COGNITIVE AND PHYSICAL FUNCTION IN INDIVIDUALS TREATED WITH
ADJUVANT FOLFOX CHEMOTHERAPY FOR COLON CANCER: PILOT STUDY

by

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Abstract

**Background:** Following chemotherapy, it is estimated that up to 95% of all cancer patients report cognitive changes such as complaints with memory and difficulty concentrating. This condition is referred to as chemotherapy-associated cognitive dysfunction or “chemo brain”. In addition, deficits in physical function are observed among those undergoing cancer treatment, as well as, long-term cancer survivors. While a decrease in physical activity participation has been shown among colorectal cancer patients over the course of chemotherapy, to date, changes in functional mobility over the course of chemotherapy has not been assessed in colon cancer patients using objective validated mobility tests. Furthermore, the association of cognitive and functional mobility dysfunction has not been explored. **Purpose:** To examine the effect of chemotherapy treatment on cognitive function, functional mobility and physical activity from baseline, to 6 months (end of chemotherapy) in individual being treated for colon cancer.

**Methods:** At baseline and end of chemotherapy, participant completed a neuropsychological test battery, which included the Stroop, Hopkins Verbal Learning Test-Revised (HVLT-R), and Trail Making A & B (TMT A&B), a 6-minute walk test (6MWT), a measure of physical function, and a functional mobility testing battery, which included timed up and go (TUG) and gait speed. Demographic information and self-reported physical activity, using the International Physical Activity Questionnaire (IPAQ), were also collected at these time points. For the analysis of neuropsychological and mobility test scores, the paired t-test was used to test for the differences and assess the change in the mean scores from the baseline to 6-months. **Results:** No significant changes were noted in the HVLT-R, Stroop, and TMT-A and -B mean scores after completion of chemotherapy compared to baseline. Compared to baseline, no significant changes were
observed for 6MWT, TUG, GS, or leisure-time physical activity after completion of chemotherapy. **Conclusions:** There were no significant changes in chemotherapy-associated cognitive, physical function, or functional mobility noted from baseline to the end of chemotherapy. In addition, physical activity levels and average time spent sitting did no change significantly. No definitive statements can be provided since the results are based on a small sample size.
Preface

BC Cancer Agency Research Ethics Board and UBC Clinical Research Ethics Board (CREB) have approved this research. Certificate number: H10-00803.
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List of Abbreviations

BMI, body mass index
FOLFOX, 5-Fluorouracil Leucovorin, Oxaliplatin
5-FU, 5-Fluorouracil
CAPOX, Capecitabine, Oxaliplatine
CAP, Capecitabine
OXAL, Oxaliplatin
HVLT-R T, Hopkins Verbal Learning Test-Revised
TR, total recall
DR, delayed recall
RET, percent retained
RDI, retention determination index
TMT, Trail Making Test
FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function
MET-hrs/week, Metabolic Equivalent of Task- hours per week
6MWT, 6-minute walk test
TUG, timed up and go
IPAQ, International Physical Activity Questionnaire; PA, Physical activity
PNQ, Patient Neurotoxicity Questionnaire,
PNP, Peripheral Neuropathy
EORTC QLQ-C29, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Colon
FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue
STPI, State-Trait Personality Inventory
CES-D, Center for Epidemiological Studies Depression Scale
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Dedication

To my sister who has been motivating me and enlightening me to become a hill seeker

To my parents – for their support and encouragement
Chapter 1: Introduction

1.1 Chemotherapy-Associated Cognitive Function

Following chemotherapy, some cancer survivors report alterations in their ability to remember, concentration or think (1-3). Research is needed to determine who is at risk of experiencing cognitive dysfunction (related to treatment type, age, baseline level of cognitive performance), and the time course of these changes (i.e., is it acute and resolves, persistent or a late effect of treatment) (4). Also, the mechanisms by which chemotherapy can cause the long-term cognitive changes are largely unknown, and the majority of research to date on cognitive dysfunction in cancer survivors has been done in breast cancer survivors (4,5).

Currently, there is little in the way of treatment options to offer cancer survivors experiencing these symptoms other than memory aids and other coping strategies. Thus, a better understanding of the extent of cognitive changes, time course and possible underlying mechanisms is crucial to developing appropriate intervention strategies, such as exercise which has been shown to be effective in improving cognitive function in older adults.

1.2 Chemotherapy-Associated Physical Function and Physical Activity

Deficits in physical function and functional mobility are observed among those with a recent cancer history, as well as, long-term cancer survivors (6). Physical function is an umbrella term for aspects of cardiovascular endurance, strength, mobility, agility, balance, and coordination (7), whereas functional mobility is defined as the ability to perform basic activities of daily living (6,7).

Although physical activity has associations with improved colon cancer-specific mortality, overall survival, recurrence- and disease- free survival in observational studies, (8-
10) physical activity levels have been shown to decrease in colorectal cancer survivors over the course of chemotherapy (11). In addition, it has been shown that, compared to national norms, 61% of colon cancer patients had a declined physical performance levels following cancer diagnosis even though they had the highest physical performance levels prior to diagnosis (12). In spite of all these concerns, changes in functional mobility using objective validated mobility tests have not been assessed among colon cancer patients over the course of chemotherapy.

### 1.3 Research Aims and Hypotheses

This study will examine the impact of chemotherapy treatment for colon cancer from baseline to 6-months (end of chemotherapy) on neuropsychological performance, physical function, functional mobility and physical activity levels. The first aim is to investigate if there are any changes in neuropsychological performance, specifically executive function, measured by Stroop Test and Trail Making Test (TMT). The second aim was to examine the changes in physical function and functional mobility, measured by the 6-minute walk test (6MWT), Timed Up and GO (TUG), and gait speed. A subset of the second aim was to examine if there is chemotherapy induced peripheral neuropathy (CIPN) assessed by Patient Neurotoxicity Questionnaire (PNQ) has contributions to physical function specifically the functional mobility. The third aim was to discover if there are any changes in self-reported physical activity levels through colon cancer chemotherapy treatment using International Physical Activity Questionnaire (IPAQ) scored as MET-minutes/week.

Chemotherapy-induced cognitive changes were expected to occur from baseline to the end of chemotherapy. Thus, it was hypothesized that there will be changes in neuropsychological performance. Physical function was expected to decline over the course of colon cancer.
chemotherapy treatment, and this would be associated with development of peripheral neuropathy symptoms. It was also hypothesized that there will be a reduction of physical activity levels over the course of colon cancer treatments. In addition, negative interaction was expected to exist between cognitive function and functional mobility, as well as, physical activity levels.

1.4 Definitions and Prevalence of Chemotherapy-Associated Cognitive Function

Following chemotherapy treatment, it is estimated that as many as 95% of cancer patients experience symptoms of cognitive dysfunction, reported as a reduced ability to think, concentrate or multitask compared to pre-diagnosis(13). These symptoms are often termed as chemotherapy-associated cognitive dysfunction or “chemo-brain”. Although cognitive dysfunction has commonly been attributed to the receipt of chemotherapy, cancer- associated factors such as anxiety, depression, or comorbid medical conditions have also been proposed to contribute to the reported cognitive dysfunction(13,14). However, in studies that statistically adjusted for these psychological factors or included patients without significant psychological distress, the chemotherapy-associated cognitive changes remained(14). A longitudinal study examined the cognitive function of 18 breast cancer patients at baseline, 6-months and 18 months after the chemotherapy treatment (2). It was reported that 33% of the patients had cognitive dysfunction before the chemotherapy treatment, while 61% of the patients had cognitive function decline 6 months after the baseline (2). Interestingly, none of the cognitive tests had statistical significant relation with anxiety or depression at any of the aforementioned time points (2).

