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Effects Of Chemotherapy-Induced-Peripheral-Neuropathy On Spatiotemporal Gait Parameters And Fall Risk In Cancer Patients After The Completion Of Chemotherapy Drug Treatment

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BY

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Approval of Successful Defense

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Lastly, and most importantly, to my wife, Stephanie Marshall, for her endless love and unwavering support, encouragement, and most notably, her patience. Without her, none of this would have been possible. I Love You.

DEDICATION

To all of those present, past and future, who have been diagnosed with cancer:

We will continue to fight.

"You beat cancer by how you live, why you live and in the manner in which you live"

-Stuart Scott

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ABSTRACT

Background: Cancer patients undergoing chemotherapy often experience chemotherapy-induced-peripheral-neuropathy, which reportedly causes gait disturbances that may increase their risk for falls. Falls are a significant event because they have been linked to serious injuries and disabilities, loss of independence, and increased mortality rates. **Purpose:** The purpose of this study was to assess whether chemotherapy-induced peripheral neuropathy is associated with spatiotemporal gait adaptations in posttreatment adult cancer survivors when compared to healthy, disease-free, age and morphologically matched controls. **Methods:** In a quasi-experimental design, 16 subjects participated in the present study. There were 8 CIPN subjects between the ages of 50–70 years of age who had a histologically confirmed stage 2–3 breast or colorectal cancer diagnosis with a confirmed treatment plan consisting of taxane- or oxaliplatin-based chemotherapy. Controls consisted of 8 age and morphologically matched subjects. The primary outcome consisted of spatiotemporal gait parameters as computed using the GAITRite walkway and software. Secondary outcomes consisted of determining fall risk using the Timed Up & Go test. **Results:** Gait velocity for CIPN patients (110. 75 cm/s, *SD* = 26.79), was significantly slower than gait velocity of the controls (147.79 cm/s, *SD* = 11.69). Step length was significantly shorter for CIPN (53.92 cm, *SD* = 23.55) when compared to the controls (77.15 cm, *SD* = 5.28). Lastly, CIPN participants had a significantly higher TUG Score (12.33 s, SD 6.25) compared to the controls (6.62 s, *SD* = 1.10). **Conclusion:** Cancer patients with CIPN displayed a slower walking velocity and shorter step length compared to healthy age and morphologically matched controls. Additional gait patterns, such as step time, step length, base of support, swing time, single support time, and double support time, were not significantly different. Also, the mean TUG score for CIPN patients were not only significantly greater than

the controls, but were also above the clinical fall risk cut off of 10.7 s, indicating fall risk. While gait speed and step length were the only significant gait variables, as noted in the literature they are key indicator for fall risk.

Chapter I

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is generally classified as a series of neuromuscular symptoms, both sensory and motor in nature, that results from nerve damage caused by the neurotoxic effects of chemotherapy drugs for the treatment of cancer (Park et al., 2013; Visovsky, 2003). It is estimated that at least 30% of patients who receive paclitaxel, docetaxel, bortezomib, thalidomide, or oxaliplatin will develop a degree of chemotherapy-induced peripheral neuropathy. The characteristics of CIPN depend upon the specific chemotherapy agent used, as well as when the agent is introduced in the treatment protocol and the dosage amount (Airley, 2009).

Symptoms of CIPN may be acute, mild or severe, transient or chronic, depending upon the treatment regime and dose of the agents and may manifest in a variety of ways, involving sensory and motor symptoms (Park et al., 2013; Postma & Heimans, 2000; Wilkes, 2007). Sensory signs and symptoms may include numbness, tingling, burning, pain, ataxia, loss of deep tendon reflex, and reduced sense of touch, vibration, and proprioception. Motor symptoms may include weakness, balance disturbances, and difficulty performing fine motor skills and a diminished or absent deep tendon reflex. Motor symptoms are less frequent due to the neurotoxic agent's inability to cross the blood–brain barrier in concentrations significant to cause harm (Bakitas, 2007; Murillo, Cox, & Oholendt, 2008; Park et al., 2013; Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007; Wilkes, 2007). The autonomic system may also be affected, resulting in constipation, urinary retention, sexual dysfunction, and altered blood pressure (Bakitas, 2007; Visovsky et al., 2007; Wilkes, 2007).

Sensory changes in the toes and feet are usually first to be noticed, followed by in the fingers and hands, progressing in a distal–proximal fashion to the ankles and wrist in a stocking-glove manner (Park et al., 2013; Wolf, Barton, Kottschade, Grothey, & Loprinzi, 2008). Chemotherapy-induced peripheral neuropathy symptoms are most commonly distributed in a bilateral and symmetrical pattern. It is not uncommon for CIPN symptoms to intensify after the neurotoxic agent has been discontinued; this is referred to as coasting and is the result of cumulating concentrations of the neurotoxic agent within the body system. In some instances, CIPN symptoms may occur gradually over a prolonged period. But it is not uncommon for CIPN symptoms to appear suddenly and intensely (Wilkes, 2007).

The impact of CIPN varies and, thus, affects patients differently. Cumulatively, CIPN symptoms may negatively alter a patient's ability to perform routine activities, functions, and behaviors. Specifically, patients experiencing CIPN symptoms will often report difficulties such as with sleeping, driving, standing, walking, climbing stairs, balancing, opening containers, holding onto things, cooking, cleaning, flipping pages of paper, wearing certain shoes and jewelry, exercising, and socializing (Speck et al., 2012; Tofthagen, 2010). The most common symptoms reported include burning, muscle aches, and sensitivity to cold (Tofthagen, 2010). Patients with CIPN reported a variety of symptoms in their feet, which included the feelings of "ice cold," "walking on hot coals," and "sandpaper on the bottom of your feet" (Tofthagen, 2010, p. E25).

The exact cause of CIPN remains elusive. However, it is currently understood that chemotherapy agents will often inflict their neurotoxic effects on axons and cell bodies of dorsal root ganglion neurons, resulting in axonal damage, which is characterized by a decrease in intraepidermal nerve fiber density and terminal arbor degeneration (Han & Smith, 2013).

Chemotherapy agents will also exert their toxicity on mitochondria, causing them to become swollen and vacuoled, as well as causing oxidative stress, resulting in inflammation. Pathologically, the dorsal root ganglion neurons and surrounding satellite cells may negatively alter the expression of various ion channels, neurotransmitters, and receptors, as well as exhibit altered gene expression. The mitochondrial dysfunction and IENF loss seem to be directly correlated to presence of pain. Cumulatively, these changes cause various sensory symptoms, such as numbness, tingling, burning, pain, and reduced sense of touch, as well as motor symptoms, such as weakness, balance disturbances, and difficulty performing fine motor skills, as frequently reported by cancer patients undergoing chemotherapy treatment (Bakitas, 2007; Han & Smith, 2013; Murillo et al., 2008; Visovsky et al., 2007; Wilkes, 2007).

Although the mechanism that causes CIPN is not well understood, it is apparent that chemotherapy agents will exert their neurotoxic effects on the body's neurons, which is the basic component of the nervous system, and transmit signals throughout the body. Neurons have three functional classes, which include sensory neurons (also called afferent neurons), motor neurons (also called efferent neurons) and interneurons, which originate and terminate in the brain or spinal cord, acting as connections between axons descending and descending within the brain or spinal cord (Magill & Anderson, 2013). Sensory neurons send neural impulses to the central nervous system (CNS), whereas motor neurons send neural impulses from the CNS to skeletal muscle fibers (Magill & Anderson, 2013).

The peripheral nervous system has three functional divisions, which are the sensory nerves, motor nerves, and the autonomic nerves. The sensory nerves sense touch, pain, temperature, position, and vibration. The motor nerves are responsible for voluntary movement, muscle tone, and coordination (Armstrong, Almadrones, & Gilbert, 2005). The small nerve

fibers are primarily composed of microtubules, which transport proteins throughout the nerve fiber. Large nerve fibers are primarily composed of neurofilaments, which comprise the axon's framework. Sensory nerves terminate at the level of the skin and extend to the dorsal root ganglion, connecting with either the dorsal column via a large fiber or the spinothalamic tract via a small fiber in the spinal cord (Armstrong et al., 2005).

The somatosensory system, which consists of muscle spindles, Golgi tendon organs, joint receptors, and cutaneous receptors, contributes the modulation of spinal pattern generators, modulation of motor commands, and perception and control of movement through sensory information. These sensory neurons provide information about mechanical stimuli, temperature changes, potential damage to the skin, body and limb movement and position, and velocity and muscle activation (Magill & Anderson, 2013; Shumway-Cook & Woollacott, 2012). Of particular interest are cutaneous receptors, which consist of mechanoreceptors, thermoreceptors, and nociceptors, and are located within sensitive areas of the skin with as many as 25,000 per square centimeter (Shumway-Cook & Woollacott, 2012). Cutaneous sensory receptors provide information about the body's orientation within the immediate environment and provide information necessary for reflexive responses.

Cumulatively, sensory receptors within the somatosensory system provide information via afferent nerve fibers to the spinal cord, which allows for the modulation of locomotion. Control of one's gait may also depend upon afferent information from additional sources, including the visual, vestibular, and proprioceptive systems (Dietz, 2002; Gandevia & Burke, 1992).

Gait has been defined as a subconscious and highly reproducible movement, that is often performed daily as one participates in their daily activities. Stable gait requires appropriate

communication between the neuronal spinal and supraspinal pattern generators, as well as sensory feedback from visual, vestibular, and proprioceptor systems. Feedback from the sensory system is believed to provide critical information for the adjustment of stride-to-stride limb trajectories in order to smooth out unintended irregularities during walking (Dietz, 2002). Therefore, peripheral sensibility is often reduced in individuals with peripheral neuropathy, which may negatively affect proprioceptive feedback, thus disrupting normal locomotion and increased variability in one's gait (Wuehr et al., 2014).

Although it has been well documented that cancer survivors who are undergoing or have undergone chemotherapy may experience peripheral neuropathy and gait disturbances, research regarding the exact changes that have occurred in their gait cycle and cause patients to report unsteady gait and frequent calls are relatively new and unknown. Alternatively, the effects that peripheral neuropathy has on gait has been well documented within the diabetic population. Specifically, it has been demonstrated that individuals with diabetic peripheral neuropathy generally display a gait that is more conservative and may be characterized by slower walking velocities and smaller step sizes (Paul, Ellis, Leese, McFadyen, & McMurray, 2009; Wrobel, Crews, & Connolly, 2009). Similar to chemotherapy-induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy (DPN) targets both sensory and motor fibers and is progressive in nature. Large and small diameter nerve fibers are affected, resulting in attenuated sensory nerve conduction, which includes large fiber thresholds for vibration and joint positions, as well as neurogenic atrophy due to axonal degeneration of motor fibers (Andersen, Gadeberg, Brock, & Jakobsen, 1997; Dyck & Thomas, 1999; Horak, Dickstein, & Peterka, 2002)

Individuals with DPN often display altered gait patterns, which may be characterized as slower, with shortened stride lengths and increased base widths, stride times, and double support

times when compared to age-matched controls (Andersen et al., 1997; Dyck & Thomas, 1999; Horak et al., 2002; Shankarappa, Piedras-Rentería, & Stubbs, 2011; Wuehr et al., 2014). Furthermore, individuals with peripheral neuropathy often display significant increases in locomotor variability. Not surprising, increased variability in the gait cycle has been found to be most correlated with falls (Dingwell & Cavanagh, 2001).

Although research indicates that sensory feedback plays a critical role in adjusting the stride-to-stride limb trajectories in order to smooth out irregularities during unperturbed movements and safely navigate and maintain balance, when the somatosensory system is compromised, as in the case of peripheral neuropathy, increased variability arises. Previous research indicates that increased stride-to-stride variability associated with one's stride length, walking speed, and double support time each independently contribute to falling (Dingwell & Cavanagh, 2001; Gandevia & Burke, 1992; Maki, 1997)

Falling is a significant event, especially for older adults, as falls have been linked to serious injuries and disabilities, loss of independence, and increased mortality. Twenty-three percent of falls in adults aged 65–69 result in death, with the rate climbing as high as 50% of falls resulting in death for adults aged 85 or older. It is estimated that of the 1.6 million new cancer diagnoses in 2013, 77% were individuals over the age of 55 (Alamgir, Muazzam, & Nasrullah, 2012). Cancer patients experiencing peripheral neuropathy have reported difficulties in walking and incidences of falls (Tofthagen, Visovsky, & Berry, 2012). In fact, it's estimated quantified that approximately 20% of patients with CIPN may fall, which is a higher percentage than age-matched controls (Mohile et al., 2009, 2011; Tofthagen, Overcash, & Kip, 2012). Stone and colleagues (2012) conducted a 6-month prospective study of cancer patients and found

that 50.3% of the patients fell during the studies follow-up period. More significantly, over one-third of the falls resulted in soft tissue injuries and 3.2% resulted in fractures.

Early research suggests that cancer patients may experience axonopathy and a compromised somatosensory system as a result of undergoing chemotherapy treatments (Han & Smith, 2013; Visovsky & Daly, 2004). It has been noted that cancer patients experiencing even mild peripheral neuropathy after receiving taxane chemotherapy may experience significant changes in postural stability as a result of their treatment, which may cause the neurotoxic effect of taxane on the somatosensory systems and the subsequent changes that occur as a result of the neurotoxicity. Furthermore, while the severity of the peripheral neuropathy experienced by the participants in this study was mild, the postural instability displayed was comparable to diabetic individuals diagnosed with severe neuropathy.

In summary, cancer patients undergoing chemotherapy may often experience varying degrees of chemotherapy-induced peripheral neuropathy (CIPN), which may result in impaired neuronal function and manifest through a loss of sensation and proprioception, disturbed nerve conduction velocities, and a reduction in muscle strength (Argyriou et al., 2013; Bakitas, 2007; Krishnan, Goldstein, Friedlander, & Kiernan, 2005; Murillo et al., 2008; Park et al., 2013; Visovsky et al., 2007; Wilkes, 2007). Chemotherapy agents have a toxic effect on the somatosensory component of the nervous system (Stillman & Cata, 2006; Wang, Lehky, Brell, & Dorsey, 2012; Wickham, 2007). This facet of the nervous system is responsible for modulating and producing coordinated gait patterns. When impaired, it may result in functional impairments that lead to walking difficulties, as reported by cancer patients (Shumway-Cook & Woollacott, 2012).

Research indicates that abnormalities or the observation of variability in gait parameters, such as cadence, stride length, swing, double support, stride length variability, and swing time variability, may increase the risk of falling (Toulotte, Thevenon, Watelain, & Fabre, 2006; Verghese, Holtzer, Lipton, & Wang, 2009). Falling is a significant event for the elderly population, as falls have been linked to serious injuries and disabilities, loss of independence, and increased mortality (Alamgir et al., 2012). It is estimated that of the 1.6 million new cancer diagnoses in 2013, 77% were individuals over the age of 55, and previous research indicated that 20% of patients with CIPN may fall, which is a higher percentage than the age-matched nondisease control (Alamgir et al., 2012; American Cancer Society, 2013; Mohile et al., 2009, 2011; Tofthagen et al., 2012).

Peripheral neuropathy may also be experienced in diabetic patients, and research suggests that the symptoms and pathophysiology of diabetic peripheral neuropathy (DPN) are similar to cancer patients with CIPN (Andersen et al., 1997; Dyck & Thomas, 1999; Horak et al., 2002; Tesfaye & Selvarajah, 2011). These diabetics display altered gait patterns characterized by slower gait velocities, shorter step lengths, and lower cadences, which may be the result of altered muscle activation times and velocity, as well as decreased joint mobility (Andersen et al., 1997; Paul et al., 2009; Savelberg et al., 2010; Sawacha et al., 2009; Thomas & Tomlinson, 1993).

Although CIPN is prevalent in cancer patients undergoing chemotherapy, evidence suggests that other patient populations, such as diabetics with peripheral neuropathy, may experience abnormal spatiotemporal gait patterns due to neuropathic symptoms. In turn these abnormalities may increase the risk of falls, yet surprisingly spatiotemporal gait parameters have not been studied in cancer patients undergoing chemotherapy (Wallace et al., 2002).

Statement of the Problem

Chemotherapy agents have a toxic effect on the somatosensory component of the nervous system, causing many cancer patients to experience chemotherapy-induced peripheral neuropathy, which may be described as loss of sensation and proprioception, disturbed nerve conduction velocities, and a reduction in muscle strength (Argyriou et al., 2013; Bakitas, 2007; Krishnan et al., 2005; Murillo et al., 2008; Stillman & Cata, 2006; Visovsky et al., 2007; Wang et al., 2012; Wickham, 2007; Wilkes, 2007). This facet of the nervous system is responsible for modulating and producing coordinated gait patterns and when impaired may result in functional impairments that lead to walking difficulties, as reported by cancer patients (Shumway-Cook & Woollacott, 2012). Diabetics commonly experience peripheral neuropathy. The presence of peripheral neuropathy has been associated with changes in gait patterns and increases in falls in this population (Andersen et al., 1997; Paul et al., 2009; Savelberg et al., 2010; Sawacha et al., 2009; Thomas & Tomlinson, 1993). Research indicates that abnormalities in gait parameters may increase the risk of falling, which is a significant event for the elderly population, as falls have been linked to serious injuries and disabilities, loss of independence, and increased mortality (Alamgir et al., 2012; Toulotte et al., 2006; Verghese et al., 2009). Copious amounts of research demonstrate the importance of the somatosensory system for gait modulation, and when this system is impaired, significant gait changes occur that increase fall risk. Nonetheless, insight into changes in gait patters of cancer patients with CIPN remains unknown. Considering the increased incidence of falls in cancer patients with CIPN, it is paramount to investigate if the same gait changes occur within cancer patients as with CIPN.

Purpose of the Study

The purpose of this study was to investigate if changes occur in spatiotemporal gait parameters of cancer patients who have undergone taxane- or platinum-based chemotherapy treatments and have been diagnosed with chemotherapy-induced peripheral neuropathy. Additionally, the level of fall risk associated with the CIPN remains a secondary variable of interest.

