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Thesis

AN ANALYSIS OF THE RELATIONSHIP BETWEEN DEPRESSION AND INFLAMMATION IN CANCER PATIENTS FOLLOWING REMISSION: PATHOGENESIS, DIAGNOSIS & COMPARISON OF TREATMENT METHODS

by

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B.S., University of Virginia, 2017

Submitted in partial fulfillment of the

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DEDICATION

I would like to dedicate this work to my family, Tracy, Paul, Benjamin, Nicholas and Samantha.

In loving memory of my uncle Douglas Leigh Jenkins, my grandparents Kendall Leigh Jenkins and Paul Wayne Jenkins, my great uncle Tom Jenkins, and my great-grandparents Robert and Adele Kluck, to the beautiful legacy you have left us. I know you have been with me every step of the way.

To all cancer patients, survivors, and their loved ones, you have battled the unimaginable, your courage and strength are unfathomable.

ACKNOWLEDGMENTS

I would like to thank my advisor, Dr. Levy for his kindness and wisdom, but especially for his faith in my abilities from day one. My sincere thanks to Dr. Offner and the BU GMS department for their guidance and support. Finally, my gratitude to Dr. Davies for her patience, understanding and continued support.

AN ANALYSIS OF THE RELATIONSHIP BETWEEN DEPRESSION AND INFLAMMATION IN CANCER PATIENTS FOLLOWING REMISSION: PATHOGENESIS, DIAGNOSIS & COMPARISON OF TREATMENT METHODS

KENDALL MARIE JENKINS

ABSTRACT

Cancer survivors typically adapt well to life following remission; however, some patients still experience lingering negative moods that may develop into depression. There are multiple factors that can contribute to depressive symptoms from somatic symptoms, to emotion and social concerns. When analyzing these contributing factors, an underlying theory of a connection between the symptoms of depression and inflammation was revealed. Although this was not shown to be a causal association, it set forward some theories on the pathogenesis of depression in cancer survivors who may have persistent inflammation following treatment. As cancer patients are a growing group due to improvements in treatment and an aging general population, early identification of high-risk survivors and research into new treatment methods is essential. Depression in survivors can lead to an inability to follow through on medical care, decreased quality of life and poorer patient health outcomes. Currently, depressive symptoms are treated primarily on an individual basis, determining if there is a common underlying biological mechanism that could help scientists develop new guidelines for the treatment of survivors.

Research studies demonstrated interdependence between conditions such as chronic pain, fatigue, sleep disturbance, cognitive impairment and depression. Current published literature on each of these conditions was explored and while each of these conditions have demonstrated connections to inflammatory pathways and specific cytokines, there does not appear to be one common underlying mechanism. Preliminary research has presented some options for future treatments that can mitigate the severity of the inflammation caused during traditional cancer therapies. These preventative measures address certain cytokine pathways that have been associated with negative side effects. As emotional and social concerns can add to a survivor's stress causing stimulation of inflammatory pathways, evidence-based methods for reducing stress have been discussed and include exercise, psychosocial and occupational therapy interventions as well as legislative advocacy for better insurance coverage.

There are some limitations in the current literature on the topic as much of the survivor research centers on patients who were diagnosed with breast cancer. There are several diverse subgroups of cancer survivors including childhood, adolescent and young adult, and adult cancer survivors, and comprehensive research should be conducted across these cohorts to ascertain which groups are at a higher risk for certain symptoms and stresses. Furthermore, research into novel treatment options has focused mainly on pharmacological solutions to the negative impacts of chemotherapy. While several studies have theorized about possible, persistent biological mechanisms underlying radiotherapy, few drugs have been suggested or developed to combat the late effects of inflammation including fibrosis. Many of the suggested treatments can be given as a co-treatment alongside of chemotherapy, radiotherapy or surgery; in the future, research should be conducted on the effects of reducing inflammatory levels in patients already in remission.

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LIST OF ABBREVIATIONS

ACS... American Cancer Society

AMPK.. Adenosine Monophosphate Activated Protein Kinase

AYA...Adolescent and Young Adult

CBT...Cognitive Behavior Therapy

CIPN ....Chemotherapy Induced Peripheral Neuropathy

CNS... Central Nervous System

CRCI ....Cancer Related Cognitive Impairment

CRF...Cancer Related Fatigue

CRH ....Corticotrophin Releasing Hormone

CRP... C-reactive Protein

CPSP ....Chronic Post-Surgical Pain

DA...Dopamine

DAMP...Damage-Associated Molecular Patterns

DNA... Deoxyribonucleic acid

DRG .... Dorsal Root Ganglion

DSM-IV ....Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

ECM...Extracellular Matrix

EPO.. Erythropoietin

FCR..Fear of Cancer Recurrence

HICP .... High Impact Chronic Pain

HPA..Hypothalamic-pituitary-adrenal

IDO Indolamine-2,3-dioxygenase

IL ....Interleukin

INF ....Interferon

MDD ....Major Depression Disorder

mTOR ....Mammalian Target of Rapamycin

NCCN ....National Comprehensive Cancer Network

NREM ....Non Rapid Eye Movement

NFκβ ....Transcription Factor Nuclear Factor κ-β

PRR ....Pattern Recognition Receptors

PTSD ....Post-Traumatic Stress Disorder

QOL ....Quality of Life

RIBE ....Radiation Induced Bystander Effect

REM ....Rapid Eye Movement

ROS ....Reactive Oxygen Species

TGF ....Transforming Growth Factor

TNF ....Tumor Necrosis Factor

INTRODUCTION

In the first part of this thesis, the comorbidity of cancer and depression will be explored, acknowledging that post-remission depression is multifactorial and has multiple potential causes, including various psychosocial and social aspects. A thorough background of these multifactorial causes will be provided. The specific aims of the paper will be listed and then explored further. They include, a review of the current literature on the pathogenesis of depression in cancer survivors, the interdependent relationship depression has with chronic pain, fatigue, sleep disturbances and cognitive impairments. Evidence-based interventions will be discussed for specific survivor populations. A final assessment will discuss the nuances of, and barriers against, providing treatment to a wide range of survivors, as well as current gaps in research and the importance of providing funding towards research for specific underserved survivor groups.

Comorbidity of Cancer and Depression

Depression affects more than 264 million people and is one of the leading causes of disability worldwide, with considerable associated public health concerns.[1] Although the study of depression can be challenging because symptoms appear on a wide spectrum from sadness to major depressive disorders, research has identified the most commonly noted symptoms as fatigue, insomnia and depressed mood. Depression can have a larger impact on patient health when comorbid with a chronic medical condition, such as anxiety (posttraumatic stress disorder (PTSD), panic disorder) or pain.

As the odds of cancer survival have improved over the past decade, with earlier detection and improvement in treatment options, cancer survivors are becoming a rapidly increasing population group. The American Cancer Society (ACS) estimates that about two-thirds of cancer survivors were diagnosed 5 or more years ago, with a subset of 17% diagnosed 20 or more years ago.[2] This population is also growing due to an increasing number of new diagnoses in a growing and aging population. The ACS estimates that almost half (47%) of the survivor population is 70 years of age or older, with only 11% of survivors being younger than 50.[2] Current cancer prevalence estimates suggest that in 2016, there were 15.5 million cancer survivors in the United States alone, with that number predicted to increase to 26.1 million by 2040.[3] The need for research on treatment options for depression in cancer survivors has become increasingly important as this vulnerable population continues to grow.

When compared to the general population, depression disproportionately impacts cancer patients at a rate of 20%, with these estimates varying according to the type of diagnostic criteria used.[4] A recent study of depression and anxiety in long-term survivors following a cancer diagnosis estimates that 17% of survivors have moderate to severe depression, with no significant difference noted between the 5 and 10 year post diagnosis cohorts.[5] Although this study surveyed survivors from a large variety of tumor entities, most research about post-remission depression comes from research centered solely on breast cancer survivors. Notably, depression in cancer survivors is often underreported, as oncologists often fail to detect or differentiate symptoms of depression within their patient populations. Diagnosis can be difficult because the somatic signs of depression overlap with common cancer symptoms and side effects of treatment (such as fatigue, changes in appetite and insomnia). Additionally, typically the medical focus is on monitoring physical health symptoms and side effects of various treatments instead of screening for depression.

There is some variation in the prevalence of depression across different types of cancer and among certain survivor subgroups, especially when considering other variables such as individual risk factors, structural level impacts (finances and community support) and psychological considerations. Many cancer survivors are able to adapt to their diagnosis and the treatments that follow, but a subset of patients experience difficulty emotionally adjusting during their survivorship period. Cancer remission survivorship for this thesis will encompasses a variety of cancer experiences including living cancer-free after treatment either for the remainder of the patient's life, until later recurrence or until the development of a second type of cancer. Survivorship will also include a range of patient histories such as, adults who have survived childhood cancers, as well as adolescent, young adult (AYA) and mature adult cancer survivors. In the following sections, depressive symptoms as well as other post-cancer related sources of emotional distress will be explored. Early diagnosis of depressive symptoms is key, as poor recognition of symptoms is linked with a reduced quality of life (QOL) for patients.

