diagnosis of cancer. Further research is needed to examine the relationship between anxiety and TNF-α in individuals newly diagnosed with colorectal cancer.

Exercising as much as usual. In this study, individuals with colorectal cancer reported decreased physical activity or *not exercising as much as usual* compared to individuals without colorectal cancer. Additionally, the study found that *not exercising as much as usual* alone independently predicted higher levels of IL-6 and predicted higher levels of CRP and TNF-α across groups. Not exercising as much as usual also predicted higher levels of the immunosuppressive cytokine IL-10 although the regression model did not reach significance.

Consistent with these findings, engagement in regular aerobic and resistance training has been associated with lower circulating levels of IL-6, CRP, and TNF-α in healthy and patient populations (Balducci et al., 2010; O'Connor et al., 2009). However, no research has examined the effect of reducing exercise frequency or intensity in individuals with cancer or other populations. Decreased physical activity has been described as an immune mediated sickness behavior that permits the reduction of energy demands so that fever and other physiologic immune responses that require energy and are necessary for the survival of the individuals can be sustained (Dantzer, 2004; Hart, 1988). Further research examining decreased physical activity and appropriateness of exercise interventions in individuals with cancer is needed.

Limitations and Future Research

Findings from this study were limited by a cross-sectional design, convenience sample, and inclusion of patients with different stages of disease receiving multiple therapies (surgery, chemotherapy, radiation therapy). Although other studies have found higher inflammatory cytokines and biomarkers in individuals with advanced versus localized cancer, this study was not sufficiently powered to provide definitive

information about this relationship ((Belluco et al., 2000; Dymicka-Piekarska, et al., 2007; Kaminska et al., 2005; Kantola et al., 2012; Ueda et al., 1994).

Despite these limitations this study provides preliminary evidence that individuals with colorectal cancer can experience alterations in levels of inflammatory cytokines and biomarkers. Having colorectal cancer independently predicted TNF-α and CRP after controlling for potential covariates. TNF-α is a pro-inflammatory cytokine that has been implicated in the expression of sickness behavior (Dantzer, 2004). CRP is an indirect marker of inflammation and may be a candidate biomarker of sickness behavior in individuals with colorectal cancer. These findings are very important and foundational to understanding sickness behavior and appropriate interventions. Further longitudinal studies are needed to assess sickness behavior and the effects of cancer and cancer treatment on inflammatory cytokine expression in individuals with colorectal cancer.

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Table 3.1
Sample Characteristics, n (%) (N = 100)

		Colorectal Cancer Group (n = 50)	Healthy Comparison Group (n = 50)	*p*
Demographic Characteristics				
Age (years)	Mean (SD)	55 (12)	58 (7)	0.11
Education (years)	Mean (SD)	15 (3)	16 (3)	0.20
Gender	Females	26 (52%)	25 (50%)	1.00
	Males	24 (48%)	25 (50%)	
Marital status	Married	16 (32%)	10 (20%)	0.25
Race[a]	White	38 (76%)	42 (84%)	0.72
	Non-white	10 (20%)	7 (14%)	
Medical Characteristics				
Body Mass Index (kg/m^2)	Mean (SD)	27.98 (7.80)	28.68 (5.73)	0.61
Other Health Problems	Yes	13 (26%)	6 (12%)	013
Current Tobacco Use	Yes	5 (10%)	7 (14%)	0.76
Psychological and Symptom Distress				
Total Mood Disturbance	Mean (SD)	13.3 (16.14)	0.14 (9.60)	< 0.001
Anxiety	Mean (SD)	4.76 (3.24)	2.58 (1.94)	< 0.001
Depressed Mood	Mean (SD)	3.00 (3.30)	1.90 (2.30)	0.06
Anger	Mean (SD)	2.98 (3.53)	2.38 (1.98)	0.30
Vigor	Mean (SD)	8.20 (4.92)	12.94 (3.59)	< 0.001
Confusion	Mean (SD)	4.56 (2.93)	2.64 (1.65)	< 0.001
Fatigue	Mean (SD)	6.20 (4.24)	3.58 (2.48)	< 0.001
Exercise				
Exercise As Much As Usual[b]	Mean (SD)	2.20 (1.16)	3.37 (0.70)	< 0.001

[a]Two colorectal cancer and one healthy participant declined to answer. [b]Missing data on one individual in the healthy comparison group.

Table 3.2

Medical and Treatment Characteristics of Individuals with Colorectal Cancer, n (%) (n = 50)

		Colorectal Cancer Group (n = 50)
Time from Diagnosis (day)	Mean (SD)	67 (49)
Tumor Location	Colon	27 (54%)
	Rectum	15 (30%)
	Rectosigmoid Junction	8 (16%)
Stage of Cancer	Stage I & II	16 (32%)
	Stage III	19 (38%)
	Stage IV & Recurrent	15 (30%)
Treatment	After diagnosis and before any treatment	20 (40%)
	After surgery only	13 (26%)
	Receiving chemotherapy and/or radiation therapy	17 (34%)

Table 3.3

Means and Standard Deviations of Inflammatory Cytokines and Biomarkers (N = 100)[a]

	Colorectal Cancer Group (n = 50) Mean ± SD[b]	Healthy Comparison Group (n = 50) Mean ± SD[b]	t	*p*
Pro-inflammatory Cytokines				
Interleukin-1	0.21 ± 0.39	0.19 ± 0.46	0.19	0.85
Tumor Necrosis Factor - α	1.93 ± 0.67	1.90 + 0.93	0.23	0.82
Interleukin-6	1.94 ± 0.90	1.53 ± 0.93	2.26	0.03
Indirect Pro-inflammatory Biomarkers				
Interleukin -1 Receptor Antagonist	2.37 ± 1.69	2.04 ± 2.07	0.87	0.39
C-Reactive Protein	1.78 ± 1.05	1.04 ± 0.59	4.36	0.00
Immunosuppressive Cytokines				
Interleukin-10	2.85 ± 0.94	2.40 ± 0.99	2.33	0.02
Transforming Growth Factor - β1	3.26 ± 0.33	3.41 ± 0.23	- 2.73	0.01
Inflammatory Cytokine Ratios				
Tumor Necrosis Factor-α/Interleukin-10	0.72 ± 0.24	0.91 ± 0.47	- 2.62	0.01
Interleukin-10/Tumor Necrosis Factor-α	1.60 + 0.69	1.34 + 0.60	2.03	< 0.05

[a]Individual assay values below the minimal detectable concentration (Min DC) were assigned a value of '0'. [b]Inflammatory cytokines and biomarkers transformed with natural log.

Table 3.4

Pearson Correlation Coefficients Between Inflammatory Cytokines and Biomarkers and Immune Function Modifiers (N = 100)

	Age	Education	BMI	Current Tobacco[a]	Anxiety[b]	Depression[b]	Exercise as Usual[c]
Pro-inflammatory Cytokines							
Tumor Necrosis Factor - α	0.04	- 0.13	0.00	- 0.02	0.22 *	- 0.03	0.14
Interleukin-6	0.06	- 0.21 *	0.12	0.13	0.11	0.02	- 0.32 *
Indirect Pro-inflammatory Biomarkers							
C-Reactive Protein	0.06	- 0.21 *	0.18	0.05	0.15	0.18	- 0.39 *
Immunosuppressive Cytokines							
Interleukin-10	- 0.09	- 0.06	0.11	- 0.07	0.16	0.13	- 0.34 *
Transforming Growth Factor - β1	- 0.12	0.04	- 0.03	0.12	0.04	0.13	0.14
Inflammatory Cytokine Ratio							
Tumor Necrosis Factor-α/Interleukin-10	0.12	0.09	- 0.01	0.11	0.01	- 0.09	0.24 *
Interleukin-10/Tumor Necrosis Factor-α	- 0.19	0.15	- 0.04	- 0.05	- 0.04	0.04	- 0.14

[a]Current tobacco use: no = 0, yes = 1. [b]Profile of Mood States-Brief Form subscale. [c]Item from Inventory of Functional Status Cancer Part C.

*$p \leq 0.05$

Table 3.5
Predictors of Tumor Necrosis Factor-alpha (N = 100)

Variable	B	SE B	β	*p*
Group	0.29	0.14	0.25	0.04
Age	0.01	0.01	0.11	0.26
Education	- 0.02	0.02	- 0.09	0.35
BMI	0.01	0.01	0.08	0.39
Current Tobacco Use	- 0.25	0.18	- 0.14	0.17
Anxiety	0.08	0.03	0.40	0.00
Depressed mood	- 0.06	0.03	- 0.28	0.02
Exercise as Usual	- 0.17	0.06	- 0.32	0.01

$R = 0.44$, $R^2 = 0.19$, $F = 2.69$, $p = 0.01$.

Table 3.6
Predictors of Interleukin- 6 (N = 100)

Variable	B	SE B	β	*p*
Group	- 0.05	0.22	- 0.03	0.83
Age	0.01	0.01	0.10	0.31
Education	- 0.05	0.03	- 0.14	0.16
BMI	0.00	0.01	0.00	0.97
Current Tobacco Use	0.24	0.28	0.09	0.39
Anxiety	0.22	0.04	0.07	0.61
Depressed mood	- 0.07	0.04	- 0.21	0.80
Exercise as Usual	- 0.33	0.10	- 0.40	0.00

$R = 0.47$, $R^2 = 0.22$, $F = 3.11$, $p = 0.00$.

Table 3.7
Predictors of C-reactive protein (N = 100)

Variable	B	SE B	β	*p*
Group	- 0.58	0.20	- 0.31	0.01
Age	0.01	0.01	0.13	0.16
Education	- 0.03	0.03	- 0.09	0.33
BMI	0.02	0.01	0.18	0.05
Current Tobacco Use	0.20	0.26	0.07	0.46
Anxiety	- 0.04	0.04	- 0.13	0.29
Depressed mood	0.03	0.04	0.81	0.42
Exercise as Usual	- 0.22	0.09	- 0.27	0.02

$R = 0.55$, $R^2 = 0.30$, $F = 4.79$, $p = 0.00$.