A prospective cohort study examined the neuropsychological test scores of 39 breast cancer patients who underwent surgery, radiotherapy, and adjuvant cyclophosphamide, methotrexate, fluorouracil (CMF) chemotherapy, and compared it to 34 age- matched control
group who only received the same type of surgery and radiotherapy (15). The cognitive domains examined included verbal function, memory, attention/concentration, and speed of information processing, motor function, visuoconstructional function, and mental flexibility. The neuropsychological testing battery consisted of Rey Auditory Verbal Learning Test (verbal memory), Fepsy finger-tapping task (motor function), Fepsy visual reaction /choice/ visual searching test (speed of information processing), Stroop Test (mental flexibility), Trail making A and B (attention/concentration and mental flexibility), Word fluency subtest from the S.A.N. test (verbal function). Compared to patients who only underwent surgery and radiation, those treated with chemotherapy had more significantly lower scores for the objective tests assessing concentration and memory. The same study undertook a second cognitive assessment with the aim to investigate the long-term sequelae and the potential reversibility of the neurotoxic effects of chemotherapy on cognitive functioning. Thus, at the 4-year follow-up, the late effects of adjuvant chemotherapy on neuropsychological functioning were examined among breast cancer patients receiving chemotherapy (n=76), and the controls who only received surgery and radiation (n=27) (16). Compared to the controls, the chemotherapy group self-reported more cognitive complains related to concentration and memory. The cognitive functioning section of the European Organization for Research and Treatment of Cancer EORTC-QLQ-C30(17), and a five point likert scale interview were used to assess self-reported cognitive complaints (16). Two years after completion of treatment, the chemotherapy group had significantly higher cognitive and depression complaints compared to controls. However, no significant differences were observed at the follow-up, suggesting that the chemotherapy group showed improvements in self-reported cognitive and depression complaints similar to the level of the control group. Thus, the cognitive dysfunction as assessed by objective neuropsychological tests, was unrelated to the
self-reported cognitive dysfunction and depression complaints and it was not affected by anxiety, depression, fatigue, and time since treatment. The neuropsychological test performance improved in all chemotherapy groups compared to controls. This study suggested that the cognitive dysfunction observed two years following chemotherapy, improved 4 years post-chemotherapy. These results indicated the possibility of transient nature of the cognitive dysfunction (16).

While the majority of studies to date examining the prevalence and time course of cancer-associated cognitive dysfunction have been conducted in women diagnosed with breast cancer, there is an interest in exploring cognitive changes in other cancer survivors. The most common cancers diagnosed in Canada are prostate, breast, lung and colorectal cancer (18). In Canada, over 23,000 men and women will be diagnosed in 2014. To date there has been one prospective study evaluated potential alterations in cognitive function in individuals being treatment for colorectal cancer (19). In individuals receiving FOLFOX4 treatment for colorectal cancer, Andreis et al. assessed cognitive impairment, visuo-spatial memory, information processing speed, verbal memory by using Mini Mental State Examination, Clock Drawing Test, Trail Making Test-A and Trail Making Test -B, and Rey Auditory Verbal Learning Test call/ recall, respectively. Andreis et al., reported improvements in the information processing speed and verbal memory at six months after chemotherapy(19). The call component of Rey Auditory Verbal Learning Test performance revealed a significant improvement for the mean differences at the end of chemotherapy as well as 6 months after chemotherapy compared to baseline. This result in alignment with the improvements reported in the tests that evaluated anxiety, depression and emotional distress, which suggest that this group of patients may have been able to minimize
the treatment effects. This is because it has been reported that depression and anxiety attribute to the chemotherapy-associated cognitive dysfunction (20).

1.5 Cognitive Domains Affected in Chemotherapy-Associated Cognitive Dysfunction

Depending on the comparison group, there is a variation in identifying the most vulnerable cognitive domains of chemotherapy-associated cognitive dysfunction. In addition, there is a significant variability in the estimate of how many cancer patients experience cognitive dysfunction due to the variety of methods of assessment (i.e., cognitive screening measures or comprehensive neuropsychological test batteries) and the inconsistency of the cognitive dysfunction definition amongst studies (21). In a metaanalysis by Jansen et al., the authors report that comparison of the neuropsychological test scores in women with breast cancer treated with chemotherapy with controls (207 cancer patients who have received local therapy only or 136 healthy individuals matched for age and education) has shown differences (reported as an effect size) in all seven domains of cognitive function; namely, attention, executive function, information processing, motor function, spatial skills, verbal memory and visual memory (3). However, when the scores of both groups were compared with normative data, significant differences were observed in only three domains, namely executive function, motor function and verbal memory (3). The negative direction of all the significant effect sizes indicated that, on average, all the neuropsychological tests’ mean scores for the patients who underwent chemotherapy were lower than the comparison group. Thus, the results from this meta-analysis support the hypothesis that chemotherapy might have negative impact on cognitive function. In addition, a meta-analysis in 2012 assessed whether chemotherapy-associated cognitive
dysfunction was consistently observed in a mixed group of cancer patients such as testicular, lymphoma, breast, leukemia; the areas of affected cognition also was identified. It was concluded that executive function and memory were the cognitive domains most affected by chemotherapy treatment (22). Interestingly, time since treatment cessation and age did not impact the chemotherapy associated cognitive function. Hodgson et al. noted that the study of chemotherapy-associated cognitive dysfunction among colorectal cancer has received little attention (22).

1.6 Proposed Biological Mechanisms for Development of Chemotherapy-Associated Cognitive Dysfunction

The mechanisms underlying chemotherapy-associated cognitive dysfunction remain largely unknown even though several candidate mechanisms have been proposed (14). Depending on the treatment regimens and the vulnerabilities of the individual, there are five main proposed mechanisms that affect the cognitive function and brain structure, namely: 1) blood-brain barrier integrity; 2) DNA damage and telomere length; 3) cytokine deregulation; 4) estrogen or testosterone reduction; and 5) genetic susceptibility (14).

1.6.1 Blood-Brain Barrier Integrity

It is known that, with the exception of methotrexate and 5-flourouracil, most systemically- administered chemotherapy agents do not cross blood-brain barrier (14). However, animal studies have reported that small doses of chemotherapy reaching the central nervous system (CNS) can enter the brain through genetically variable drug transporters at the blood-brain barrier. The gene multi-drug resistance (MDR-1) encodes P-glycoprotein (P-gp), which is
expressed at the capillary endothelial cells and is responsible for transporting toxic substances out of the cells. Animal studies have shown that deficiency in P-gp leads to higher concentration of peripheral administration of chemotherapy agent. This leads to cell death and reduced cell division of structures relevant to cognition, namely the sub-ventricular zone, the dentate gyrus of the hippocampus, and the corpus callosum (14). It has been suggested that patients who have less efficient efflux pumps and have deficits in DNA-repair mechanisms are more likely to develop cognitive dysfunction before and after treatment. Low efficiency efflux pumps lead to greater toxin exposure in the brain, and greater DNA damage, and as a result the immune response become deregulated (14).

1.6.2 DNA Damage and Telomere Length

The therapeutic efficacy of standard chemotherapy is achieved through DNA damage (14). One of the primary mechanisms of standard chemotherapy for targeting the tumor cells is to cause DNA damage of fast dividing cells, meanwhile affecting normal cells. Toxic exposure, namely chemotherapy, leads to a common source of DNA damage called oxidative stress, which induces single or double strand breaks. Therefore, DNA damage in CNS is one of the proposed mechanisms for chemotherapy-associated cognitive dysfunction. Lower telomere length and telomerase activity can also lead to poor cognitive performance (14). Several studies have shown that oxidative stress and chemotherapy influence the rate of telomere shortening (23-25).

Interestingly, through pre- and post-chemotherapy treatment blood analysis, a cross-sectional study (n=73) investigated potential factors that predict chemotherapy-induced hematological toxicity in colorectal cancer patients undergoing adjuvant chemotherapy (24). It was shown that short peripheral blood mononuclear cell telomere length is a strong predictor of the 5-
flourouracil (5-FU) toxicity among colorectal cancer patients (24). Thus, chemotherapy exposure causes DNA damage and telomere shortening, which in turn induces an immunological response (24). Therefore, telomere length denoting the proliferative capacity of a cell can be used as a predictor of 5-FU-induced toxicity and a measure of a cell’s response ability to chemotherapy. Specific to cognitive changes, it is imperative to compare the clinical patterns and correlates of cognitive function associated with chemotherapy by investigating the molecular biology aspect of these changes.

1.6.3 Cytokine Deregulation

Cytokines have important roles in the regulation of pro-inflammatory responses as well as CNS function. Increased levels of inflammatory cytokines namely, IL-6, -8, and -10, have been observed at pre- and post- chemotherapy treatment specifically at the acute levels among cancer patients (14). Cytokine deregulation associated with chemotherapy leads to neurotoxicity and neuronal damage. Unregulated cytokine levels may also contribute to the DNA damage and oxidative stress. Similarly, DNA damage triggering cytokine dysregulation leads to chronic inflammation resulting in oxidative stress (14). Thus, understanding of the feedback cycle and interaction between the DNA damage cytokine dysregulation as well as oxidative stress is crucial for deducing the mechanisms responsible for the chemotherapy-associated cognitive dysfunction.