Depression Diagnosis Methods

Many cancer survivors experience emotional distress that does not meet the criteria for major depressive disorder (MDD); there are many potential sources of the distress for survivors. The National Comprehensive Cancer Network (NCCN) Distress Guidelines notes that the term emotional distress encompasses a wide range of symptoms from common feelings of vulnerability, sadness and fears of recurrence, to disabling problems such as depression, anxiety, isolation and existential crisis.[6] Many physicians diagnose depression using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), which is an official source of definitions related to mental illness. To meet the DSM-IV criteria for MDD set by the American Physician Association, a patient must have five or more of the following symptoms (listed in Table 1) over a two-week period with a notable difference or change from the patient's baseline.[7]

Table 1: Diagnostic Criteria for Major Depressive Disorder
Table taken from Kennedy, 2008 [7]

Symptoms of Major Depressive Disorder
Depressed mood or irritability
Loss of interest or pleasure in daily activities
Weight change (significant, 5%) or change in appetite
Insomnia or hypersomnia
Change in activity
Fatigue, lack of energy
Feelings of guilt or worthlessness
Diminished ability to concentration, more indecisiveness
Thoughts of death or suicide

Psychosocial assessment and treatment were not considered an important aspect of quality care for cancer patients until a report in 2007 from the Institute of Medicine called *Cancer Care for the Whole Patient*.[6] This report was based on work from the NCCN panel and called for frequent screenings of symptoms of emotional distress. It also highlighted the importance of developing a treatment plan that incorporated referrals to psychosocial resources, as needed.[6] These guidelines emphasize the importance of identifying, monitoring, documenting and treating distress at all stages of cancer treatment, including follow up care during remission.

There are multiple different ways to diagnose depression; these assessments can be completed through print tests, online or clinical interviews. It is essential to find a balanced method that is easy to administer (so that the proper recommendations and referrals can be placed quickly), but that also maintains a high sensitivity and selectivity for defining further treatment options. There are various scaling assessments based on numerical ratings, verbal descriptions and visual analogs. Most times, severity and identification of symptoms are done through subjective reporting from the patient; however, some symptoms such as cognitive impairment can be diagnosed using performance measures. Observational data collected over time by a therapist could also help support subjective reporting from the patient. The NCCN recommends that screening questions be asked at regular intervals especially when there are changes in health status or treatment or if the patient is complaining of multiple, new somatic symptoms.[8] In cancer survivors it is important to track these symptoms at least once a year, in order to identify which patients are most at risk and treat their negative moods before they further develop into a chronic condition.

Multifactorial Causes of Depression

Depression can be caused from a wide variety of factors including somatic symptoms, emotional distresses, and social and structural concerns; it is generally acknowledged that these factors can be contributary (Figure 1).

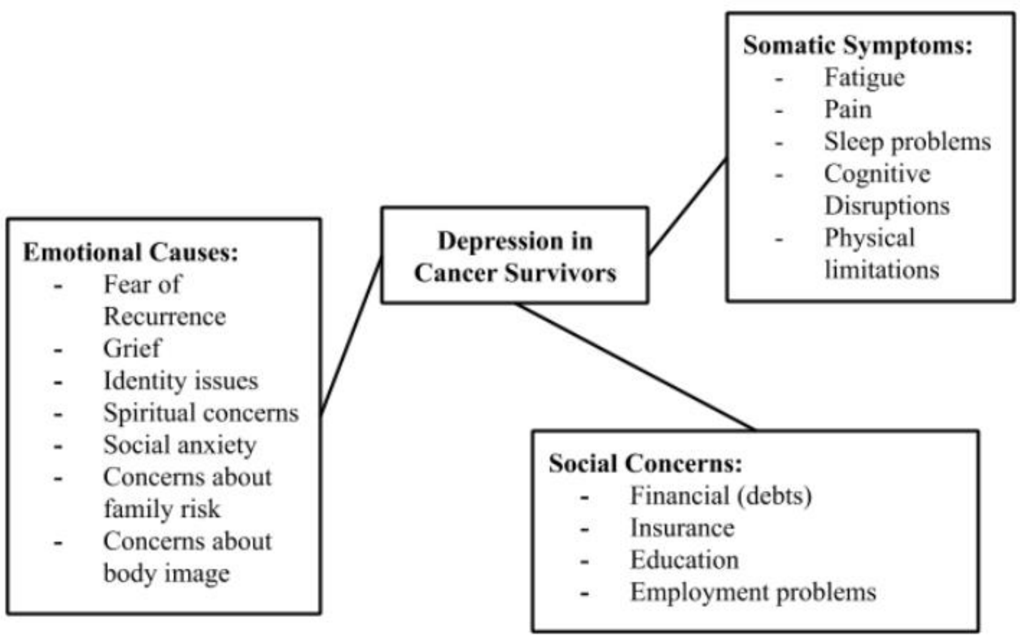

Figure 1. Multifactorial Causes of Depression. Depression is a multifactorial disorder, the emotional causes, social concerns and somatic symptoms listed above do not act in isolation. These factors can interact to increase the patient's vulnerability to depression. Figure taken from Yi, 2017.[8]

Emotional Causes of Depression

When analyzing potential emotional causes of depression, one of the notable differences between depression in the general population and depression amongst cancer survivors is the impact of fear of cancer recurrence (FCR). FCR is defined as fear or worry about the possibility that cancer may return or progress. It is one of the most commonly reported problems among adult cancer survivors and is often an unmet need within the community.[9] Studies of short-term and long-term cancer survivors demonstrate no significant change in FCR over time, with FCR persisting at a modest intensity for most long-term survivors.[10] Because FCR is a long-term and late effect concern for many cancer patients, it is important to consistently monitor symptoms after their treatment ends in order to identify and address FCR symptoms in a timely manner within a clinical setting. The most consistent predictor of FCR is younger age in survivors, with significant evidence also supporting an association between more physical symptoms or treatment side effects and FCR.[11] An assessment of FCR in cancer survivors of the 10 most common cancers indicates that 1 year after their diagnosis 68.1% of patients had FCR, and more than half had concerns about the future (57.7%).[12] This is a major concern for the survivor community as FCR is related to poorer QOL, and an increased risk for depression in cancer survivors.

Emotional concerns among survivors are also common, a Livestrong survey assessment of 2910 post-treatment cancer survivors noted that 90% reported at least one emotional concern with less than half receiving care (47%).[13] Emotional distress (defined on page 2) can be caused by grief, identity issues, and social anxiety following remission.

Particularly in cancer survivors, emotional stress can stem for the extreme uncertainty they face due to possible recurrence. These feelings could be exacerbated by the effects that the cancer and its treatment has had on survivors' jobs, families, physical appearances, abilities, finances, and independence. These factors along with inadequate coping strategies, a history of mental history preexisting a cancer diagnosis or insufficient communication with health care providers can all put survivors at a higher risk for developing depression.[14] It's important to screen for these concerns by collecting a detailed patient history, an oral record taken by a physician or therapist could help determine the future course of treatment.

It should be noted that the remission transition period that follows the end of a patient's treatment, can be especially difficult as patients typically lose the safety net of active medical treatment and supportive medical workers.[15] This re-entry back into their former roles can be difficult if their persistent symptoms are juxtaposed against expectations set by themselves or their support network to swiftly return to their life before diagnosis. This disconnect, between where they are and where they feel that they should be, can cause survivors to feel that they do not have the tools to express what they experienced and may cause them emotional distress.

Somatic Symptoms Linked to Depression

Fatigue is the most common symptom reported by survivors across multiple cancer types; typically, this lack of energy will gradually resolve after treatment is ceased, but not all survivors experience such an improvement. Cancer related fatigue

(CRF) is defined as a subjective sense of emotional, physical and/or cognitive exhaustion related to cancer and/or cancer treatment that is distressing, persistent and not proportional to their exertion during recent activity. Patients report that CRF is typically more severe, persistent and debilitating than "normal" fatigue caused by lack of sleep or overexertion.[16] Fatigue has an interdependent relationship with several other common symptoms that cancer survivors experience, including pain and sleep disturbance.