Research Question

1. Do significant changes occur in spatial gait parameters within individuals diagnosed with CIPN as a result of undergoing either taxane- or platinum-based chemotherapy agents?
2. Do significant changes occur in temporal gait parameters within individuals diagnosed with CIPN as a result of undergoing either taxane- or platinum-based chemotherapy agents?
3. Does a significant change occur in fall risk within individuals diagnosed with CIPN as a result of undergoing either taxane or platinum based chemotherapy agents?

Hypothesis

1. There will be *significant* differences in spatial gait parameters between individuals diagnosed with CIPN and age- and morphologically matched controls.
2. There will be *significant* differences in temporal gait parameters between individuals diagnosed with CIPN and age-and morphologically matched controls.
3. There will be *significant* differences in fall risk between individuals diagnosed with CIPN and age- and morphologically matched controls.

Chapter II

REVIEW OF THE LITERATURE

The American Cancer Society (2013) estimated that as of January 1, 2013, there were 13.7 million Americans living with a history of cancer. This number is expected to increase, as it is estimated that 1,685,210 new cancer cases are expected to be diagnosed in 2013 (Siegel, et al., 2016). From 1975 to 1977, an individual diagnosed with cancer had a 49% chance of surviving 5 years past his or her initial cancer diagnosis. Today, an individual with a cancer diagnosis has a 68% chance of surviving at least 5 years past his or her initial diagnosis (Siegel et al., 2016). Given this increased 5-year relative survival rate, it is of paramount importance to address and evaluate how a cancer survivor's quality of life and ability to function are affected by the cancer treatment process.

Cancer is a general term used for a disease that consists of more than 200 various types that can occur at any point throughout the lifespan, with different growth rates and abilities to spread or metastasize, resulting in varying treatment options and prognoses. Despite the numerous types of cancers, when viewed at the cellular and molecular levels, there are only a few variations of cancer based upon alterations in genetics and defective cell functions (Eggert, 2010). In global terms, cancer is uncontrolled cell growth and proliferation that develops as a result of the accumulation of mutations or genetic abnormalities within a cell. Genes can experience mutations, which cause the cell to increase activity (oncogenes), or mutations, which result in a decrease in cellular activity (tumor suppressor genes). Regardless of the process, the result is a nonfunctional cell that will begin to multiply due to its resistance to the normal cell signaling process. The mutated cells, resistant to apoptosis, which is preprogrammed cell death, will grow uncontrollably and multiply, forming masses of nonfunctional tissue that will take over

the space of functional tissue, ultimately causing various malfunctions that disturb normal processes throughout the body (Pecorino, 2008).

Cancer cells exhibit cellular characteristics that definitively separate them from normal, healthy cells. A primary characteristic that separates cancer cells from normal cells is that cancer calls can grow and divide absent of receiving signals from the various environmental and growth factors that are normally needed for cells to divide. Additionally, unlike normal healthy cells, cancer cells can ignore growth inhibitory signals. The ability to ignore these signals may be due to mutations that allow cancer cells to short-circuit the growth factor pathways, resulting in unchecked and unregulated cell growth (Pecorino, 2008).

Cancer cells can avoid apoptosis, which is preprogrammed cell death. Noncancerous cells, in response to damage to their DNA or simply as part of the cell cycle, will be destroyed and removed by apoptosis. However, cancer cells have the ability to evade apoptosis signals and continue to proliferate (Pecorino, 2008). Cancer cells also possess unlimited replicative potential. Normal cells contain autonomous counting devices that determine the cell's finite replication potential. The counting devices are telomeres, which are located at the ends of chromosomes. As cells replicate, the telomeres shorten until they reach a length that halts further replicative processes. However, telomeres of cancer cells are altered and stay a consistent length despite constant replication, which allows cancer cells to possess unlimited replicative potential (Pecorino, 2008).

Normal, healthy cells receive oxygen and nutrients from blood vessels. The number and architecture of these blood vessels remain relatively constant. Cancer cells are able to induce angiogenesis, which is the creation of new blood vessels. This process is important for cancer cells as the growth of new blood vessels is needed in order to feed the continuously proliferating

tumor. Lastly, whereas normal cells will remain in relatively the same location throughout their life span, cancer cells possess the ability migrate to various other parts of the body, a process called metastasis (Pecorino, 2008).

Treating cancer can be difficult because not all cancer cells behave in the same manner (Schneider, Dennehy, & Carter, 2003). Ultimately, the primary goal of cancer therapies, such as chemotherapy and radiation therapy, are to cause cell death. Traditional cancer treatments include chemotherapy, radiation therapy, and surgery, which effectively cause cell death (Navarro & Mejía Vázquez, 2010). The goal of these treatments is to achieve and maintain remission.

Additionally, due to the difficulty in destroying cancer cells, many normal cells are destroyed in the process, resulting in negative physiological side effects to normal tissues and body functions (Courneya & Friedenreich, 2011; Schneider et al., 2003). Many of the body systems, such as the immune system, cardiovascular and pulmonary system, musculoskeletal system, and gastrointestinal system, will experience extreme toxicities (Courneya & Friedenreich, 2011; Schneider et al., 2003).

The physiological toxicities to the various bodily system experienced by cancer survivors may also have negative effects on their psychosocial well-being and quality of life. Many cancer survivors struggle to cope with physical losses, such as loss of hair or loss of one or both breasts, the colon, the jaw, or other body part(s). Cancer survivors may experience drastic weight fluctuations, as well as the development of lymphedema, which is a swelling of an appendage. Actual or perceived changes in body image may result in anger and/or depression. The extent of the toxicities and the specific system that is damaged, as well as the extent of the psychological disturbances that may accompany actual or perceived physical changes, may depend on the

specific therapy utilized, as well as the intensity of that therapy (Courneya & Friedenreich, 2011; Schneider et al., 2003).

Chemotherapy is often used in combination with other treatments, such as surgery or radiation, and is a form of drug therapy that causes cellular death (Airley, 2009). Chemotherapy may be administered orally or intravenously and is dispersed in repeated courses over a 3- to 6-month period. Chemotherapy drugs work by targeting rapidly dividing cells and disrupting the cells' ability to replicate. Chemotherapy drugs cannot differentiate between normal, quickly dividing cells and cancer cells. Consequently, noncancer cells are also destroyed in the process. For example, hair cells are among those that are rapidly dividing and are often destroyed by chemotherapy, resulting in loss of hair by the patient. The rapidly dividing cells that comprise human skin are also affected by chemotherapy drugs, which can routinely produce rashes and dry skin. The cells that line the inside of human guts and mouths divide at a similar rate as cancer cells; therefore, chemotherapy typically affects these cells as well, causing various side effects such as mouth sores, nausea, vomiting, and fatigue (Airley, 2009).

Due to the fact that chemotherapy agents will target normal, rapidly diving cells, patients undergoing chemotherapy may potentially experience one or more countless side effects. A common side effect of chemotherapy is chemotherapy-induced peripheral neuropathy (CIPN).

Symptoms of CIPN may be acute, mild or severe, transient or chronic, depending upon the treatment regime and the dose of the agents. They may manifest in a variety of ways, involving sensory and motor symptoms (Park et al., 2013; Postma & Heimans, 2000; Wilkes, 2007). Sensory signs and symptoms may include numbness, tingling, burning, pain, ataxia, loss of deep tendon reflex, and reduced sense of touch, vibration, and proprioception. Motor symptoms may include weakness, balance disturbances, and difficulty performing fine motor

skills and a diminished or absent deep tendon reflex. Motor symptoms are less frequent due to the neurotoxic agent's inability to cross the blood–brain barrier in concentrations significant enough to cause harm (Bakitas, 2007; Murillo et al., 2008; Visovsky et al., 2007; Wilkes, 2007). The autonomic system may also be affected, resulting in constipation, urinary retention, sexual dysfunction, and altered blood pressure (Bakitas, 2007; Visovsky et al., 2007; Wilkes, 2007).

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The characteristics of CIPN depend upon the specific chemotherapy agent used, as well as when the agent is introduced in the treatment protocol and the dosage amount. Induction chemotherapy is the initial administration of the therapy, the goal of which is to achieve significant cytoreduction, resulting in complete remission (Airley, 2009).

Consolidation/intensification chemotherapy is administered once remission has been achieved in order to ensure the disease remains in remission, thus increasing overall patient survival rates. Adjuvant chemotherapy is administered once the disease has been eradicated by localized treatment, such as surgery or radiation. Neoadjuvant chemotherapy agents are administered prior to local therapy to ensure maximal effect of localized therapy. For example, an agent may be administered to shrink the tumor prior to surgery (Airley, 2009).

Maintenance chemotherapy is administered in lower doses over a prolonged period. This form of treatment is most often administered in an outpatient or community clinic with the goal of prolonged remission (Airley, 2009). Salvage chemotherapy is an agent given when all other treatments have failed, with the purpose of controlling the disease and/or providing palliative care. Lastly, combination chemotherapy is the administration of a combination of agents, thus maximizing the effectiveness of the agents to kill the tumor cells throughout various points of the cell cycle (Airley, 2009).

Although chemotherapy agents will vary in the timing of administration, they also vary in their chemical composition, resulting in several distinct classes of agents. The incidence of CIPN and subsequent symptoms depend unto the class of the chemotherapy agent used and the parts of the nervous system that may be targeted by the various classes of agents (Armstrong et al., 2005; Wilkes, 2007). Platinum compounds consist of cisplatin, carboplatin, and oxaliplatin. CIPN has been reported in 57%–92% of cancer patients who received cisplatin (Armstrong et al.,

2005; Wilkes, 2007). Cisplatin has been known to cause sensory symptoms that progress to a mixture of sensorimotor symptoms and may also affect the autonomic nerves. The occurrence depends on the type of platinum analog, total daily dose, and total regimen dose. The risk of developing CIPN symptoms increases as the cumulative dose reaches 300 mg/m² (Armstrong et al., 2005; Wilkes, 2007). Research has indicated that cisplatin will affect large axon fibers, causing axonal swelling, loss of sense of position, and vibration. Cisplatin has been associated with Lhermitte's sign, which is a lightning-like sensation that begins in the neck and may extend posteriorly down the legs during neck flexion. The cause for these symptoms is postulated to be the result of dorsal column irritation within the spinal cord (Armstrong et al., 2005; Wilkes, 2007). Motor dysfunction is typically seen after sensory loss (Armstrong et al., 2005; Wilkes, 2007). CIPN typically presents late in the treatment or after the treatment has been completed (Armstrong et al., 2005; Wilkes, 2007).

Oxaliplatin has been shown to cause CIPN symptoms in 82% to 92% of cancer patients (Armstrong et al., 2005; Wilkes, 2007). It is believed that oxaliplatin will interfere with ion conductance within the axon, thus affecting the neuron's ability to become "excited" (Armstrong et al., 2005; Wilkes, 2007). Oxaliplatin has been associated with two types of neuropathy. The first is similar to that of cisplatin in that the large fibers are primarily targeted, causing distal sensory neuropathy. The second type of neuropathy is acute in that it may occur within 30–60 min of the infusion. Cancer patients may develop dysesthesias of the hands and feet, jaw tightness, and a sensation of loss of breath (Armstrong et al., 2005; Wilkes, 2007). Acute neuropathy symptoms have been reported to be exacerbated by exposure to the cold, as well as the dose and infusion time of a particular agent. The risk for developing symptoms increases as the cumulative dose reaches 750 to 800 mg/m² (Armstrong et al., 2005; Wilkes, 2007).

A recent prospective study investigated the incidence and severity of acute oxaliplatin-induced peripheral neuropathy in 170 patients diagnosed with metastatic colorectal cancer. The patients, who had a mean age of 63.7 years, received either a combination of leucovorin, 5-fluoruracil, and oxaliplatin, or a combination of capecitabine and oxaliplatin. The National Cancer Institute's Common Toxicity Criteria were used to assess severity of accumulation oxaliplatin sensory and motor neuropathy symptoms. Sensory and motor nerve conduction studies were performed on the ulnar, radial, peroneal, and sural nerves and were repeated after six courses (oxaliplatin planned dose, 510 mg/m²) and 12 courses (oxaliplatin planned dose, 1,020 mg/m²) of the cepecitabine regiments and after four courses (oxaliplatin dose, 520 mg/m²) and eight courses (oxaliplatin dose, 1,040 mg/m²; Argyriou et al., 2013).

Argyriou and colleagues (2013) found that 85.9% of the patients experienced acute oxaliplatin-induced peripheral neuropathy and 72.4% of patients experienced chronic oxaliplatin-induced peripheral neuropathy with the worst symptoms associated with the cumulative dosages of oxaliplatin (Spearman rho = 0.171; $p = .026$). The incidence of acute oxaliplatin-induced peripheral neuropathy was also significantly correlated with the incidence ($r = 0.601$; $p < .001$) and severity ($r = 0.702$; $p < .001$) of chronic oxaliplatin-induced peripheral neuropathy. Argyriou and colleagues (2013) also noted that sensory action potentials in all three sensory nerves experienced deterioration. Thus, the results of the study suggest that oxaliplatin may induce acute and chronic peripheral neuropathy, which was accompanied by amplitude deterioration of sensory action potentials, which was linked to chronic neuropathy (Argyriou et al., 2013). The conclusion reached by Argyriou and colleagues (2013) is consistent with previous research, which has shown oxaliplatin to cause sensory peripheral neuropathy accompanied by changes in nerve conduction velocities.

Taxanes, which are plant-derived poisons, include paclitaxel and docetaxel, and will often cause microtubular aggregation (Armstrong et al., 2005; Wilkes, 2007). Chemotherapy-induced peripheral neuropathy associated with pacelitaxel and docetaxel depends on the agent used, administration schedule, cumulative dose, and whether or not it is combined with another agent (Armstrong et al., 2005; Wilkes, 2007). It has been reported that 59% to 78% of patients who receive doses of at least 200 mg/m² and up to a cumulative dose of 1,400 mg/m² of paclitaxel may experience neuropathy that is mild to moderate in nature (Armstrong et al., 2005; Wilkes, 2007). Peripheral neuropathy symptoms associated with docetaxel, which occur in 20% to 58% of cancer patients, are usually not present until the cumulative dose exceeds 600 mg/m². Docetaxel has been known to cause damage to small fibers, resulting in sensorimotor symptoms (Armstrong et al., 2005; Wilkes, 2007).

The incidence of taxane-induced peripheral neuropathy is contingent on various factors, such as the treatment schedule, single dose per course, and cumulative dose. Other factors, such as prior or simultaneous administration of platinum compounds or vinca alkaloids, age, preexisting peripheral neuropathy due to other medical conditions, such as hereditary ones associated with nutritional agents, paraneoplastic, diabetes mellitus, and alcohol abuse. It is suggested that when patients receive a combination of paclitaxel plus cisplatin or paclitaxel plus carboplatin, peripheral neuropathy may present as axonal, predominately sensory peripheral neuropathy that is mild to severe. Patients who receive paclitaxel plus cisplatin may experience peripheral neuropathy 69.2% of the time, whereas patients who receive paclitaxel plus carboplatin may experience peripheral neuropathy 66.6% of the time (Argyriou, Koltzenburg, Polychronopoulos, Papapetropoulos, & Kalofonos, 2008).

Vinca alkaloids, which consist of vincristine, vindesine, and vinblastine, have been associated with peripheral neuropathy. Vincristine has been associated with the greatest effects (Armstrong et al., 2005; Wilkes, 2007). Vincristine has been shown to cause peripheral neuropathy in 57% of cancer patients when the cumulative dose exceeds 6 mg/m². Vincristine, which may cause aggregation of microtubules, thus causing degeneration and atrophy of peripheral nerve fibers, may cause the symptoms of pain and temperature sensation (Armstrong et al., 2005; Wilkes, 2007).

The chemotherapy agent bortezomib has been shown to cause CIPN symptoms in 35% of patients. The symptoms are most often sensory in nature and rarely involve motor deficits. Thalidomide has been associated with CIPN symptoms in 25% to 81% of patients. Lastly, thalidomide predominantly causes sensory symptoms, with the risk of symptom development increasing as the cumulative dose exceeds 400 mg/m² (Armstrong et al., 2005; Wilkes, 2007).

Although all cancer cells have six common characteristics, there are over 200 different types of cancer. The heterogeneity of cancer is reflected in the various treatment types. Chemotherapy is a general term for a variety of classes of drugs that may be administered alone or in combination with other treatments, as well as at various times throughout the cancer journey. Despite the numerous types of chemotherapy agents, a common side effect is chemotherapy-induced peripheral neuropathy.

Pathophysiology of Chemotherapy Induced Peripheral Neuropathy

The symptoms patients experience are due to the neurotoxic effects chemotherapy agents have on the peripheral nervous system. Briefly, the nervous system has two main components: the central nervous system (CNS) and the peripheral nervous system (PNS). The central nervous system consists of the brain and spinal cord. The human system is continuously immersed with

sensory information from a variety of sources from the environment, as well as from movement, touch, awareness of the body in space, sight, sound, and smell. During high-order motor behaviors, such as walking, the brain and central nervous system (CNS) must correlate the various sensory inputs with motor outputs in order to control the body as it moves and interacts with the environment (O'Sullivan & Schmitz, 2007). The CNS will use this information to modulate movement by both feedback and feedforward control. Feedback control occurs during movement, in which sensory information is used to monitor and adjust active movement. Feedforward control is proactive and utilizes sensory information that has been learned through previous experience to send signals prior to the movement to allow anticipatory postural adjustments to be made to control posture or movement. Thus, sensory information plays critical roles in movement in that sensory information will aid in the selection of proper motor actions in response to the environment and adapt and shape motor programs through feedback, allowing for corrective actions to occur in response to a dynamic environment (O'Sullivan & Schmitz, 2007).