1.6.4 Reduction in Estrogen or Testosterone Levels

It has been shown that estrogen and testosterone are neuroprotective and play an important role in maintaining the telomere length(26). In addition, reduction of estrogen associated with natural menopause is linked to changes in cognitive function, specifically the
working memory (14). Chemotherapy for breast cancer is linked with accelerated menopause and subsequent decrease in estrogen levels (14,27). Chemotherapy treatment-induced reduction of circulating levels of estrogen and testosterone regulate neural repair (14). Thus, through having an independent effect or an interaction with chemotherapy, reduced circulating levels of estrogen and testosterone leads to reduction of the ability to maintain telomere length. Therefore, although not well studied, it is suspected that reduction of estrogen might attribute to chemotherapy-associated cognitive dysfunction independently or exacerbates chemotherapy effects on cognitive changes (14).

1.6.5 Genetic Susceptibility

There are genetic risk factors that increase the vulnerability to cognitive dysfunction associated with chemotherapy treatments. These include genetic variability in the blood–brain barrier transporters, DNA repair mechanisms, and rate of telomere shortening, cytokine regulation, neural repair as well as neurotransmission. Polymorphism is the natural variation in a gene, DNA sequence, or chromosome resulting in the occurrence of different morphs of a phenotype (14). Polymorphism of brain-derived neurotrophic factor, which is associated with neuronal repair and axonal growth, leads to reduction of neuronal repair mechanisms. This neurotrophic factor is expressed in pre-frontal cortex of the brain, as well as, the hippocampus. In addition, polymorphisms in certain neurotransmitters, particularly catechol-O-methyltransferase, are linked to chemotherapy-associated cognitive dysfunction and lead to reduction of neurotransmitter activity levels (14). Overall, the specific mechanisms for the chemotherapy-associated cognitive dysfunction remain to be elucidated.
1.7 How to Measure Chemotherapy-Associated Cognitive Dysfunction

How to measure chemotherapy-associated cognitive dysfunction has been a key issue in the research field. Self-reported complaints were generally not reflected in objective tests of cognitive function (3). Thus, these tests may not be sufficiently sensitive to catch the more subtle changes in cognitive function that are reported by cancer survivors, compared to the population the tests were developed for, such as demenia (28).

In 2011, the International Cognition and Cancer Task Force (ICCTF) aimed to summarize the literature to determine the cognitive domains most impacted by chemotherapy, namely executive function, memory, and processing speed, and published recommendations of neuropsychological tests that are the most appropriate to capture chemotherapy-associated cognitive dysfunction, based on a review of the available literature (4). The recommended tests for assessing the learning and verbal memory, executive function, and processing speed domains included the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination. Due to the sensitivity in assessing dementia, availability of six alternate forms, reduced number of list items and learning trials, HVLT-R has been argued to be suitable for sequential assessment of individuals with severely impaired cognitive function compared to other verbal learning measures, such as the Rey Auditory Verbal Learning Test (29). In addition, the ICCFT recommended that studies also include measures of working memory (executive function, and complex attention). The ICCTF also pointed to areas in the field that required further research and recommended that the ideal study design for examining the effect of chemotherapy treatment are, prospective, longitudinal trials with baseline cognitive assessments (before treatment) and long-term follow up (4). The pre-treatment measure was recommended since results of
longitudinal studies to date have shown that 20-30% of patients have low cognitive performance before chemotherapy treatment begins (30). This suggests the need to assess cognitive function prior to chemotherapy to adequately assess the impact of chemotherapy on cognitive function. In addition, excluding patients with cognitive performance below age-appropriate norms may not necessarily be the most appropriate approach, since these individuals may be at even greater risk for cognitive decline with chemotherapy (4).

In summary, according to the findings of meta-analyses and the ICCTF report, future research must be conducted on chemotherapy-associated cognitive dysfunction in cancer types such as colorectal cancer, which has received little attention. There is a consensus that many factors affecting the results of the neuropsychological testings remain to be elucidated. Furthermore, further investigation is required to explore the associated biological and psychological mechanisms, role of genetic factors, impact of various chemotherapy treatments, and the effect of endocrine therapy, as well as radiotherapy.

In 2013, a prospective, longitudinal, cohort study (n=189) of breast cancer survivors treated with chemotherapy investigated the association of neuropsychological test performance and self-reported cognitive complaints. The neuropsychological test battery consisted of Wechsler Test of Adult Reading, California Verbal Learning Test, Wechsler Memory and intelligence Scale, Brief Visuospatial Memory Test, and Trail making Test. Self-reported cognitive complaints was assessed using the Patient’s Assessment of Own Functioning Inventory, which have four subscales including memory, higher-level cognition measuring executive function, language and communication, and motor-sensory perception (31). Compared to healthy controls, self-reported elevated memory (p=0.003) and executive function (p=0.01) complaints were statistically higher among cancer patients. These complaints had statistically
significant associations with domain-specific neuropsychological test performances in visual memory ($R^2 = 0.16$), psychomotor speed ($R^2 = 0.19$), and executive function ($R^2 = 0.21$).

In addition, compared to healthy controls, the cancer patients’ performance was lower in the domain-specific neuropsychological test performances in visual memory ($p = 0.03$), psychomotor speed ($p = 0.01$), and executive function ($p = 0.09$). This was the first study to demonstrate that subjective cognitive complaints reflected objective neuropsychological performance (31).

1.7.1 Mini Mental State Examination

As per the ICCTF recommendations, a baseline screen of cognitive function using the mini-mental state examination (MMSE) can be conducted in order to screen for frank cognitive impairment. A score of less than 23 is commonly used in clinical practice to denote an increased risk of Alzheimer’s disease (32). This test has also been validated and deemed reliable among psychiatric patients namely, dementia syndromes, affective disorder, affective disorder with cognitive impairment (i.e., “pseudodementia”), mania, schizophrenia, and those with personality disorders (32,33). This test assesses orientation to time and place, attention/concentration, language, constructional ability, and immediate and delayed recall (33). The inter-rater reliability is above 0.65 and it can be enhanced with more precise administration and scoring criteria (32). The test-retest reliability estimates of conducting the test in intervals of less than two months ranged from 0.80 to 0.95 (32).

1.7.2 Stroop Test

Stroop Test evaluates the executive function domain of the brain. During the Stroop Test, study participants are asked to disregard the verbal content of the word while reporting the words’ colour. Thus, the “colour-word interference effect” refers to the aforementioned decrease
in color-naming speed (34). It has been reported that among individuals with intact cognitive function, the ability of reading the colour words presented in colored ink is as fast as when they are presented in black ink (34). However, when asked to report the colour of the ink rather than the word itself, the time to complete the task increases significantly (34). The test-retest reliability at a one-month interval between the test sessions is reported as a reliability coefficient of 0.91 (34). Furthermore, the test-retest reliability has also been examined in individuals with known neuropsychological symptoms. In a study using the Central Nervous System Vital Sign battery test, which included the Stroop Test, in 169 healthy controls and 144 neuropsychiatric-subjects aged 7–90, the test-retest reliability of the Stroop Test was reported as an ICC of 0.87 (35). Neither age nor clinical status had any effect on the reliability (35). However, in another cross-sectional study among healthy Dutch-speaking patients aged 24 to 81 years (n=1788) demographic data such as age, sex and education profoundly affected the, speed-dependent Stroop scores (i.e., time to complete a subtest, which is a continuous variable) as opposed to accuracy measures (i.e., the errors made per Stroop subtest, a discrete variable) (36). A significant age and low education level interaction was found for the Stroop inference scores representing declines in executive function with aging. This decline was more distinct among those with lower level of education (36).