In addition to fatigue, survivors also commonly report pain, insomnia and/or physical limitations. Chronic pain is a frequent complication of cancer and cancer treatments; pain is considered chronic when the patient reports experiencing pain on most days in the past 6 months. Pain in survivors can be linked to residual tissue damage from the cancer itself or damage from the resulting cancer therapies.[17] Sleep disturbances, another common complaint, manifest in one of three ways, inability to obtain the necessary amount or quality of sleep, failure to sustain sleep continuity (disrupted sleep), or events that occur during sleep that interrupt the sleep cycle.[18] These disturbances can be caused by a variety of factors in survivors including lifestyle and environmental stresses as well as the effects of the cancer or the cancer treatment.

Both chronic pain and sleep disturbances are generally associated with serious physical and emotional consequences including decreased QOL, depression, and decreased life span. Finally, some physical limitations that survivors have reported include, problems with their heart, lungs, vision, hearing and oral health, as well as lymphedema, neuropathy, sexual dysfunction and cognitive impairments. Often these physical limitations can be specifically linked to the type of tumor or the type of treatment the patient received. For example, several studies of breast cancer patients have demonstrated a link between cognitive impairment and chemotherapy, indeed neuroimaging demonstrates alterations in brain structure and function following treatment.[19] These physical limitations and cognitive impairments could be connected to the fatigue, chronic pain and sleep disturbance experienced by many survivors.

Since cancer patients are living longer following their diagnosis recent studies have been focusing on the impact that cancer has on aging, and what survivors can expect in terms of QOL and life span. Recent studies on breast cancer survivors have noted accelerated aging following remission based on aging-related symptoms (energy level, depression, sleep disruption, daily functional impairments and potential for recurrence). In one study, survivors reached the probability for functional limitations 5-10 years before women in the cancer-free cohort.[20] These functional limitations can impact a cancer survivor's ability to complete daily activities and may affect the capacity in which survivors can return to work or school, contributing to possible emotional distress.

Social Concerns Possibly Contributing to Depression

The financial cost of cancer treatment can be a heavy burden to survivors. The annual medical costs of cancer were estimated to be 157.7 billion dollars in 2020, a 27% increase in cost since 2010.[21] Due to this increase, more third-party payers have begun shifting these growing costs onto the patients in the form of copayments. This increased financial burden can negatively affect care, causing patients to forgo or delay medical care and/or follow up care or discontinue necessary and useful medications that they can no longer afford. Concerns about large medical bills, being unable to pay for care and possible bankruptcy can contribute to a depressed mood or emotional distress. Patients that are in school or employed during their diagnosis may suffer from a lost sense of identity and may experience limited employment following remission because of health problems related to their diagnosis or treatment, therefore, leading to additional financial concerns.

Common Cancer Treatments

Understanding the methods of cancer treatments is essential to treating depression in survivors, as the biological mechanisms that occur during these treatments can cause symptoms that persist past the duration of the therapy. The most common methods of treatment for cancer are surgery, radiation and chemotherapy. Surgery is the primary treatment method for removing obvious cancerous tissue, especially solid tumors. Ionizing radiation is a common local therapy for cancer; it is directed to impact only the region containing the tumor. Radiotherapy works either as the primary method of treatment or as a supplement to chemotherapy or surgery. Approximately half of all cancer patients receive some form of radiation therapy during their treatment.[22] The therapy works by inducing deoxyribonucleic acid (DNA) damage in target cells through destroying the chemical bonds (producing reactive oxygen species, ROS, which damage DNA) or by directly destroying DNA and the regulatory proteins necessary for DNA repair.[23] The underlying requirement for this treatment to work is the assumption that the healthy cells are more capable at repair than the cancer cells, as DNA damage kills any affected cells, healthy or otherwise.

Chemotherapy involves applying chemicals or drugs to destroy cancer cell, and it has more systemic effects than radiation. There are a variety of chemotherapy drugs which are classified based on their mechanism of action. They include: alkylating agents (damage DNA), anti-metabolites (replace building parts of DNA and RNA), antibiotics (interfere with enzymes needed for replication), topoisomerase inhibitors (prevent unwinding of DNA during replication), mitotic inhibitors (prevent cell division), corticosteroids (relieve side effects of other drugs).[24] Chemotherapy can be helpful in treating cancer cells that have metastasized throughout the body, as the drugs transverse throughout the body during treatment.

Specific Aims

The specific aims of this thesis include:

1. A comprehensive review of literature to characterize the nature and prevalence of depression following cancer remission.

2. An investigation into the current evidence for the pathogenesis of post-remission depression (acknowledging that there are multifactorial causes).

3. An assessment of the interdependent relationship between chronic pain, fatigue, sleep disturbance, cognitive impairment, depression and inflammation especially the relation between cytokine pathways and connections to the innate immune system.

4. A summary of the most appropriate depression intervention options currently available for different survivor populations post-remission.

PUBLISHED STUDIES

Pathogenesis of Post-Remission Depression

In order to explore the pathogenesis of depression in cancer survivors, the various biological mechanisms for the main factors linked to post-remission depression will be explored; these include chronic pain syndrome, fatigue, sleep disruption and cognitive impairment. When exploring these factors, the biological mechanisms of certain cancers and cancer treatments that are associated with depression will also be addressed. In particular, the link between depression and inflammation will be highlighted, especially the biological mechanisms of certain cytokine pathways and connections to the innate immune system.

Chronic Pain Syndrome in Cancer Survivors

The prevalence of pain in cancer survivors varies based on the type of cancer, the presence of comorbidities, and initial pain management. A report from the ACS found that 34.6% of cancer survivors reported having chronic pain and 16% of survivors reported having high-impact chronic pain (HICP, chronic pain with significant activity restrictions).[25] There was a noted increase in pain levels generally based on lower levels of education and income, and among survivors of bone, kidney, throat and uterine cancers.[25] Pain in cancer patients typically arises due to the disease or treatment, however there are some cases where pain can arise in muscles or connective tissue. In these cases, inactivity and deconditioning can predispose the patient to chronic pain, because fatigued patients are more at risk for muscle injuries.[27] Collecting a detailed patient history to figure out the potential cause of the survivor's chronic pain can be helpful in determining pain management strategies.

Pain in survivors can be initially caused by the tumor itself and persist into their remission period. The direct invasion of the tumor into tissue or bone can cause nociceptive somatic and visceral pain.[27] Peripheral neuropathies can be caused directly by the tumor itself if it is present within the nervous system, like brain or spinal tumors. However, most types of persistent pain in survivors are not due to the cancer itself but can be linked to cancer treatments. Chemotherapy can cause chemotherapy-induced peripheral neuropathy (CIPN, damage to the peripheral nerves that can cause weakness, numbness, and pain in extremities). Ionizing radiation therapy can lead to late effect radiation toxicity, and surgical intervention can cause persisting pain syndromes.[28] Understanding these long-term side effects could help oncologists and cancer patients make educated decisions about the different types of treatments.

As cancer is evolving into chronic illness, managing chronic pain in survivors has become a serious concern for patients who now face months, years or potentially a lifetime of coping with chronic pain. Optimizing pain control and maintaining or improving the patient's functioning is the main goal. Patients struggling with pain management report having more financial difficulties, decreased QOL (due to an increase in health and financial burdens) and report more symptoms mood disorders, like depression.[29] Pain management should be assessed throughout a patient's remission period in order to provide them with resources should late-effect symptoms develop.

Most research about chronic pain experienced by cancer survivors centers around CIPN. CIPN is a common side effect of exposure to the chemotherapeutic agents used for treatment, the degrees of incidence range from 10% to 100% depending on the study.[27] The timing of the onset and extent of severity depends on a couple of factors, most importantly comorbidity of conditions such as diabetes, liver insufficiency, and alcohol-related neuropathy or the cotreatment of multiple neurotoxic agents during therapy.[27] The persistency of symptoms varies on the type of agent used as well as the dosage, with no guarantee that with cessation of treatment there will be a resolution of the pain. Posttreatment painful peripheral neuropathy has been linked in current research to the use of the following agents, vincristine, platinum, taxanes, thalidomide, and bortezomib.[30] The pathophysiology of CIPN varies upon the agent, however typically the underlying mechanism is predominately sensory across most cases, with motor nerve involvement noted as being less common.[28] These antineoplastic agents interfere with neuronal functioning by affected peripheral nerve structures, as they preferentially accumulate and bind in the dorsal root ganglion.[31] Understanding the biological mechanisms behind these negative side effects can help physicians make decisions about the length of such cancer treatments and screen for patients who might be more at risk because of the agents used in their treatment.

Both neuronal and non-neuronal cells play a role in the pathogenesis of CIPN. Macrophages and T-lymphocytes can communicate with neurons and Schwann cells through the release of cytokines, allowing for neuron-immune system communication. Cell dysfunction and the increased activation of macrophages can lead to abnormal cellular signaling changing the expression of genes and mediators (such as the pro-inflammatory cytokines listed in Table 2) that are linked to pain and apoptosis. Understanding which cytokines have a demonstrated connection to CIPN is essential as other symptoms of depression such as fatigue and cognitive impairment also have connections to these pro-inflammatory mediators.