Table 3.8
Predictors of Interleukin – 10 (N = 100)

Variable	B	SE B	β	*p*
Group	- 0.09	0.24	- 0.04	0.72
Age	0.00	0.01	- 0.02	0.86
Education	0.00	0.04	0.01	0.96
BMI	0.01	0.01	0.08	0.40
Current Tobacco Use	- 0.28	0.31	- 0.09	0.38
Anxiety	0.02	0.05	0.36	0.72
Depressed mood	0 00	0.04	- 0.01	0.93
Exercise as Usual	- 0.26	0.11	- 0.29	0.02

$R = 0.36$, $R^2 = 0.13$, $F = 1.70$, $p = 0.11$.

Table 3.9

Predictors of Transforming Growth Factor – beta 1 (N = 100)

Variable	B	SE B	β	*p*
Group	0.20	0.07	0.34	0.01
Age	0.00	0.00	- 0.14	0.18
Education	0.01	0.01	0.05	0.65
BMI	0.00	0.00	- 0.08	0.44
Current Tobacco Use	0.08	0.09	0.09	0.38
Anxiety	0.00	0.01	0.02	0.88
Depressed mood	0.02	0.01	0.17	0.19
Exercise as Usual	- 0.01	0.03	- 0.04	0.76

$R = 0.38$, $R^2 = 0.14$, $F = 1.88$, $p = 0.07$.

Table 3.10

Predictors of TNF-α/IL-10 ratio (N = 100)

Variable	B	SE B	β	*p*
Group	0.24	0.09	0.31	0.01
Age	0.00	0.00	0.09	0.39
Education	- 0.02	0.02	- 0.13	0.23
BMI	0.00	0.01	- 0.02	0.86
Current Tobacco Use	0.04	0.12	0.03	0.78
Anxiety	0.03	0.02	0.23	0.10
Depressed mood	- 0.03	0.02	- 0.19	0.14
Exercise as Usual	- 0.01	0.04	- 0.02	0.85

$R = 0.35$, $R^2 = 0.12$, $F = 1.54$, $p = 0.16$.

Table 3.11

Predictors of IL-10/TNF-α ratio (N = 100)

Variable	B	SE B	β	*p*
Group	- 0.36	0.16	- 0.27	0.03
Age	- 0.01	0.01	- 0.19	0.07
Education	0.04	0.03	0.17	0.11
BMI	0.00	0.01	- 0.02	0.84
Current Tobacco Use	0.08	0.21	0.04	0.70
Anxiety	- 0.06	0.03	- 0.25	0.08
Depressed mood	- 0.04	0.03	0.16	0.20
Exercise as Usual	0.03	0.07	0.04	0.72

$R = 0.36$, $R^2 = 0.13$, $F = 1.63$, $p = 0.13$.

CHAPTER IV

COGNITIVE SYMPTOMS AND INFLAMMATION

Introduction

Colorectal cancer affects individuals of all racial and ethnic groups and is the third most common cancer for both men and women. The overall life time risk of developing the disease is 1 in 20 (American Cancer Society, 2013). Individuals with colorectal cancer can experience cognitive symptoms and impaired function before and during treatment for the disease (Patti, Saitta, Cusumano, Termine, & Di Vita, 2011; Vardy, 2007; Walker et al., 1996). Changes in cognitive function can be distressing and affect an individual's ability to learn, work, and achieve personal goals (Boykoff, Moieni, & Subramanian, 2009). At this time, little is known about biologic mechanisms that may underlie cognitive changes. One potential mechanism is the immune system's response to the cancer and cancer treatments (Cleeland et al., 2003; Hart, 1988). Specifically, inflammatory cytokines are produced in the tumor microenvironment or in response to tissue injury associated with cancer treatments. These proteins can communicate with the brain to induce symptoms and behavioral responses or 'sickness behaviors' that generally support the immune system and the survival of the individual. However, persistent or excessive production of inflammatory cytokines can be detrimental. Cognitive symptoms and impaired function appear to occur alongside sickness behaviors in individuals with cancer and may be a cytokine-induced response to the cancer and/or cancer treatments (Cleeland et al., 2003; Meyers, Albitar, & Estey, 2005).

Indirect evidence for a role of inflammatory cytokines in cognitive deficits comes from studies assessing the side effects of immunotherapy in individuals with chronic myelogenous leukemia, colorectal cancer, melanoma, and renal cell carcinoma. Specifically, patients treated with interleukin-2 (IL-2) and interferon-alpha (IFN-α) have been found to be impaired on measures of global cognition (Mini-Mental State Exam) and on measures of specific cognitive domains including directed attention, working memory, and long-term memory (Consistent Long-term Retrieval, Controlled Oral Word Association Test, Corsi's Spatial Test, Digit Span Backward, Digit Symbol Test , TMT A & B, Spatial Working Memory Test, Stockings of Cambridge, Zazzo's Attention) (Capuron, Ravaud, & Dantzer, 2001; Caraceni et al., 1993; Denicoff et al., 1987; Scheibel, Valentine, O'Brien, & Meyers, 2004; Walker et al., 1997). One study, by Bender and colleagues (2000), did not observe significant changes in cognitive function in patients treated with immunotherapy for melanoma. However, researchers did observe a non-significant deterioration in directed attention and working memory in individuals receiving high dose interferon (Trail Making B). Finally, serious neurologic events have been associated with cytokine therapy including acute confusion, seizures, and altered states of consciousness (Buter, de Vries, Sleijfer, Willemse, & Mulder, 1993; Denicoff et al., 1987; Kirkwood et al., 1985; Nethersell, Smedley, Katrak, Wheeler, & Sikora, 1984), implicating an overexpression of cytokines as a potential mechanism in cognitive symptoms.

To date, only one study has assessed the relationship between endogenous inflammatory cytokine expression and cognitive symptoms in individuals with cancer. The study, by Meyers and colleagues (2005), assessed inflammatory cytokine expression

(interleukin-1 receptor antagonist, interleukin-6, tumor necrosis factor-α) and cognitive symptoms in 54 patients newly diagnosed with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) before any treatment. Researchers found that higher levels of interleukin- 6 (IL-6) were associated with poorer performance on a measure of directed attention and working memory (Trail Making B). This study suggests that an over expression of inflammatory cytokines may underlie changes in directed attention and working memory function in individuals with cancer before any treatment.

Thus, the objective of this study was to further explore the relationship between cognitive function and endogenous levels of inflammatory cytokine expression in a combined group of individuals with and without colorectal cancer. The study measured pro-inflammatory cytokines (interleukin-1β, IL-1β; interleukin-6, IL-6; tumor necrosis factor-α, TNF-α), indirect pro-inflammatory biomarkers (interleuking-1 receptor antagonist, IL-1RA; C-reactive protein, CRP), and immunosuppressive cytokines (interleukin-10, IL-10; transforming growth factor-β1). The cognitive measures included attention (Attention Network Test, ANT), directed or controlled attention and working memory (Digit Span, Trail Making, Attentional Function Index), and long-term memory (Rey Auditory Verbal Learning Test, Everyday Memory Questionnaire). The study tested the hypothesis that lower performance and perceived effectiveness on measures of attention, directed attention and working memory, and long-term memory will be related to elevated serum levels of pro-inflammatory cytokines, indirect pro-inflammatory biomarkers, and immunosuppressive cytokines.

Methods

Study Design, Sample, and Setting

This study used a cross-sectional design to assess the relationship between cognitive symptoms and inflammatory cytokines and biomarkers. The sample of men and women with and without cancer was included to ensure sufficient variance in the key cognitive and immune function variables. One hundred participants were recruited from a university medical center in the Midwest. For individuals with colorectal cancer (n = 50), participants were assessed within six months of a diagnosis of primary or recurrent colorectal cancer. For individuals without colorectal cancer (n = 50), participants were assessed within twelve months of a negative colonoscopy. Eligibility requirements included: being 30 years of age or older and being able to read and write English. Individuals were excluded for conditions that could affect cognitive function including: a history of untreated or unstable mental disorder, learning disability, head injury, drug or alcohol abuse, and central nervous system disease. Individuals were also excluded for a diagnosis of malignancy other than the new diagnosis colorectal cancer or a history of skin cancer.

Measures

Cognitive Measures

Cognitive Function Screen. The Mini Mental State Exam (MMSE) was used to screen potential participants and ensure that individuals participating in this study had intact cognitive functioning. The MMSE is a brief test consisting of 11 questions that measure orientation, memory, attention and language (Folstein, 2000). Similar to other studies assessing cognition in healthy individuals and individuals with cancer, a score of

greater than 24 was used to indicate no serious cognitive impairment (Cimprich & Ronis, 2001; Patti et al., 2011).

Attention. The Attention Network Test (ANT) was used to measure overall attentional function (Fan, McCandliss, Sommer, Raz, & Posner, 2002). This computerized test assessed three networks of attention including: alerting, orienting, and executive control. Participants are asked to determine if a middle arrow in a group of arrows or flankers points to the left or right. Sometimes the arrows and flankers are accompanied by cues that provide information about when or where the middle arrow will occur. An overall mean accuracy and response time for correct answers was computed and used for attentional function in the data analyses. For a detailed description of the measure and how it is scored see Fan and colleagues (2002). The ANT has established reliability and validity (Fan et al., 2002; Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010).

Directed Attention and Working Memory. Digit Span (DS), the Trail Making Test (TMT) and the Attentional Function Index (AFI) were used to measure directed attention and working memory.

Digit Span (DS) is a standardized test with two parts: Digit Span Forward (DSF) and Digit Span Backward (DSB). DSF asks participants to recall a series of numbers in the order presented. DSB asks participants to recall a series of numbers in reverse order. The score is the number of digits recalled before two failed attempts. DS has established reliability and validity and is a sensitive measure of directed attention and working memory deficits in individuals with cancer (Cimprich, 1998; Cimprich & Ronis, 2001; Lezak, 2004; Small et al., 2011).