1.7.3 Hopkins Verbal Learning Test-Revised

Hopkins Verbal Learning Test-Revised (HVLT-R) assesses verbal learning and memory, specifically as immediate recall, delayed recall, and delayed recognition. This test has adequate psychometric properties such as validity, sensitivity to change over time, test-retest reliability, and the accessibility of the test in different languages (4). The test-retest reliability coefficients of HVLT-R have been reported for total recall (r = 0.74), learning (r = 0.41), delayed recall (r =
The reliability and construct validity of the measures on HVLT-R have been demonstrated among elderly adults. The specificity (0.83) and sensitivity (0.83) for detecting dementia among elderly and ethnically diverse community-dwelling population have been well demonstrated (37). In addition, significant association has been found between younger age and better HVLT-R performance. One study measured the practice effects during repeated administrations of HVLT-R memory tests with and without alternate forms (38). It was reported that when alternate verbal learning memory test forms are used, practice effects were significantly reduced (38).

### 1.7.4 Trail Making Test

Trail Making Test is the most commonly used neuropsychological test incorporated in testing batteries for clinical practice; it includes two parts: TMT-A and TMT-B (39). TMT targets the executive functions and processing speed of cognitive domain. TMT-A requires visuoperceptual abilities. TMT-B primarily targets the episodic memory domain. TMT-B also reflects the psychomotor speed, mental flexibility, and task switching abilities. For both parts, the time of completion is recorded for the task where subjects are asked to draw lines in order to connect the circles containing number in an ascending order. However, TMT-B has an added task of alternating between numbers and alphabet letters (39). One study claimed a significant practice effect for only TMT-A over the course of three administrations in 6-month interval; the reliability of TMT-A was reported as 0.94 while 0.67 for TMT-B (39). The inter-rater reliability for TMT-A and -B has been reported as 0.94 and 0.90, respectively. TMT has adequate sensitivity to measure executive functions, processing and psychomotor speed. Therefore, the high inter-rater reliability, validity, and suitability of the test to multinational application indicate
that the TMT-A and -B have adequate and reliable psychometric properties (39). According to ICCFT suggestions for the examination of specific cognitive domains namely, processing speed and visual memory, this test has been recommended in studies of cognitive function in cancer patients and survivors (4).

1.8 Proposed Risk Factors for Chemotherapy-Associated Cognitive Dysfunction Development

There are many confounding factors influencing inter- and intra-subject variability in reported chemotherapy-associated cognitive dysfunction among cancer patients. In addition to age and education level as outlined above, the factors that influence the vulnerability of an individual to chemotherapy-associated cognitive dysfunction include, type of chemotherapy regime, genetics, menopausal status, and the prescribed chemotherapy regimen (40).

First, the type of chemotherapy received may impact susceptibility. It has been shown that the extent of cognitive dysfunction may differ according to the chemotherapy regimen prescribed (14). Using a battery of neuropsychologic tests, a cross-sectional study assessed cognitive functioning of 34 breast cancer patients treated with high-dose chemotherapy plus tamoxifen, 36 patients treated with standard-dose chemotherapy plus tamoxifen, and 34 control patients who did not receive chemotherapy. Those treated with higher dose chemotherapy had 8.2 times higher risk of cognitive impairment compared to controls (41). However, the standard-dose chemotherapy group did not show a statistically significant elevated risk of cognitive impairment compared to controls. Thus, higher chemotherapy dose results in higher rate of cognitive decline compared to standard dose (41). However, the standard-dose chemotherapy group did not show a statistically significant elevated risk of cognitive impairment compared to controls. Thus, higher chemotherapy dose results in higher rate of cognitive decline compared to
standard dose (41). In a prospective longitudinal study of cognitive performance, the impact of high-dose cyclophosphamide, thiotapecarbo-platin (CTC) chemotherapy (n = 28), was compared to standard-dose fluorouracil, epirubicin, cyclophosphamide (FEC) chemotherapy group (n = 39), and to a healthy control group (n = 60), as well as, stage-I breast cancer patients who had received no systemic chemotherapy (n = 57) (42). Cognitive decline was higher among those breast cancer patients treated with high-dose chemotherapy as opposed to standard-dose chemotherapy, and this study confirmed the findings from the earlier cross sectional study with the same population by van Dam et al. (41,42). In addition, a four-year follow-up of this study, individuals who had received chemotherapy had a higher risk of late cognitive dysfunction than the control group (n=27), which did not receive chemotherapy (16). However, no elevated risk was found among those who received standard-dose fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy in the original study (42).

Second, genetic variability of blood- brain transporters can differ across cancer patients(14). It has been shown that with the exception of methotrexate and 5-flourouracil, systemic administration of most of chemotherapy agents does not lead to chemotherapy crossing the blood- brain barrier. However, patients with different polymorphisms of gene MDR-1or other transporter genes could be more susceptible for having higher levels of chemotherapy. Similarly, animal studies have shown that small doses of chemotherapy could cause cell death and reduction of brain cell division, which interfere cognitive function (14).

Third menopausal status as well as the endogenous estrogen and testosterone levels of female and male patients, respectively may play a role in susceptibility to developing cognitive issues. Although it has been shown that cognitive functioning is affected by the neuro-protective influence of systemic estrogen levels, in a population-based study (n=241), neither the
menopausal status nor the blood estrogen levels affected the cognitive performance among the pre- and post-menopausal healthy women (43). Specific to cancer survivors, in the longitudinal study by Schagen et al. outlined previously, no association was found between cognitive performance and menopausal status after comparing the changes in cognitive performance between the patients with no changes in menopausal status following chemotherapy and those who became postmenopausal after treatment (42).
Chapter 2: Physical Function and Functional Mobility

2.1 Prevalence in Colon Cancer Survivors

A reduction in self-reported physical function has been reported with cancer treatments (6,44,45), specifically with objective measures of cardiorespiratory fitness and strength in prospective interventions in breast cancer survivors(46), and in as self-reported in cross-sectional studies of lung, colon, and prostate cancer survivors (47). However, the physical function and functional mobility of colon cancer patients over the course of chemotherapy has not been assessed using objective validated tests.

Based on the physical functioning scales of the Short-Form Health Survey (SF-36), deficits in physical function are observed among recent and long-term cancer survivors (6). A retrospective study, analyzed the data from the 1999–2002 National Health and Nutrition Examination Survey were analyzed. The aim was to compare the proportion of restrictions and limitations in physical performance and activity among 279 recent and 434 long-term cancer survivors, and among 9370 individuals with no reported cancer history. All cancer types were included in this report (6). The prevalence of physical performance limitations was 1.5–1.8 times higher among recent (54.4%) and long-term cancer survivors (52.7%) compared to those with no cancer history (21.2%) (6). Thus, having a cancer history is associated with increased prevalence of physical performance limitations. These findings are consistent with findings from the Iowa Women's Health Study, which was a large population-based cohort study of postmenopausal women who were followed into their elderly years (48). Using a 5-item self-reported assessment of functional health designed for elderly, community-dwelling individuals, the prevalence of functional limitation was reported among 1068 five-year survivors and 23501 non-cancer survivors. It was reported that 30 -50% increased prevalence of functional limitations occurred
among cancer survivor after five year or more, in activities requiring mobility and strength (48). Analysis of functional limitations by cancer site among 5-year cancer survivors revealed a statistically significant higher prevalence of functional limitations for the breast cancer patients compared to those with no previous cancer history (OR =1.37, 95% CI = 1.14 to 1.65) (48).

Among colon cancer patients specifically, in individuals receiving surgery and adjuvant treatment, one cohort study that included a variety of cancer survivors groups (breast, colon, lung, or prostate cancer) indicated significant decline in physical function across all cancer survivors despite having high levels prior to diagnosis. For this study, a retrospective physical function assessment was done using the 10-item subscale of Short Form-36 (SF-36) (12). As the retrospective outcome assessment, patients were asked to recall their physical function 3 months prior to cancer diagnosis. Age, cancer site and stage of disease did not predict the reported levels of physical function prior to diagnosis, but following diagnosis, the changes in physical function was varied by the cancer site and cancer treatments. The cancer sites included breast, colon, lung, or prostate cancer (12). Treatment modalities included chemotherapy, different types of surgery depending on the cancer site, and radiation. Compared to population-based norms values for nine geographic areas of the United States, colon cancer patients had higher than average performance levels prior to diagnosis (49). However, compared to national norms for patients 55 to 64 years of age, following cancer treatments, 61% of study participants had a one or more quartiles decline in physical performance level, which is clinically meaningful (12). This decline in physical performance was greater in colon cancer patients than that observed for lung, breast, and prostate cancer patients (12). The predictors of the physical dysfunction were receiving surgery, chemotherapy, and radiation treatments (12). In a subset of patients where physical function remained as high as pre-diagnosis, it was noted that these individuals received
less aggressive cancer treatments (12). In addition, declined functional status was influenced by comorbidity only among colon cancer patients meaning that comorbidity had a higher impact on poorer functional status (12).