Table 2: Pro-inflammatory Mediators Linked to Chemotherapy-Induced Peripheral Neuropathy
Abbreviations: Chemotherapy-Induced Peripheral Neuropathy (CIPN), Tumor Necrosis Factor (TNF), Interleukin (IL). Table taken from Wang, 2012 [31]

Mediators	Connection
TNF-α, IL-1β, IL-6	When Schwann cells undergo phenotype modulation, they can release these cytokines which induce macrophage infiltration and neuroinflammation.[32] Schwann cells control demyelination by degrading myelin through a matrix metalloproteinase dependent pathway which can promote macrophage recruitment and activation.[33, 34]
TNF- α, IL-1β	Can stimulate sensitive A- and C- fibers, which can cause unprompted discharges which are related to allodynia (pain to stimuli that does not typically cause pain, such as light touch) and hyperalgesia (increased sensitivity to pain).[35]
TNF- α, IL-1β	These cytokines can induce action potentials to discharge by increasing the Na^+ and Ca^{2+} concentrations at the nociceptor peripheral terminals. An increase in these concentrations causes increased excitability in the membrane thus reducing the pain threshold.[35,36,37]

Chemotherapy is not the only cancer treatment that can lead to chronic pain syndrome in survivors; a less researched area is chronic pain following radiation treatment. Chronic pain can be caused by certain side effects following radiotherapy, and these side effects can be classified as acute (occurring within a few weeks following completion of a course of radiotherapy) or late (occurring 90 days following treatment, potentially lasting multiple years). Recently focus on the late effects has been accentuated as the average cancer survivor's life expectancy is increasing, and because while the early effects tend to resolve, the late effects are often irreversible or are demonstrated to progress in severity overtime.[38] Late side effects that can appear during remission appear to be caused by the inflammatory reactions that follow the regional damage to tissue during the initial stages of the therapy. These reactions can cause fibrosis and atrophy in tissues, even vessels or nerves which can cause nerve damage. This nerve damage can lead to pain that develops after cessation of therapy, which can in some cases persist for the duration of a survivor's life.

Even though avoiding non-cancerous tissues is high priority for oncologists during radiotherapy, there is evidence that even cells which are not directly impacted by the ionizing radiation can still be negatively impacted. An indirect mechanism of collateral damage can be induced in cells neighboring the irradiated cells called radiation induced bystander effects (RIBEs). These neighboring cells can then undergo harmful cellular processes, which can alter gene expression, causing damage to the mitochondria or increasing cell apoptosis through intracellular ROS levels.[28] This can help eliminate surrounding cancerous tissue without having to directly target it, but it can also be harmful to surrounding healthy tissue. It is difficult with radiotherapy, to find a balance between the therapeutic benefits and the resulting toxicity. Oncologists have to weigh the costs of extending therapy to ensure the cancer is gone against the potential late-effect symptoms that could develop due to a lengthier treatment plan.

Another significant side effect of radiotherapy is the development of fibrosis, this is induced during the period before the onset of late effect symptoms, during which there is a biological response at the cell and tissue level. The activation of cytokine cascades occurs during an intermediate phase after the appearance of the early effects, and before the late effects which can induce fibrogenesis. The early effects of radiotherapy include DNA damage response, apoptosis and necrosis, and these all occur within minutes to several days following irradiation. During this time period some healthy fibroblasts die, and some become epigenetically remodeled fibroblasts, but these effects typically resolve quickly following treatment. In the days to weeks following radiotherapy the intermediate effects occur, including tissue regeneration, inflammation, mutagenesis and RIBEs. These intermediate effects are typically silent (presenting few to no symptoms) taking place during the "latent period" experienced by the patient; during this time some fibroblasts develop into fibrotic myofibroblasts. Most chronic pain begins months to years after treatment when the fibrotic myofibroblasts produced in the months following treatment produce an aberrant extracellular matrix (ECM) accumulation causing late symptoms such as fibrosis and organ failure.[39] Preventative measures can reduce the formation of fibrotic tissues, but research should also be conducted on which treatments are best for patients who are already living with these restrictions.

Fibrogenesis occurs and excessive amounts of extracellular matrix and collagen are deposited during the body's misguided wound healing response, and this biological mechanism can cause serious pain for survivors. If the fibrosis is occurring in the gut mucosa, ischemia can occur due to vascular sclerosis causing chronic abdominal pain due to gut dysmotility or obstruction.[28] This particular fibrotic process begins with a localized inflammatory pathway that is stimulated by the reactive oxygen and nitrogen species generated by the radiotherapy. The primary mediator for this biological response is transforming growth factor beta (TGF-β).[40] Typically TGF-β is released from local platelet cells and generated by inflammatory cells at the beginning of an immune response in order to resolve inflammation and promote tissue repair. However, in cases with unresolved inflammation, levels of TGF-β can rise too high leading to the development of fibrosis. This process can be compounded due to the dose of radiotherapy, amount of tissue treated, prolongation of therapy or concurrent treatment of chemotherapy. This highlights a need for more research in order to scale back treatment when possible or identify survivors who are at a higher risk for developing chronic pain.

Another cause of pain in cancer survivors is chronic post-surgical pain (CPSP). CPSP is defined as pain present for more than 2 to 3 months following surgery, not including surgical or pre-existing pain or continuing malignancy or chronic infection.[41] The risk of developing CPSP depends on the type of operation and surgical technique. Persistent postsurgical pain has been noted as clinically relevant for 10-50% of patients undergoing common operations, including surgical treatment for breast cancer.[42] The mechanisms of CPSP are complex and not thoroughly researched or understood, many of the syndromes are believed to be neuropathic and related to changes in the nervous system.

Psychological and emotional distress are common in people with chronic pain, appearing in approximately 90% of adult patients with chronic pain symptoms.[43]

Anxiety, depression and PTSD are the most common psychiatric disorders comorbid with chronic pain, and patients with these comorbidities report having significantly more functional limits which can contribute to further depressive disorders.[43] Current research indicates a clear connection between pain syndromes and depression, noting that patients with pain syndromes are at a two-fold risk for developing coexisting depression. This association only strengthens with an increase in severity of either condition.[44] Appropriate management or treatment of an underlying pain syndrome can be helpful in treating survivors diagnosed with depression.

Fatigue and Sleep Disturbance in Cancer Survivors

Fatigue is one important somatic symptom needed to meet the diagnostic criteria for MDD (Table 1) and is prevalent within the survivor population. There are several factors that contribute to the symptom burden of CRF including the direct effects of the tumor, treatment-related effects (due to chemotherapy, radiotherapy, surgery, other medications), and comorbidities (malnutrition, infection, depression, anxiety) (Figure 2).[45] Studies of long-term cancer survivors indicate that approximately 25-33% patients have fatigue that persists up to 10 years after their initial cancer diagnosis.[16] Clinically relevant levels of CRF were found to be present in 29% of cancer survivors for up to 6 years following treatment, and the presence of CRF was associated with high levels of disability.[46] Current research indicates that up to 66% of patient with depression present with symptoms of fatigue such as low energy and listlessness.[47] This makes sense as, fatigue and depression conditions have significant overlap in symptom and cause of development, research suggests that they may contain similar underlying mechanisms as well.[48]