The Trail Making Test (TMT) is a standardized test with two parts: Trail Making Test A (TMT A) and Trail Making Test B (TMT B). TMT A asks participants to draw a line to connect consecutively numbered circles. TMT B asks participants to draw a line to connect consecutively numbered and letter circles, alternating between the two. The time taken to complete each part is the score. TMT has established reliability and validity and is a sensitive measure of directed attention and working memory deficits in individuals with cancer and in individuals receiving immunotherapy for cancer (Bond, Dietrich, & Murphy, 2012; Denicoff et al., 1987; Hermelink et al., 2007; Meyers et al., 2005; Meyers, Byrne, & Komaki, 1995; Reitan, 1979; Scheibel et al., 2004; Walker et al., 1997).

The Attentional Function Index (AFI) is a self-report measure that asks participants to rate their function on tasks in daily life that require directed attention and working memory from 0 (not at all) to 10 (extremely well or a great deal). The score is the mean of all 13 items. The AFI has established reliability and validity and is a sensitive measure in individuals with cancer (Cimprich, Visovatti, & Ronis, 2011). The internal consistency coefficient has been reported as 0.76 to 0.94 in cancer patients and healthy individuals (Cimprich et al., 2011). In this study, the Cronbach alpha was 0.91.

From these measures, two scores were computed and used in the data analyses: a standardized total composite score for objective measures (DS, TMT) and a total mean score for the subjective measure (AFI). The standardized total composite score was determined by transforming scores on DS and TMT to Z scores based on the mean and standard deviation of each test for the entire sample and then summing the Z scores.

Because higher scores on DS and lower scores on TMT indicate better function, scores on the TMT were reversed.

Long-term Memory. The Rey Auditory Verbal Learning Test and the Everyday Memory Questionnaire were used to measure long-term memory. The Rey Auditory Verbal Learning Test (RAVLT) is a standardized test that asks participants to recall words from a 15-word list. Participants are presented with one word list (List A) five times followed by a second word list (List B) once. After each presentation, participants are asked to recall the words on the list. After recalling the final list (List B), participants are asked to immediately recall List A as well after a short 30-minute delay. The number of words recalled on the delayed recall condition was the score used for long-term memory in this study. The RAVLT has established reliability and validity (Schmidt, 1996). Word list learning is a sensitive measure of long-term memory deficits in individuals with cancer and individuals receiving immunotherapy for cancer (Scheibel et al., 2004; Wefel, Vardy, Ahles, & Schagen, 2011).

The Everyday Memory Questionnaire (EMQ) is a self-report measure that asks participants to rate the frequency of forgetting on tasks that require long-term memory function from 1 (not at all in the last month) to 7 (several times a day). The score is the sum of all 28 items. The EMQ has established reliability and validity and has been positively correlated with objective measures of long-term memory in older adults (Cornish, 2000; Sunderland, Watts, Baddeley, & Harris, 1986). It has an internal consistency coefficient of 0.90 (Cornish, 2000). In this study, the Cronbach alpha was 0.90.

Inflammatory Cytokines and Biomarkers.

Selected inflammatory cytokines and biomarkers were chosen from previous research examining cancer-related symptoms and the acute phase response in colorectal cancer (Bellone et al., 2001; Berghella, Pellegrini, Del Beato, Adorno, & Casciani, 1997; Lee et al., 2004; Meyers et al., 2005; Narai et al., 2002; Orre et al., 2009; Rich et al., 2005; Shim, Kim, Han, & Park, 1999; Wang et al., 2010). The study measured pro-inflammatory cytokines (IL-1-β, IL-6, TNF-α), indirect pro-inflammatory biomarkers (IL-1RA, CRP), and immunosuppressive cytokines (IL-10, TGF-β1). Blood specimens were collected from all participants in the morning or early afternoon to control for diurnal variations in inflammatory cytokine expression. Five milliliters of blood was drawn into serum separator tubes by trained phlebotomy staff using sterile technique. Collected blood was separated according to standard procedures and stored at $\leq$ - 70 °C for batch analyses after all participants completed testing. Serum levels of interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-10 (IL-10) were measured using Millipore's High Sensitivity Human Cytokine Magnetic Bead panel (HSCYTMAG-60SK), interleukin-1 receptor antagonist (IL-1RA) was measured with Millipore's Human Cytokine/Chemokine Magnetic Bead panel (HCYTOMAG-60K), transforming growth factor-β1 (TGF-β1) was measured with R & D System's DuoSet ELISA development kit (DY240) and C-reactive protein (CRP) was measured with R & D System's DuoSet ELISA development kit (DY 1707).

All inflammatory cytokines and biomarkers were assayed in duplicate and results are reported as the mean of the two measurements. An inflammatory cytokine ratio was also computed. Specifically, the pro-inflammatory cytokine ratio was determined by

dividing TNF-α levels by IL-10 levels and the anti-inflammatory cytokine ratio was determined by dividing IL-10 levels by TNF-α levels.

Adjunct Measures

Patient characteristics that might affect cognitive and immune function were measured using: the Profile of Mood States Brief Form (POMS-BF), the Inventory of Functional Status Cancer (IFS-CA), a demographic questionnaire, and a medical chart audit form. Characteristics that have been associated with cognitive deficits as well as higher circulating levels of inflammatory cytokines and biomarkers include: age, years of education, anxiety, depressed mood, presence of other health problems, changes in hormones, current tobacco use, a higher body mass index, and reduced exercise (Ahles et al., 2010; Belluco et al., 2000; Bender et al., 2006; Chung & Chang, 2003; Cimprich, 1998, 1999; Cimprich, So, Ronis, & Trask, 2005; Galizia et al., 2002; Hermelink et al., 2007; Merriman et al., 2010; Musselman et al., 2001; Narai et al., 2002; O'Connor et al., 2009; Schilder et al., 2010; Skaali, Fossa, & Dahl, 2011; Vearncombe et al., 2009).

The Profile of Mood States-Brief Form (POMS-BF) is a self-report measure that asks participants to rate how they have been feeling during the past week from 1 (not at all) to 4 (extremely). The POMS-BF includes six subscales that measure anxiety, depression, anger, vigor, fatigue, and confusion. The anxiety, depression, and fatigue subscales were used in this study. Scores on the subscales are the mean of the five items in the subscale. The internal consistency coefficients for the six subscales have been reported from 0.86 to 0.93 in individuals with cancer (Cimprich, 1999). In this study, the Cronbach alpha was 0.76 for anxiety, 0.81 for depressed mood, and 0.88 for fatigue.

The inventory of Functional Status Cancer (IFS-CA) is a self-report measure that asks participants to rate their ability to perform everyday activities (Tulman, Fawcett, & McEvoy, 1991). The IFS-CA includes an item that assesses any changes in usual exercise in the past few weeks from 1 (not at all/never exercise as much as usual) to 4 (all the time/fully exercise as much as usual. The IFS-CA is a sensitive measure in detecting changes in activities of daily living in individuals with cancer (Tulman et al., 1991; Visovatti et al., 2009).

A demographic questionnaire and medical chart audit form were used to assess patient characteristics including: age, education, presence of other health problems, changes in hormones, colorectal cancer history, tobacco use, and body mass index.

Study Procedures

The institutional review board at a midwest university and health system approved the study. All participants provided written informed consent. Participants completed neuropsychological testing and self-report measures in a quiet room and had blood specimens drawn by trained staff at the health system. Most participants completed all testing on the same day. However, a few participants had blood specimens drawn with routine blood tests on a separate day within 14 days of cognitive and adjunct measures. The principal investigator obtained informed consent and administered neuropsychological tests and self-report measures. Testing procedures included: administering the immediate recall trials of the RAVLT followed by other objective measures of attention and memory in random order (ANT, DS, TMT) and then the delayed recall trial of the RAVLT. The self-report measures were administered in

random order after the objective measures. Time to complete neuropsychological tests and self-report measures was approximately 60 minutes.

Data Analysis

Descriptive statistics including means and standard deviations for continuous variables and frequencies for categorical variables were used to describe the sample. The relationship between each cognitive and immune variable was assessed by Pearson Correlation coefficients and only those inflammatory cytokines and biomarkers that had a significant relationship with the cognitive variables were included in multiple regression models. Separate multiple linear regression models were constructed to assess the relationship between each cognitive variable and each significant inflammatory cytokine or biomarker controlling for covariates which may be related to cognitive and immune function. Inflammatory cytokines and biomarkers had a skewed distribution and were log transformed using the natural log to be consistent with other biobehavioral studies examining inflammatory cytokines and biomarkers in individuals with cancer (Bower et al., 2011; Bower et al., 2009). Serum levels of IL-1β and IL-1RA were very low and fell outside the detectable range in greater than 20% of participants. As such, they were not included in the correlation or multiple linear regression analyses.

Results

Sample Characteristics

Demographic characteristics. The sample consisted of 100 men and women including 50 individuals newly diagnosed with primary or recurrent colorectal cancer and 50 individuals without colorectal cancer. Participants ranged in age from 36 years to 79 years and had a mean age of 56 years (SD =10). Participants were mostly Caucasian

(80%), married or in a partnered relationship (80%), and employed outside the home (59%). They were also highly educated with a mean of 16 years (SD = 3) of education. See Table 4.1.

General health characteristics. The majority of participants were overweight (27%) or obese (37%) and the remaining participants were underweight (3%) or normal weight (33%). Most did not smoke (88%). Of the 51 women included, most were postmenopausal (65%).

Medical characteristics. The sample consisted of 50 individuals newly diagnosed with primary colorectal cancer (96%) or recurrent colorectal cancer (4%). All participants had adenocarcinoma. Approximately 32% had stage I or II, 38% had stage III, and 30% had stage IV disease or recurrent cancer. Most participants were assessed before chemotherapy or radiation therapy (66%).

Psychological distress and physical activity characteristics. Participant scores on the POMS-BF and IFS-CA exercise item are presented in Table 4.2. In general, participants reported low to moderate levels of mood disturbance including anxiety (*M* = 3.67, SD 2.87), depressed mood (*M* = 2.45, SD 2.88), and fatigue (*M* = 4.89, SD 3.70). For the IFS-CA exercise item, 64% of participants reported *exercising as much as usual* most or all of the time.