2.2 Measurement of Physical Function and Functional Mobility

Studies to date in cancer survivors have focused primarily on subjective self-report measures of physical function and mobility. However, there is emerging interest in using objective assessments of physical function and mobility to monitor change overtime in this population. Objective measures of physical performance obtained close to the time of cancer diagnosis may predict overall survival or 2-year progression to disability (44). Four hundred and thirty one individuals diagnosed with cancer during the first 6 years of follow-up were identified from the Health, Aging and Body Composition study, which was a prospective cohort of 3075 well-functioning older adults. Objective physical function and mobility measures completed at set intervals included 20m and 400-m long-distance corridor walk test. In this subset of identified cancer survivors, these outcomes were examined as predictors of survival and disability. Objective assessments of lower extremity physical performance predicted subsequent disability in older adults with a new cancer diagnosis (44).

Objective tests were also used in a in a case study of an 81- year old breast cancer patient before, during, and after undergoing neurotoxic chemotherapy treatment (45). The short physical performance battery (7), was used, which included a balance test, 4-m walk test, chair stands, and gait speed, was used to assess mobility in. There was a significant decline in balance and functional mobility during chemotherapy treatment, which persisted at two and half years-post-treatment (45).
In spite of all these concerns, there is still a gap in the literature on the prognosis for chemotherapy-associated functional mobility dysfunction among colon cancer patients. Therefore, for this study, 6-minute walk test (6MWT), Timed Up and GO (TUG), and gait speed were included in the physical function and mobility testing battery in order to examine the changes in physical function and functional mobility with treatment for colon cancer.

2.2.1 Six Minute Walk Test
The 6MWT is a commonly used test to represent an individuals’ sub-maximal level of functional capacity. This test measures the maximum distance walked in six minutes without running or jogging. It has been reported that the distance walked in a 6MWT is correlated with VO2peak ($r =$ 0.59 - 0.73) specifically in breast cancer survivors (50), as well as cancer patients (51). The test is reported to be easy to administer, well tolerated, and more reflective of daily living activities than the other walk tests (52).

This test has been reported to be valid and reliable in healthy elderly, cancer, cardiac, and pulmonary patients (51) The ICC for test-retest reliability of 6-MWT walking distance has been reported as 0.93 in breast and colorectal cancer patients (51). In addition, the feasibility of using the 6MWT to measure functional exercise capacity has been tested in a variety of populations, including individuals with severe intellectual and sensory disabilities (53). The test-retest reliability for the 6MWT is reported as ICC ranging between 0.86-0.96 among those with severe intellectual and sensory disabilities (53).
2.2.2 **Timed-Up and Go**

Functional mobility can be assessed using a standardized test TUG while gait speed assesses physical function. TUG is a timed test for measuring how long the patient takes to stand up from a chair without using their arms, walk 3 metres, turn, and return to a seated position. Intra-tester and inter-tester reliability of TUG have been reported as ICC of 0.99 and 0.98 among elderly populations (54). Through correlation of TUG scores with measurements obtained for gait speed, construct validity has been supported (Pearson r = 0.75). According to a study that evaluated the reliability of six physical performance tests in older adults with dementia, the relative reliability of TUG and gait speed was shown to be excellent, with ICC of 0.90-0.95 (55).

2.2.3 **Gait Speed**

The gait speed assesses the speed the patient normally walks for 4 meters. This test is scored by dividing the time for completion of the test by the distance walked (4 metres) Gait speed measurements are considered highly reliable in people without known impairments (56). Multiple studies have demonstrated gait speed to be a powerful predictive measure of declines in physical function and mortality (56-58). In addition, it has been suggested that gait speed alone may perform as well as a summary measure of gait speed, balance, and chair stands (57,58).
Chapter 3: Physical Activity

3.1 Definitions and Prevalence of Physical Activity in Colon Cancer Survivors

Physical activity is defined as any bodily movement produced by skeletal muscles that require energy expenditure (59). In intervention studies, physical activity has been shown to improve health-related quality of life, physical function and fitness as well as fatigue levels in colon cancer patients and survivors (60). In addition, there is emerging observational evidence that being physically active following diagnosis can reduced risk of recurrence and improved survival (8,9,61-64).

A prospective observational study of 832 patients with stage III colon cancer enrolled in a randomized adjuvant chemotherapy trial investigated the impact of physical activity on colon cancer recurrence and survival. Compared to the inactive group (<3 MET hour per week), significantly improved disease- and recurrence- free survival was reported for those who engaged in 18-26.9 MET- hours/week after stage III colon cancer diagnosis. In addition, it was reported that during post-operative adjuvant chemotherapy, women who engaged in higher physical activity (> 25 MET- hours/week) had improved survival compared to the physically inactive group (hazard ratio=0.55) (8). These results were independent of physical activity prior to cancer diagnosis (8). In addition, deficits in physical function may lead to restrictions in daily physical activity participation or vice versa.

Although it is well documented that both occupation- and leisure time-related physical activity are inversely related to the colon cancer outcomes, physical activity participation has shown to decrease in colorectal cancer survivors over the course of chemotherapy (11,65). In a prospective study of 431 colorectal cancer patients, compared to pre-diagnosis, there was a significant reduction in strenuous physical activity participation (more than 150 min per week) at
the end of chemotherapy (28.8 ± 106.2 vs. 11.8 ± 95.9 min, p = 0.042). In the physical activity questionnaire, exercise intensity was defined as mild (minimal effort, no perspiration), moderate (not exhausting, light perspiration), and strenuous (heart beats rapidly, sweating) during free time in a typical week. Furthermore, the percentage of patients achieving the current American College of Sports Medicine Guidelines for Cancer Survivors (at least 150 min of vigorous to moderate intensity physical activity per week) was reduced from 27% before diagnosis to 10% during treatment (11).

Using seven questions from NHANES 1999–2002, a population-based study of mixed cancer survivors assessed physical performance limitations among 279 recent and 434 long-term cancer survivors, and 9370 individuals with no reported cancer history (6). These questions asked about difficulty with different components of activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (6). Among those with history of cancer, the prevalence of restrictions in physical activity participation was 31% compared to those with no history of cancer (6). Interestingly, these limitations were reported many years following cancer diagnosis and were not mediated by age (6). The authors concluded that having a cancer history is associated with decreased physical activity participation (6). In summary, to date, the change in physical function of colon cancer patients and its impact on physical activity has not been explored (6,66).
3.2 Measurement of Physical Activity

Heart rate monitors, pedometers, and accelerometers are objective methods for the assessment and quantification of the amount and intensity of physical activity in a field setting. These methods all have advantage and limitations, including burden on participant in having to be done on the device for several days.

For the use of heart rate monitors, the linear relationship between heart rate and oxygen consumption (VO2) is relied on. However, this relationship is inclined to many confounding variables at the lower end of individual’s physical activity levels (67). Individual’s heart rate can be affected by factors other than body movements such as psychological stress, caffeine, smoking, and many other medications.

Another approach is the use of motion sensors that detect body movement, namely pedometers or accelerometers (67). The mileage walked or the number of steps taken over a period of time can be estimated using pedometer. One of the limitations of pedometers include the inability to assess the intensity or pattern of activities performed since it only detects the total steps or counts over the observational period of running or walking (67). Accelerometer measures accelerations produced by body movements. It quantifies the magnitude and direction of the acceleration, referred to by the dimensionless ‘counts’. Although accelerometer provides an objective assessment of overall physical activity, limitations exist in recording horizontal or upper-body movements. Another limitation of the accelerometer and pedometer include the lack of ability to report on the information of the specific activity and they are limited to reporting only total daily physical activity (68).