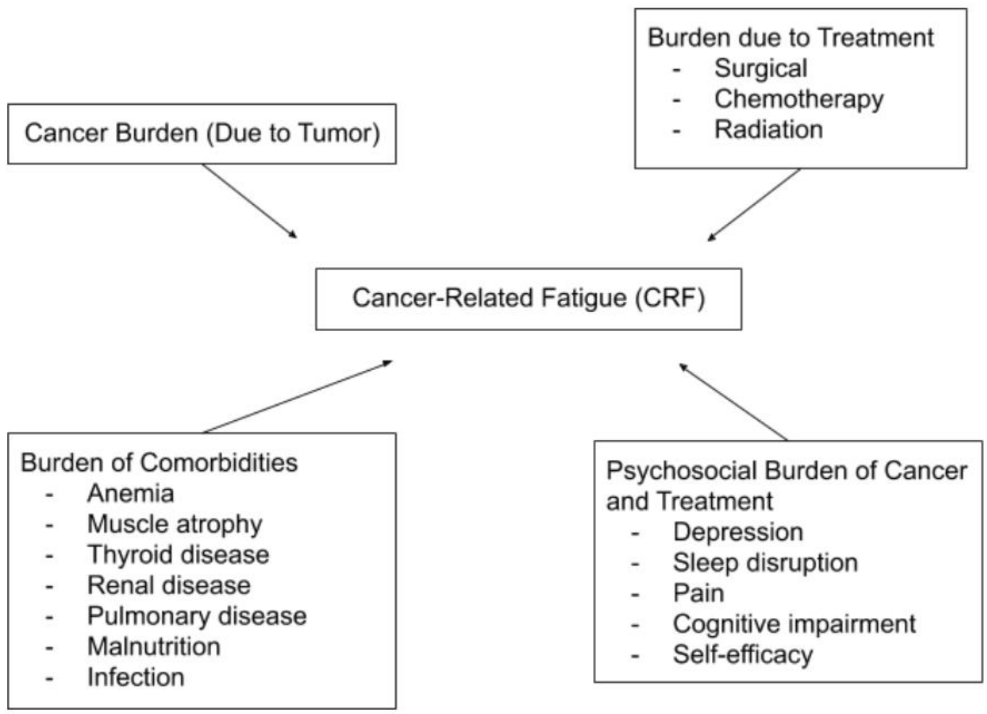

Figure 2. Multiple Aspects of Cancer Related Fatigue. Cancer related fatigue (CRF) is a broad term that covers fatigue symptoms caused by a varies of possible sources. In the figure above only the late effects of the cancer treatment burden and the psychosocial burdens associated with cancer and its subsequent treatment will be explored. In order to identify CRF in cancer survivors, patients should be screened frequently, and physicians should collect a detailed patient history on potential contributing factors and comorbidities to determine the best course of treatment. Figure taken from Wang, 2012 [45]

The central theory on fatigue suggests that CRF develops in the brain and spinal cord, also known as “central fatigue”, defined as difficulty initiating or maintaining voluntary activity, manifesting in an inability to complete tasks requiring self-motivation (for example, “I feel exhausted all the time”).[49] Peripheral fatigue is the decline in physical performance due to inadequate functioning, either cardiorespiratory, metabolic or physiological (for example, “I get tired while exercising”).[50] Both types of fatigue have been reported in cancer patients and survivors, and they can be distinguished using both patient-reported and physician-reported measures. It is especially important to identify the type of fatigue before considering treatment options. To determine the most effective pharmacological approach to the problem, scientists have been studying the possible biological factors that contribute to the symptoms of CRF. Several studies support a strong connection between proinflammatory cytokines and CRF, suggesting that elevated cytokines could be potential contributors to CRF symptoms, although it should be acknowledged that there are many different theories about biological mechanisms that could lead to CRF. [50]

Studies into possible connections between fatigue and inflammation have yielded some avenues for future research in cancer survivors suffering from CRF. Elevated cytokine level, especially tumor necrosis factor alpha (TNF- α), are often observed in research studies on fatigue promoting medical conditions.[51] Additionally, fatigued survivors have demonstrated elevated functional cytokine response (greater production of interleukin 6 (IL-6) and TNF-α) in research studies, when compared to their control counterparts.[52] Activation of such proinflammatory cytokine networks by tumors or their subsequent treatment can lead to symptoms of fatigue in survivors through signaling in the central nervous system (CNS). In animal studies, the cytokine TNF-α lead to an increase in non-rapid eye movement (NREM) and a decrease in rapid eye movement (REM) sleep, and the cytokine IL-6 was noted to produce fragmented sleep, leading to fatigue symptoms.[53] It is possible that activation of the innate immune system can influence CNS functions including neurotransmitter metabolism, behavior, sleep-wake cycles, and regional brain activity.[54] Negatively impacting these CNS functions can lead to fatigue, sleep disturbance and other factors that can lead to depressive mood symptoms. In research studies, activation of pro-inflammatory cytokines has demonstrated a connection to increases in depressive mood symptoms,[55] while a pharmacological block of such inflammatory activity improved sleep and reduced severity of depressive mood symptoms.[56,57] This inflammatory response can persist following treatment as the patient's body attempts to deal with alterations in cytokine homeostasis and possible continued pathogenesis. Although there are correlations between patients diagnosed with CRF and increased levels of specific proinflammatory cytokines, the biological mechanism of causation is less clear.

Fatigue and depression have also been strongly correlated with sleep disturbances such as insomnia. Although reports of sleep problems decrease in cancer patients as they go into remission, 51% of long-term cancer survivors report high sleep disturbance and a subset of 20% of survivors still report poor sleep quality 9 years after being diagnosed.[58] General sleep disruptions are usually evaluated as one of the components of a cluster of symptoms including depression and fatigue. Insomnia is a specific kind of sleep disruption, identified by difficulty falling asleep and staying asleep or nonrestorative sleep. Even within the general population, insomnia and other sleep disruptions are associated with lower QOL, an increase in the number of accidents and days spent in bed with decreased activity.[59] Several research studies note insomnia as a risk factor for new-onset or recurrent depression across patients of all ages. The comorbidity of depression and sleep disturbance can also impact the trajectory of a patient's depression negatively affecting episode severity, duration and/or relapse rates.[60] Most important, early treatment of CRF is important as elevated levels of fatigue predict shorter periods of recurrence-free survival and a decrease in life expectance.[61]

Cognitive Impairment in Cancer Survivors

Cancer-related cognitive impairment (CRCI) in survivors is not limited to chemotherapy or central nervous system cancers. There are many cognitive deficits that can result from the tumor itself, the type or treatment and/or psychological consideration present before a cancer diagnosis. These deficits may negatively impact survivors' QOL regarding their ability to return to work, maintain social relationships, remain self-confident or keep their autonomy.[62] According to longitudinal studies in cancer patients, up to 30% of patients have experienced CRCI and up to 35% have experienced CRCI in the months or years following remission.[63] CRCI can vary in symptoms from subtle to dramatic, it can be temporary or persistent, and stable or progressive. It was first reported as phenomena linked to chemotherapy treatments, however more current research has investigated the associations between radiation therapy and hormonal therapies and CRCI. CRCI is a broad term that covers many subclusters of cognitive impairment, such as memory, executive functioning, motor dexterity, retention and consolidation of memory, working memory, attention and psychomotor speed.

Several research studies have reported associations between cytokines and cognitive impairment in cancer patients, such as notably high levels of inflammatory factors in cancer patients before, during and up to 5 years following the start of their treatment.[64,65,66] Specific cytokines, such as IL-6 and TNF-α have been associated with diminished verbal memory 5 years following treatment.[67] However, these studies have not determined if the relationship between inflammation and cognitive impairment is a causal link. There are proposed theories for the link between the two, and it is possible that inflammation could induce chromosomal instability and epigenetic changes that could explain long-term cognitive deficits. Pro-inflammatory cytokines could cross the blood-brain barrier and then induce a release of local cytokines that could cause neurotransmitter dysregulation, oxidative stress and decreased neuroplasticity and/or neurogenesis.[67] It's also possible that inflammation could induce epigenetic changes and/or chromosomal instability leading to persisting cognitive problems. Most research on CRCI has been focused on finding what populations of cancer patients or survivors are most at risk and what contributing factors could be (Figure 3), but survivors could benefit from research on treatments that target the underlying biological mechanism.

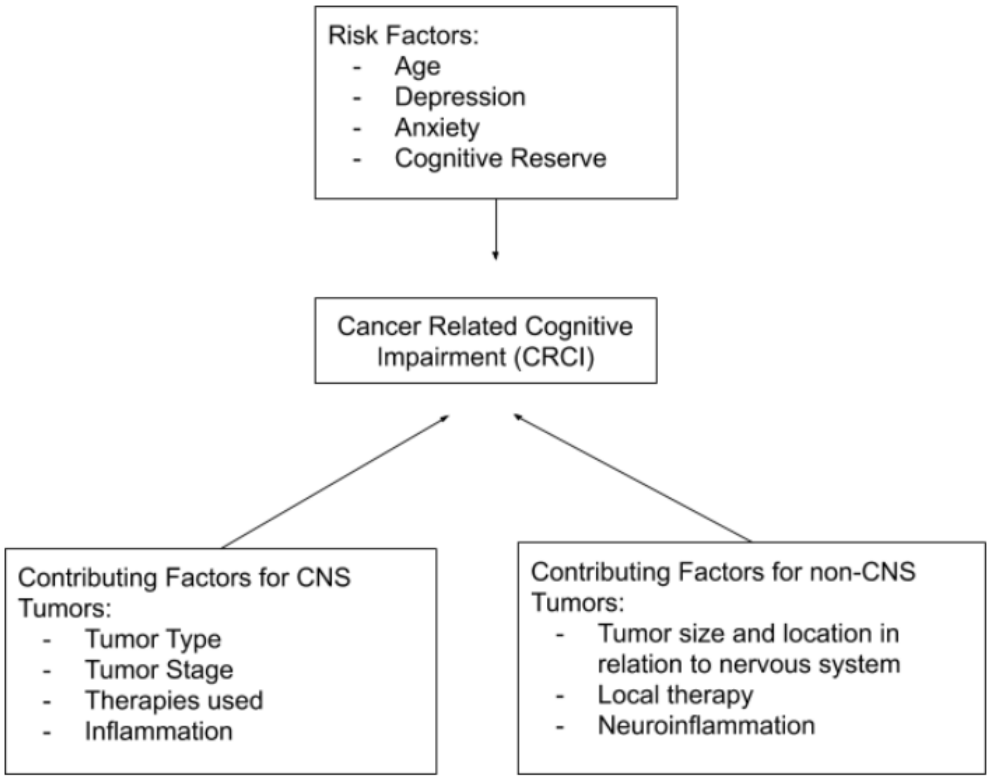

Figure 3. Risk Factors and Contributing Factors for Cancer Related Cognitive Impairment (CRCI). Research on CRCI has focused on discovering the contributing factors for CRCI in an attempt to determine future methods of treatment as currently there is no common standard of care for clinical management. Treatment of CRCI should be adjusted based on whether the tumor originates in the CNS or not. Research indicates that in CNS cancers, the tumor itself causes most of the damage, while in non-CNS tumors, patient often have cognitive decline linked to their treatment modalities. Figure taken from Janelsins, *et al*. 2014 [63]