The main task of the PNS is to convey signals of information, such as sense of touch, pain, temperature, position, and vibration sense, from the periphery to the CNS. The responsibility for signal transmission belongs to the neuron, which is the basic component of the nervous system and is composed of three distinct structures: the cell body, the dendrites, and the axon (Magill, 2013). The neuron generates electrical signals from one part of a cell to another part of the same cell or a neighboring cell. For most neurons, this electrical signal will cause the release of neurotransmitters, which are chemical messengers that allow cells to communicate with one another (Cuccurullo, 2010). Each neuron has a cell body (or stoma) within which the cell's nucleus and ribosomes reside. Branching out from the cell body are dendrites, which are responsible for receiving signals from other cells. The long extension from the cell body is

called the axon, and may also be referred to as the nerve fiber (Cuccurullo, 2010). The axon extends from the cell body and carries the output signal to other cells. The axon can vary in length, ranging from a few microns to over a meter (Cuccurullo, 2010).

Neurons are classified according to their function. A neuron may either receive or send information by a neural impulse. A signal may be sent to, from, or within the central nervous system, which is composed of the brain and spinal cord. Neurons have three functional classes, which include sensory neurons (also called afferent neurons), motor neurons (also called efferent neurons), and interneurons, which originate and terminate in the brain or spinal cord, acting as connections between axons descending within the brain or spinal cord (Magill & Anderson, 2013). Sensory neurons send neural impulses to the central nervous system (CNS), whereas motor neurons send neural impulses from the CNS to skeletal muscle fibers (Magill & Anderson, 2013).

The PNS is composed of afferent and efferent divisions. The afferent neurons will transmit information from sensors located in the periphery to the CNS, whereas the efferent neurons will transmit signals from the CNS to muscles or glands (Widmaier, Raff, & Strang, 2006). The peripheral nervous system has three functional divisions, which are the sensory nerves, motor nerves, and the autonomic nerves. The sensory nerves sense touch, pain, temperature, position, and vibration sense. The motor nerves are responsible for voluntary movement, muscle tone, and coordination. The autonomic nerves are responsible for the control of intestinal motility, blood pressure, and involuntary muscles (Widmaier et al., 2006).

Anatomically, the afferent nerves of the peripheral nervous system are composed of small and large fibers. The small fibers are unmyelinated and consist of nerves that sense pain and temperature. The large nerve fibers are myelinated and consist of nerves that sense position and

vibration, as well as motor control (Armstrong et al., 2005). The small nerve fibers are primarily composed of microtubules, which transport proteins throughout the nerve fiber. Large nerve fibers are primarily composed of neurofilaments, which comprise the axon's framework. Sensory nerves terminate at the level of the skin and extend to the dorsal root ganglion, connecting with either the dorsal column via a large fiber or the spinothalamic tract via a small fiber in the spinal cord (Armstrong et al., 2005).

The somatosensory system, which consists of muscle spindles, Golgi tendon organs, joint receptors, and cutaneous receptors, contributes to the modulation of spinal pattern generators, modulation of motor commands, and perception and control of movement through sensory information. Specifically, there are several different types of receptors at the end of the afferent nerves, which provide information with regard to length and tension in muscles and tendons, sense of joint positions, as well as heat, cold, touch, pressure, and skin of body parts affected by the action of muscles.

Collectively, these distinct receptors and their afferent nerves, which may be referred to as the somatosensory system, provide the CNS information with respect to muscle length and tension, movement of the joints, the effect of movement on the overlying skin, as well how the body is interacting with the external environment. The CNS will interpret this information and send a command via efferent nerves to implement an action (Widmaier et al., 2006). These sensory neurons will provide information about mechanical stimuli, temperature changes, potential damage to the skin, body and limb movement and position, as well as velocity and muscle activation (Magill & Anderson, 2013; Shumway-Cook & Woollacott, 2012). Of particular interest may be cutaneous receptors, which consist of mechanoreceptors, thermoreceptors, and nociceptors, which are located within sensitive areas of the skin, with as

many as 25,000 per square centimeter (Shumway-Cook & Woollacott, 2012). Cutaneous sensory receptors provide information about the body's orientation within the immediate environment and provide information necessary for reflexive responses. Cumulatively, sensory receptors within the somatosensory system provide information by afferent nerve fibers to the spinal cord, which allows for the modulation of locomotion.

The neurotoxic effects of chemotherapy agents on the peripheral nervous system are wide-ranging, targeting many components of the peripheral nervous system, such as the axons and cell bodies of dorsal root ganglion neurons, and resulting in axonal damage, which is characterized by a decrease in intraepidermal nerve fiber density and terminal arbor degeneration (Han & Smith, 2013). Chemotherapy agents will also exert their toxicity on mitochondria, causing them to become swollen and vacuoled, as well as create oxidative stress, causing inflammation. Pathologically, the dorsal root ganglion neurons and surrounding satellite cells may negatively alter the expression of various ion channels, neurotransmitters, and receptors, as well as exhibit altered gene expression. The mitochondrial dysfunction and IENF loss seem to be directly correlated to the presence of pain. Cumulatively, these changes cause various sensory symptoms, such numbness, tingling, burning, pain, and reduced sense of touch, as well as motor symptoms, such as may include weakness, balance disturbances, and difficulty performing fine motor skills, which are frequently reported by cancer patients undergoing chemotherapy treatment (Bakitas, 2007; Han & Smith, 2013; Murillo et al., 2008; Park et al, 2013; Visovsky et al., 2007; Wilkes, 2007).

Although there is a wide range of neuronal targets for various chemotherapy agents, it is estimated that platinum drugs (antineoplastic agents), such as cisplatin and oxaliplatin, may generally target the DRG and ion channels. Oxaliplatin may cause an acute peripheral

neuropathy by causing the nodal axonal voltage-gated sodium and calcium channels to become dysfunctional (Argyriou, Bruna, Marmiroli, & Cavaletti, 2012). In animal models, rats treated with oxaliplatin did not experience degeneration of peripheral nerve axons (A-fibers and C-fibers), but there was a partial loss of intraepidermal nerve fibers, which was accompanied by a reduction in sensory nerve conduction velocity that lasted well after the cessation of treatment, suggesting deficits may be chronic rather than acute. There was no reduction in motor nerve conduction velocity. The rats treated with oxaliplatin also experienced slower and more irregular and spontaneous discharges patterns in A-fibers and C-fibers, swollen and vacuolated mitochondria, and mechano-allodynia, mehcano-hyperalgesia, and cold-allodynia, which is consistent with patient-reported symptoms (Xiao, Zheng, & Bennett, 2012). It has also been proposed that platinum compounds will alter the tertiary structure of DNA by forming intrastrand adducts and interstrand crosslinks, thus inducing apoptosis and causing neuronal apoptosis through oxidative stress and mitochondrial dysfunction (Argyriou et al., 2012).

Taxanes, such as paclitaxel and docetaxel, are thought to disturb the function of the microtubules of the mitotic spindle, thus negatively affecting axonal transport, which may evoke the typical “dying-back” pattern. Taxanes will also evoke certain cellular processes, such as macrophage activation in both the DRG and peripheral nerve, as well as microglial activation within the spinal cord, which has been postulated to contribute to the development of taxane-induced peripheral neuropathy. Recent studies suggest that paclitaxel may cause the axonal microtubules to undergo a massive polar reconfiguration, which is often accompanied by impaired organelle transport, resulting in degeneration of intraepidermal terminal arbors of primary afferent neurons, and is associated with increased incidence of swollen and vacuolated axonal mitochondria in A-fibers and C-fibers (Argyriou et al., 2012). Furthermore, paclitaxel

and docetaxel can induce a ganglionopathy that attacks the cell bodies, particularly those of the dorsal root ganglia (DRG), or myelinopathy with primary segmental demyelination. Taxanes have been known to affect sensory neurons, especially myelinated nerve fibers of vibration sensation and proprioception. Nerve biopsies have shown that taxane-induced peripheral neuropath are mostly ganglionopathic in nature, rather than axonopathic (Argyriou et al., 2008).

Taxane-induced peripheral neuropathy may most often present a sensory neuropathy, although motor neuropathy is not uncommon. The primary affected fibers are the thick myelinated nerve fibers conducting sensation and sense of position. Symptoms may also include loss of pain and temperature sensation and loss of tendon reflexes (Argyriou et al., 2008). Electrophysiological abnormalities include decrease or loss of sensory response, slower motor conduction velocities, or F-wave latency delay, suggesting primary demyelination, as well as the possibility that damage has also occurred to the myelin-Schwann cells. Secondary demyelination may also occur, which consists of minor increases in distal latency and decreased conduction velocity (Argyriou et al., 2008). It has also been noted that sural nerves may experience reduced or loss sensory nerve potentials velocity (Argyriou et al., 2008).

While taxanes may produce a symmetric, axonal neuropathy that is predominately sensory in nature, motor neuropathy may occur but is often difficult to recognize because of the very mild weakness that occurs in muscles. However, when motor neuropathy does occur, reduction occurs in the compound muscles action potential response that can be noted, which indicates axonal loss, highlighted by electromyography (EMG), showing active denervation changes in the distal muscles of the lower limb velocity (Argyriou et al., 2008).

Two to 3 days after paclitaxel treatment, myopathy with proximal weakness and myopathic EMG changes are known to occur. High doses of taxanes have been known to cause

severe myalgia, particularly in the shoulder and paraspinal muscles. Biopsies of nerves subjected to taxanes have shown nerves to experience axonal degeneration and have reduced myelinated nerve fiber density and loss of large-fiber velocity (Argyriou et al., 2008). However, recent research using *in vivo* chronic animal models of CIPN in female Wistar rats what were administered cisplatin, paclitaxel, or a combination of both, found that while there was a decrease in nerve conduction velocity, there was no change in myelin structure (Gilardini, 2012). Thus, the exact pathophysiology of CIPN remains unknown at this time.

The risk for developing CIPN can be further increased in individuals who have been previously been diagnosed with diabetes, alcohol-related peripheral neuropathy, ischemic disease, vitamin deficiencies, renal insufficiency, prior exposure, or concurrent use of neurotoxic agents (Armstrong et al., 2005; Wilkes, 2007). Additionally, the incidence and severity of CIPN depends upon the intensity and duration of a single dose, as well as the total number of doses and any prior or concurrent doses. Furthermore, any prior or concurrent exposure to cisplatin may increase the incidence and severity of CIPN. A medical history of diabetes and alcohol abuse can also affect the incidence and severity of CIPN (Jaggi & Singh, 2012). Although CIPN may reverse itself once the agent has been stopped, many times CIPN symptoms may be irreversible (Wilkes, 2007).

Due to the neurotoxic effect of chemotherapy agents, the CNS may not receive vital information. As such researchers have begun investigating the effects of chemotherapy agents on the somatosensory system. Visovsky and Daly (2004) evaluated the change in CIPN symptoms within cancer survivors undergoing chemotherapy. To evaluate the presentation of CIPN and changes in nerve function, Visovsky and Daly evaluated the vision, hearing, deep tendon reflexes, vibratory sense, cutaneous sensation, gait, balance, muscle strength, and

orthostatic blood pressure of cancer survivors undergoing chemotherapy. Measures were assessed at baseline, which was before the participants started receiving chemotherapy. The participants were reassessed at 4 weeks and 12 weeks into treatment. Gait and balance were assessed using portions of the Tinetti Performance-Oriented Assessment of Balance and Gait instrument, which requires the participant to display mobility and balance throughout a series of maneuvers. The investigators observed gain initiation, step height, step length, step symmetry, step continuity, path deviation, trunk stability, walk stance, and turning while walking. The test is a valid and reliable measure that focuses on maintenance of position, postural responses to voluntary movement, and perturbation and gait mobility. The test is simple to administer; however, the scoring criteria are vague. Thus, it is difficult to detect small changes in spatiotemporal gait parameters (O'Sullivan & Schmitz, 2007). Visovsky and Daly (2004) also assessed deep tendon reflexes using Babinski's reflex hammer, vibratory sense using a tuning fork, cutaneous sensation using Semmes-Weinstein monofilaments, and muscle strength using a handheld dynamometer (Visovsky & Daly, 2004).

Visovsky and Daly (2004) observed changes in vision, hearing, deep tendon reflexes, vibratory sense, cutaneous sensation, balance, muscle strength, and orthostatic pressure; gait remained unchanged. Although the changes in outcomes may not have been statistically significant, Visovsky and Daly noted that this may be due to the small, homogenous sample size. Furthermore, an interesting finding in the present study was that the participants experienced an 18% decline in dynamic balance but no changes in gait. This discrepancy may by a function of the tool, as the Tinetti Performance-Oriented Assessment of Balance and Gait instrument uses a vague scoring criterion and thus cannot detect small changes in spatiotemporal gait parameters. However, the Tinetti Performance-Oriented Assessment of Balance and Gait may not have been

the best tool to use, as a recent study suggested that to assess risk of falls for those with neuropathy, either the Functional Reach test, Timed Up and Go test, the Berg Balance Scale, or the Dynamic Gait Index may be more appropriate (Jernigan, Pohl, Mahnken, & Kluding, 2012). More specifically, Jernigan and colleagues (2012) suggested that in the clinical setting sensitivity is the most important measure because high sensitivity corresponds to more true positives and fewer false negatives. Thus, the Timed Up and Go test may be a better test to asses fall risk due to its high sensitivity of 90% and high diagnostic accuracy at 88.9%. Furthermore, Visovsky and Daly stated the data may have been more accurately and consistently captured had a highly trained examiner performed the data collection. The examiners in this study are experienced nurse practitioners; thus, their lack of expertise on the clinical measures may have resulted in inherent intrasubject variability. However, the results of the current study suggested a trending decline in peripheral nerve function through treatment and the current clinical outcomes used, thus warranting further investigation.

Lastly, an interesting finding in the present study was that participants experienced an 18% decline in dynamic balance, as well as a reporting of recurrent falls, which are significant events, especially in the older population, as falls have been linked to serious injuries and disabilities, loss of independence, fear of falling, and increased mortality rates (Kelsey, Procter-Gray, Hannan, & Wenjun, 2012; Visovsky & Daly, 2004).

Hilkens, Verweij, Vecht, Stoter, and van den Bent (1997) conducted a series of case reports of cancer survivors undergoing chemotherapy treatment with docetaxel, a taxane-based agent. Common symptoms experienced throughout the case reports were sensory signs and symptoms that started with paresthesia and numbness in the hands and feet. The case reports insinuated a loss of tendon reflexes and vibratory perception, along with disabling pain, which

suggested involvement of small, unmyelinated nerve fibers. In conjunction with patient-reported numbness and paresthesia, several of the patients reported a loss of dexterity and an increasingly unsteady gait (Hilkens et al., 1997).

Hile, Fitzgerald, and Studenski (2010) conducted a case study to investigate the severity and impact of neurotoxic chemotherapy on one individual. The individual being studied was diagnosed with breast cancer and received paclitaxel after undergoing a curative mastectomy. Before the patient began taxane chemotherapy, baseline testing was administered, which consisted of the Short Physical Performance Battery and quantified standing, walking, and repeated chair stands. The patient's baseline testing indicated an active woman with no functional deficits of neuropathic symptoms. However, after three cycles of paclitaxel therapy over the course of 12 weeks, the patient experienced a 50% decline in her performance-based measures. The patient now required a cane for walking as her gait became unsteady and decreased by 0.46 m/s. Additionally, at 12 weeks, the patient scored 1/4 for balance (3.6 s semitandem), 3/4 for gait (0.74 s), and 1/4 for chair stands (16.9 s), as well as reported difficulties in performing mobility-related tasks and a higher incidence of falls. Furthermore, testing revealed a significant decrease in balance (Hile et al., 2010). The results of this case study suggested that chemotherapy may have a deleterious impact on physical function. Even more important is the reporting of recurrent falls, which are significant events, especially in the older population, as falls have been linked to serious injuries and disabilities, loss of independence, fear of falling, and increased mortality rates (Kelsey et al., 2012). Therefore, research suggested that certain chemotherapy agents may negatively affect proprioception and sensory feedback, thus impairing certain aspects of function and mobility.

In summary, chemotherapy-induced peripheral neuropathy is characterized by multiple sensory changes, which include mechanical allodynia, cold allodynia, slowing of sensor nerve conduction velocity, and loss of heat sensitivity. Although the exact pathophysiology of CIPN remains unclear, research suggested decreases in intraepidermal nerve fiber density and terminal arbor degeneration, which are associated with mitochondrial dysfunction, mitotoxicity, and oxidative stress (Han & Smith, 2013). Cumulatively, CIPN causes a host of uncomfortable and painful sensations throughout the periphery of a cancer patient's extremities.

In addition to the unconformable and often painful sensory nature of chemotherapy-induced peripheral neuropathy, CIPN may also cause a loss of peripheral sensation, proprioception, and lower-extremity muscle weakness, which may interfere with balance and gait (Tofthagen et al., 2012).

Motor activity, such as gait, is the result of the integration of neuronal signal of the motor control systems within the central and peripheral nervous system (Shumway-Cook & Woollacott, 2012). Motor control may be defined as the "ability to regulate or direct the mechanisms essential to movement" (Shumway-Cook & Woollacott, 2012, p. 3). Movement is the result of three factors and their interactions with one another. These three factors are the individual, the task, and the environment (Shumway-Cook & Woollacott, 2012).

Although there may be just three factors that interact to produce movement, the way in which these three factors interact is complex, resulting in multiple theories of motor control and how movement is controlled. The first of the two leading theories is related to motor programs, or the central pattern generator (CPG), which is a neural circuit of networks that generate rhythmic motor patterns without the influence of sensory or descending inputs (Kelso, 1995). A central pattern generator (CPG) is a genetically defined (inherited) central organization located

within the brain stem or spinal cord. It is theorized that there are specific patters of motions, such as for walking and swimming, and that these patterns may be multifunctional, producing several variations within a movement. For example, during gait, one may walk, run, skip, hop, bound, or jump (Kelso, 1995).

According to the motor program theory, a set of commands defines and shapes an action, which is then modified by sensory information. A stimulus (a command neuron) will trigger and initiate the CPG's action in the brain. The CPG will then send rhythmic, oscillating instructions to the musculature. These signals (instructions) create limb movement that are often characterized as reciprocal and repetitive in nature (MacKay-Lyons, 2002).