Relationship Between Cognitive and Immune Function Variables

Scores on cognitive and immune variables are described in paper 2 and 3. Significant correlations between cognitive and immune variables tended to be domain specific and are presented in Table 4.3. For directed attention and working memory, bivariate correlation analyses found that higher serum levels of IL-6 and CRP were

associated with poorer performance on the Standardized Total Composite Score ($r = -0.29$, $p < 0.001$; $r = -0.37$, $p < 0.001$ respectively). Additionally, bivariate correlation analyses found that higher serum levels of CRP and lower serum levels of TGF-β1 were associated with lower scores on the AFI indicating perceptions of poorer directed attention and working memory function ($r = -0.29$, $p < 0.001$; $r = 0.30$, $p < 0.001$ respectively). Finally for long-term memory, bivariate correlation analyses found that higher serum levels of TNF-α and IL-6 were associated with poorer performance on the RAVLT delayed recall score with small to moderate correlations ($r = -0.20$, $p < 0.05$; $r = -0.28$, $p < 0.01$ respectively). There were no significant relationships between inflammatory cytokines and biomarkers and the ANT overall accuracy and response time scores or scores on the EMQ.

Immune Predictors of Attention and Memory Function

Multiple linear regression analyses were performed to further assess the relationship between cognitive variables and immune variables controlling for possible covariates. Only those cognitive measures that had a significant relationship with one or more immune variables were examined. Specifically, three separate multiple linear regression models were constructed using the Standardized Total Composite Score, the Attentional Function Index (AFI), and the Rey Auditory Verbal Learning Test delayed recall condition (RAVLT-delayed recall) as the dependent variables. Scores from the Attention Network Test and the Everyday Memory Questionnaire were not correlated with immune variables and were not included in the regression analyses. See Table 4.3 for correlations between cognitive and immune function variables. Possible covariates included age, gender, education, medication that can affect cognitive function, colorectal

cancer, anxiety, depressed mood, fatigue, and exercise as usual. See Table 4.4 for correlations between cognitive function variables and possible covariates. See Table 4.5 for correlations between immune function variables and possible covariates. See Tables 4.8, 4.11, and 4.14 for final regression models.

The model for the Standardized Total Composite Score included immune variables that were significantly related to the Standardized Total Composite Score (IL-6, CRP) as well as other variables that were related to the Standardized Total Composite Score, IL-6, and/or CRP (age, education, medication that can affect cognitive function, colorectal cancer diagnosis, depressed mood, exercise as usual) as determined by bivariate correlation analyses. Independent variables for the AFI self-report model differed from the Standardized Total Composite Score model. In particular, TGF- β1, anxiety, and fatigue were correlated with the AFI and included in the model. In contrast, age was not correlated with the AFI and thus not included in the model. Finally, independent variables for the RAVLT delayed recall condition model differed from both the Standardized Total Composite Score and the AFI models. In comparison to the Standardized Total Composite Score model, TNF-α, gender, and anxiety were correlated with the RAVLT and included in the RAVLT model. Depressed mood was not correlated with the RAVLT and thus not included in the RAVLT model. In comparison to the AFI model, age and gender were correlated with the RAVLT and included in the RAVLT model. CRP, TGF-β1, depressed mood, and fatigue were not correlated with the RAVLT and therefore not included in the RAVLT model.

Standardized Total Composite Score. To determine possible predictors of performance on tasks requiring directed attention and working memory measures,

separate multiple linear regression models were constructed using the standardized total composite score as the dependent variable. Each significant immune variable (IL-6, CRP) was entered separately as well as together with selected covariates as independent variables. See Tables 4.6 to 4.8. CRP was the only immune variable that predicted scores on the standardized total composite score. Specifically, higher serum levels of CRP ($t = -2.24$, $p = 0.03$), older age ($t = -3.22$, $p < 0.01$), and fewer years of education ($t = 3.21$, $p < 0.01$) predicted lower scores on the standardized total composite score accounting for 32% of the variance, multiple $R = 0.567$ $F(7, 91) = 6.17$, $p < 0.001$. CRP also predicted scores on the standardized total composite score when both IL-6 and CRP were entered as independent variables. Findings from this regression model were similar to the regression model that included only CRP as an independent variable. See Table 4.8. Interestingly, although bivariate correlation analyses found that IL-6 and the standardized total composite score were significantly related, IL-6 did not independently predict scores on the standardized total composite score after controlling for possible covariates. It is possible that IL-6 may have shared the variance with other independent variables in the model reducing it's unique contribution to the standardized total composite score. Inflammatory processes have been associated with a number of biobehavioral factors as well as stressful life events (new diagnosis of cancer) and depression (O'Connor et al., 2009). In particular, higher IL-6 levels have been found in cancer patients with depression compared to cancer patients without depression and healthy controls (Musselman et al., 2001).

Attentional Function Index. To determine possible predictors of perceived effectiveness on common tasks of directed attention and working memory, separate

multiple linear regression models were constructed using the AFI score as the dependent variable. Each significant immune variable (CRP, TGF-β1) was entered separately as well as together with selected covariates as independent variables. See Table 4.9 to 4.11. TGF-β1 was the only immune variable that predicted scores on the Attentional Function Index when entered individually. Specifically, lower serum levels of TGF-β1 ($t = 3.51$, $p < 0.01$) and greater fatigue ($t = -4.11$, $p < 0.01$) predicted lower scores on the AFI accounting for 45% of the variance, multiple $R = 0.67$, $F(8, 90) = 9.24$, $p < 0.001$. However, when both CRP and TGF-β1were entered as independent variables in the model, both significantly predicted scores on the AFI. Specifically, higher serum levels of CRP ($t = -2.18$, $p = 0.03$), lower serum levels of TGF-β1 ($t = 4.11$, $p < 0.01$), and greater fatigue ($t = -4.02$, $p < 0.01$) predicted lower scores on the AFI accounting for 47% of the variance, multiple $R = 0.69$, $F(8, 90) = 9.92$, $p < 0.001$. See Table 4.11. The increase in R squared of this regression model suggests that the inclusion of both CRP and TGF-β1 in the model predicted more fully scores on the AFI (i.e. better model than CRP alone).

Rey Auditory Verbal Learning Test – delayed recall. To determine possible predictors on tasks requiring long-term memory, separate multiple linear regression models were constructed using the RAVLT 30-minute delayed word recall condition as the dependent variable. Each significant immune variable (TNF-α, IL-6) was entered separately as well as together with selected covariates as independent variables. See Table 4.12 to 4.14. IL-6 was the only immune variable that predicted the number of words recalled on the delayed recall condition of the RAVLT. Specifically, higher IL-6 levels ($t = -2.09$, $p = 0.04$), older age ($t = -2.98$, $p < 0.01$), fewer years of education ($t =$

2.30, p = 0.02), and male gender (t = 3.50, p < 0.01) predicted lower scores on the RAVLT- delayed recall condition accounting for 35% of the variance, multiple R = 0.59, F (8, 89) = 5.92, p < 0.001). Interestingly, when both TNF-α and IL-6 were included in the regression model, neither pro-inflammatory cytokine predicted scores on the RAVLT-delayed recall condition. Regression analyses showed no multicollinearity. As such, a likely explanation is that IL-6 shared the variance with TNF-α reducing its unique contribution to scores on the RAVLT.

Discussion

One potential mechanism underlying cognitive symptoms in individuals with cancer is an over expression of inflammatory cytokines related to the immune system's response to the cancer and cancer treatments. Given that little research has examined the relationship between physiologic levels of inflammatory cytokine expression and cognitive symptoms, the goal of this study was to begin to characterize this relationship. The sample included individuals with and without colorectal cancer. The inclusion of individuals without cancer allowed for the assessment of this relationship in a larger population of individuals who may be experiencing cognitive symptoms and/or elevated cytokines from other non-cancer factors (i.e. aging, other health problems and behaviors). The study found that serum levels of IL-6, CRP, TGF-β1 and TNF-α were associated with performance on cognitive measures and/or subjective perceptions of cognitive function. Furthermore, the associations tended to be domain specific. In particular, when controlling for possible covariates, 1) higher serum levels of CRP predicted poorer performance on tasks requiring directed attention and working memory and 2) higher serum levels of CRP and lower serum levels of TGF-β1 predicted poorer self-report of

directed attention and working memory function. In addition, TNF-α and IL-6 were correlated with performance on the RAVLT, however after controlling for covariates neither pro-inflammatory cytokine predicted scores on the RAVLT-delayed recall condition in the final regression model. These findings will be discussed below.

Relationships between inflammatory cytokines and biomarkers and cognitive function

Pro-inflammatory cytokines and indirect pro-inflammatory biomarkers: IL-6, TNF-α and CRP. Consistent with previous studies examining the relationship between inflammatory cytokines and cognitive function, this study found that higher circulating levels of IL-6 were associated with poorer performance on measures of directed attention and working memory as well as long-term memory (Krabbe et al., 2005; Meyers et al., 2005; Vollmer-Conna et al., 2004). Interestingly, after controlling for possible covariates, IL-6 did not predict performance on measures of directed attention and working memory (individually or together with CRP) or performance on a measure of long-term memory. However, after controlling for covariates, IL-6 did predict performance on the long-term memory measure when entered individually. One possible explanation for these findings is that IL-6 shared the variance with other immune variables and biobehavioral factors. IL-6 is one of the primary cytokines that is induced in response to an immune challenge and operates as part of a cascade of cytokines to amplify and maintain a pro-inflammatory response (Cavaillon, Adib-Conquy, Fitting, Adrie, & Payen, 2003; Mant et al. 2008). IL-6 is also thought to have a primary role in inducing symptom and behavioral responses that support the immune system and the

survival of the individual (Konsman, Parnet, & Dantzer, 2002). As such, further research is needed to clarify the relationship between IL-6 and cognitive symptoms.

No prior studies were found that examined the relationship between TNF-α or CRP and cognitive function. Bivariate correlation analyses found that higher serum levels of TNF-α were associated with poorer performance on a measure of long-term memory. However, after controlling for possible covariates, TNF-α did not predict performance on the long-term memory measure (individually or together with IL-6). Similar to IL-6, this finding may suggest that TNF-α shared the variance with other immune variables and biobehavioral factors in the model. TNF-α is an important cytokine in the initiation of the inflammatory response and along with IL-6 has been associated with the amplification and maintenance of the inflammatory response (Cavaillon, Adib-Conquy, Fitting, Adrie, & Payen, 2003; Mant et al. 2008). Indirect markers of TNF-α have been associated with fatigue in individuals with cancer suggesting a role for this cytokine in symptoms and behavioral changes that accompany the systemic inflammatory response (Bower et al., 2002; Bower et al., 2011; Wang et al., 2012).