There is minimal research on whether the underlying pathogenesis of cognitive impairment continues following the cessation of treatment and remission in survivors. Researchers are unsure whether the cognitive impairments that occur due to the cancer or cancer treatments are reversible; current studies are exploring what could happen if the inflammation levels are lowered. When considering how to treat cognitive impairment as a possible cause of depression in survivors, oncologists should take preventative measure in the initial course of therapy to reduce the risks of impairment. This could reduce one of the factors that could contribute to post-remission depression. Before, during and after treatments, cognitive assessments should be performed not only to collect research on the side effects of certain treatments, but also to curtail or adjust certain treatments that may lead to poorer QOL for the survivor.

Association between Depression and Inflammation in Cancer Survivors

Cancer survivors suffer from several symptoms as a result of the cancerous tumor itself and/or from the treatment they receive for that tumor. These symptoms can cause treatment delays, premature termination of treatment, or impair functional abilities causing significant distress, if unchecked they can potentially lead to depression. There is ongoing research on possible biological mechanisms that underlie or contribute to the development of some of these symptoms simultaneously. Several theories note that systemic inflammation caused by tumor-host interactions could cause some of the symptom clusters that underlie depression in survivors.

Symptoms caused by systemic inflammation in humans are similar to “sickness behavior”, the physiological and behavioral responses demonstrated in animals after they are administered proinflammatory cytokines.[68] Additional human research indicates connections between proinflammatory cytokines and somatic symptoms; in one study symptoms were assessed over a 12-week period in melanoma patients being treated with interferon-alpha (INF-α) as an immunotherapy option. Within 2 weeks patients experienced fatigue, wasting, and pain, and later in the study patient began to experience symptoms of depression and cognitive impairment. Because of the associated symptoms, patients were also randomized to receive a selective serotonin reuptake inhibitor antidepressant or a placebo two weeks before the start of the treatment. Patients taking antidepressants demonstrated an improvement in symptoms, and a decrease in the severity of the pain, cognitive impairment and depressive symptoms they exhibited. Wasting and fatigue symptoms however, improved to a lesser degree.[68] Studies on the impacts of cytokines on humans' emotional and cognitive functioning are very limited because most studies occur in populations of severely ill patients, calling into question the interference of other preexisting medical conditions, and the dose necessary to induce symptoms could compromise the cognitive performance or emotional wellbeing of the study's participants. Evidence from the existing studies suggest that inflammatory cytokines TNF-α, IL-1 and IL-6 can mediate this "sickness behavior",[69] although future research is necessary to determine if this is a casual relationship.

In healthy individuals, cytokines provide homeostasis and manage immune system control through positive and negative feedback mechanisms within the innate portion of the immune system. There is a balance between pro-inflammatory cytokines and anti-inflammatory cytokines that can be altered by the tumor-host interactions in cancer; in studies of advanced cancer patients the pro-inflammatory cytokines seem to predominate.[70] Cytokines IL-6 and TNF are reported to induce synthesis of C-reaction protein (CRP), which can be measured as a marker of systemic inflammation.[71] CRP could potentially be used to identify patients with inflammation-associated depression, should a causal link be identified. The inflammatory process can be stimulated when tissues are destroyed either by the tumor or by the treatment method. Tissue damage causes damage-associated molecule patterns (DAMPs) to form on the injured tissues, which can then bind onto pattern recognition receptors (PRRs) on leukocytes, such as macrophages, and activate the production of cytokines (Figure 4).

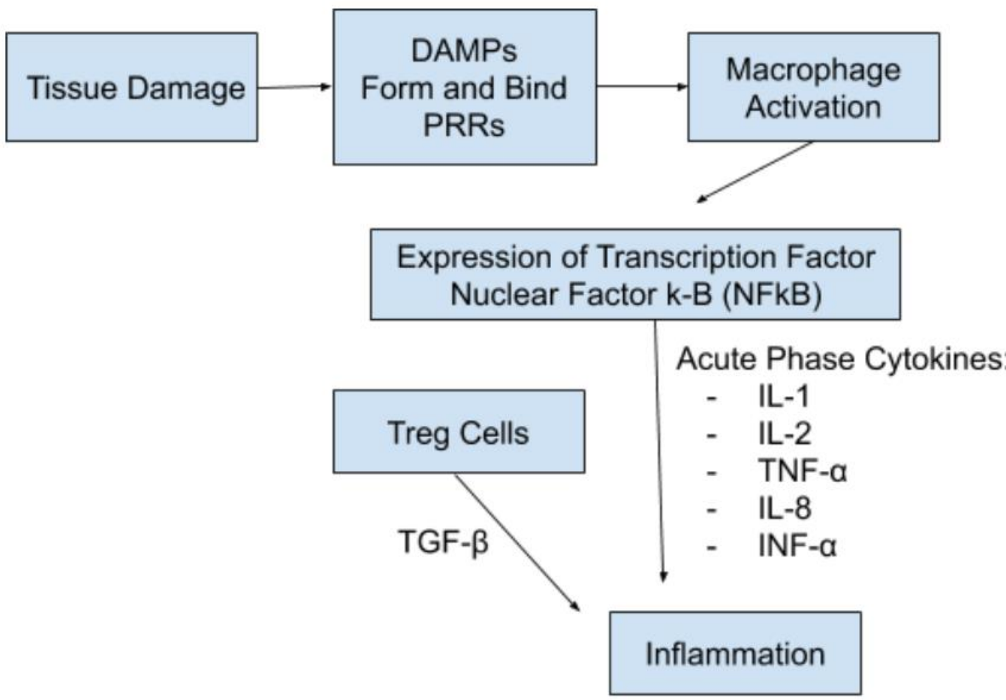

Figure 4. Inflammation and Cytokines Related to Tissue Damage in Cancer Survivors. Research on the biological mechanisms that underlie inflammation in cancer patients could help scientists develop pharmacological treatments to help reduce the symptoms that survivors experience. Current literature suggests that inflammation persists in survivors after the cessation of treatment, treating that inflammation by blocking part of the pathway may leads to a reduction in some of the symptoms that survivors experience. Figure taken from Bierhaus, 2003.[73]

Factors other than tissues damage can contribute to the development of inflammation. For example, ionizing radiation and some chemotherapeutic agents have demonstrated the ability to directly stimulate NFκβ independently of any tissue damage which can further increase the expression of cytokines.[72] Additionally, research shows that healthy patients who underwent a stress test demonstrated increased NFκβ expression.[73] In other research studies, TNF-α has been observed to increase the activity and expression of serotonin and noradrenaline reuptake transporters.[74] This causes a lower concentration of serotonin and noradrenaline at the synapses, which has been linked to depressive behaviors.[75] It is important to understand these pathways of inflammation when considering treatment options for depression as these cytokines have been linked to biological mechanisms that could lead to symptoms linked to depression.

Proinflammatory cytokines have also been shown to increase the secretion of corticotrophin releasing hormone (CRH), which can cause behavioral changes. Clinical studies have provided evidence that frequent alterations in regulating stress hormones, such as elevated secretions of CRH, can cause anxiety- and depressive-like symptoms.[76] In animal studies, INF-α has been shown to decrease concentrations of dopamine (DA), by reducing the expression of DA receptors, the release of striatal DA and the conversion of phenylalanine to tyrosine (which reduces formation of DA downstream in the brain).[74] Decreased DA levels can lead to feelings of anhedonia and other depressive symptoms, demonstrating a possible link between these pro-inflammatory mediators and depression.[77] Other pro-inflammatory cytokines, such as TNF-α, have also been shown to cause a decrease in DA concentration, through activation of an enzyme known as indolamine-2,3-dioxygenase (IDO), which can degrade tryptophan (a precursor for serotonin), leading to depressive symptoms.[78] In addition to decreasing levels of serotonin, IDO can also stimulate the release of catabolites that are proinflammatory and neurodegenerative to brain tissue. The effects of these catabolites, particularly on the hippocampus, have been linked to the development of depression.[79] These connections are important to keep in mind throughout the thesis as the cluster and somatic symptoms of depression are listed and connected to inflammation through various proinflammatory cytokines. Identifying how depressive symptoms can be associated to inflammation can provide researchers with new treatment ideas to explore.