Although research indicates that CPGs are primary contributors to motor control, sensory and reflexive processes are needed in order to modify these commands to allow for adaptations to the changing environment; thus, central pattern generators are not the sole determinants of a movement (Shumway-Cook & Woollacott, 2012). Premovement information, such as posture and body orientation, are used by individuals to prepare for movement, as well as various reflex mechanisms, which will aid in the generation of rapid connections in order to successfully perform an action in dynamic environments (Schmidt & Wrisberg, 2008). In this theory, the brain stem controls both the CPG and the reflexes that mediate the afferent inputs to the spinal cord. The spinal reflex pathways and descending pathways merge information within a common spinal interneuron to integrate various information (Dietz, 2002). The supraspinal descending tracts provide inputs that help shape the output patterns of CPGs. The mesencephalic locomotor region (brain stem) transmits information to the flexors and extensor neurons during flexion and extension muscle activations throughout the gait cycle. The descending tracts also aid in the stabilization of gait rhythms (MacKay-Lyons, 2002).

The second of the two leading theories is systems theory, which states that in order to understand the neural control of movement, one must understand the system's characteristics in which the movement occurs, as well as the external and internal forces that are acting on the body (Bernstein, 1967). Bernstein (1967) studied the body as a whole mechanical system that has mass and is subject to external forces, such as gravity, and internal forces, such as inertial and movement-dependent forces. Bernstein suggested that even though two central commands may be equal, the two resulting movements may be quite different due to the interplay between external forces and variations within initial conditions. Bernstein also suggested that many interacting systems play a role in movement integration (Bernstein, 1967). Bernstein put forth the idea that the body, as a mechanical system, has multiple degrees of freedom that must be controlled during movement. For example, the body contains numerous joints that can flex, extend, and sometimes rotate, which will complicate movement. Bernstein hypothesized that control of the various degrees of freedom is hierarchical in nature in that the higher portions of the nervous system will control the lower portions of the nervous system, which in turn will activate synergies, or groups of muscles, that act as a unit (Shumway-Cook & Woollacott, 2012).

Over the years, Bernstein's system theory has evolved into the dynamical systems theory, which states that when the individual parts of a system are combined, the individual elements will start to behave collectively, resulting in an ordered way (Shumway-Cook & Woollacott, 2012). When applied to motor control, dynamical systems theory may predict movement based on the elements involved and their interactions, ignoring any specific commands or motor programs of the nervous system (Shumway-Cook & Woollacott, 2012). Dynamical systems theory states that a new behavior pattern will occur when there is a change in the system, called the "control parameter." A control parameter is a variable that alters a system's behavior. For

example, as an animal's walking velocity increases, it will reach a certain velocity that dictates the animal's behavioral change from a walk to a trot (Shumway-Cook & Woollacott, 2012). This is in stark contrast to the theory of central pattern generators, as the dynamical system deemphasizes the existence of central nervous system commands (Shumway-Cook & Woollacott, 2012).

A key concept in dynamical systems theory is that of variability and its role in movement control (Shumway-Cook & Woollacott, 2012). Dynamical systems theory states that human movement functions optimally due to its inherent variability, which may consist of the variations that normally occur during motor performance throughout multiple task repetitions. In the central pattern generator theory, variability is the result of errors that occur during motor performance and assumes that these errors can be reduced through skill acquisition, which results in decreases in variability and error (Shumway-Cook & Woollacott, 2012). On the other hand, dynamical systems theory views variability as positive, as it allows for flexible and adaptive strategies to occur as the environment changes, which is essential for normal movement to occur. In this theory, a lack of variability may result in injury, whereas excessive variability results in movement impairments, such as with persons with ataxia (Shumway-Cook & Woollacott, 2012). Thus, dynamical systems theory views a small amount of variability as positive because it indicates highly stable and preferred movement patterns, which is called an attractor state. An example of an attractor state with walking is a person walking at various speeds who, barring outside influences, will walk at a preferred state that is the most energetically efficient (Shumway-Cook & Woollacott, 2012).

The dynamical systems theory does have its limitations. Although this theory does take into consideration all of the contributors to movement, such as muscles and skeletal systems, as

well as gravity and inertia, it does minimize the role of the nervous system. The dynamical system states that the nervous system in isolation does not predict movement, which is contrary to central pattern generator theory (Shumway-Cook & Woollacott, 2012).

Despite these differences, both theories of motor control must incorporate the basic systems of control: open-loop and closed-loop control systems. The primary difference between these two systems is that a closed-loop system involves feedback, whereas an open-loop system does not. In human movement, such as walking, the feedback is afferent information sent by various sensory receptors to the control center, which will provide modulation of movement while it is in progress (Magill & Anderson, 2013).

Regardless of the theory, movement depends on the coordinated integration of the individual, the task, and the environment. From the CPG perspective, movement is the result of a central command that sends signals via inherent neural networks. From the dynamical system theory (DST) perspective, movement is based on the elements involved and their interactions, ignoring any specific commands. Furthermore, although the origin of movement may be very different between these two theories, both CPG and DST rely on peripheral sensory information and joint receptor and muscle spindle information sent via afferent pathways for the modulation of locomotion. Previous research using animal subjects has shown that when sensory nerves are cut (deafferented), commands can still be processed and locomotion is generated. However, the resulting locomotion is unmodulated and often sloppy and uncoordinated. Research has shown that, even though CPGs allow for locomotion to occur in the absence of proprioception, afferent feedback is a prime contributor in the generation of stable and modulated movement (MacKay-Lyons, 2002). Specifically, afferent feedback provides position sense, direction, and force movement, resulting in rhythmic movements (MacKay-Lyons, 2002).

Whereas a central pattern general (CPG) may provide a movement command, load receptors in the muscles and tendons provide important information that allows for a smooth gait pattern. For instance, load receptors located in the tibias anterior provide information to the CNS that aids in the regulation of the activation time and duration for the gastrocnemius. Receptors in the hip provide afferent formation that is critical during phase transitions for different movement patterns (Dietz, 2002).

Thus, sensory information plays a critical role in movement in that sensory information will aid in the selection of proper motor actions in response to the environment and adapt and shape motor programs through feedback, allowing for corrective actions to occur in response to a dynamic environment (O'Sullivan & Schmitz, 2007). Sensory feedback control plays a critical role in adjusting stride-to-stride limb trajectories in order to smooth out irregularities during unperturbed movements and safely navigate and maintain balance (Gandevia & Burke, 1992). Sensory information and information provided by Golgi tendon organs and muscle spindles provide critical information for the generation of rhythmic alternating contractions in muscles, indicating that sensory information plays a role in locomotion. Specifically, sensory information contributes to stepping frequency. Furthermore, joint receptors and the muscle spindle afferent (from stretch hip flexors) contribute to the regulation of phase transitions and timing of when the legs should swing forward, thus contributing to the rhythm of gait (Dietz & Duysens, 2000; Shumway-Cook & Woollacott, 2012).

Sensory information and proprioceptive information are also critical for the regulation and control of one's body position through locomotion. The ability to maintain postural stability during locomotion is a key and fundamental task. Postural control, which may be defined as the ability to control one's body position in space, and maintaining an appropriate relationship

between one's body segments and between the body and the environment for a task are critical in order to keep the body stable and oriented. Postural stability, also known as balance, is the ability to control the center of mass in relationship to the base of support. The center of mass is defined as a point that is at the center of the total body mass (Shumway-Cook & Woollacott, 2012). The base of support is defined as the area of the body that is in contact with the support surface. Previous research indicates that the central nervous system will control the body's center of mass in order to maintain postural control. Another term and concept critical to postural control is center of pressure. The body will generate forces in order to control the motion of the center of mass. The center of pressure is the center of the distribution of the total forces applied to the supporting surfaces. The center of pressure moves continuously around the center of mass to keep it within the base of support (Shumway-Cook & Woollacott, 2012).

Every task requires an orientation component and stability component, and these requirements will change depending upon the task and the environment. During locomotion, postural control ensuring orientation and stability is essential. During gait, the body's center of mass (center of gravity) does not stay within the base of support of the feet; thus, the body is in a constant state of imbalance. However, individuals do not always fall while walking because normally the foot that swings forward during gait is placed ahead of and lateral to the center of gravity as it moves forward, keeping the center of mass relative to the moving base of support (Shumway-Cook & Woollacott, 2012).

Therefore, there are several neural components that are critical for postural control, such as motor processes, which are the organization of muscles to perform actions such as swinging the leg forward; sensory/perceptual processes, which consist of organizing and integrating various visual, vestibular, and somatosensory systems; and lastly high-level cognitive processes

for interpreting the information provided by the sensory and perceptual process in order to produce an appropriate action. According to dynamical systems theory, postural control is due to the complex interactions of various body systems working cooperatively to control the body's orientation and stability (Shumway-Cook & Woollacott, 2012).

Thus, the generation, maintenance, and regulation of gait requires input from specific neuronal mechanisms, such as afferent feedback and proprioceptive information and neuronal circuits in the spinal cord, thus shaping a movement pattern. There are three reflex systems that contribute to the modulation of gait: the monosynaptic reflex, which is mediated by Ia afferent nerves; the cutaneous reflexes, which is mediated by the skin afferents; and the polysynaptic reflexes, which integrate afferent inputs from a variety of sources (Dietz, 2002).

The monosynaptic reflex, also known as the spinal stretch reflexes or myotatic reflex, is a preprogrammed response by the body due to a stretch stimulus in the muscle. When a muscle spindle is stretched, the spinal cord receives a signal immediately and responds by having that muscle contract. The myotatic reflex is critical for posture and gait because if the body begins to deviate due to an obstacle or change in terrain, the stretch reflex will quickly counter interruption and ensure the body's center of mass is over the base of support. Furthermore, during gait, this reflex, such as the H-reflex of the soleus, may provide compensation for irregularities in the ground. However, it still remains unclear as to the magnitude of the functional impact the stretch reflex has during gait. The monsynaptic reflex system is very sensitive to small inputs, thus only responding to small irregularities on the ground. So, the afferent input that is selected in response to what is occurring in the body's external environment is critical because the neuronal signals of the muscle stretch or length is not enough to control the body during gait. Body control requires a combination of afferent inputs (Dietz, 2002).

The second reflex system is the cutaneous system. Muscles will respond to sensory nerves that are induced by electrical stimuli. Various limb muscles will have this response mechanism that has a latency similar to that of spinal pathways. Cutaneous leg muscle reflexes are motor task specific, providing profound modulation that depends on the context in which they are evoked. Cutaneous leg reflexes are also nerve specific, which appears to be important for function, and may include central pattern generators (Dietz, 2002).

Lastly, polysynaptic reflexes are mediated by muscle proprioceptive input from group 2 afferent fibers, which are static muscle spindles or skin. From a functional perspective, polysynaptic reflexes may be particularly important for function because they may provide compensatory responses during gait that are more complex than simple stretch–reflex responses. The polysynaptic pathway integrates inputs from muscle, joint, and cutaneous afferents, and combines these inputs with commands from supraspinal centers to common spinal interneurons. The polysynaptic reflex has both excitatory and inhibitory connections for both extensors and flexors. The polysynaptic reflex sensory input determines direction, velocity, and amplitude of the bodily adjustments through specific patterns of leg muscle activation needed by individuals to maintain their center of gravity over their feet (Dietz, 2002).

Afferent information for locomotion will be provided from a variety of sources. In addition to receptions in the skin and muscles, afferent information will be provided from visual and vestibular sources. Spinal reflex pathways and descending pathways will converge on a common interneuron in which these inputs will be integrated. For examples, activity from the length sensors in muscles (i.e., the muscle spindles) will be reduced by visual feedforward information. Additionally, proprioceptor information from the leg muscles during gait may determine the amount and degree of influence of vestibulospinal input to stabilize the body

during movement. On the other hand, the amount and degree of vestibulospinal input will be increased when there is a loss or decrease in somatosensory information (Dietz, 2002).

In summary, gait is a complex behavior. A stable gait is characterized by postural control, which may be accomplished through the production of coordinated rhythmic patterns of muscle activation in the lower extremities and trunk and which moves the body forward in the desired direction, maintaining the body's center of mass and center of pressure within the established base of support, producing the needed posture dynamic stability throughout locomotion.

As a result, during a stable gait pattern, the body can respond to environmental challenges, such as avoiding obstacles; negotiate uneven terrain; and change speed and direction as required (Shumway-Cook & Woollacott, 2012). A disruption in the somatosensory system may result in decreased gait modulation and adaptation, interfering with and disturbing a normal gait cycle. A gait cycle is a series of cyclical movements, beginning when the foot contacts the ground, which is most often the heel. This is denoted as the 0% point and is beginning of the gait cycle, which is also known as heel contact or heel strike. The gait cycle is 100% complete when the same foot again makes contact with the ground (Neumann, 2002). A stride, which also is another term for gait cycle, is the events and their sequences that take place between successive heel contacts of the same foot. A step, on the other hand, is the sequence of events that occurs within successive heel contacts of opposite feet. Therefore, a gait cycle has two steps: a right step and a left step (Neumann, 2002).

A gait cycle may be simply described by its most basic spatial descriptors, which include the length of a stride and the length of a step. Stride length may be defined as the distance between two successive heel contacts of the same foot, whereas step length may be defined as

the distance between successive heel contacts of the two different feet. A normal stride length is approximately 72 cm (Neumann, 2002). Step width is also an important spatial descriptor of gait and may be defined as the lateral distance between the heel centers of two consecutive foot contacts. Step width is normally between 7 and 9 cm (Neumann, 2002). Furthermore, foot angle may be defined as the angle between the line of progression of the body and the long axis of the foot. A normal foot angle is 7 degrees (Neumann, 2002).

The gait cycle may be further divided into two major phases: stance and swing (Neumann, 2002). The stance phase begins at right heel contact and continues as long as the right foot remains on the ground. The stance phase ends when the right toe comes off the ground. The swing phase begins when the right toe lifts off the ground and ends when the right heel makes contact with the ground once again. Normally, individuals will spend 60% of their time in stance phase and 40% of their gait cycle in swing phase (Neumann, 2002).

The basic temporal gait descriptors consist of cadence, stride time, and step time (Neumann, 2002). Cadence may be defined as the number of steps per minute; this may also be referred to as step rate. Additionally, stride time is defined as the time for a full gait cycle, and step time is defined as the time for completion of a right or a left step (Neumann, 2002). Walking speed, which is a combination of spatial and temporal measures, informs the distance covered in a given amount of time and may be the best functional measure of an individual's ability to walk. Normal gait speed is 1.37 m/s (Neumann, 2002).

The adaptation of gait to environmental demands depends in part upon the somatosensory system, which consists of various sensory and proprioceptors that provide the input to modulate the gait pattern. The proprioceptors convey information about the body and the environment to the spinal cord via afferent nerves (Dietz, 2002). However, these are the same nerves in which

chemotherapy agents exert their toxic affect. Tofthagen and colleagues (2012) found that as the chemotherapy dosages increased, the presences of neuropathic symptoms increased and muscle strength and balance decreased, causing greater difficulty in performing the tasks of walking and driving.

Although gait is a subconscious and highly reproducible movement performed daily, previous research suggests that when certain gait characteristics deviate from the normal, an individual may be at higher risk for falls. Research indicates that the majority of falls experienced by the elderly will occur during walking. As with individuals with CIPN, aging will result in desensitization of motor units, as well as decreased perceptions of high-frequency vibrations, touch, proprioception, and pressure stimuli, indicating a disturbed somatosensory system (Prince, Corriveau, Hebert, & Winter, 2007). Further investigation has shown that elderly individuals who fall will display slower gait speeds, decreases in step length, and increases in double support times (Shumway-Cook & Woollacott, 2012). Additionally, elderly adults who fall will exhibit increased variability within swing time and stride length, which has been shown to predict fall risk (Verghese et al., 2009). Increased variability within spatiotemporal gait parameters has been associated with increased fall risk (Maki, 1997)

Falling is a significant event, especially for older adults, as falls have been linked to serious injuries and disabilities, loss of independence, and increased mortality. Twenty-three percent of falls in adults aged 65–69 resulted in death, with the rate climbing as high as 50% of falls resulting in death for adults aged 85 or older. It is estimated that of the 1.6 million new cancer diagnoses in 2013, 77% were individuals over the age of 55 (Alamgir et al., 2012). Previous studies have indicates that 20% of patients with CIPN may fall, which is a higher percentage than age-matched controls (Mohile et al., 2009, 2011; Tofthagen et al., 2012). Stone

and colleagues (2012) conducted a 6-month prospective study of cancer patients and found that 50.3% of the patients fell during the follow-up period. More significantly, more than one-third of the falls resulted in soft tissue injuries and 3.2% resulted in fractures. Bylow et al. (2008) reported that 34% of prostate cancer patients undergoing androgen deprivation therapy fell over the course of 6 months. Bylow et al. also noted that these patients experienced significant deficits in physical performance as measured by reduced gait speed, balance, and lower body strength. In a very recent study, Gewandter and colleagues (2013) investigated the correlations between chemotherapy-induced peripheral neuropathy, functional impairments, and prevalence and falls. Of the 471 participants with CIPN, 12% reported having fallen in the 3 months prior to the study and 27% of the participants had impairment in functional capacity. The participants who reported a fall also had higher (worse) sensory and motor neuropathy scores. Those who fell reported struggling to hold a pen, which resulted in difficulty writing, as well as trouble with walking (Gewandter et al., 2013).

A study conducted by Tofthagen et al. (2012) evaluated the risk factors for falls in a group of patients with CIPN. The participants received paclitaxel, docetaxel, oxaliplatin, or cisplatin and reported at least one symptom of CIPN. Tofthagen and colleagues found that fallers received higher cumulative doses of chemotherapy and a higher number of neuropathic symptoms as noted by higher score on the Chemotherapy Induced Peripheral Neuropathy Assessment Tool self-report questionnaire as a whole, as well as on both the symptom experience and interference items of the questionnaire. The participants whom fell more also reported more severe muscle weakness, loss of balance, and increased interference with walking and driving. An interesting finding was that participants who received paclitaxel or docetaxel were more likely to have fallen then those who received a platinum-based agent, such as

okaliplatin. It was also interesting to note that Tofthagen and colleagues did not find a significant difference between fallers and nonfallers in terms of age, gender, stage of disease, or any other demographic characteristic (Tofthagen et al., 2012)

Although the literature often generally cites that cancer patients report functional impairments, such as difficulties in walking, there is limited research examining specific gait parameters deficits. Gait parameters are significant because research shows that spatiotemporal gait characteristics, such as cadence, stride length, swing, double support, stride length variability, and swing time variability, may be indicators of risk for falling. Specifically, research indicates that slower gait speeds, decreases in step length, and increases in double support times may increase the risk of falling (Toulotte et al., 2006; Verghese et al., 2009). Similar to individuals with CIPN, aging will result in desensitization of motor units, as well as decreased perceptions of high-frequency vibrations, touch, proprioception, and pressure stimuli, indicating a disturbed somatosensory system (Prince et al., 2007).