Bivariate correlation analyses also found that higher serum levels of CRP were associated with poorer performance and perceived effectiveness on tasks requiring directed attention and working memory. When controlling for covariates, CRP remained a significant predictor of performance on measures of directed attention and working memory (individually and together with IL-6) and perceived effectiveness on cognitive tasks (with TGF-β1). This novel finding is important and suggests a role for this CRP in the expression of cognitive symptoms. CRP is an acute phase protein that is induced by

pro-inflammatory cytokines (primarily IL-6) as part of the systemic inflammatory response to an immune challenge (Pepys & Hirschfield, 2003). It has an important role in binding to/recognizing foreign pathogens and damaged cells (Gabay & Kushner, 1999; Pepys & Hirschfield, 2003). Additionally, it can activate the complement system and induce inflammatory cytokines (Gabay & Kushner, 1999; Pepys & Hirschfield, 2003). CRP has been associated with fatigue in cancer survivors suggesting a role for this protein in the expression of sickness behaviors (Bower et al., 2009; Orre et al., 2009, Wratten et al., 2009).

Immunosuppressive cytokines: Transforming Growth Factor-β1. To date, no research studies were found that examined the relationship between TGF-β1 and cognitive function. In this study, higher serum levels of TGF-β1 were associated with better perceived effectiveness on tasks that require directed attention and working memory. When controlling for possible covariates, TGF-β1 remained an independent predictor of scores on the self-report measure of directed attention and working memory (individually and together with CRP). This was an unexpected finding and may suggest that some inflammatory cytokines are associated with neuroprotective processes. TGF-β1 is critical for the development and maintenance of human tissue and has an important role in regulating the response as well as tissue remodeling and repair (wound healing) (Ariel & Timor, 2012). Importantly, preclinical studies suggest that TGF-β1 may support the survival of adult neurons as well as control microglial activation and inflammation within the brain (Caraci, 2009). TGF-β1 has not yet been associated with sickness behaviors or ameliorating sickness behaviors. Further research is needed to confirm this finding and further assess the relationship between TGF-β1 and cognitive function.

Other inflammatory cytokines, biomarkers, and ratios: IL-1β, IL-1RA, IL-10, TNF-α/IL-10, and IL-10/TNF-α. In this study correlation and multiple regression analyses did not include IL-1β or IL-1RA because serum levels of these cytokines were very low and fell outside the detectable range in greater than 20% of the sample. However, IL-10 and the inflammatory cytokine ratios were included in bivariate correlation analyses but no significant relationships were found between these immune variables and cognitive variables. As such, IL-10 and the inflammatory cytokine ratios were not included in regression analyses. Further research in larger samples is needed to assess the relationship between IL-1β, IL-1RA, IL-10, and the inflammatory cytokine ratios and cognitive symptoms.

Immune Predictors of Cognitive function: Final Regression Models

Separate multiple linear regression models were constructed to assess the relationship between each cognitive variables and each significant immune variable controlling for colorectal cancer, medications that may affect cognitive function and other possible covariates significantly related to cognitive and immune variables in the model. See Tables 4.8, 4.11, and 4.12. When controlling for possible covariates, age, education, gender, and fatigue were found to be significant predictors of cognitive performance and self-report along with the inflammatory cytokines and biomarkers described below indicating the importance of considering these covariates in future analyses. Patient characteristics that did not predict cognitive performance or perceived performance on measures of attention and memory included having colorectal cancer, body mass index, current tobacco use, taking medication that might affect cognitive function, depressed

mood, anxiety, or exercising as much as usual. Demographic and biobehavioral predictors have been discussed in previous papers.

C-reactive protein. After controlling for possible covariates and significant immune variables, higher serum CRP levels predicted poorer performance and perceptions of performance on tasks requiring directed attention and working memory. This finding is congruent with the study's hypothesis that higher levels of inflammatory cytokines and biomarkers would be associated with poorer performance on cognitive measures. Interestingly, this study found that CRP was a significant predictor of a single cognitive domain suggesting that different cytokines may be associated with different cognitive symptoms or losses in function.

Transforming Growth Factor-β1. After controlling for possible covariates and significant immune variables, higher serum levels of TGF-β1 were associated with better perceived effectiveness on tasks requiring directed attention and working memory. This was an unexpected finding and may suggest that some inflammatory cytokines are associated with reduced vulnerability to cognitive symptoms. TGF-β1 was also a significant predictor of a specific cognitive domain lending further support for the idea that specific cytokines may influence specific cognitive domains.

Limitations and Future Research

Limitations of this study include a cross-sectional design, convenience sample, and inclusion of a combined group of individuals with and without colorectal cancer. Findings from this study cannot be generalized to individuals with cancer without further replication and clarification in larger samples.

Despite these limitations this study provides preliminary evidence of a relationship between cognitive symptoms and an over expression of inflammatory cytokines and biomarkers. Additionally, findings from this study suggest that an overexpression of specific cytokines may predict domain-specific losses in function and symptoms. Finally, this study found a relationship between higher levels of an immunosuppressive cytokine and better cognitive function suggesting that some inflammatory cytokines may have a neuroprotective role in inflammation. Further research is needed to examine the relationship between specific inflammatory cytokines and cognitive domains in healthy individuals and patients with chronic illnesses like colorectal cancer.

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Table 4.1
Sample Characteristics (N = 100)

		%
Demographic characteristics		
Age, years	36-79, mean 56, standard deviation 10	
Education, years	9-22, mean 16, standard deviation 3	
Gender	Female	49
	Male	51
Marital status	Single	26
	Married/Partner	74
Race[a]	White	80
	Non-white	14
Employed outside home	Yes	59
Medical characteristics		
Body mass index, kg/m^2	17-57, mean 28, standard deviation 7	
Colorectal cancer	Yes	50
Other health problems[b]	Yes	81
Taking medication that affects cognitive function[c]	Yes	38
Taking Medication that affects immune function[d]	Yes	68
Current Tobacco Use	Yes	12

[a]Three participants declined to answer. [b]Other health problems include: benign skin lesions, cardiovascular disease(Hypertension, hyperlipidemia), endocrine disease (diabetes mellitus, hypothyroidism), gastrointestinal disease (GERD, diverticulosis, hemorrhoids), immune disorders (allergies, arthritis), musculoskeletal disease (lower back pain, osteoporosis), pulmonary disease (COPD, Sleep Apnea), renal disease (nephrolithiasis) and mood disorders (depression, anxiety). [c]Medications that could affect cognitive function included: antianxiety, antidepressants, narcotics, and medications for insomnia. [d]Medications that could affect immune function included: allergy medications, aspirin and other NSAIDs, statins, ophthalmic cyclosporine, inhaled corticosteroids, prednisone, antibiotics, antiviral medication, antifungal medication, chemotherapy, and antioxidants.

Table 4.2

Means and Standard Deviations of Physical and Psychological Symptoms (N = 100)

	Mean ± SD	Range
Profile of Mood States: Brief Form[a]		
Total Mood Disturbance	6.72 ± 14.78	-19 - 51
Anxiety	3.67 ± 2.87	0 - 14
Depression	2.45 ± 2.88	0 - 14
Anger	2.68 ± 2.86	0 - 17
Vigor	10.57 ± 4.90	0 -20
Fatigue	4.89 ± 3.70	1 - 17
Confusion	3.60 ± 2.55	0 - 13
Inventory of Functional Status: Cancer[b]		
Exercise as Much as Usual	2.78 ± 1.21	1 - 4

[a]Total Mood Disturbance Scale computed by summing the anxiety, depressed mood, anger, confusion and fatigue subscales and subtracting the vigor subscale. Total range of scores for the Total Mood Disturbance Scale is between – 20 and 100. Total range of scores for each subscale is between 0 and 20. [b]Total range of score for the item exercise as much as usual is between 1 and 4.

Table 4.3
Pearson Correlation Coefficients Between Cognitive Function Variables and Inflammatory Cytokines and Biomarkers (N = 100)

Variables[a]	1	2	3	4	5	6	7	8	9	10	11	12
1. TNF-α	-	-	-	-	-	-	-	-	-	-	-	
2. IL-6	0.46*	-	-	-	-	-	-	-	-	-	-	
3. CRP	- 0.08	- 0.30*	-	-	-	-	-	-	-	-	-	
4. IL-10	0.37*	0.56*	0.14	-	-	-	-	-	-	-	-	
5. TGF -β1	0.00	- 0.04	0.13	- 0.05	-	-	-	-	-	-	-	
6. TNF-α/IL-10	0.35*	- 0.04	- 0.21*	- 0.59*	0.03	-	-	-	-	-	-	
7. IL-10/TNF-α	- 0.49*	0.12	0.15	0.51*	- 0.05	- 0.77*	-	-	-	-	-	
8. ANT Error rate	0.08	- 0.12	- 0.11	- 0.14	- 0.03	0.13	- 0.16	-	-	-	-	
9. ANT Reaction Time	- 0.07	0.19	0.19	0.06	- 0.13	- 0.08	0.04	- 0.23*	-	-	-	
10. Standardized Total Composite Score	- 0.10	- 0.29*	- 0.37*	- 0.18	- 0.04	0.11	- 0.04	0.25*	- 0.34*	-	-	
11. Attentional Function Index	- 0.05	- 0.14	- 0.29*	- 0.14	0.30*	0.07	- 0.07	0.01	- 0.10	0.13	-	
12. RAVLT delayed recall	- 0.20*	- 0.28*	- 0.09	- 0.11	0.00	- 0.09	0.08	0.19	- 0.14	0.33*	0.01	-
13. EMQ	0.01	0.08	- 0.09	0.15	- 0.15	- 0.04	0.10	0.02	0.00	0.07	- 0.43*	- 0.03

Note. ANT = Attention Network Test; Standardized Total Composite Score = zDSF + zDSB – zTMTa – zTMTb; RAVLT delayed recall = Rey Auditory Verbal Learning Test 30 minute delayed recall condition; EMQ = Everyday Memory Questionnaire.
[a]Numbers in Columns correspond to numbers in top row
*$p < 0.05$.