As a subjective method, questionnaires have been identified as an appropriate way to measure physical activity that is feasible and has a low patient burden. They are valid for gross
classification of physical activity level (e.g., low, moderate, highly active) for any population (68). However, lack of comparability of various physical activity questionnaires used across studies has been identified as one of the major limitations preventing comparison amongst studies aiming to quantify physical activity levels. Thus, the International Physical Activity Questionnaire was developed as an instrument to monitor physical activity cross-nationally (59). Fourteen centers from 12 countries collected the reliability and validity data for the IPAQ long format. The long format of IPAQ form using “last 7-day recall” is recommended for research and clinical setting requiring more detailed assessment (59). In validation work, the test-retest spearman’s reliability coefficient for the IPAQ long form was reported as 0.80, indicating a very good reliability (59). Pooled data for concurrent validity ($r= 0.67$) as well as criterion validity ($r=0.33$) was investigated in order to assess the agreement between the short and long IPAQ format and to compare the physical activity recorded by the self-report and accelerometer. The high validity of IPAQ is due to its ability for assessment of frequency, intensity, and duration of physical activity, as well as an emerging concern, which is sedentary behavior.
Chapter 4: Chemotherapy Induced Peripheral Neuropathy

4.1 Definitions and Prevalence

In addition to cognitive dysfunction, chemotherapy induced peripheral neuropathy (CIPN) is a common neurological adverse effects of chemotherapeutic agents. Chemotherapy treatments exert a direct effect on peripheral nerves and this is manifested as CIPN. The most common neural target of CIPN is the dorsal root ganglion of the primary sensory neurons. The severity of CIPN is dose-dependent and can persist long after completion of chemotherapy. One study utilized quantitative sensory testing to examine the changes in the primary afferent fibers of 52 colorectal cancer patients compared to healthy controls (69). The occurrence of subclinical peripheral neuropathy was exhibited in almost all colorectal cancer patients before the initiation of chemotherapy (69). A common treatment approached for colon cancer includes the use of a platinum- based compound called oxaliplatin, which induces two clinically distinct form of neurotoxicity namely acute and chronic. The acute is due to nodal and axonal dysfunction as opposed to chronic sensory form, which is induced by the morphologic and functional changes in dorsal root ganglion cells.

The main risk factor for acute CIPN is cumulative dose levels of oxaliplatin, and acute CIPN is reported to occur in up to 22% of cancer patients (70). The prevalence of chronic CIPN ranges from 60-75% patients treated with oxilipatin-based regiments (70). The risk factors for this chronic presentation of CIPN are the cumulative oxaliplatin dose, time of infusion, and the existence of peripheral neuropathy prior to chemotherapy initiation. Although it is expected that the long-term effect of platinum-induced neurotoxicity resolve within a year after discontinuing the treatment, CIPN might remain persistently due to long-term accumulation of platinum compounds in dorsal root ganglion (69). To date there is no research on the role of CIPN on
objectively assessed physical function, functional mobility, or physical activity levels in colon cancer survivors.

### 4.2 Measurement of Chemotherapy Induced Peripheral Neuropathy

A standardized objective approaches have not been developed for the quantitative measurement of Chemotherapy Induced Peripheral Neuropathy (CIPN). While sensory testing has been used to a limited degree (69), a correlation between quantitative measurements and clinical symptoms has not been established yet. CIPN can be subjectively measured as a component of several self-report instruments that have been validated in cancer survivors, such as the Functional Assessment of Cancer Therapy (FACT), Gynecologic Oncology Group, neurotoxicity (GOG-Ntx), Neuropathic Pain Scale (NPS), Patient Neurotoxicity Questionnaire (PNQ), Peripheral Neuropathy Scale (PNS), EORTC QoL questionnaire (QLQ), quantitative sensory testing (QST), scale for chemotherapy-induced long-term neurotoxicity (SCIN), total neuropathy score (TNS), total neuropathy score clinical version (TNSc), total neuropathy score, reduced version (TNSr), thermal threshold (TT), and vibration threshold (VT) along with other four toxicity rating scales: World Health Organization (WHO), Eastern Cooperative Oncology Group (ECOG), Ajani, and National Cancer Institute of Canada – Common Toxicity Criteria (NCIC-CTC) (71).

One common approach to measuring CIPN is using the PNQ. In a cohort of 300 breast cancer patients, CIPN was assessed using two patient-based questionnaires (PNQ, FACT and GOG-) and one physician-based scale (NCIC-CTC 2.0). Compared to the aforementioned tools, the PNQ showed a greater sensitivity and revealed a greater impact of CIPN on daily living activities (72). In addition, prospective evaluation of CIPN in patients treated with weekly
paclitaxel as part of treatment of breast cancer has evidenced the superior sensitivity of the PNQ over (NCIC-CTC 2.0) (71).

The PNQ has two versions. One version is for administration in studies where chemotherapy treatments include taxanes, cisplatin, and carboplatin. The second version is for administration in studies where chemotherapy treatment included oxaliplatin. A randomized, multi-institutional phase III trial of adjuvant taxane chemotherapy used the PNQ to examine the impact of chemotherapy among 300 Japanese breast cancer patients receiving adjuvant chemotherapy (72). According to 61 physicians’ perspectives, the utility and diagnostic value of the PNQ was shown to be useful and highly acceptable for collection of CIPN information (73). One important factor in the PNQ is the presence of formal assessment of the effect of CIPN on a list of pre-defined daily life activities (72). Therefore, for this study, as an assessment of CIPN the PNQ was used to examine if there is any correlation between CIPN and the physical function, functional mobility, or physical activity.
More recently, a positive link between cognitive function, physical function, and usual physical activity levels has been reported in older adults (74), as well as, in individuals with Alzheimer's and Parkinson’s disease or post-stroke patients (75,76). Longitudinal studies have shown that physical activity participation lead to a less cognitive decline over time. One longitudinal study assessed the use of cardiorespiratory fitness as a predictor of cognitive performance over 6 years or with level of cognitive function on tests performed 6 years later in 349 healthy older adults (77). The assessed cognitive domains included working memory, processing speed, attention, and general mental functioning (77). In the longitudinal Health, Ageing, and Retirement survey, less cognitive decline was reported after 2.5 years among individuals who participated in any type of regular physical activity, especially vigorous activities more than once a week (78). A prospective, cohort study of dementia has suggested an association between higher levels of regular physical activity with reduced risk of subsequent cognitive impairment among 4615 elderly Canadian population aged 60 years or over who completed a 5-year follow up study (79), age-, sex-, and education-adjusted analyses revealed the association between high levels of physical activity and reduced risks of cognitive impairment (odds ratio, 0.58; 95% confidence interval, 0.41-0.83) (79). Interestingly, this significant dose-response relationship was observed only among women (79). In addition, 3-year follow-up studies of 1090 subjects aged 60 years or over have reported that those who were limited to indoor physical activity had higher relative risk of developing dementia compared to those without limitations (80).

There is emerging evidence for the relationship in clinical populations as well. A meta-analysis which included 30 randomized controlled trials (2020 participants) reported that adults
with dementia and related cognitive impairments benefit from physical activity due to the beneficial effects on physical fitness (effect size = 0.69) and cognitive function (effect size = 0.57) (81). In addition, exercise intervention studies provide a strong support for the impact of physical exercise on cognition. Significant increases in cardiorespiratory fitness, have led to the enhanced cognitive performance in older adults (82). Thus, cognitive decline in older age can be protected through engagement in moderate and vigorous physical activities (78,82).

5.1 Proposed Mechanisms

Several mechanisms have been proposed for the protective role of physical activity or exercise on cognitive function. These include decreased blood pressure, sustained cerebral blood flow, enhanced cerebral metabolic demands, larger hippocampal volumes, and inhibited platelet accumulation (83).

5.2 Physical Activity, Physical Function and Cognitive Dysfunction

While improvement in aerobic capacity (84), muscular strength (85), and walking distance, have been reported in randomized controlled trials of exercise in breast cancer patients (86), the clinical effect of an exercise intervention on cognitive dysfunction among cancer patients is still unknown.