More current research has also shown that cancer patients may display a decrease in postural stability as a result of somatosensory changes that occur as a result of taxane chemotherapy (Tofthagen et al., 2012; Wampler et al., 2007). Specifically, Wampler and colleagues (2007) conducted a prospective study that evaluated postural stability of women who received paclitaxel or docetaxel for treatment of breast cancer and compared them to matched health controls. Because vision acuity plays a role in postural control, as well as in the neurological and visual system, inclusion criteria required participants to have a corrected low-contrast visual acuity better than 20/60 and corrected high-contrast visual acuity better than 20/40 (Wampler et al., 2007).

The participants in both the breast cancer and healthy control groups completed one testing session each. To establish intrarater reliability, women in the breast cancer group returned and repeated all tests within 1 week of initial testing. The participants in the breast cancer group were tested within 30 days of completing the final treatment of taxane infusion. Testing included several quantitative peripheral neuropathy measures, which included the total neuropathy score, the modified neuropathy score, quantitative touch thresholds, quantitative vibration thresholds and nerve conduction studies (Wampler et al., 2007).

Several measures were used to assess postural control. Center of pressure (COP) data were collected using a Kistler force plate to assess stability under four static positions: eyes open with head straight, eyes open with head back 40°, eyes closed with head straight, and eyes closed with head back 40°. The NeuroCom Sensory Organization Test (SOT) was used to assess dynamic postural stability by way of a composite equilibrium score and a mean equilibrium score. The SOT required the participants to stand as steady under six different conditions. Three trials were performed for each condition. The six conditions challenged the sensory system and increased in difficulty. The first condition required the participants to keep their eyes open on a stable platform and a nonmoving visual surround. The tests then progressed by removing visual feedback (by closing eyes), altering visual feedback (by moving the surround), or altering somatosensory feedback (rotating the platform in the sagittal plane). The calculated equilibrium score represented the amount the participant swayed during the various conditions. Also included was the Timed Up and Go (TUG) test, which has been established as a clinical measure of balance that assesses the relationships between the various measures of postural control (Wampler et al., 2007).

Wampler and colleagues (2007) found that the breast cancer patients treated with taxane chemotherapy experienced a mild yet significant peripheral neuropathy and a significant increase in mean TUG scores when compared to the healthy controls. Furthermore, the participants with breast cancer displayed poorer static and dynamic postural control, especially during the conditions that required the participants to close their eyes, which required the participants to increasingly rely on their somatosensory and vestibular input for postural stability. Wampler and colleagues (2007) concluded that women treated with taxanes may experience significant changes in postural stability as a result of their treatment, which may cause the neurotoxic of effect of taxane on the somatosensory systems and the subsequent changes that occur as a result of the neurotoxicity. Furthermore, it was noted that while the severity of the peripheral neuropathy experienced by the participants in this study was mild, the COP velocities, as measured by the force plate, as well as their SOT scores from their first three conditions, were comparable to diabetic individuals diagnosed with severe neuropathy. (Wampler et al., 2007).

An additional interesting finding from the study conducted by Wampler and colleagues (2007) was that the modified TNS was moderately correlated with the total SOT score (r = -.66, p = .02) and explained just 44% of the variance in SOT scores. This suggested that other pathological changes may be occurring as the result of chemotherapy and may contribute to postural instability (Wampler et al., 2007). Tofthagen and colleagues (2012) suggested that it is important to note that other factors may contribute as well. Treatment-related side effects, such as fatigue, generalized weakness, atrophy, anemia, and poor performance status, may also increase fall risk in those who undergo chemotherapy for treatment of cancer. Generalized weakness may be the result of anemia, fatigue, and muscle weakness. Anemia, which is a common side effect of cancer treatment, reduces the amount of red blood cells in the body and

thus reduces the oxygen-carrying capability. This may result in tiredness and fatigue, which may be primary factors in fall incidences (Tofthagen et al., 2012).

Although there has been a minimal amount of research done with respect to the mechanisms of falls often reported by cancer patients, the effects that peripheral neuropathy has on gait have been well documented within the diabetic population. Specifically, it has been demonstrated that individuals with diabetic peripheral neuropathy generally display a gait that is more conservative and may be characterized by slower walking velocities and smaller step sizes (Paul et al., 2009; Wrobel et al., 2009). Furthermore, as many as 62% of diabetics with peripheral neuropathy may fall (Wallace et al., 2002).

Similar to chemotherapy-induced peripheral neuropathy (CIPN), diabetic peripheral neuropathy (DPN) targets both sensory and motor fibers and is progressive in nature. Large- and small-diameter nerve fibers are affected, resulting in attenuated sensory nerve conduction, which includes large fiber thresholds for vibration and joint positions, as well as neurogenic atrophy due to axonal degeneration of motor fibers (Andersen et al., 1997; Dyck & Thomas, 1999; Horak et al., 2002)

Patients with DPN may experience symptoms that are sensory in nature and may include burning, tingling, shooting (“electric shock”), lancing (stabbing), and numbness. Symptoms may be present in both the upper and lower extremities and follow the “glove and stocking” distribution pattern, in which symptoms may initially present in the toes and fingers and progress proximally. Individuals may also experience motor deficits, characterized by weakened muscles, particularly in the lower extremity. DPN may also be the result of disruptions in the anatomy and function within the somatosensory system, which may be caused by endoneurial hypoxia

brought on by poor oxygen diffusion to the small blood vessels of the lower limbs (Tesfaye & Selvarajah, 2011).

The pathophysiological mechanisms of DNP are not completely understood but may be related to the intermittent hyperglycemic damage of neurons that may increase the spontaneous C-fiber firing, which may be the result of remodeling of voltage-gated ion channels (Shankarappa et al., 2011). Additionally, several other mechanisms have been postulated, such as changes in the disruption and expression of calcium and sodium channel, altered expression of neuropeptides and peripheral blood flow, atrophy, and degeneration to axons, damage to small fibers. Lastly, possible mechanisms may also include an increase in oxygen-free radicals, which cause oxidative stress and ischemia of nerves, mitochondrial disruptions, and reduced intraepidermal nerve fiber density and autonomic dysfunction (Kaur, Pandhi, & Dutta, 2011; Tesfaye & Selvarajah, 2011). It has also been proposed that DPN is caused by endoneurial hypoxia brought on by poor oxygen diffusion to the small blood vessels of the lower limbs. Despite the uncertainty in pathophysiology, it is clear that peripheral neuropathy affects both sensory and motor fibers and is progressive in nature. Large- and small-diameter nerve fibers are affected, resulting in attenuated sensory nerve conduction, which includes large-fiber thresholds for vibration and joint positions. Small-fiber thresholds for pain and temperature are also affected (Dyck & Thomas, 1999; Horak et al., 2002).

In addition to a decrease in nerve conduction information resulting in attenuated afferent and proprioceptive information, individuals with diabetic peripheral neuropathy also exhibit weakened knee and ankle muscle strength caused by neurogenic atrophy due to axonal degeneration of motor fibers (Andersen et al., 1997; Thomas & Tomlinson, 1993). There is a significant decrease in muscle compartment cross-sectional area in both the proximal and distal

levels of the lower leg, resulting in impaired ankle dorsiflexors and plantarflexors (Andersen et al., 1997).

Thus, individuals with DPN often display altered gait patterns, which may be characterized as slower, with shortened stride lengths and increased base widths, stride times, and double support times compared to age-matched controls (Allet et a., 2008; Paul et al., 2009; Wrobel et al., 2009). The altered gait patterns may be due to the impaired proprioceptors and sensorimotor functions, which negatively affect the afferent feedback that is necessary to successfully modulate locomotion (Andersen et al., 1997; Dyck & Thomas, 1999; Horak et al., 2002; Shankarappa et al., 2011).

Individuals with diabetic peripheral neuropathy may display gait patterns characterized by slower speeds, shortened stride lengths, greater double support times, decreased ankle moments and powers, and decreased vertical and anterior–posterior ground reaction forces. Dingwell and Cavanagh (2001) investigated if these changes also resulted in locomotor variability, as increased locomotor variability is associated with increase incidences of falls. Participants included 14 diabetic individuals with significant neuropathy, as determined by Semmes-Weinstein filaments and a biothesiometer for vibration testing. Participants were compared to 12 gender-, age-, height-, and weight-matched healthy controls (Dingwell & Cavanagh, 2001).

Three strain gauge electrogoniometers were placed across the approximate joint centers of the hip, knee, and ankle of the right leg to measure sagittal plane motion. To measure upper-body dynamic stability, a triaxial accelerometer was attached to the base of the sternum to measure accelerations of the upper body in the anterior–posterior, vertical, and mediolateral

directions. Each participant walked around a 200-m open-level indoor walking track at a natural pace. Data were collected at 66.7 Hz (Dingwell & Cavanagh, 2001).

Dingwell and Cavanagh (2001) found that the participants with peripheral neuropathy walked slower and took smaller steps compared to the control group. Furthermore, the participants with peripheral neuropathy displayed significant increases in locomotor variability, and variability in the gait cycle was most highly correlated with falls. Specifically, as variability increased, fall risk increased (Dingwell & Cavanagh, 2001).

The findings by Dingwell and Cavanagh (2001) have since been confirmed in various other studies. Paul and colleagues (2009) evaluated gait parameters of individuals with diabetic peripheral neuropathy (DPN) with individuals without DPN. Of the 30 participants recruited, 15 had DPN whereas the remaining 15 did not have DPN. Paul et al. used the GAITRite walkway to evaluate various spatiotemporal parameters, such as step length and duration, duration of single and double support, velocity, and cadence. The primary outcome was gait velocity. For all of the gait variables measured, Paul and colleagues found that there was a statistically significant difference in gait parameters within individuals with DPN. Specifically, individuals with DPN had significantly slower walking velocities, as well as shorter step length, but longer step times. Individuals with DPN also displayed greater double support times and a slower cadence compared to individuals without DPN (Paul et al., 2009).

Furthermore, Camargo et al. (2015) investigated the relationships between balance, ankle muscle strength, and spatiotemporal gait parameters in individuals with diabetic peripheral neuropathy. The spatiotemporal gait parameters were evaluated by recording the time it took the participants to walk predetermined distances during self-selected walking speeds and maximal walking speeds. Balance was evaluated using the Timed Up and Go (TUG) test. Compared to

healthy controls, individuals with DPN displayed significantly different spatiotemporal gait parameters and scores on the TUG test. Specifically, individuals with DPN had shorter step lengths and slower cadence and gait speeds in both self-selected walking speed and maximal walking speed. Results also indicated the individuals with DPN took greater amounts of time to perform the test, suggesting DPN individuals display functional deficits when ambulating (Camargo et al., 2015).

Wuehr and colleagues (2014) evaluated the influence of peripheral neuropathy on walking patterns of 18 neuropathic individuals compared to age-matched controls. The participants presented with significant peripheral neuropathy in their legs and feet as a result of various etiologies that consisted of type 2 diabetes, vitamin B12 deficiency, ethyl toxicity, and idiopathic peripheral neuropathy. Walking velocity, as well as cadence, base width, stride length, stride time, double support time, double support time percentage, swing time percentage, and stance time percentage, were analyzed for each trial and leg separately using the GAITRite system.

Wuehr and colleagues (2014) found that peripheral neuropathy directly affected gait variability between strides in both the mediolateral plane (base width) and fore–aft plane (stride time and stride length). Specifically, individuals with peripheral neuropathy displayed significant variability in heel strike magnitudes, regardless of walking speed, which is significant considering mediolateral adjustments are primarily controlled by integrated sensory feedback (Wuehr et al., 2014). Fore–aft locomotion, which is thought to be stabilized by biomechanical regulation, should not be affected by a deficit in the sensory system. However, individuals with peripheral neuropathy, and thus deficient peripheral sensory systems, displayed significant variability in both stride length and stride time. Variability was more present at slower walking

speeds, which is when locomotion is relies highly on active sensory feedback (Wuehr et al., 2014).

In summary, many patients who receive chemotherapy as part of their treatment for cancer are likely to experience CIPN in one form or another, which can cause a variety of debilitating symptoms due to peripheral nerve toxicities caused by the chemotherapy agents (Murillo et al., 2008; Visovsky et al., 2007; Wilkes, 2007). Specifically, chemotherapy agents may disrupt axonal transport, resulting in diminished or absent deep tendon reflexes, hyperesthesias, hypoesthesias, paresthesias, pain, loss of temperature and vibration sense, loss of proprioception, and motor neuropathy (Murillo et al., 2008; Visovsky et al., 2007; Wilkes, 2007). Cancer survivors who receive chemotherapy for cancer treatment may experience a disruption to the somatosensory systems which may negative effect the sensory feedback that is necessary to produce a coordinated and balanced gait (Magill & Anderson, 2013; Murillo et al., 2008; Visovsky et al., 2007; Wilkes, 2007). Research indicates that cancer survivors who have undergone chemotherapy report gait disturbances and higher incidences of falls (Bylow et al., 2008; Gewandter et al., 2013; Mohile et al., 2009, 2011; Stone et al., 2012; Tofthagen et al., 2012; Wampler et al., 2007). Although the literature has not evaluated specific changes in spatiotemporal gait parameters in cancer patients, previous research indicates that individuals afflicted with peripheral neuropathy as a result of various etiologies will display altered gait patterns characterized by smaller step and stride lengths, wider step widths, increased double support times, and slower walking speeds (Dingwell & Cavanagh, 2001; Toulotte et al., 2006; Verghese et al., 2009; Wuehr et al., 2014). Furthermore, individuals with peripheral neuropathy will display increased variability within these same parameters, which is significant considering that increased variability is associated with increased falls (Dingwell & Cavanagh, 2001; Maki,

1997). As a result, patients experiencing peripheral neuropathy, regardless of the etiology, experience fall rates that are higher than individuals without peripheral neuropathy. However, investigation of changes within spatiotemporal gait parameters has provided insight as to the changes in gait that individuals with peripheral neuropathy due to diabetes and vitamin deficiencies. Research has not investigated changes within the spatiotemporal gait parameters of cancer patients experiencing CIPN. Therefore, considering the common pathophysiologies of peripheral neuropathy between diabetic peripheral neuropathy and chemotherapy-induced peripheral neuropathy and evaluating spatiotemporal gait patterns such as stride length, cadence, and velocity within individuals diagnosed with CIPN may provide insight into the gait interference and incidences of falling that patients with CIPN have reported within the literature.

Chapter III

METHODS

Cancer survivors who receive chemotherapy for cancer treatment may experience a disruption to the somatosensory systems, which may negatively affect the sensory feedback which aides in the coordinated and balance required in gait (Magill & Anderson, 2013; Murillo et al., 2008; Visovsky et al., 2007; Wilkes, 2007). Research indicates that cancer survivors who have undergone chemotherapy report gait disturbances and higher incidences of falls (Bylow et al., 2008; Gewandter et al., 2013; Mohile et al., 2009, 2011; Stone et al., 2012; Tofthagen et al., 2012; Wampler et al., 2007). Although the literature has not evaluated specific changes in spatiotemporal gait parameters, research has indicated an association between cadence, stride length, swing, double support, stride length variability, and swing time variability. Specifically, research indicates that slower gait speeds, decreases in step length, and increases in double support times may increase the risk of falling (Toulotte et al., 2006; Verghese et al., 2009). Thus, evaluating spatiotemporal gait patterns within individuals diagnosed with CIPN who are at a risk for falls may provide insight into the gait interference that increases the risk of falling as reported in the literature by patients with CIPN.

Therefore, the purpose of this study is to assess whether chemotherapy-induced peripheral neuropathy is associated with spatiotemporal gait adaptations in posttreatment adult cancer survivors when compared to healthy, disease-free, age- and morphologically matched controls.

Participants

Sixteen participants between the ages of 50 and 70 were recruited for participation. Eight of the participants had a histologically confirmed stage 2–3 breast or colorectal cancer diagnosis with a confirmed treatment plan consisting of taxane- or oxaliplatin-based chemotherapy as confirmed by an oncologist. Participants also had a confirmed diagnosis of chemotherapy-induced peripheral neuropathy according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Subjects were excluded if they had a history of peripheral neuropathy (i.e., hereditary peripheral neuropathy associated with nutritional agents and paraneoplastic), known peripheral neuropathy, or diseases that may contribute to peripheral nerve damage, such as diabetes, renal insufficiency, alcohol abuse, vitamin B12 deficiency, HIV, and vasculitis. Subjects were excluded if they had central or peripheral neurologic disease, brain or spinal cord metastases, orthopedic problems that affect balance, or vestibular system or visual disease. Subjects were excluded if they had corrected low-contrast visual acuity worse than 20/60 and a corrected high-contrast visual acuity worse than 20/40. Subjects, who had participated in regular exercise, as defined as 150 min of light-to-moderate intensity exercise per week over the past year, were excluded from this trial. Subjects were also excluded if they used a walking aide.

Design

This study was a quasi-experimental design.

Variables

The variables included both spatial and temporal gait parameters. The spatial gait parameters consisted of step length and base of support. Step length was measured from the heel center of the current footprint to the heel center of the previous footprint on the opposite foot, by

the GAITRite walking system. H-H base of support, or base width, was measured as the vertical distance from the heel center of one footprint to the line of progression formed by two footprints of the opposite foot, as measured by the GAITRite walking system.