Table 4.4

Pearson Correlation Coefficients Between Cognitive Function Variables and Potential Cognitive Function Modifiers (N = 100)

Variables [a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Age	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2. Education	-0.02	-	-	-	-	-	-	-	-	-	-	-	-	-
3. Gender[b]	-0.18	-0.12	-	-	-	-	-	-	-	-	-	-	-	-
4. Medication: CF[c]	0.06	-0.12	0.27*	-	-	-	-	-	-	-	-	-	-	-
5. Colorectal Cancer[d]	0.16	0.13	-0.02	-0.29*	-	-	-	-	-	-	-	-	-	-
6. Other Health Problems[e]	0.26*	0.06	0.04	0.12	0.18	-	-	-	-	-	-	-	-	-
7. Anxiety	-0.26*	-0.18	0.03	0.00	-0.38*	-0.06	-	-	-	-	-	-	-	-
8. Depressed Mood	-0.15	-0.21 *	-0.03	0.04	-0.19	-0.10	0.60*	-	-	-	-	-	-	-
9. Fatigue	-0.12	-0.12	0.09	0.14	-0.36*	-0.02	0.53*	0.56*	-	-	-	-	-	-
10. ANT Accuracy	-0.09	-0.06	-0.06	-0.11	0.15	-0.02	-0.10	-0.11	0.06	-	-	-	-	-
11. ANT Reaction Time	0.45*	-0.20	0.04	0.25*	-0.19	0.07	0.03	-0.01	0.02	-0.23*	-	-	-	-
12 Standardized Total Composite Score	-0.25*	-0.38*	0.07	-0.08	0.20*	-0.03	-0.08	-0.21*	-0.09	-0.25*	-0.34*	-	-	-
13. AFI	0.07	0.22*	-0.17	-0.21*	0.32*	0.03	-0.37*	-0.35*	-0.57*	0.01	-0.10	0.13	-	-
14. RAVLT delayed recall	-0.39*	0.21*	0.31*	-0.14	-0.02	-0.09	0.14	0.08	0.14	0.19	-0.14	0.33	0.01	-
15. EMQ	-0.13	-0.02	0.10	0.15	-0.10	0.24*	0.23*	0.12	0.19	0.02	0.00	0.07	- 0.43*	-0.03

Note. Med: CF = taking medication that may affect cognitive function; ANT = Attention Network Test; Total Composite Score = Standardized Total composite Score = zDSF + zDSB – TMTa –zTMTb; AFI = Attentional Function Index; RAVLT delayed recall condition = Rey Auditory Verbal Learning Test 30 minute delayed recall condition; EMQ = Everyday Memory Questionnaire.

[a] Numbers in Columns correspond to numbers in top row. [b] Gender: 1 = male, 2 = female. [c] Medication: CF: 0 = no, 1 = yes. [d] Colorectal cancer: 1 = yes, 2 = no. [e] Other health Problems: 0 = no, 1 = yes.

*$p < 0.05$.

Table 4.5

Pearson Correlation Coefficients Between Serum Levels of Inflammatory Cytokines and Biomarkers and Potential Immune Function Modifiers

Variable[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Age	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2. Education	-0.02	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3. BMI	-0.03	-0.06	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4. Med: CF[b]	0.06	-0.12	0.05	-	-	-	-	-	-	-	-	-	-	-	-	-
5. Med: IF[c]	0.15	0.01	-0.02	0.14	-	-	-	-	-	-	-	-	-	-	-	-
6. CRC[d]	0.16	0.13	0.05	-0.29*	-0.09	-	-	-	-	-	-	-	-	-	-	-
7. Tobacco[e]	0.01	-0.13	-0.03	0.03	-0.08	0.06	-	-	-	-	-	-	-	-	-	-
8. Anxiety	-0.26*	-0.18	0.09	0.00	-0.02	-0.38*	0.22*	-	-	-	-	-	-	-	-	-
9. Depressed	-0.15	-0.21*	0.14	0.04	-0.05	0.19	0.03	-0.60*	-	-	-	-	-	-	-	-
10. Exercise	0.12	0.22*	-0.06	-0.35*	-0.08	0.52	0.04	-0.37*	-0.33*	-	-	-	-	-	-	-
11. TNF-α	0.04	-0.13	0.12	0.10	0.05	-0.02	-0.02	0.22*	0.02	-0.26*	-	-	-	-	-	-
12. IL-6	0.06	-0.21*	0.00	0.12	0.07	-0.22*	0.13	0.11	-0.03	-0.38*	0.49*	-	-	-	-	-
13. CRP	0.06	-0.21*	0.18	0.33*	0.14	-0.40*	0.05	0.15	0.18	-0.43*	-0.08	0.30*	-	-	-	-
14. IL-10	-0.09	-0.06	0.11	0.13	0.01	-0.23*	-0.07	0.16	0.13	-0.33*	0.37*	0.56*	0.14	-	-	-
15. TGF -β	-0.12	0.04	-0.03	- 0.17	-0.08	-0.27*	0.12	0.04	0.13	0.08	-0.00	-0.04	0.13	-0.05	-	-
16.Pro-ratio	-0.12	-0.09	-0.01	- 0.16	-0.04	-0.26*	0.11	0.01	-0.09	0.10	-0.35*	- .04	-0.21*	-0.60*	0.03	-
17. Anti-ratio	-0.19	0.15	-0.04	0.17	-0.03	-0.20*	-0.05	- 0.04	0.04	- 0.05	-0.49*	0.12	0.15	-0.51*	-0.05	-0.77*

Note. BMI = body mass index; Med: CF = taking medication that can affect cognitive function; Med: IF = taking medication that can affect immune function; CRC = colorectal cancer, Tobacco = current tobacco use, Pro-ratio = TNF-α/IL-10; Anti-ratio = IL-10/TNF-α.

[a] Numbers in columns correspond to numbers in top row. [b] Med: CF, 0 = no, 1 = yes. [c] Med: IF, 0 = no, 1 = yes. [d] CRC, 1 = yes, 2 = no. [e] Tobacco, 0 = no, 1 = yes.

p * < 0.05.

Table 4.6

Predictors of Standardized Total Composite Score with IL-6 (N = 100)

Variable	B	SE B	β	*p*
IL-6	- 0.40	0.27	0.15	0.14
Age	- 0.08	0.02	- 0.29	< 0.01
Education	0.27	0.09	0.29	< 0.01
Medication: CF	0.36	0.50	0.07	0.47
Depressed Mood	- 0.15	0.09	- 0.17	0.09
Exercise as Usual	0.16	0.27	0.07	0.54
Colorectal Cancer	0.57	0.53	0.11	0.28

$R = 0.55$, $R^2 = 0.30$, $F = 5.62$, $p < 0.001$.

Table 4.7

Predictors of Standardized Total Composite Score with CRP (N = 100)

Variable	B	SE B	β	*p*
CRP	- 0.63	0.28	- 0.23	0.03
Age	- 0.08	0.02	- 0.29	< 0.01
Education	0.27	0.08	0.29	< 0.01
Medication: CF	0.59	0.50	0.11	0.24
Depressed Mood	- 0.11	0.08	- 0.13	0.19
Exercise As Usual	0.19	0.25	0.08	0.46
Colorectal Cancer	0.34	0.53	0.07	0.52

$R = 0.57$, $R^2 = 0.32$, $F = 6.17$, $p < 0.001$.

Table 4.8

Predictors of Standardized Total Composite Score with IL-6 and CRP (N = 100)

Variable	B	SE B	β	*p*
IL-6	- 0.33	0.27	- 0.12	0.22
CRP	- 0.58	0.28	- 0.21	< 0.05
Age	- 0.07	0.02	- 0.27	< 0.01
Education	0.26	0.09	0.27	< 0.01
Medication: CF	0.54	0.50	0.10	0.28
Depressed Mood	- 0.13	0.08	- 0.15	0.12
Exercise as Usual	0.08	0.27	0.04	0.76
Colorectal Cancer	0.34	0.53	0.07	0.53

$R = 0.58$, $R^2 = 0.33$, $F = 5.61$, $p < 0.001$.

Table 4.9

Predictors of Attentional Function Index with CRP (N = 100)

Variable	B	SE B	β	*p*
CRP	- 0.14	0.17	- 0.08	0.41
Education	0.07	0.05	0.11	0.21
Medication: CF	- 0.25	0.31	- 0.08	0.42
Anxiety	- 0.04	0.06	- 0.08	0.51
Depressed mood	0.01	0.06	0.02	0.88
Fatigue	- 0.20	0.05	- 0.45	< 0.01
Exercise as Usual	0.12	0.16	0.08	0.48
Colorectal Cancer	0.08	0.34	0.02	0.82

$R = 0.62$, $R^2 = 0.38$, $F = 6.90$, $p < 0.001$.

Table 4.10

Predictors of Attentional Function Index with TGF-β1 (N = 100)

Variable	B	SE B	β	*p*
TGF-β1	1.62	0.46	0.29	< 0.01
Education	0.06	0.05	0.11	0.19
Medication: CF	- 0.19	0.29	- 0.06	0.51
Anxiety	- 0.05	0.06	- 0.09	0.41
Depressed mood	- 0.02	0.06	- 0.04	0.73
Fatigue	- 0.19	0.05	- 0.43	< 0.01
Exercise as Usual	0.18	0.15	0.12	0.25
Colorectal Cancer	- 0.16	0.32	- 0..05	0.62

$R = 0.67$, $R^2 = 0.45$, $F = 9.24$, $p < 0.001$.

Table 4.11

Predictors of Attentional Function Index with CRP and TGF-β1 (N = 100)

Variable	B	SE B	β	*p*
CRP	- 0.36	0.16	- 0.20	0.03
TGF-β1	1.94	0.47	0.35	< 0.01
Medication: CF	- 0.08	0.29	- 0.02	0.78
Anxiety	- 0.07	0.06	- 0.12	0.26
Depressed mood	- 0.02	0.06	- 0.04	0.68
Fatigue	- 0.18	0.05	- 0.42	< 0.01
Exercise as Usual	0.13	0.15	0.09	0.37
Colorectal Cancer	-0.37	0.33	- 0.12	0.26

$R = 0.69$, $R^2 = 0.47$, $F = 9.91$, $p < 0.01$.