DISCUSSION

Treatment of Symptoms Clustered with Depression in Cancer Survivors

Chronic Pain Syndrome

Depression has many different contributing factors (listed in Figure 1) and some of the somatic symptoms, such as chronic pain can be linked to certain cancer treatment options, such as chemotherapy, radiotherapy and surgery. While there are options for mitigating chronic pain for patients in remission, oncologists should also consider what groups are at high risk for the development of chronic pain syndrome and what options there are for preventing the development of such symptoms. Physicians should review a plan with patients prior to starting treatment and discuss how they will modify the dosing of certain neurotoxic agents if symptoms begin to interfere with the patient's ability to complete daily activities or lead to decreases in their QOL. Furthermore, patients that are older in age, and have a history of pre-existing neuropathy, diabetes or alcoholism, or have had a more than average number of chemotherapy cycles, are more at risk for development of CIPN.[80] Knowing these risk factors can help health professionals educate patients about the symptoms they may develop and introduce more regular assessments for the development of these symptoms to prevent future impacts on patients' QOL.

The possible causes of CIPN have already been discussed, as chemotherapeutic agents are believed to accumulate in the dorsal root ganglion (DRG) of neurons and nerve terminals, some therapies are focusing on nerve-protection. Erythropoietin (EPO) is a cytokine produced in the kidneys that functions to regulate hematopoiesis. EPO in animal studies has been shown to enhance nerve regeneration and promote function recovery following injuries to peripheral nerves.[81] These neuroprotective and neurotrophic properties signify it may be beneficial in the treatment of CIPN. EPO is already currently being used as a treatment for anemia in cancer patients undergoing chemotherapy (specifically paclitaxel and cisplatin), and it has proposed that EPO be used as a co-treatment to potentially prevent or reverse the neurotoxic effects of the treatment.[82] However, more research needs to be conducted on this topic because in some studies, recombinant EPO has been associated with tumor progression.[83] Other nerve-protective treatments include N-acetylcysteine and glutathione for platinum based treatments; N-acetylcysteine is an antioxidant which increases the blood concentration of glutathione. Glutathione can prevent the accumulation of platinum in DRG because it has a high affinity for heavy metals.[84] This seems to be a promising area of research for preventing the development of neurotoxicity. When researching this antioxidant drug, scientists should consider whether it will decrease the effects of platinum-based chemotherapies on treatment of cancerous tumors.

There are ion channel-targeted therapies that are being explored as well; this is because chemotherapeutic drugs can result in reduced thresholds for excitability in peripheral nociceptors (Table 2).[35] Treatments for the inflammation that could cause this reduction in threshold will be discussed in the next paragraph, but there are ways to treat CIPN at the level of the ion channels as well. Mexiletine is a compound that is known to block sodium channels, its testing in animals has suggested that it can reverse the effects of allodynia caused by oxaliplatin and vincristine.[85] Other options include calcium and magnesium infusions, it was proposed that oxalate can metabolize from oxaliplatin and cause neurotoxicity by chelating with calcium and magnesium, potentially causing neurotoxicity.[86] Calcium and magnesium are necessary for the functioning of the ion channels in nerve membranes, and so these infusions were presumed to theoretically prevent or decrease the severity of oxaliplatin-induced neurotoxicity. There have been mixed results on whether an infusion of calcium and magnesium before a chemotherapy treatment reduced the symptoms of CIPN compared to the placebo, so the utility of such treatment needs to be explored further.[87,88] Most of these options are still in research stages and should only be considered as future, potential treatments.

In the published literature section, Table 2 focuses on associations between specific pro-inflammatory mediators and biological mechanisms that can lead to the symptoms of CIPN. The focus was placed on potential connections between inflammation and CIPN as inflammation has been noted to possibly underlie many of the cluster and somatic symptoms associated with depression. There are some drugs that are being explored for their anti-inflammatory properties, for example, Metformin which is typically used to treat diabetes. Recently an assessment of the intraperitoneal administrations of metformin demonstrated prevention of mechanical allodynia and numbness in mice treated with cisplatin.[89] Metformin is believed to activate the adenosine monophosphate activated protein kinase (AMPK) pathway, and activation of AMPK is believed to inhibit nociceptive progress by inhibiting the mammalian target of rapamycin (mTOR) pathway. Metformin also acts in an anti-inflammatory manner by decreasing pro-inflammatory mediators, such as TNFα and IL-6 cytokines, and suppressing macrophage response (Table 2).[84] There is another anti-inflammatory drug being explored called minocycline; it works by inhibiting monocyte activation and therefore decreasing pro-inflammatory cytokine release.[90] Minocycline has been shown to prevent mechanical sensitivity following administration of certain chemotherapeutic agents in animals.[91] This may be the best possible research pathway forward as minocycline has exhibited anti-inflammatory and anti-apoptotic properties as well as anti-tumorigenic potential.[84]

There are very few clinical trials for treatments of radiation-induced neuropathies, and the exact biological mechanism for the development of these chronic pain syndromes is unknown. Preventative measures include, reducing the dose and volume of radiotherapy when possible, and identifying patients that have serious comorbidities. Most treatment options are based on treating symptoms, because no definitive curative strategies have been presented. In survivors who underwent radiation treatment and developed chronic pain syndrome, systemic administration of local anesthetics has been explored.[92] Pain can be treated pharmacologically with non-opioid anti-inflammatories, muscle relaxers (such as benzodiazepines for paresthesia), or membrane-stabilizing drugs (that can reduce nerve hyperexcitability).[93] Topical medications like corticosteroids can help control acute inflammation associated with radiation induced fibrosis, although it does little to reduce the fibrosis itself.

Reducing stimuli that could increase the progression of radiation induced chronic pain is also helpful. Steps include, working with patients to control their diabetes or high blood pressure or discontinue alcohol abuse, avoiding medications that are fibrogenic or drugs that could cause potential neuromuscular toxicity (statins), as well as avoiding local trauma from new surgeries.[93] Physical therapy is also recommended to maintain function and prevent joint stiffness which can cause pain or lead to activity limitation which can cause muscle atrophy from disuse. There have been no definitive studies determining a causality relationship between CIPN, psychological distress and fatigue, however studies recommend quick clinical interventions for survivors with high CIPN as they report clinically relevant higher levels of fatigue.[82] Current research also notes that patients with CIPN who experience fatigue should be screened for psychological distress as CIPN survivors comorbid with anxiety and depression tend to report the most fatigue.[82]

Treating the Somatic Symptoms of Depression

In Table 1 the diagnostic criteria for MDD are listed. Of the nine listed standards, sleep disturbances, fatigue and diminished ability to concentrate (as related to CRCI) will be discussed, listing possible treatment options for each somatic symptom.

Fatigue and Sleep Disturbances

Cancer survivors that experience CRF are often told by physicians to adjust to changes in their functional ability by limiting activities to conserve energy and relying on others when possible to complete activities they cannot.[94] However, recent research indicates the exact opposite may be better, cancer survivors that engage in regular exercise experience physical and mental benefits that reduce symptoms of CRF. The benefits include increased functional capacity, diminished depression, and improved QOL.[95] Yoga therapy has been tried with breast cancer survivors, with a noted improvement in fatigue and vigor.[96] Multicomponent changes in physical activity have been reported to improve fatigue and depressive symptoms immediately after starting such interventions and in the 3 months following intervention.[97] Exercise programs should be adjusted and personalized by physicians or medical researchers for each survivor on the basis of their health status, the treatment that they received, their target health outcome and their disease trajectory.

According to Figure 2 there are multiple causes of CRF, it is possible that the recommended exercise that seems to alleviate the symptoms of CRF could be addressing the underlying symptoms of CRF including depression, pain and/or sleep disturbance since they are all interrelated. While most clinicians focus on treating the comorbidities or contributing factors associated with CRF (listed in Figure 2) using pharmacological interventions (antidepressants, steroids, benzodiazepines), many cancer patients still experience CRF even after successful clinical treatment.[98] Therefore, nonpharmacologic behavioral interventions should be considered, including exercise, meditation, nutrition, and sleep therapy.