The temporal gait parameters consisted of velocity, step time, swing time, single support time, and double support time. Velocity was defined as dividing the distance traveled by the ambulation time and was expressed in centimeters per second (cm/sec). Step time was defined as the time in seconds elapsed from first contact of one foot to first contact of the opposite foot. Swing time was initiated with the toe off and ended with the heel strike. It was defined as the time elapsed between the last contact of the current footfall to the first contact of the next footfall on the same foot and was expressed in seconds (s). Single support was defined as the time elapsed between the last contact of the current footfall to the first contact of the next footfall of the same foot and was measured in seconds (s). Swing time is equal to the single support time of the opposite foot. Lastly, double support time was defined as the period when both feet are on the floor. Initial double support occurs from the heel contact of one footfall to the toe-off of the opposite footfall and is measured in seconds (s). Fall risk was defined as the time it took to complete the Timed Up and Go test. Research suggested that a time of greater than 10.7 s indicated risk for falls (Jernigan et al., 2012).

Measurements

The GAITRite system was used to measure all spatio temporal parameters of gait. It is an electronic pathway that is 8.2 m in length. Through an interface bale, the electronic pathway connects to a personal computer. The electronic pathway is made up of a series of sensory pads that are inserted in grid formation between a layer of vinyl (top cover) and foam rubber (bottom cover). The active area is 61 cm wide and 732 cm long. The sensors are placed 1.27 cm apart

and are activated by mechanical sensors. There are a total of 27,648 sensors. Data from the activated sensors are collected by a series of onboard processors and transferred to the computer through a serial port. The sampling rate of the system is 8 Hz. Visually, the walkway resembles a carpet runner and is portable (Webster, Wittwer, & Feller, 2004).

Fall risk was assessed using the valid and reliable Timed Up and Go test (TUG), which is a mobility test used to measure basic mobility skills (Webster, Wittwer, & Feller, 2004). The measurement outcome for the TUG is the time it takes to rise up out of a chair, walk 3 m away from the chair, walk 3 m back to the chair, and return to the seated position. The time it takes to complete this task is recorded. Previous research indicates that a time of greater than 10.7 s indicates risk for falls (Jernigan et al., 2012).

Procedures

Potential subjects were recruited through the placement of an Institutional Review Board (IRB)–approved advertisement flyer (see Appendixes A and B) on bulletin boards located throughout the Seton Hall University (SHU) community, as well as the surrounding SHU community. Participants were also recruited from Saint Michael's Medical Center, located in Newark, NJ. See Appendix E for the research flyer. A snowballing sampling technique method was used to recruit participants (Portney & Watkins, 2009).

Upon seeing the study research flyer, potential subjects contacted the primary investigator (PI) by either the e-mail address or phone number listed on the flyer (see Appendix B). Upon being contacted, the PI scheduled a meeting with the potential subject at the South Orange Campus of Seton Hall University, 400 South Orange Avenue, South Orange, New Jersey, in Corrigan Hall Room 67 (Functional Human Performance Lab) in order to review the inclusion and exclusion criterion for participation. The PI also met participants at the Cancer

Center at Saint Michael's Medical Center, which was a second testing site. The subjects were instructed to wear a T-shirt or sweatshirt, shorts or sweatpants, and a pair of comfortable walking shoes or sneakers to the testing sessions. Upon arrival to the testing session site, subjects were required to read an informed consent form. Subjects were given the opportunity to ask questions. If, after reviewing the consent forms and asking any related questions, the potential subjects were still willing to volunteer to participate, they were required to sign the consent forms and were advised that they could withdraw from the study at any time.

Following the signing of the informed consent forms, the PI administered the prescreen tool (see Appendix C) to those who met the study inclusion and exclusion criteria. The subjects' responses were recorded. An answer of *yes* to any of the questions indicated that the subject did not fit the inclusion and exclusion criteria and thus could not participate in the present study. If the subject did not qualify for participation, the subject was thanked for being willing to volunteer. Those subjects who met the study inclusion criteria proceeded to the data collection portion of the study.

Data collection began with the completion of the top portion of the Participant Data Collection Sheet (see Appendix D), which included the subject's cancer diagnosis, name of the chemotherapy agent received, age, sex, height, and weight. Prior to the collection of the spatiotemporal parameters of gait using the GAITRite system and risk of falls by the Timed Up and Go test, subject height and right/left leg length were measured (from the greater trochanter to the floor) using a standardized, flexible cloth tape. These data were required by the GAITRite software.

Next, following standard protocol, the Timed Up and Go test was performed to assess fall risk. The Timed Up and Go test required the subjects to raise their body out of a chair, walk 3 m

down a hallway, turn around, walk 3 m back to the chair, and sit back down in the chair. To set up the test, a 3-m (9.8-ft.) walkway was measured and marked on the floor using colored tape. The floor of the walkway was clear of any objects. A standard-height chair (seat height, 46 cm; arm height, 67 cm) was positioned at the beginning of the walkway. The subjects began by sitting on the standard chair, placing their back against the chair, and resting their arms by their sides.

The PI demonstrated the test prior to the subject performing the test. After the demonstration, PI instructed the subject to walk at a self-selected pace. When the subject was ready, the PI said "Go," indicating to the subject to get up out of the chair, walk the 3-m distance away from the chair, walk the 3-m distance back to the chair and sit back down. The stopwatch was started upon the "Go" command from the PI and was stopped when the subject's butt made contact with the seat upon sitting back down. The time it took to complete the test was recorded on the Individual Participant Data Collection Sheet (see Appendix B). Fall risk was indicated by a timed score of greater than 10.7 (Jernigan et al., 2012)

Jernigan and colleagues (2012) suggested that because in the clinical setting, sensitivity is the most important measure, as high sensitivity corresponds to more true positives and fewer false negatives. The Timed Up and Go test is a good test to assess fall risk due to its high sensitivity of 90%, 88.5% specificity, and high diagnostic accuracy at 88.9% when a modified cutoff score is applied. Subjects who volunteered to be in the control group were also assessed for fall risk.

After the completion of the Timed Up and Go test, the GAITRite was used to compute the spatiotemporal gait parameters (step length, step time, and walking speed). Before initiating walking on the GAITRite, the PI set up the location. For each trial, subjects were instructed to

initiate walking from a non sliding standing spot mat located at the midpoint of the start line placed 2 m before the beginning edge of the GAITRite carpet. This allowed walking to be initiated from the same location at every trial and permitted a steady state of ambulation to be achieved prior to stepping on the GAITRite walkway. The subjects were informed to negotiate the entire length of the 5.18-m GAITRite carpet walkway at a steady pace while looking straight ahead. Three trials were performed.

Data Analysis

The present study contained two groups: a control group, which consisted of healthy, disease free, age and morphologically matched controls, and an intervention group, which consisted of cancer survivors diagnosed with CIPN. The independent variable was the presence of CIPN. There were multiple dependent variables, which included the participants' TUG score and spatiotemporal gait parameters obtained from the GAITRite. Thus, the research question was answered by using a one-way MANOVA comparing each of the spatial and temporal variables between the two groups. An alpha level of 0.05 was used (Field, 2009).

Chapter IV

RESULTS

The purpose of this study was to investigate if changes exist in the spatiotemporal gait parameters of cancer patients who have completed chemotherapy for the treatment of cancer compared to age and morphological matched controls. A total of 16 subjects participated in the present study. Of the 16 subjects, 8 had CIPN, and the remaining 8 subjects were the age and morphologically matched controls.

Table 1 indicates that both of the groups had 6 females and 2 males. Table 2 indicates that the mean age of the CIPN participants was 61.38 years (*SD* = 7.24) and the mean age of the control participants was 62.25 years (*SD* = 3.77). Table 2 shows that the mean weight of the CIPN participants was 76.45 kg (*SD* = 18.48), whereas the mean weight of the control participants was 72.42 kg (*SD* = 8.88). Table 3 indicates that 5 of the participants had breast cancer and 3 participants had colon cancer. Of the types of chemotherapy received, 1 participant received pacelitaxel, 4 participants received taxanes, and 3 participants received oxaliplatin.

Table 4 indicates that age was normally distributed for CIPN D (7) = .224, $p > .05$ and control, D (7) = .122, $p > .05$. Table 4 shows that weight was normally distributed for CIPN D (7) = .584, p> .05 and control, D (7) = .117, p> .05. Table 4 also denotes that height was normally distributed for CIPN D (7) = .832, p> .05 and control D (7) = .936, p> .05. Lastly, as indicated in table 5, BMI was normally distributed for CIPN D (5) = .901, p> .05 and control, D (7) = .884, p> .05.

Table 1

Participant Gender

	Participant type	*N*
Females	CIPN	6
	Control	6
Males	CIPN	2
	Control	2

Table 2

Descriptive Statistics

	Participant type	*N*	Mean	Std. deviation	Std. error mean
Age (yrs.)	CIPN	8	61.38	7.42	2.63
	Control	8	62.25	3.77	1.33
Weight (kg)	CIPN	8	76.45	18.48	6.53
	Control	8	72.42	8.88	3.14
Height (cm)	CIPN	8	158.05	14.35	5.07
	Control	8	167.90	9.44	3.34
BMI (kg/m^2)	CIPN	8	27.71	6.34	2.24
	Control	8	24.85	2.37	.84

Table 3

Cancer Participant Descriptive

		Chemotherapy type		
Cancer type	*n*	Paclitaxel	Taxane	Oxaliplatin
Breast Cancer	5	1	4	
Colon Cancer	3			3

Table 4

Evaluating Descriptive Data for Normal Distribution

	Participant type	Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	*df*	Sig.	Statistic	*df*	Sig.
Age	CIPN	.159	8	.200	.888	8	.224
	Control	.267	8	.097	.861	8	.122
Weight (Kg)	CIPN	.189	8	.200	.937	8	.584
	Control	.223	8	.200	.859	8	.117
Height (cm)	CIPN	.289	8	.048	.832	8	.062
	Control	.157	8	.200	.936	8	.576
BMI	CIPN	.210	8	.200	.901	8	.296
	Control	.265	8	.103	.884	8	.205

Table 5 indicates that there was equal variability with age, F (1, 14) = 4.01, $p > .05$. Table 5 shows that the assumption of homogeneity of variance for weight had been violated, F (1, 14) = 6.59, $p < .05$. Table 5 shows that there was equal variability with height, F (1, 14) = .145, $p > .05$, but homogeneity of variance was not violated. Lastly, as displayed in Table 5, the assumption of homogeneity of variance for BMI had also been violated, F (1, 14) = 10.10, $p < .05$.

Table 5

Evaluating the Descriptive Data for Homogeneity of Variance

	Levene statistic	*df*1	*df*2	Sig.
Age (years)	4.01	1	14	.065
Weight (kg)	6.59	1	14	.022
Height (cm)	.145	1	14	.709
BMI	10.10	1	14	.005

An independent *t* test was used to evaluate if the participant characteristics of the CIPN group were significantly different or similar to the participant demographics of the control group.

As four independent *t* tests were run on the same data, a Bonferroni correction was applied to reduce the risk of making type 1 error (Field, 2009). As indicated in Table 6, there was no significant difference in age, t (14, = –.297, $p > .05$ or weight, t (10.071) = .556, $p > .05$, between the two groups. Table 6 also denotes that there was no significant difference in height, t (14) = -1/622, $p > .05$, or BMI, t (8.913) = 1.196, $p > .05$, between the two groups. Therefore, there was no significant differences between the participant characteristics of the two groups other than the presence of chemotherapy-induced peripheral neuropathy.

Table 6

Independent t *Test to Compare Descriptive Data Means*

		t test for equality of means		
		t	*df*	Sig. (2-tailed)
Age	Equal variances assumed	-.297	14	.771
	Equal variances not assumed	-.297	10.385	.772
Weight	Equal variances assumed	.556	14	.587
(kg)	Equal variances not assumed	.556	10.071	.590
Height	Equal variances assumed	-1.622	14	.127
(cm)	Equal variances not assumed	-1.622	12.100	.131
BMI	Equal variances assumed	1.196	14	.251
	Equal variances not assumed	1.196	8.913	.262

With the results of the independent *t* test indicating that two groups were the same with regard to their demographic characteristics, a one-way MANOVA was conducted to determine if significant differences exist between the dependent variables. Before a one-way MANOVA was ran, the assumptions for the test were first tested. The assumptions tested consisted of multivariate normality, the linear relationship between the dependent variables, the homogeneity of variance–covariance matrices, and multicollinearity (Field, 2009)

The first assumption tested was multivariate normality by use of the Shapiro-Wilk test (Field, 2009).

Table 7

Assessing Normal Distribution of Gait Parameters

		Kolmogorov-Smirnov			Shapiro-Wilk		
	Participant type	Statistic	*df*	Sig.	Statistic	*df*	Sig.
TUG	CIPN	.340	8	.007	.643	8	.001
	Control	.183	8	.200*	.899	8	.284
Velocity	CIPN	.184	8	.200*	.950	8	.708
	Control	.203	8	.200*	.911	8	.358
R_Step_Time	CIPN	.218	8	.200*	.784	8	.019
	Control	.179	8	.200*	.903	8	.308
R_Step_Length	CIPN	.291	8	.045	.791	8	.023
	Control	.202	8	.200*	.912	8	.372
R_HH_Base_Support	CIPN	.141	8	.200*	.945	8	.658
	Control	.219	8	.200*	.943	8	.642
R_Swing_Time	CIPN	.172	8	.200*	.937	8	.582
	Control	.272	8	.083	.820	8	.046
R_Single_Support_Time	CIPN	.228	8	.200*	.881	8	.194
	Control	.185	8	.200*	.955	8	.761
R_Double_Support_Time	CIPN	.213	8	.200*	.947	8	.679
	Control	.197	8	.200*	.896	8	.265

Table 7 indicates that the data for the TUG test for the CIPN group, D (7) = .643, $p < .05$, were not normally distributed. But the TUG data for the control group were normally distributed, D (7) = .899, $p > .05$. Velocity data for the CIPN group, D (7) = .950, $p > .05$, as well as data for the control group, D (7) = .911, $p > .05$, were normally distributed. Table 7 depicts that data for the right step time of the CIPN group, D (7) = .784, $p < .05$, were not normally distributed, whereas data for the control group was normally distributed, D (7) = .903, $p > .05$. Furthermore, CIPN data for base step length, D (7) = .791, $p < .05$, were not normally distributed, whereas data for control were normally distributed, D (7) = .912, $p > .05$. Base of support data for both the CIPN group, D (7) = .945, $p > .05$, and control group, D (7) = .943, $p > .05$, were normally distributed. Swing time data for the CIPN group, D (7) = .937, $p > .05$, were

normally distributed, whereas swing time data for the control group were not normally distributed, D (7) = .820, $p < .05$. Table 7 indicates that single support time for the CIPN group, D (7) = .881, $p > .05$, and the control group, D (7) = .955, $p > .05$, were normally distributed. Lastly, Table 7 depicts that double support time data for the CIPN group, D (7) = .947, $p > .05$, and control group, D (7) = .896, $p > .05$, were both normally distributed. Although Table 7 indicates violations of the assumption of normal distribution, however, a one-way MANOVA was still conducted, as the test is robust enough (Field, 2009).

The second assumptions tested was if there was homogeneity of variance-covariance matrices by use of the Leven's test (Field, 2009). Table 8 displays the results of Levene's test, which assesses homogeneity of variance/covariance. As indicated in Table 8, there was no significant difference in variability for TUG data, F (1, 14) = 3.84, $p > .05$. Table 8 also indicates that velocity, F (1, 14) = 32.44, $p > .05$, and step time, F (1, 14) = 3.28, $p > .05$, also satisfied the assumption of homogeneity of variance/covariance.

Table 8

Leven Test for Homogeneity of Variance-Covariance

	Levene statistic	*df*1	*df*2	Sig.
TUG	3.84	1	14	.070
Velocity	2.55	1	14	.133
R_Step_Time	3.28	1	14	.092
R_Step_Length	4.00	1	14	.065
R_HH_Base_Support	2.58	1	14	.131
R_Swing_Time	2.56	1	14	.132
R_Single_Support_Time	.74	1	14	.403
R_Double_Support_Time	1.07	1	14	.319

Base of support, F (1, 14) = 2.58, $p > .05$, and swing time, F (1, 14) = 3.84, $p > .05$, also satisfied the assumption of homogeneity of variance/covariance. Lastly, as depicted in Table 8, single support time F (1, 14) = .74, $p > .05$ and double support time, F (1, 14) = 1.07, $p > .05$, data also satisfied the assumption of homogeneity of variance/covariance (Field, 2009).

The third assumption addressing a linear relationship between the dependent variables for each of the independent variables using scatterplot matrices (Field, 2009). Figure 1 indicates that there was a linear relationship between TUG and velocity for the independent variables, thus satisfying the MANOVA assumption. Figure 2 indicates that there was a linear relationship between step time and step length for the independent variables, thus satisfying the MANOVA assumption.

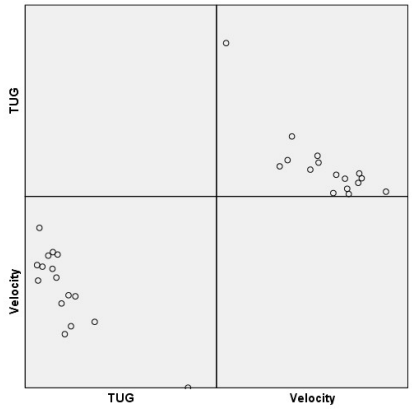

Figure 1. Linear relationship for TUG and velocity.

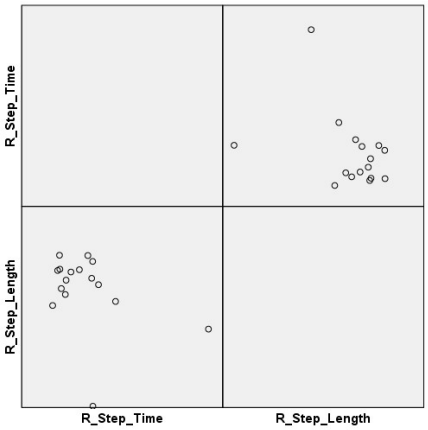

Figure 2. Linear relationship for step time and step length.