Table 4.12

Predictors of RAVLT delayed recall with TNF-α (N = 99)

Variable	B	SE B	β	*p*
TNF-α	- 0.97	0.51	- 0.18	0.06
Age	- 0.09	0.03	- 0.28	< 0.01
Education	0.25	0.10	0.22	0.02
Gender	2.02	0.58	0.32	< 0.01
Medication: CF	- 1.21	0.64	- 0.19	0.06
Anxiety	0.16	0.11	0.15	0.14
Exercise as Usual	0.22	0.32	0.08	0.49
Colorectal Cancer	- 0.34	0.68	- 0.05	0.62

$R = 0.59$, $R^2 = 0.34$, $F = 5.79$, $p < 0.001$.

Table 4.13

Predictors of RAVLT delayed recall with IL-6 (N = 99)

Variable	B	SE B	β	*p*
IL-6	- 0.67	0.32	- 0.20	0.04
Age	- 0.09	0.03	- 0.28	< 0.01
Education	0.24	0.10	0.21	0.02
Gender	2.03	0.58	0.33	< 0.01
Medication-CF	- 1.06	0.63	- 0.16	0.10
Anxiety	0.12	0.11	0.11	0.28
Exercise as Usual	0.17	0.33	0.06	0.61
Colorectal Cancer	- 0.54	0.67	- 0.09	0.42

$R = 0.59$, $R^2 = 0.35$, $F = 5.92$, $p < 0.001$.

Table 4.14

Predictors of RAVLT delayed recall with TNF-α and IL-6 (N = 99)

Variable	B	SE B	β	*p*
TNF-α	- 0.47	0.56	- 0.09	0.41
IL-6	- 0.55	0.36	- 0.16	0.13
Age	- 0.10	0.03	- 0.27	< 0.01
Education	0.22	0.10	0.19	0.04
Gender	1.98	0.58	0.32	< 0.01
Medication-CF	- 1.26	0.63	- 0.20	0.05
Exercise as Usual	0.04	0.32	0.01	0.91
Colorectal Cancer	- 0.64	0.66	- 0.10	0.33

$R = 0.59$, $R^2 = 0.34$, $F = 5.83$, $p < 0.001$.

CHAPTER V

CONCLUSIONS

Individuals with cancer can experience cognitive symptoms at diagnosis, during primary and adjuvant therapy, and up to 20 years after treatment for the disease (Cimprich, 1998; Cimprich & Ronis, 2001; Koppelmans et al., 2012; Wefel, Vardy, Ahles, & Schagen, 2011). Few research studies have examined cognitive symptoms in individuals with colorectal cancer and little is known about mechanisms that may underlie cognitive symptoms in cancer survivors. One potential mechanism is the immune system's response to the cancer and cancer treatments (Cleeland et al., 2003; Hart, 1988; Kent, Bluthe, Kelley, & Dantzer, 1992). Specifically, inflammatory cytokines produced in response to an immune challenge can communicate with the brain to induce symptoms and behaviors or 'sickness behavior' that generally support the immune system's response and the survival of the individual (Konsman, Parnet, & Dantzer, 2002). Sickness behavior responses include fatigue, malaise, anorexia, hyperalgesia, decreased physical and social activity and changes in sleep pattern and architecture (Cleeland et al., 2003; Hart, 1988; Kent, Bluthe, Kelley, & Dantzer, 1992; Watkins & Maier, 2000). These sickness behavior responses appear to occur alongside cognitive changes (Cleeland et al., 2003). Thus, this study hypothesized that cognitive symptoms reported by colorectal cancer survivors may be a part of the immune system's response to the colorectal cancer and associated treatments. The goal of this dissertation

study was to describe cognitive and immune function in individuals with colorectal cancer and to begin to characterize the relationship between cognitive symptoms and inflammatory cytokine and biomarker expression. The study used a cross-sectional comparative design and included individuals newly diagnosed with primary or recurrent colorectal cancer and healthy individuals without colorectal cancer. The following section will review findings, discuss limitations, make recommendations for future research, and discuss implications for future nursing practice.

Improving Colorectal Cancer Survivorship

Cognitive Symptoms in Colorectal Cancer

When assessing cognitive function in colorectal cancer survivors, this study found that patients with colorectal cancer performed and perceived their function to be significantly worse on tasks requiring directed attention and working memory but not long-term memory when compared to individuals without colorectal cancer. It is not clear why individuals with colorectal cancer did not have deficits in long-term memory given findings from preclinical studies suggesting that inflammatory cytokine expression can impair hippocampal dependent memory processes.

Further analyses found that after controlling for covariates, having colorectal cancer remained an independent predictor of worse performance on objective measures of directed attention and working memory. Additionally, fatigue was found to be an independent predictor of performance on a self-report measure of directed attention and working memory after controlling for covariates. These findings are important because they are the first to identify deficits in a specific cognitive domain in individuals with colorectal cancer. Directed attention and working memory are cognitive processes that

allow an individual to focus on important information in the environment and to hold and manipulate information so that higher cognitive activities can be achieved. As such, they are critical to learning, reasoning, and problem solving. Problems with directed attention and working memory can make it difficult for an individual newly diagnosed with cancer to make treatment decisions, manage work demands and family needs, and cope with the illness. The finding that fatigue severity predicted worse perceived effectiveness on common tasks that require directed attention and working memory was an unexpected finding that may provide a window into potential mechanisms that underlie cognitive symptoms in colorectal cancer survivors. Specifically, multiple factors may influence the expression of cognitive symptoms and some of these factors may share a common biological mechanism while other factors may be associated with different mechanisms and make unique contributions. Understanding the mechanisms associated with cognitive symptoms is important for colorectal cancer survivorship as it will allow for the application and/or development of targeted interventions to support attention and memory function, reduce distress and improve quality of life.

Inflammatory Cytokines and Biomarkers Expression in Colorectal Cancer

When assessing immune function in colorectal cancer, this study found that patients with colorectal cancer had significantly higher serum levels of IL-6, CRP and IL-10 and significantly lower serum levels of TGF-β1 compared to individuals without colorectal cancer. However, after controlling for covariates, having colorectal cancer was an independent predictor of higher serum levels of TNF-α and CRP. Interestingly, indirect makers of TNF-α activity and CRP also have been associated with sickness behaviors such as fatigue in individuals with cancer (Bower, et al., 2002; Bower et al.,

2011; Bower, et al., 2009; Orre, et al., 2009; Wang, et al., 2010; Wang, et al., 2012; Wratten, et al., 2004). These findings are important because few studies examining immune function in colorectal cancer have controlled for biobehavioral factors that may affect inflammatory cytokine and biomarker expression making it difficult to interpret results. In this regard, findings from this study that controlled for biobehavioral factors provide preliminary evidence that TNF-α and CRP are associated with a systemic inflammatory response or an acute phase response in individuals with colorectal cancer. These findings also suggest that TNF-α and CRP may be sensitive biomarkers of sickness behavior including cognitive symptoms in individuals with colorectal cancer. As such, they are very important and foundational to understanding immune mediated responses in individuals with colorectal cancer.

Cognitive Symptoms and Inflammatory Cytokines and Biomarkers in Colorectal Cancer

Cognitive and immune function was assessed in the combined group of individuals with and without cancer to ensure sufficient variance on cognitive and immune variables. When assessing the relationship between cognitive symptoms and the expression of inflammatory cytokines and biomarkers, this study found that serum levels of TNF-α, IL-6, CRP, and TGF-β1 were associated with performance on cognitive measures and/or perceptions of cognitive function on self-report measures. Further, the study found that 1) higher levels of CRP specifically predicted poorer performance on tasks requiring directed attention and working memory and 2) higher serum levels of CRP and lower serum levels of TGF-β1 predicted poorer self-report of directed attention and working memory function. This study is the first to report a relationship between

higher circulating levels of CRP and specific cognitive domain – namely directed attention and working memory. CRP is an indirect marker of pro-inflammatory activity and findings suggest that cognitive symptoms may be associated with the systemic inflammatory response and immune-mediated symptoms and behaviors. This study is also the first to report a relationship between lower circulating levels of TGF-β1 and poorer perceived effectiveness on tasks requiring directed attention and working memory. Interestingly, preclinical studies suggest that TGF-β1 may be necessary for regulation of the inflammatory response, neuroplasticity and neurogenesis (Ariel & Timor, 2012). As such, this finding may suggest that this immunosuppressive cytokine has a neuroprotective role. Finally findings from this study may suggest that different cytokines may be associated with different cognitive symptoms or losses. Together these findings raise important questions about the relationship between cognitive symptoms and inflammatory cytokine expression and provide a direction for future research.

Limitations

This study has certain limitations that need to be considered when interpreting results. First, the study used a convenience sample. As such, patients who enrolled in this study may have differed in an important way from patients who declined to participate. Of the 30% who declined to participate, the main reasons for refusal was feeling overwhelmed. Given that psychological distress can affect both cognitive function and the expression of inflammatory cytokines and biomarkers, individuals who declined to participate may have been more likely to experience cognitive symptoms as well as have higher levels of inflammatory cytokines and biomarkers. Therefore, findings from this study may have been conservative and not fully captured the

differences in cognitive and immune variables between individuals with and without cancer.

Second, this study used a cross-sectional design and collected data at one time point within six months of a new diagnosis of primary or recurrent cancer. Most patients were assessed after colonoscopy and before any treatment, some individuals were assessed after surgery only, and the rest were receiving chemotherapy and/or radiation therapy at the time of the research visit. Findings indicate that individuals with colorectal cancer were impaired on measures of directed attention and working memory and had higher serum levels of inflammatory cytokines and biomarkers. However, it is unclear whether the expression of cognitive symptoms or inflammatory cytokines and biomarkers may be associated with the cancer and cancer diagnosis or the cancer treatments or some combination of both.