Previous animal studies have shown that 5-FU crosses the blood brain barrier and accumulates in brain tissue(87). It has been shown that in healthy rodents adjuvant chemotherapeutic agents used for breast cancer treatment (e.g. methotrexate (MTX) and 5-FU) induced impairments in cognitive tasks namely; the Morris water maze and novel object recognition (88,89). Thus, a 2x2 study design investigated the potential role of physical activity in ameliorating the chemotherapy-induced cognitive impairments in healthy rats (90). In order to
reflect clinically equivalent cumulative dose of combined oxaliplatin and 5-Flourouracil (5-FU) and to confirm that these doses produced measurable cognitive impairments, the rats were injected with a combination of 5-FU (75 mg/kg) and oxaliplatin (8 mg/kg) in two intra-peritoneal injections. The oxaliplatin injection was reduced to 8 mg/kg in order to prevent the rat’s running wheel ability to be influenced by the likelihood of peripheral neuropathy. After allocating the rats to receive chemotherapy, the effect of 5-FU, oxaliplatin, and the combination of 5-FU/oxaliplatin were examined by the cognitive tasks such as the Morris water maze and novel object recognition, and fear conditioning. The same cognitive tasks were conducted after the 4-week exercise intervention where the rats were given access to running wheel overnight. The sedentary rats treated with 5-FU/oxaliplatin displayed significantly worse object recognition (memory task) than all other groups. Interestingly, there was no significant difference between the 5-FU/oxaliplatin-exercise rats and the control rats; this means that the poor performance on a memory task induced by 5-FU/oxaliplatin treatment was ameliorated by physical activity. This study concluded that 4-weeks access to running wheel improved the performance on the hippocampal-dependent memory tasks since hippocampus is one of the regions of the brain, which appears to be preferentially affected with the combined treatment of 5-FU and oxaliplatin (90).

To date there have been no studies examining the impact of physical activity or interventions to delay or prevent the development of chemotherapy-associated cognitive dysfunction during or after diagnosis of colorectal cancer. However, based on the link between higher levels of physical activity and reduced cognitive decline in older adults, it is possible that lower levels of physical activity may contribute to cancer-associated cognitive dysfunction.
Therefore, it is crucial to explore the association and examine if there are any possible interactions between the changes in neuropsychological performance and physical function as well as self-reported physical activity levels among colon cancer patients.
Chapter 6: Methods

6.1 Participant Information

Approval was obtained from the British Columbia Cancer Agency (BCCA) Research Ethics Board prior to the commencement of this longitudinal pilot study. English speaking colon-cancer patients of age 18 years or older were recruited if they were scheduled by their oncologists to receive 5-fluorouracil/oxaliplatin (FOLFOX) as an adjuvant chemotherapy treatment for colon cancer at British Columbia Cancer Agency (BCCA)-Vancouver. Participants were excluded if they had already started chemotherapy treatment, scored less than 23 on the baseline Mini Mental State Examination (MMSE), took medications for any condition that may have altered cognitive testing such as clinical depression, anxiety and neurological disorder, or had history of substance abuse.

6.2 Sample Size

No pilot data for sample size calculation was available since at the time of the study commencement there were no published longitudinal studies examining the cognitive and physical function among colon cancer patients. Previous studies have used other neuroimaging and neuropsychological tests for the breast cancer population, thus their sample size and power calculation would not be reflective of this pilot study. Therefore, our aim was to assess the feasibility of obtaining prospective measures of cognitive function, physical function, and mobility prior to and following chemotherapy in colon cancer survivors, as well as to gather data to inform further studies in as many participants as possible within a 12-month recruitment window.
6.3 Study Protocol

Eligible participants were referred to the study by oncologists at BCCA-Vancouver. Referred participants were then contacted for a phone-screen by study staff to establish eligibility. During the phone screen, the participant was informed about the duration of each visit (approximately four hours, which included a measure of electroencephalography (EEG), which will not be discussed in this thesis) at University of British Columbia (UBC) and timing of the two proposed study visits, namely within two weeks prior to chemotherapy and two weeks after last chemotherapy dose. If the individual was eligible and interested in participating, the baseline study visit was booked. At the first visit, the participant signed the informed consent form. The study visits took place at the Friedman Building Multi-Purpose Room on the UBC campus.

Demographic factors (i.e., age, sex, past medical history and medications) were collected by self-report questionnaire. Cancer treatment information (i.e., cancer stage, chemotherapy treatment start date, amount/duration of chemotherapy) was collected by chart abstract under the direction of Dr. Howard Lim. The consistency of the order in which the outcome measures were obtained was maintained the same through data collection for all participants. The neuropsychological testing was completed prior to the physical function and mobility testing. The neuropsychological test battery, which follows the ICCTF recommendations, included the Stroop, HVLT-R, and TMT (4). Before conducting the neuropsychological testing, the MMSE was completed. In addition, the MMSE was performed for the 6-month testing visits in order to document any intellectual changes that might have occurred with time and to assess the effects of potential chemotherapeutic changes on cognitive function. The physical function and mobility testing battery included 6MWT, TUG, and gait speed. At the end of each visit, participant was asked to complete the patient self-report of chemotherapy induced peripheral neuropathy and
usual physical activity over the last seven days, using that International Physical Activity Questionnaire (59).

6.4 Outcome Measures

6.4.1 Neuropsychological Test Battery

The Stroop Test measures aspects of executive function, selective attention, and cognitive flexibility (34). During the test, the participant was asked to focus on a computer screen. Three coloured response keyboard pad (i.e., blue, red, and yellow) were introduced to the participant. Words appeared on the screen written in blue, red, or yellow ink. The computer presented a randomly chosen selection of 258 coloured word or “stimuli” to the participant. When a word appeared, the participant was asked to respond to the colour the word that is written in, not the word itself by pressing the appropriate key on a coloured response pad (i.e. the word yellow printed in blue should be responded as blue). The stimuli can be congruent (i.e., the word yellow is written in yellow) or incongruent (i.e., the word blue is written in yellow). A five-minute practice trial was conducted in order for the participant to understand the process. For the scoring, the time to complete and the number of errors, as a measure of accuracy, were recorded. The main outcome variables of interest were the reaction time for congruent and incongruent accurate trials, the percent accuracy of congruent and incongruent trials, as well as the interference score. This score refers to the time that it takes to suppress the reading of the word in which the colour is written in plus the time to name the colour. Strauss et al. have specified that the Stroop interference reveal the ability of an individual to “suppress a habitual response in favor of an unusual one” (91).

TMT measures executive function, attention, sequencing, mental flexibility, visual search, and motor function. TMT consist of two parts (i.e. Part A&B). For the TMT-A, the
participant drew lines to connect 25 circles with sequential numbering (i.e., 1,2,3) in an ascending order. For TMT-B, the same task was completed, however the circles now include both numbers (1 –13) and letters (A – L), and the participant had to alternate connecting a number, then a letter in ascending order. For both parts, a practice sample trial was conducted for better understanding of the process. Scoring for both forms was expressed in terms of time in seconds required for completion of each Part A and B of the test. If errors are made, the participant was re-directed to correct and keep going. The time difference between the trials (TMT-B minus TMT-A) was also calculated.

HVLT-R is a brief assessment of immediate recall, delayed recall, and recognition. It was originally designed to provide a brief measure of episodic verbal memory. The research assistant read 12 words aloud to the participant. Then, the participant attempted to immediately recall as many of the words as possible in any order; scored as the number of correct words recalled. This process was repeated two more times for a total of three free-recall trials. Then the other paper-and-pencil test (i.e., TMT A and B) and Stroop were completed to allow for the appropriate time (20-25 min) for the delayed recall trial or trial four in which, participants were asked to recall as many words as possible after a 20-25 min delay. The participant was then asked to complete a delayed trial by trying to free recall as many words as possible from the original list; scored as the number of correct words recalled. Adding the correct responses recorded for the three learning trials lead to the score for the total recall. The delayed recall score reflected the correct responses obtained in trial four. Finally, a discrimination trial, called the delayed recognition trial, was completed. This consisted of a randomized list of words that included 12 target words (from the original list) and 12 non-target words (6 semantically related false-positives and 6 semantically unrelated false-positives) read aloud to the participant. The participant had to
identify if the word read was part of the original list. This was scored as recognition discrimination index, which was calculated by subtracting the total number of false-positives from total number of true-positives. The retention percentage was also calculated (the score of fourth trial was divided by the higher score from either the second or third trial, then the result was multiplied by 100).

The test-retest reliability coefficients of HVLR-R have been reported for total recall (r = 0.74), learning (r = 0.41), delayed recall (r = 0.66), percentage retained (r = 0.39), and the recognition discrimination index (r = 0.40) (37). An equivalent, alternate form was given at the end of study visit to avoid a learning effect (38). The main outcome variables of HVLT-R were the total recall, delayed recall, retention percentage, and recognition discrimination index.