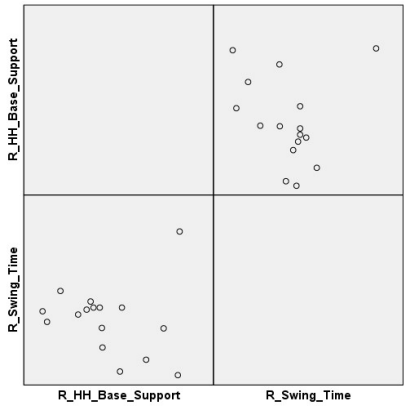

Figure 3. Linear relationship for base of support and swing time.

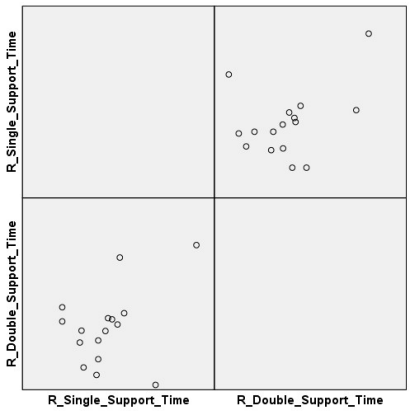

Figure 4. Linear relationship for single and double support time.

Figure 3 indicates that there was a linear relationship between base of support and swing time for the independent variables, thus satisfying the MANOVA assumption. Figure 4 indicates that there was a linear relationship between single and double support time for the independent variables, thus satisfying the MANOVA assumption.

The last assumption test was multicollinearity by use of the Pearson's correlation coefficient. The dependent variables did not display a high level of correlation, which was indicated by a Pearson product value of .90 or higher (Field, 2009). As indicated in Table 9, none of the dependent variables were highly correlated because all Pearson correlations were below 0.90. Thus, the assumption was satisfied (Field, 2009).

Table 9

Pearson Correlations for Multicollinearity

		TUG	Velocity	R_Step_Time	R_Step_Length	R_HH_Base_Support	R_Swing_Time	R_Single_Support_Time	R_Double_Support_Time
TUG	Pearson Correlation	1	-.835**	.800**	-.601*	.397	.587*	.624**	.634**
	Sig. (2-tailed)		.000	.000	.014	.127	.017	.010	.008
	N	16	16	16	16	16	16	16	16
Velocity	Pearson Correlation	-.835**	1	-.723**	.691**	-.205	-.621*	-.576*	-.625**
	Sig. (2-tailed)	.000		.002	.003	.446	.010	.020	.010
	N	16	16	16	16	16	16	16	16
R_Step_Time	Pearson Correlation	.800**	-.723**	1	-.364	.346	.815**	.811**	.775**
	Sig. (2-tailed)	.000	.002		.166	.189	.000	.000	.000
	N	16	16	16	16	16	16	16	16
R_Step_Length	Pearson Correlation	-.601*	.691**	-.364	1	-.056	-.313	-.341	-.364
	Sig. (2-tailed)	.014	.003	.166		.836	.238	.196	.166
	N	16	16	16	16	16	16	16	16
R_HH_Base_Support	Pearson Correlation	.397	-.205	.346	-.056	1	-.116	.072	.505*
	Sig. (2-tailed)	.127	.446	.189	.836		.668	.791	.046
	N	16	16	16	16	16	16	16	16
R_Swing_Time	Pearson Correlation	.587*	-.621*	.815**	-.313	-.116	1	.889**	.341
	Sig. (2-tailed)	.017	.010	.000	.238	.668		.000	.196
	N	16	16	16	16	16	16	16	16
R_Single_Support_Time	Pearson Correlation	.624**	-.576*	.811**	-.341	.072	.889**	1	.366
	Sig. (2-tailed)	.010	.020	.000	.196	.791	.000		.164
	N	16	16	16	16	16	16	16	16
R_Double_Support_Time	Pearson Correlation	.634**	-.625**	.775**	-.364	.505*	.341	.366	1
	Sig. (2-tailed)	.008	.010	.000	.166	.046	.196	.164	
	N	16	16	16	16	16	16	16	16

Table 10 indicates the mean Timed Up and Go (TUG) time for the CPN participants was 12.33 s (*SD* = 6.25), whereas the mean TUG time for the control was 6.62 s (*SD* = 1.10). The CIPN group had a mean step time of .55 s per step (*SD* = .08), whereas the control had a mean step time of .52 s per step (*SD* = .02). As displayed in Table 10, the mean step length for the CIPN group was 53.92 cm per step (*SD* = 23.55), whereas the mean step length for the control was 77.15 cm per step (*SD* = 5.28). The CIPN group mean base of support was 8.77 cm (*SD* = 3.00), whereas the control group had a mean base of support of 7.87 cm (*SD* = 1.97). The mean swing time for the CIPN group was .44 s per step (*SD* = .04), whereas the mean swing time for the control group was .43 s per step (*SD* = .02). The mean single support time for the CIPN group was .44 s per step (*SD* = .05), whereas the mean single support time for the control group was .43 s per step (*SD* = .03). Lastly, Table 10 indicates that the mean double support time for

the CIPN group was .24 s per step (*SD* = .07), whereas the mean double support time for the control group was .18 s per step (*SD* = .07).

Table 10

Dependent Variable Descriptive Statistics

	Participant type	Mean	Std. deviation	*N*
TUG(s)	CIPN	12.33	6.25	8
	Control	6.62	1.10	8
	Total	9.48	5.24	16
Velocity	CIPN	110.75	26.79	8
	Control	147.79	11.69	8
	Total	129.27	27.65	16
R Step Time	CIPN	.55	.08	8
	Control	.52	.02	8
	Total	.54	.06	16
R Step Length	CIPN	53.92	23.55	8
	Control	77.15	5.28	8
	Total	65.53	20.39	16
R HH Base Support	CIPN	8.77	3.00	8
	Control	7.87	1.97	8
	Total	8.32	2.49	16
R Swing Time	CIPN	.44	.04	8
	Control	.43	.02	8
	Total	.43	.03	16
R Single Support Time	CIPN	.44	.05	8
	Control	.43	.03	8
	Total	.44	.04	16
R Double Support Time	CIPN	.24	.07	8
	Control	.18	.04	8
	Total	.21	.07	16

Next, a one-way MANOVA was performed to determine if a significant difference existed between the mean TUG and one or more of the spatiotemporal gait values. A one-way MANOVA was performed due to having more than one dependent variable. Table 10 displays the results of the one-way MANOVA.

Table 11 indicates that there was no significant difference in TUG scores or spatiotemporal gait parameters between the control group and participants with chemotherapy-induced peripheral neuropathy, F (8, 7) = 2.45, $p > .05$, partial $\eta^2 = .74$. Pillai's trace test statistics were used because, as indicated in Table 7, there were violations of the assumptions of normal distribution. Therefore, due to the conservative nature of Pillai's trace, it was the more appropriate test to use when violations existed because it is robust to these violations (Field, 2009).

Table 11

MANOVA Output

Effect		Value	*F*	Hypothesis *df*	Error *df*	Sig.	Partial Eta Squared
Intercept	Pillai's Trace	1.00	2141.86	8.00	7.00	.00	1.00
	Wilks' Lambda	.00	2141.86	8.00	7.00	.00	1.00
	Hotelling's Trace	2447.83	2141.86	8.00	7.00	.00	1.00
	Roy's Largest Root	2447.83	2141.86	8.00	7.00	.00	1.00
Participant type	Pillai's Trace	.74	2.45	8.00	7.00	.13	.74
	Wilks' Lambda	.26	2.45	8.00	7.00	.13	.74
	Hotelling's Trace	2.80	2.45	8.00	7.00	.13	.74
	Roy's Largest Root	2.80	2.45	8.00	7.00	.13	.74

Table 12 displays the results of multiple analyses of variance run to determine if any of the dependent variables differed for the deponent variables. Because 8 ANOVAs were run, a Bonferroni correction was applied, adjusting the alpha to decrease to risk of making a type 2 error. The original alpha level of .05 was divided by 8 to determine the new alpha level of .006.

Using the correct alpha level, only velocity was noted to be significantly different between the control group and CIPN group, F (1, 16) = 12.85, p = .003, partial η^2 = .48.

Table 12 displays the results of multiple Kruskal-Wallis H test, which was performed given that the data was not normally distributed. Since 8 Kruskal-Wallis H test were performed, a Bonferroni correction was applied, adjusting the alpha to decrease the risk of making a type 2 error. The original alpha level of .05 was divided by 8 to determine the new alpha level of .006. Effect size was calculated using the equation, $n^2 = \frac{H-k+1}{n-k}$, where H was the value obtained in the Kruskal-Wallis test, n^2 is eta squared, 'k' was the number of groups, and 'n' was the total number of observations (Tomczak & Tomczak, 2014).

Table 12

Kruskal-Wallis H Test Output

	TUG	Velocity	R_Step_ Time	R_Step_ Length	R_HH_ Base_ Support	R_Swing_ Time	R_Single_ Support_Time	R_Double_ Support_Time
Chi-Square	11.29	7.46	.40	8.04	.54	.04	.00	3.19
df	1	1	1	1	1	1	1	1
Asymp. Sig.	.001	.006	.529	.005	.462	.833	.958	.074

Using the correct alpha level, velocity was found to be significantly different between the control group and CIPN group, $X^2(1) = 7.46$ p = .006; $n^2 = 0.43$. Step length was also found to be significantly different between the control group and CIPN group, $X^2(1) = 8.04$, p = .005, $n^2 = 0.47$. Lastly, the TUG time was also found to be significantly different between the control group and the CIPN group, $X^2(1) = 11.29$, p = .001; $n^2 = 0.69$.

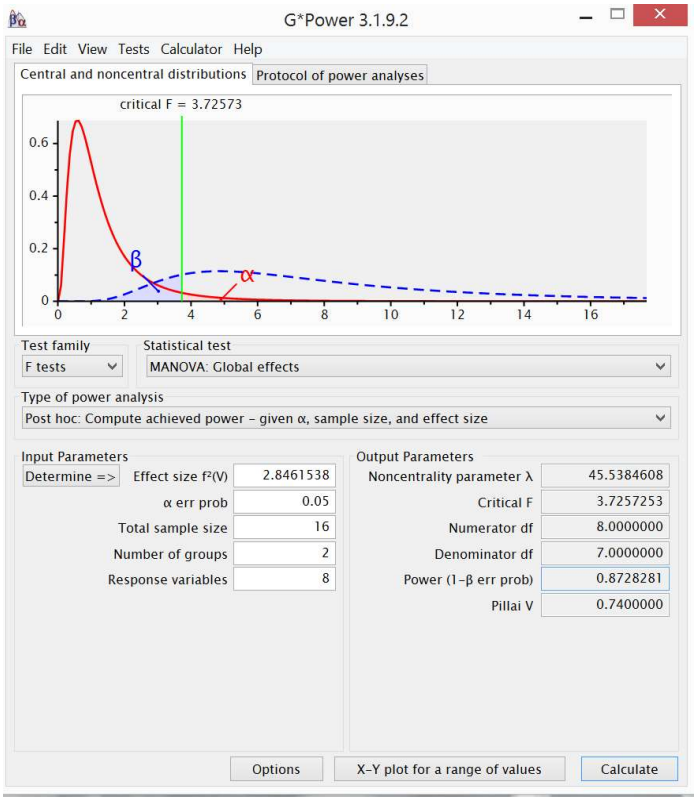

Figure 5. G-power analysis.

As indicated in figure 5, a large partial eta squared lead to a large effect size (2.85). Additionally, it was found that the power for the present study was .87, which satisfied the .8 threshold (Field, 2009).

Chapter V

DISCUSSION

With screening measures and treatment options improving, the number of people surviving a cancer diagnosis is increasing (Siegel et al., 2012). However, many cancer survivors are dealing with long-term physical and emotional side effects that negatively impact their health and overall quality of life (Rowland & Bellizzi, 2014). A common functional impairment experienced by cancer patients who received chemotherapy is chemotherapy-induced peripheral neuropathy (CIPN) (Stubblefield et al., 2009). It is estimated that the incidence rate of CIPN is 30%–70% dependant up on various factors, such as the class of chemotherapy agent and/or the cumulative dosage of the agent (Mantyh, 2006). Taxanes, such as paclitaxel, are commonly used to treat breast cancer, causing CIPN in 57%–83% of patients (Stubblefield et al., 2009).

Chemotherapy-induced peripheral neuropathy symptoms are often described as paraesthesia-like numbness and/or pain, which occurs in a stocking-and-glove distribution (Argyriou et al., 2012). Cancer patients with CIPN often report difficulties in walking, in that they feel unsteady and have a reduced sense of balance (Grisold, Cavaletti, & Windebank, 2012; Visovsky & Daly, 2004; Wampler et al., 2007). The impaired balance and gait reported by cancer patients has been linked to increased fall risk, potentially causing significant limitations in the ability to perform tasks of daily living (Quasthoff & Hartung, 2002; Stubblefield et al., 2009; Tofthagen et al., 2012; Windebank & Grisold, 2008). However, little is known about the specific gait impairments that may be caused by CIPN and if these gait impairments contribute to the increase in fall risk (Wampler et al., 2007). Furthermore, little is known about the compensation strategies employed by cancer patients with CIPN to manage these functional deficits.

Therefore, the purpose of this study was to investigate possible changes in spatiotemporal gait patterns of cancer patients with CIPN.

In the present study, it was found that CIPN subjects gait velocity (110.75 cm/s) was significantly slower than control subject's walking velocity (147.79 cm/s). Furthermore, the step length of those with CIPN (53.92 cm) was significantly shorter than the step length of the control subjects (77.15 cm). This studies finding that individuals with CIPN do have slower gait velocities is noteworthy because it supports a study done by Verghese et al. (2009) who found that individuals with gait speeds between 70 and 100 cm/s were more like to fall then individuals with gait speeds above 100 cm/s. Furthermore, Verghese et al. (2009) found that a decrease in gait velocity by 10 cm/s increased fall risk by 7% and thus concluded that gait velocity is a simple and quick way to assess fall risk.

Moreover, the CIPN participants in this current study had a gait velocity of 110. 75 cm/s (*SD* = 26.79), which is above the upper threshold 100 cm/s that Verghese et al. (2009) found to predict falls. However, the participants in the present study had a mean age of 61. 38 years (*SD* = 7.42), whereas the mean age of the participants in the study by Verghese et al. (2009) was 80.5 years. Thus, despite the age difference of approximately 20 years, the difference in gait velocity between those with CIPN and the participants in the study by Verghese et al. (2009) was 10 cm/s. This suggests that the presence of CIPN may negatively impact individuals' gait to the extent that they will develop a gait pattern similar to that of someone who is 20 years their senior.

Additionally, a decrease in gait velocity was found in this study and is concerning as decreased velocity has been found to be directly associated with an increase in fall risks, (Espy et al., 2010). The mean Timed-Up & Go (TUG) time for those with CIPN was 12.33 seconds (SD = 6.25), which was significantly greater than the mean TUG time for the control group which

was 6.62 (SD = 1.10). Moreover, the mean TUG time by those with CIPN was well above the score of 10.7 seconds which researchers suggest is indicative of fall risk (Jernigan et al., 2012). Therefore, the results further support that those with CIPN are at a higher risk of falling.

Not only was there a significant difference in gait velocity in this study, but individuals with CIPN consistently displayed significantly shorter step lengths; with a mean step length of 53.92 cm, which was significantly shorter than the control step length of 77.15 cm.

In the literature various clinical assessments are used to evaluate fall risk including the Timed-Up-and-Go (TUG). While the TUG test has demonstrated its clinical effectiveness in assessing fall risk, the TUG does not evaluate kinetic differences that are specific to the impairment that may be influence fall risk in all populations (Schulz et al., 2010). Thus researchers have used the Maximum Step Length (MSL) test which assesses both dynamic balance and leg strength. Clinically, a decrease in the MSL test is associated with an increase decade of life and performance on clinical assessments that are used to predict falls; as MSL decrease, fall risk increases (Cho et al., 2004; Lindermann et al., 2003; Schulz et al., 2013). Research indicates that the majority of falls experienced by the elderly and individuals with diabetic peripheral neuropathy will have gait patterns that are consistent with shortened step lengths (Paul, Ellis, Leese, McFadyen, McMurray, 2009; Shumway-Cook & Woollacott, 2012). Thus, the findings in the present study of decreased step length in individuals with CIPN can be associated with increased fall risk.

While previous research suggest that peripheral nerve dysfunction results in lower extremity impairments and functional limitations, such as a decrease in gait speed, the findings of the present study are not entirely consistent with previous research because previous research in diabetics with peripheral neuropathy suggested that in the presence of peripheral neuropathy,

gait patterns should undergo significant changes; in this study only gait velocity and step length were significantly different. A plausible reason for the inconsistencies between the results of the present study and previous research may be due to several limitations. First, the presence of CIPN was determined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, in which patients can simply report numbness and tingling; so, the extent of the damage to peripheral nerves was not quantified nor was the fiber types affected by the chemotherapy agents specified. This is a significant limitation because the types of fibers affected by the chemotherapy agents may explain why only velocity was found to be significantly different. While type Ia, type Ib, and type 2 fibers may be the primary fibers providing afferent feedback for the reflex arcs involved in gait mediation, these may not be the main fibers affected by the chemotherapy agents (Argyriou et al., 2012; Mantyh, 2006).

In the literature it has been suggested that unmyelinated C fibers and myelinated Aδ fibers, which are sensory fibers called nociceptors, may in fact be the primary targets on which the chemotherapy agents exert their neurotoxic effects. Unmyelinated C fibers and myelinated Aδ fibers can detect a variety of stimulus that can be both physical and chemical in nature. Although primary afferent neurons have their cell bodies in the dorsal root ganglion and transmit information from peripheral tissue to the spinal cord, unmyelinated C and myelinated Aδ fibers only project to superficial layers of the spinal cord. Primary afferent sensory fibers can detect nonnoxious sensations, such as light touch, vibration, and proprioceptive stimuli, whereas unmyelinated C and myelinated Aδ fibers can detect noxious chemical, thermal, and mechanical stimuli. It is also postulated that the unmyelinated C and myelinated Aδ fibers generate the pain that is caused by antitumor therapies, such as chemotherapies that include taxanes and platinum-

based compounds, causing chemotherapy-induced peripheral neuropathy (Argyriou et al., 2012; Mantyh, 2006).