The study results were limited by sample size. Although, this study had sufficient power to detect medium effects in group differences on most cognitive and immune measures, a larger sample would have been required to detect differences in two inflammatory cytokines and biomarkers that had lower levels of detection. Specifically, IL-1β was detected in 26% of individuals with colorectal cancer and 20% of individuals without colorectal cancer. IL-1RA was detected in 50% of individuals with colorectal cancer and 40% of individuals without colorectal cancer.

Finally, this study included individuals with varying stages of cancer but did not permit analyses of differences by stage of disease. A larger sample size of individuals with colorectal cancer would have allowed for the analyses and possible detection of

cognitive and immune differences amongst individuals with varying stages of colorectal cancer.

Recommendations for Future Research

There are multiple recommendations for future research. First, there is a need to continue to describe cognitive symptoms in individuals with colorectal cancer using neuroscience theory to guide the assessment. This study found alterations in directed attention and working memory but not long-term memory. These are novel findings that need to be confirmed in a larger sample using a combination of domain specific neuropsychological measures that take into consideration gender differences.

Second, this study assessed inflammatory cytokine and biomarker expression as a first step toward examining the relationship between cognitive and immune function in individuals with colorectal cancer. The study found that TNF-α and CRP were over expressed in individuals with colorectal cancer compared to healthy controls after controlling for biobehavioral factors that may affect the immune variables. Few studies in colorectal cancer have assessed inflammatory cytokines and biomarkers while controlling for possible covariates making it difficult to interpret findings. As such, future research is needed to confirm findings and clarify patterns of inflammatory cytokine and biomarker expression in individuals with colorectal cancer.

Third, this study found a relationship between CRP and TGF-β and a specific domain of cognitive function, namely direction attention and working memory function. Further, this study found that higher levels of TGF-β were associated with better cognitive function suggesting that some inflammatory cytokines may support attention and memory function. These novel findings need to be confirmed. Additionally, further

research that assesses and describes patient characteristics associated with an increase in the expression of inflammatory cytokines and cognitive deficits would be helpful in identifying vulnerable individuals.

Fourth, individuals with colorectal cancer reported greater psychological and symptom distress and reduced physical exercise. In particular fatigue was found to independently predict self-report directed attention and working memory function. This was an interesting and unexpected finding. Further research is needed to examine specifically the relationship between fatigue and cognitive function as well as more broadly the relationship between distress and reduced physical activity and cognitive and immune function in individuals with colorectal cancer. Additionally, these findings need to be further examined within the context of sickness behavior responses in colorectal cancer.

Fifth, there is a need to assess cognitive and immune function in a larger sample of colorectal cancer survivors. In particular, the present study had difficulty detecting group differences in IL-1β and IL-1RA. Future studies with a larger sample would also allow for the assessment of the effects of advanced cancer on the expression of cognitive symptoms and inflammatory cytokines and biomarkers. It is possible that individuals with advanced colorectal cancer are more vulnerable to cognitive symptoms given prior studies finding greater inflammatory cytokine and biomarker expression in patients with advanced cancer compared to individuals with localized disease.

Finally, this cross sectional study examined cognitive and immune function during the first six months after diagnosis with primary or recurrent cancer and found that individuals with colorectal cancer may experience deficits in directed attention and

working memory and an overexpression of inflammatory cytokines and biomarkers. Future longitudinal studies are needed to confirm these preliminary findings and to examine the effects of diagnosis and treatment on cognitive and immune function over the illness trajectory.

Implications for Nursing Practice and Research

The goal of nursing is to optimize the health and abilities of an individual and to alleviate suffering (American Nurses Society, 2013). In oncology, nurses have an important role in assessing symptoms and behavioral responses to the cancer and cancer treatments and intervening to improve function and reduce distress. This study provides preliminary evidence that individuals newly diagnosed with primary or recurrent colorectal cancer can experience deficits in directed attention and working memory. Cognitive symptoms can interfere with daily functioning including an individual's ability to learn, work, and attain personal goals (Boykoff, Moieni, & Subramanian, 2009) Cognitive symptoms have also been associated with significant distress, feelings of helplessness, and reduced quality of life (Boykoff et al., 2009). Additionally, this study found an association between cognitive symptoms and an over expression of inflammatory cytokines and biomarkers suggesting that cognitive symptoms may be a part of a systemic immune response to the cancer and cancer treatments. Understanding the expression of cognitive symptoms within this context has important implications for both the development of targeted interventions as well the timing of interventions as poorly timed interventions have the potential of exacerbating an already stressed immune system bringing harm to the individual. Assessing cognitive function and intervening to

improve cognitive function in colorectal cancer survivors as well as directions for future nursing research will be discussed further below.

Assessing Cognitive Symptoms in Colorectal Cancer

Cognitive assessments of individuals with colorectal cancer should include sensitive measures of both cognitive performance and self-report. Unfortunately, at this time there are no recommended cognitive assessments for nurses in the clinical setting. Findings from this study and findings from other studies examining cognitive symptoms in individuals with cancer, suggest that some neuropsychological tests are sensitive to detecting deficits in cognitive performance in cancer survivors (Wefel et al., 2011). However, these tests can be lengthy and require advanced training and skills in the administration and interpretation of findings. Thus, these tests are not suitable for the clinical setting. Further research is needed to develop a sensitive objective test for oncology nurses to use to screen for cognitive symptoms in the clinical setting.

Self-report measures of cognitive performance are also a critical component of cognitive assessments and can provide important information about an individual's performance on daily activities that require directed attention and working memory. This study used the Attentional Function Index (AFI) and found it to be a sensitive measure in detecting cognitive problems in individuals with colorectal cancer. The AFI has established reliability and validity in individuals with cancer (Cimprich, Visovatti, & Ronis, 2010). Further, it is brief, and easy to score and interpret. As such, it would be a useful self-report measure to be included alongside neuropsychological measure (s) in a cognitive assessment for cancer-related cognitive symptoms.

In summary, this study found preliminary evidence of cognitive problems in the domains of directed attention and working memory in individuals with colorectal cancer. At this time there are no recommended tests or questionnaires to assess cognitive function in cancer survivors in the clinical setting. As such, there is a critical need for research to develop a sensitive cognitive assessment that includes measures of both cognitive performance and self-report. The AFI was a sensitive self-report measure in this study and is recommended for inclusion in a cognitive assessment for individuals with colorectal cancer.

Intervening to Improve Cognitive Function and Reduce Distress in Colorectal Cancer

Interventions to improve cognitive function in cancer survivors require an understanding of potential mechanisms that may underlie symptoms. In this regard, there were three important findings from this study. First, this study found that individuals with cancer experienced an overexpression of inflammatory cytokines and biomarkers. Second, this study found a significant relationship between cognitive symptoms and inflammatory cytokine expression. Finally, this study found that both cognitive symptoms and an overexpression of inflammatory cytokines were associated with other biobehavioral factors. These are important findings because they suggest that an overexpression of inflammatory cytokines may underlie cognitive symptoms in individuals with colorectal cancer. Additionally, they also suggest possibilities for interventions such as modifying biobehavioral factors to improve cognitive function and/or reduce inflammatory cytokine expression. Specifically, interventions to decrease psychological distress, decrease fatigue, and/or increase physical activity may hold

promise in reducing inflammatory cytokine expression and improving cognitive function. Promoting healthy behaviors may also be an important intervention as body mass index, tobacco use, and alcohol intake have been associated with an over expression of inflammatory cytokines (O'Connor et al., 2008). However, in developing interventions to reduce inflammation and improve cognitive function researchers must consider whether the intervention has the potential to add additional stress to the immune system and/or compromise cancer control. For example, although cardiovascular fitness has been shown to lower circulating levels of inflammatory cytokines, acute exercise has been associated with an exponential increase in inflammatory cytokines (O'Connor et al. 2009). If the intervention has the potential to alter the immune response and harm the individual important questions about the doses of the intervention and the timing of the intervention need to be asked. With this in mind interventions aimed at optimizing cognitive function and not aimed at altering the immune response may be most appropriate for individuals with advanced disease and/or individuals newly diagnosed with cancer during the initial phase of the illness when the immune system is responding to both the presence of malignant cells and tissue injury associated with cancer treatments. One potential intervention aimed at reducing mental or attentional fatigue is having the individual engage in activities that rest and/or restore directed or controlled attention such as spending time in nature or enjoying a scenic view from a window (Cimprich, 2003). This intervention has proven efficacy in women with breast cancer, who like individuals with colorectal cancer, can experience mental or attentional fatigue related to the many cognitive demands associated with a diagnosis and treatment of

cancer. Further research is needed to evaluate the efficacy of this intervention in colorectal cancer.

In summary, this study suggests that there may be a relationship between cognitive symptoms and inflammatory cytokine and biomarker expression in individuals with colorectal cancer. This study also found that certain biobehavioral factors were associated with the expression of cognitive symptoms and inflammatory cytokine expression. As such, modification of some of these biobehavioral factors including psychological distress, fatigue and physical activity may reduce the expression of cognitive symptoms and/or inflammatory cytokine expression. However, the relationship between cognitive and immune function also suggests that interventions need to be appropriately timed and dosed so as to not to harm the individual. Interventions that focus on optimizing an individual's cognitive function such as spending time in nature may be most appropriate for individuals with advanced disease and/or individuals newly diagnosed with colorectal cancer undergoing treatment for the disease.

Directions for Future Nursing Research

This study provided new information about the role of immune responses in cognitive symptoms in cancer survivors and suggests that such symptoms may be a part of a cluster of immune mediated sickness behavior responses. Future research examining symptom clusters is needed to increase knowledge of immune responses in colorectal cancer and to allow for the development of new strategies for symptom management.

More broadly, current findings from this study suggest that biological mechanisms may underlie symptoms and behavioral responses. This has important implications for nurse researchers who are assessing and developing interventions for

symptoms and behaviors in other acute and chronic illnesses. Increased knowledge of biological mechanisms associated with symptoms will allow for the development of interventions to manage symptoms and improve quality of life across the trajectory of the illnesses. It may also allow for the design of personalized interventions to address the multiple biobehavioral factors that may influence the expression of symptom and behaviors.

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