Considering the associations between inflammation and CRF (page 21-22), research on pharmacological treatments should be explored, including cytokine antagonists, anti-inflammatories and other drugs that can inhibit cytokine signaling. One trial in cancer patients receiving chemotherapy demonstrated that a TNF-α-blockade was able to reduce symptoms of CRF.[99] Future clinical research studies should monitor specific inflammatory biomarkers in order to optimize records on treatment response characteristics. Given the connections between psychological stresses and inflammatory mechanisms, cognitive behavioral therapies (CBT) should also be considered if the goal is to treat inflammation as an underlying cause of CRF. CBT typically teaches patients how to overcome maladaptive thought patterns and allows them to explore emotional readjustment.[100] Research on behavioral coping mechanisms such as relaxation training, emotional regulation skills and establishment of healthy sleep-wake habits could help reduce psychological stressor that contribute to depression.[53] A study in patients with an underlying inflammatory condition, noted that emotional regulation therapy (which includes mindfulness practices) was more effective at improving depressive mood outcomes than CBT (which included exercises designed to restructure dysfunctional thought).[101] In the study, benefits in the levels of proinflammatory cytokines were seen after 16 weeks in patients who had an improvement in depression symptoms. So, therapies outside of the more traditionally recommended CBT should be considered when treating survivors with diverse needs.

Cognitive Impairment

Usually in clinical management of CRCI physicians begin with nonpharmacologic interventions, such as occupational therapy, cognitive rehabilitation, instruction on coping strategies or behavioral modification, and mindfulness exercises. Some research studies on the effectiveness of attention retraining and instruction on compensatory strategies have demonstrated promise in addressing complaints about cognitive functioning and mental fatigue in patients with cancer.[102] It is important to address CRCI using all available resource, including if possible, access to psychologists, occupational specialists and/or speech and language pathologies to fully support diverse survivor needs. Survivors who have this kind of multidisciplinary support demonstrate improved independence and employment outcomes.[103]

Other pharmacological treatments can be recommended by physicians, for patients actively undergoing chemotherapy, psychostimulants can be prescribed to treat the neurotoxic fatigue and negative cognitive side effects.[104] However, these medications are usually only recommended for the limited duration of the patient's chemotherapy, and their ability to improve cognitive functioning in survivors needs to be researched further. One study of breast cancer survivors found that madafinil was able to improve cognitive performance by enhancing attention and memory skills.[105] This should be an area of future research as most studies have identified attention, memory, and information processing as the cognitive domains that are more frequently influenced by cancer and its subsequent treatments.

Addressing Emotional Causes of Depression

In Figure 1, some of the emotional causes of depression are listed, including FCR, grief, identity issues, spiritual concerns, and concerns about family risk and/or body image. When addressing the most prevalent emotional disturbance, FCR, it is important to consider the severity. A moderate level of FCR can be healthy for patients, fostering self-monitoring habits that can help patients identify early symptoms of recurrence. However high levels of FCR can lead to intrusive thoughts, avoidance of any reminders of cancer, hypervigilance and/or increased emotional distress.[106] There are very few evidence-based strategies for treating FCR, some controlled research trials note that “fear of progression” has been shown to decrease significantly in patient test groups that undergo CBT when compared to their no-intervention counterpart.[107] Several studies show the benefits of both individual and group interventions, but there are few studies on internet-based methods, which could benefit survivors that live in rural areas who don’t have easy access to clinicians that are trained in specialized interventions. Additionally, some survivors with FCR may be reluctant to return to a hospital-like setting or may be unable to afford the indirect costs of therapy like taking time or work and traveling.

Identity issues are another emotional struggle cancer survivor may face, especially survivors of childhood cancers. There is evidence that chronic illnesses can negatively affect the formation of a person’s identity, and there are several variables that underlie that formation that should be explored further including adaption to the diagnosis, disease process and treatment and familial or peer support.[108] One explanation for disruption in adolescent identity formation for survivors, is that socialization with peers is important for a child’s development. Survivors likely experienced a limitation to this socialization due to the requirements of their treatment. Although many studies have shown that a strong support system of friends and families can positively benefit survivors and help protect against the development of depression;[109] but not many studies have explored the effect peer support can have on identity formation or prevention against developing depressive symptoms in adolescents.

Another part of a survivor’s identity that can be negatively impacted is their body image following treatment. This has been documented in research on AYA cancer survivors; when asked questions about body image, sexuality and fertility this survivor population reported feeling less attractive than the control group because of their scars and they noted lower satisfaction with their sexual function.[110] There seems to be an unmet need amongst AYA survivors for support and information when reintegrating into their normal social lives during remission. Furthermore, the impact of scarring on body image and self esteem has also been noted in childhood cancer survivors. Surveys have noted that scarring, disfigurement and persisting hair loss have adversely impacted psychological functioning and QOL in survivors.[111] This highlights the importance of having medical practitioners involved in the treatment of childhood cancer be more aware of concerns in order to facilitate interventions such as coping skills and emotional adjustment strategies for patients that are at high risk. Additionally, steps should be taken to minimize scaring during the initial diagnosis and subsequent treatment. Most body image research studies in adult cancer survivors are restricted to breast cancer and face and neck cancer survivors, research should be expanded to consider emotional concerns for a diversity population of survivors.

Addressing Social or Environmental Causes of Depression

Figure 1 lists many of the social concerns that cancer survivors experience including fear regarding financial debts, insurance coverage, and educational and employment opportunities, all of which can be contributing factors for the development of depression. There are many factors that can contribute to financial debts for cancer survivors including, out of pocket medical costs, indirect costs (productivity loss or patient time costs), general medical debt, depletion of assets and bankruptcy. Cancer patients have been noted to have almost four times higher mean expenditures, estimated at around $16,000, per patient than control persons without cancer.[112] There is variation in expense estimates based on the age group, insurance coverage, and service type received by the survivor. Outside of an added medical cost burden, nearly one third of survivors report limitations outside of work and one fourth reporting feeling less productive at work.[113] Reports amongst breast cancer survivors specifically estimates that survivors will have on average 42 total work loss days (a combination of absentee and disability days), translating to ~$8000 (in 2000 US dollars).[113] It is more difficult to estimate the future costs of loss of productivity amongst childhood and AYA cancer survivors.

Insurance coverage is another concern experienced by survivors. One study on childhood cancer survivors noted life insurance discrimination during the initial years following completion of treatment.[114] Health insurance coverage among adult survivors of cancer generally is comparable to that of adults in the control population, but survivors are more likely to have public insurance. Research shows that survivors who are uninsured or publicly insured are more likely to delay or miss medical care due to the cost burden, with 20.9% of survivors reporting delaying or missing care; that number increases to 68% for survivors without insurance.[115] Missing or delaying necessary medical care can lead to adverse health outcomes for patients.

It is essential that medical practitioners put high risk patients in touch with the hospital's billing department to see if they are eligible for any financial assistance.

Furthermore, patient should have assistance with understanding what treatments are covered by their insurance, especially features that could address psychosocial costs such as support groups or buddy services and the availability of home health care services for survivors with limited mobility following cancer treatment. It is important for the general population and health care providers to support legislation that ensures high-quality insurance that covers both required and elective cancer treatments and services, there is a need for low co-pays, premium and deductibles to make care more affordable for survivors.

Areas of Future Research

Inflammation has implications in the pathogenesis of multiple conditions including chronic pain, fatigue, sleep disturbances, and cognitive impairment, all of which have been associated with the development of depressive symptoms. A deeper understanding of the nature of inflammation in relation to depression could allow for a more top-down approach to treatment, versus the current method of treating specific symptoms individually. Should a connection between inflammation and depression be established, further research on the pathogenesis of persistent inflammation in cancer survivors, either due to cancer itself or the subsequent therapies, will allow for the development of more effective treatments.

As treatment for depression is an unmet need among cancer survivors, it is important for physicians to constantly screen throughout the remission period, not just for the somatic symptoms and diagnostic criteria of MDD, but also for emotional and social concerns that can increase the patient's risk for development. Although there are no evidence-based interventions for inflammation in the treatment of depression or the cluster symptoms of depression, there are several promising areas of future research. The benefits of exercise, psychosocial and occupational therapies have been noted, as well as the importance of taking preventative measures during initial treatments.

The majority of research on cancer survivors is within the smaller subset of breast cancer survivors. The research field needs to be expanded to include a wide variety of patient histories, including survivors of different cancer types and backgrounds including childhood, AYA and adult survivors. Different groups of survivors are at higher risk for certain emotional or social concerns that an contribute to the development of depressive symptoms. More research on these diverse subgroups could allow physicians to identify survivors who have more risk factors, and allow them to address these concerns with their patients earlier to prevent negative impacts on survivors' health outcomes and QOL.

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CURRICULUM VITAE

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