Previous research supports this hypothesized mechanism of the neurotoxic effects of chemotherapy on the nerves, as cancer patients diagnosed with CIPN have various sensory signs and symptoms that start with paresthesia and numbness in the hands and vibratory perception, along with disabling pain, which suggests involvement of small, unmyelinated nerve fibers (Hilkens et al., 1997). However, Visovsky and Daly (2004) found no effect on deep tendon reflex using Babinski's reflex hammer, which suggests that the type Ia, type Ib, and type 2 afferent nerves that innervate Golgi tendon organs and muscles spindles and their corresponding reflex mechanisms are intact. This is a significant observation because it is proposed in the literature that these three reflex mechanisms are most responsible for mediating gait (Dietz, 2002).

Conversely, a more recent study by Kneis and colleagues (2015) found that cancer patients who received taxane chemotherapy demonstrated prolonged H-reflex latency, as well as changes in H-reflex sensitivity associated with modulated spinal excitability. These findings suggest that chemotherapy agents may have a neurotoxic effect on the Ia afferent fibers of muscle spindle and Golgi tendon organs that are part of the monosynaptic reflex arcs. The authors also noted that cancer patients with CIPN displayed increased postural sway. However, the study did not find a correlation between H-reflex latency and center-of-pressure sway path. Therefore, although evidence supports that unmyelinated C and myelinated Aδ fibers may experience a neurotoxic effect due to chemotherapy, and possibly even type Ia afferent fibers part of reflex arcs, the primary fibers that experience the neurotoxic effect of thermotherapy may not be prime gait mediators, which may explain why there were no significant differences found in

spatial and temporal gait parameters other than velocity between those with CIPN and their healthy and morphologically matched controls (Kneis et al., 2015).

A second explanation for the inconsistencies in the present study with previous research is that although unmyelinated C and myelinated Aδ fibers may experience a neurotoxic effect due to chemotherapy, individuals may develop compensatory behaviors due to the loss of sensory input caused by CIPN. Gait is the result of afferent information from visual, vestibular, and proprioceptive systems. These three system do not operate independently; the body uses somatosensory information from all bodily sources in order to shape functional movement. When the contribution of somatosensory information is attenuated, or lost, such as in the case of peripheral neuropathy, the vestibular system provides a greater contribution to posture and balance (Horak & Hlavacka, 2001; Simoneau et al., 1995).

Mergner, Huber, and Becker (1997) postulated that vestibular information descends down body segments where it meets and fuses with ascending somatosensory information, combining to provide coordinates as to where the body is in space (Mergner & Rosemeier, 1998). Thus, when somatosensory information is lessened, the body still receives vestibular sensory information to regulate body movement. The vestibular system may primarily mediate the trunk during gait, which is important to note because the trunk may have a greater influence on gait stability then lower body segments because the trunk has a larger body mass. Therefore, it needs a greater amount of stability while walking (Creath, Kiemel, Horak, & Jeka, 2008; Deshpande & Zhang, 2014). Furthermore, the vestibular system may be a greater mediator of stability during gait. Thus, although CIPN patients may have attenuate somatosensory afferent feedback, more noticeable changes in spatiotemporal gait parameters other than gait velocity were not found due

to the intact vestibular information that is critical for trunk control and walking accuracy (Deshpande & Zhang, 2014).

Although previous research has established the importance of afferent feedback for the mediation of gait, the extent of the mediation remains unknown. Decreased gait velocities may not only be due to the neurotoxic effect of the chemotherapy agents but also due to the presence of pain. Individuals with CIPN commonly report symptoms that include burning, muscle aches, sensitivity to cold, and feelings of "walking on hot coals" or "sandpaper on the bottom of your feet"; cancer patients experiencing CIPN often report varying degrees of pain (Tofthagen, 2010; p. E25). The presence of pain alone is associated with a decrease in walking velocity; a recent study that evaluated Gait parameters in individuals with foot pain related to gout found that those individuals with gout-related foot pain walked significantly slower (Stewart, 2016). A study by van den Hoorn, Hug, Hodges, Bruijn, and van Dieën (2015) investigated if nociceptive stimulation and induced pain affect gait stability. Previous research suggests that musculoskeletal pain is associated with fall risk and has a negative impact on stability (Asai, Misu, Sawa, Doi, & Yamada, 2015; de Zwart et al., 2015; Kitayuguchi, Kamada, Okada, Kamioka, & Mutoh, 2015; Ross, Mavor, Brown, & Graham, 2015).

It is hypothesized that individuals who are experiencing pain will adapt their motor program to protect injured tissues. The adaptations may increase joint stability because the muscles are less responsive in order to reduce pain. For example, if pain is presence in the calf, the calf muscle may not be as responsive, as indicated by a decrease in contractions, resulting in a decrease in the range of motion the ankle joint may undergo during gait (Hodges & Tucker, 2011; Lund, Donga, Widmer, & Stohler, 2011; van Dieën, Selen, & Cholewicki, 2003). The combination of increased joint stiffness, decreased responsiveness of the tissues, and the

presence of impaired nociceptive afferent fibers, with decreasing proprioceptive acuity and the inability to regulate force, may result in a decrease in stability (Brumagne, Cordo, Lysens, Verschueren, & Swinnen, 2000; Descarreaux, Blouin, & Teasdale, 2005; Hodges et al., 2011; Lee, Cholewicki, Reeves, Zazulak, & Mysliwiec, 2010; Matre, Arendt-Nielsen, & Knardahl, 2002; Salomoni, Ejaz, Laursen, & Graven-Nielsen, 2013; van den Hoorn, Bruijn, Meijer, Hodges, & van Dieën, 2012).

Van den Hoorn and colleagues (2015) found that nociceptive irritation of the calf and back muscled decrease gait stability at low walking speed. Greater effects were seen in the calf than in the low back, which puts forth the idea that the gait adaptations may depend on the specific muscle. The findings of van den Hoorn and colleagues that the presence of pain can affect gait stability at lower walking speeds and that the specific muscle affected also plays a critical role are important to note because cancer patients with CIPN, as well as individuals with diabetic peripheral neuropathy (DPN), often report pain in their lower legs, specifically their feet and calves (Tofthagen, 2010). Thus the presence of pain in the lower extremities by individuals with CIPN is significant because the decrease in gait speed could be caused not by the decrease in afferent feedback but simply by the presence of pain because it is suggested that individuals who are experiencing pain may undergo motor adaptations to protect the painful/injured tissues, resulting in a decrease in gait velocity (Hodges & Tucker, 2011; Lund et al., 2011; van Dieën et al., 2003).

Lastly, the slower walking velocities may not be due to the attenuated afferent feedback or presence of pain but may be due to a deconditioning effect experienced by cancer patients that has been documented to occur while undergoing treatment for cancer.

A stable and successful gait that allows individuals to safely navigate their environment requires an appropriate amount of muscular strength and joint range of motion (Neumann, 2002; Shumway-Cook & Woollacott, 2012). Chemotherapy and radiation therapy may often cause muscle atrophy and muscles weakness (Mustian et al., 2009). Certain chemotherapy agents may cause pulmonary fibrosis and abnormal development of pulmonary tissue, resulting in coughing, dyspnea, fatigue, and overall decreased functional capacity (Schneider et al., 2003). It is estimated that 30% of cancer survivors will decrease their physical activity levels upon receiving a cancer diagnosis, and up to 70% of cancer survivors do not meet the U.S national recommendations for exercises and physical activity (Blanchard, Courneya, & Stein, 2008; Blanchard, Denniston, & Backer, 2003). Thus, due to the decreased amount of physical activity and the effects of cancer therapies, many cancer patients experience a deconditioning effect, which could cause slower gait velocities and decrease step length. Ko, Stenholm, Metter, and Ferrucci (2012) found that a decrease in gait speed was associated with decreases in range of motion within the hip, knee, and ankle. Ko and colleagues (2012) also found that a slower gait velocity was also associated with a decrease in maximum isokinetic knee extensor strength, suggesting that muscle strength is a contributing factor in gait velocity. Thus, as the body becomes weaker and stiffer, as indicated by decrease joint range of motion, gait will also become slower. This association between gait and a deconditioned body may also explain the slower gait in those with CIPN because the participants in the present study were nonexercisers as defined by the inclusion criteria, which required that they not participate in more than 150 min of regular physical activity per week. The chemotherapy treatments undergone by those with CIPN may have caused a deconditioning effect, resulting in loss of muscle strength that may also have been a contributing factor to the significantly slower walking velocities. However, the present study

did not evaluate and quantify this possible deconditioning effect and compare the physical status of those with CIPN to those without CIPN, as well as the physical condition between the two groups.

Chapter V1

SUMMARY AND CONCLUSIONS

As improvements continue to be made in screening measures and treatment options, the number of cancer survivors will increase. However, many cancer survivors will face long-term physical health effects and functional impairments due to chemotherapy-induced peripheral neuropathy (CIPN). Neuropathy is associated with postural and functional impairments. In cancer patients with CIPN, impairments may manifest as gait or balance disorders, which may be linked to higher rates of falling, limiting activities of daily living. However, the exact nature in which CIPN affects the spatiotemporal mechanism of gait remains largely unknown (Kneis et al., 2015).

The results of this study indicate that cancer patients with CIPN displayed a slower walking velocity and shorter step length, resulting in a higher risk of falls, compared to healthy, age and morphologically matched controls. Additional gait patterns, such as step time, base of support, swing time, single support time, and double support time, were not significantly different. Also, while the mean TUG score for CIPN patients was not only significantly greater, but was also above the clinical fall risk cut off of 10.7 s, indicating fall risk. Both gait speed and step length are key indicators for fall risk; slower gait velocities and shorter step lengths are associated with increased fall risk (Espy et al., 2010; Schult et al., 2013; Verghese et al., 2009)

Despite the findings that gait velocity and step length is significantly reduced in individuals with CIPN, there were several limitations to the present study. First, the presence of CIPN was determined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, in which patients can simply report numbness and tingling. Therefore, the extent of the damage to peripheral nerves was not quantified. Secondly, it remains unknown if the cause

of decreased gait velocity was due to the neurotoxic effect of the chemotherapy agents on the afferent nerve fibers that provide gait mediation or if the decreased gait velocity was due to the presence of neuropathic pain, or a combination of both. Lastly, gait velocity may also have been slowed due to a deconditioning effect caused by the treatment process. But this possible deconditioning effect was not accounted for in the present study.

Future research studies should address the limitations of the present study and investigate the effect (if any) of the deconditioning caused by chemotherapy treatments on gait velocity. Future studies might also investigate the timing during a chemotherapy regimen of taxane or oxaliplatin, during which the gait velocity may decrease. Future research might also investigate other chemotherapeutic agents that case CIPN, such as vincristine, and if the same changes in gait velocity occur.

In conclusion, the finding that gait velocities and step length were significantly slower in individuals with CIPN, as well as increased risk of falls as assessed by the TUG test, is very meaningful because slower gait velocities and shorter step lengths are associated with increased fall risk, which was demonstrated by the CIPN participant's mean TUG score.

Although this significant association was found, it remains unknown if the cause of the decreased gait velocity, shortened step length, and increased risk of falls as assessed by the TUG test, was the neurotoxic effect of the chemotherapy agents on the afferent nerve fibers that provide gait mediation or if the decreased gait velocity was due to the presence of neuropathic pain or a deconditioning effect caused by the treatment process. Nevertheless, the study findings aid in understanding the effects of chemotherapy-induced peripheral neuropathy on spatiotemporal gait parameters in cancer patients post chemotherapy drug treatment and assist in addressing functional limitations in CIPN patients

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‘

APPENDIXES

Appendix A

IRB APPROVAL LETTER

Saint Michael's
MEDICAL CENTER

September 15, 2015

Mr. Timothy F. Marshal
School of Health and Medical Sciences
Seton Hall University
400 South Orange Avenue
South Orange, NJ 07079

Dear Mr. Marshal:

The amended Protocol and Patient Flyer you submitted were approved by the Institutional Review Board on September 15, 2015, for use with the following protocol:

> The Effect of Chemotherapy-Induced-Peripheral-Neuropathy on Spatial-Temporal Gait Parameters in Cancer Patients After the Completion of Chemotherapy Treatment.(Protocol Amendment and Patient Flyer) – Low Risk - # 34/14

If any changes/modifications are made to this protocol, you must notify the Institutional Review Board immediately. If any changes/modifications are made, a new and complete application must be submitted for approval. All adverse effects or deaths must be reported immediately to the IRB.

According to the terms of the initial one-year approval, you must report back to the IRB as directed on the progress of the investigation. You must request an extension of this protocol for an additional twelve month period, if needed, by writing to the Chairman of the IRB. A brief report must be included with the request for an extension of approval, including the number of patients involved, age, sex, major diagnoses and a brief summary of results. Failure to submit a report to the Saint Michael's Medical Center IRB prior to study expiration will result in expiration of IRB approval and study procedures at your site must cease. These actions require reporting to the Sponsor. Please note that continuation of research after expiration of the IRB approval is a violation of Federal Regulations. Upon completion of every study, a brief summary of results must be sent to the IRB.

For studies involving drugs for inpatient use, the drug must be deposited with the pharmacy for dispensing. In addition, two copies of the consent form must be signed by the patient. One copy will be kept on the patient's chart, the other filed in the pharmacy.

Sincerely,

Constantinos A. Costeas, M.D.
Chairman
Institutional Review Board

db

cc: Dean Brian Shulman
Mary Ruzicka, Ph.D., IRB

Appendix B

RECRUITMENT FLYER

RESEARCH STUDY:
ADULT VOLUNTEERS *POST* TREATMENT FOR CANCER

WHO: Adults, between the ages of 50-70 years of age, with Breast OR Colorectal Cancer, stage 2-3, who have completed taxne-based or oxaliplatin-based chemotherapy.

WHAT: The purpose of this study is to assess whether chemotherapy-induced-peripheral-neuropathy is associated with spatial-temporal gait adaptations in post-treatment adult cancer survivors when compared to healthy, disease free, age and morphologically matched controls.
In order to analyze walking characteristics, the GAITRite system will be used, which is a 14-foot walkway carpet embedded with pressure sensors connected to a computer. Subjects will be asked to walk the length of the 14-foot electronic walkway carpet.

RISKS: There is a minimal risk to the subject for participation in this study. To reduce the risk of falling, all participants will wear a Velcro adjustable gait safety waist belt and be closely guarded by the primary researcher investigator.

BENEFITS: Previous research indicates that cancer survivors who receive chemotherapy for cancer treatment may experience a disruption to the somatosensory systems which may negative effect the sensory feedback that is necessary to produce a coordinated and balance gait. Research indicates that cancer survivors who have undergone chemotherapy report gait disturbances and higher incidences of falls.

Voluntary Nature of the Study: Participation is completely voluntary and subjects can withdraw at any time with no penalty, prejudice or questions asked.

Anonymity and Confidentiality: All information will be kept strictly confidential and anonymous by encoding names with random numbers and separately securing the name/number key from subject data.

WHERE: Cancer Center at Saint Michael's Medical Center
OR
Seton Hall University, 400 South Orange Avenue, South Orange, NJ, 07079
Corrigan Hall Room 67 (Functional Human Performance Lab)

IF INTERESTED: Please Contact the Primary Investigator, Timothy F. Marshall, to determine closest location

CONTACT: Tim Marshall, M.S., ACSM/ACS-CET
tim.marshall@student.shu.edu or 908-510-5546

Appendix C

PRE-SCREEN TOOL

Age:

Chancer Diagnose:

Chemotherapy Agent Received:

History of muscular-skeletal injury or fracture in past 6 months? yes no
If yes briefly describe:
_____

History of neuromuscular disease? yes no

History of HIV? yes no

History of vasculitis? yes no

History of central or peripheral neurologic disease? yes no

History of spinal cord metastases? yes no

History orthopedic issues that affect balance? yes no

History of uncontrolled diabetes? yes no

History renal insufficiency? yes no

History of vitamin B12 deficiency? yes no

History of debilitating arthritis? yes no

History of vestibular involvement or dizziness when turning head or looking up/down? yes no

History of uncorrected visual impairment? yes no

History of falling while ambulating over past year: yes no
(Note: a fall here is defined as an unexpected event where a person stumbles and either strikes an object or comes to rest at a lower level such as the ground)

Do you use a walking aid (i.e. cane, walker)? yes no

Do you presently have lower extremity weakness, limited motion or pain? yes no

Do you have at minimum a middle school level of education? yes no

(For females) are you pregnant? yes no

Do you exercise? yes no

Appendix D

DATA COLLECTION SHEET

Participant Data Collection Sheet

Participant #:_____

Name:_____Date:_____ ☐Intervention ☐ Age/Morphologically Matched Control

Cancer History

Cancer Diagnosis:_____

Name of Chemotherapy Agent Received:_____

Classification of Chemotherapy Agent: ☐ Oxaliplatin ☐Taxane ☐ Paclitaxel

Time Since Last Chemotherapy Treatment:_____

Biometric Data

Age:_____ Sex: ☐Male ☐Female

Height:_____ Weight:_____ BMI:_____

Leg Length:_____

Spatial Variable	Value
Line of Progression	
Stride Length	
Step Length	
H-H Base of Support	
Leg Length	
Step Width	
Stride Width	

Temporal Variable	Value	Temporal Variable	Value
First Contact		Terminal Double Support	
Heel Contact		Terminal Percent Double Support	
Last Contact		Total Double Support	
Toe Off		Percent Total Double Support	
Step Time		Stance Time	
Stride Time		Percent Stance Time	
Gait Cycle Time		Contact Phase	
Ambulation Time		Midstance Phase	
Velocity		Propulsive Phase	
Mean Normalized Velocity		Swing Time	
Stride Velocity		Percent Swing Time	
Single Support		Heel-Off/On	
Percent Single Support		Walk Ratio	
Initial Double support		Heel Percent	
Percent Initial Double Support		Midfoot Percent	
		Toe Percent	

Timed Up & Go Score (s):_____