6.4.2 Physical Function and Mobility

The components included in the physical function and mobility testing were 6MWT, TUG, and gait speed. The purpose of 6MWT is to assess aerobic endurance using the standardized protocol from the American Thoracic Society (92). The participant was asked to walk as far as possible in 6 minutes without running or jogging back and forth on a pre-set 15 m course. The number of laps (30 meters per lap) was counted with partial laps measured by distance, and a total distance in meters covered within the six minutes represented the score. The ICC for test-retest reliability of 6MWT walking distance is reported as 0.93 in breast and colorectal cancer patients (51).

The TUG measures functional mobility. This test assesses how many seconds it takes the participant to stand up from a chair without using their arms, walk three meters, turn, and return to a seated position. Data obtained during the two-recorded trials was averaged for the recorded
score. Intra-tester and inter-tester reliability have been reported as ICC of 0.99 and 0.98 among elderly populations (54).

Gait speed was measured using a standard protocol by Hardy et al (93). The participant was asked to walk normally for 6 meters on a flat level course with markers placed at the end of the first meter and at meter five. This provides a 4 m segment for which the time to complete this distance is recorded in seconds using a stopwatch. Gait speed is scored by dividing the time for completion of the test by the distance walked (4 metres). Intra-rater reliability, inter-rater reliability, and test-retest reliability have been reported as high for gait speed (ICC=0.90–0.96, r=0.89–1.00) (54).

**6.4.3 Peripheral Neuropathy**

Chemotherapy induced peripheral neuropathy (CIPN) is a common and persistent side effects of chemotherapy treatment (72). One of the drugs in the FOLFOX regimen is oxaliplatin, which belong to a group of alkylating agent class of chemotherapy drugs known as platinum-containing compounds that are most likely responsible for developing peripheral neuropathy. CIPN may negatively impact balance and mobility (45). The Peripheral Neuropathy Questionnaire (PNQ) was administered to examine if there is any association between CIPN and physical function. The PNQ for oxaliplatin is a self-report questionnaire and identifies the incidence and severity of sensory and motor disturbances. In addition, PNQ includes an activity limitations checklist which the patients complete, using categories of “None” (grade A), “mild” (grade B), and “moderate” (grade C) “moderate to severe” (grade D) or “severe” (grade E) response option. Grade A, B and C responses indicate “no interference with daily activities.
6.4.4 Usual Physical Activity

The Long Format International Physical Activity Questionnaire (IPAQ) (last 7 days) was used to assess five domains including usual physical activity levels in job-related, transportation, housework, house maintenance, recreation, sport, and leisure-time as well as total time spent sitting (59). The scoring is divided into categorical score (low, moderate, high) and continuous score, which is expressed as MET-min per week. The ICC for test-retest reliability of IPAQ has been reported for the five domains including usual physical activity levels in work (0.74), transportation (0.61), domestic (0.80), vigorous (0.84), moderate (0.86), walking (0.54), and total activity (0.90); ICC was greatest among leisure-time physical activity (0.90) (94). The test-retest reliability of sitting recall between visits in the IPAQ long forms was generally good with more than four-fifths of the coefficients above 0.70 (59).

6.4.5 Psychosocial Outcomes

Participants completed five additional questionnaires during the study visit to measure key psychosocial factors that may change related to cancer treatment and could potentially impact the association of treatment and the main study outcomes. The Functional Assessment of Cancer Therapy – Cognition (FACT-Cog) was administered to examine self-reported perceived cognitive function (95). The European Organization for Research and Treatment of Cancer (EORTC-QLQ-C29) was administered to examine health-related quality of life (17). The Functional Assessment of Cancer Therapy–Fatigue (FACT-F) was administered to assess magnitude of fatigue (96). Finally, the State-Trait Personality Inventory (STPI) was administered to evaluate anxiety levels (97), and the Center for Epidemiologic Studies Depression Scale (CES-D) was administered to assess level of depression (98).
6.4.4.1 Statistical Analysis

Descriptive statistics were generated for participant demographic and disease-related characteristics. In addition, using SPSS software for the data analysis, the mean, mode, standard deviation (SD) and 95% confidence intervals for the neuropsychological and mobility test scores were summarized. The continuous outcome variable was cognitive function performance and the categorical explanatory variable was the two time points. For the analysis of neuropsychological, physical function and mobility test scores, as well as the self-reported physical activity scores, the Paired-Sample Wilcoxon Signed Rank Test was employed. This enabled us to test for the differences between the time points and assess the changes in the mean scores from the baseline to 6-months. The level of significance with p-value <0.05 was the indicative criterion for determining if the differences were statistically meaningful.
Chapter 7: Results

7.1 Patient Characteristics

Baseline participant characteristics are reported in Table 7.1. This study consisted of three males and four females, with a mean age of 53 years and mean body mass index of 25.1 kg/m². Years of education obtained, ranged from 13 to 19 years, with a mean of 15.4 (SD= 2.5) years. All the female subjects were pre-menopausal during the study timeframe. For all the subjects, the type and grade of colon cancer was adenocarcinoma, and stage III, respectively. The median number of positive nodes was two. All patients had undergone surgery and received FOLFOX chemotherapy intravenously. However, three patients were prescribed oral fluorouracil (5-FU), which is called capecitabine. The median amounts of capecitabine, 5-FU and oxaliplatin were 10850, 44578, and 1240 (mg/m²), respectively. The median planned percent dosages of capecitabine, 5-FU, and oxaliplatin were 67.20%, 90.92 %, and 78.60%, respectively.
<table>
<thead>
<tr>
<th>Demographic and Medical Characteristics of Study Participants</th>
<th>Mean (SD) or n (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>53 (3)</td>
<td>50-56</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td>15.4 (2.5)</td>
<td>13.0-19.0</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (57%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (43%)</td>
<td></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>168.8 (8.2)</td>
<td>156.0-180.0</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>71.9 (14.7)</td>
<td>53.1-99.0</td>
</tr>
<tr>
<td><strong>BMI kg/m²</strong></td>
<td>25.1 (3.6)</td>
<td>21.93-32.70</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>5 (71%)</td>
<td></td>
</tr>
<tr>
<td>Never married/</td>
<td>2 (29%)</td>
<td></td>
</tr>
<tr>
<td><strong>Menopausal status (women only)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>4 (100%)</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of colon cancer (Adenocarcinoma)</strong></td>
<td>7 (100%)</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Number of positive nodes</strong></td>
<td>2 (Median)</td>
<td>1-11</td>
</tr>
<tr>
<td><strong>Treatment approach</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>7 (100%)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7 (100%)</td>
<td></td>
</tr>
<tr>
<td>FOLFOX (IV)</td>
<td>4 (57%)</td>
<td></td>
</tr>
</tbody>
</table>

| **Chemotherapy Dose received**                              |                   |       |
| Median amount of CAP                                        | 10850             | 7500-11550 |
| Median amount of 5-FU                                       | 44578             | 40000-50080 |
| Median amount of OXAL                                       | 1240              | (526-1740) |
| Median % dosage of CAP                                      | 67.20             | (46.90-97.10) |
| Median % dosage of 5-FU                                     | 90.92             | 83.33-97.05 |
| Median % dosage of OXAL                                     | 78.60             | (31.31-96.11) |

Legend: Data are presented as mean (SD) if not stated otherwise
Abbreviations: BMI, body mass index; FOLFOX, 5-Fluorouracil, Leucovorin, Oxaliplatin; 5-FU, 5- Fluorouracil; CAPOX, Capecitabine, Oxaliplatine; CAP, Capecitabine; OXAL, Oxaliplatin
7.2 Objective Neuropsychological Measures

Compared to baseline, there was no significant difference in the HVLT-R (i.e., total recall, delayed recall, retention percentage, retention discrimination) after completion of chemotherapy compared to baseline (Table 7.2) (Figure 7.1-4). There was also no significant difference in TMT-A (31.3 ± 12.6 s at baseline vs. 31.1 ± 10.9 s after completion of chemotherapy, p=0.97), TMT-B (63.8 ± 14.5 s at baseline vs 63.9 ± 26.4, p= 0.99), and TMT Difference (32.5 ± 11.6 s at baseline vs 32.9 ± 18.8 s after completion of chemotherapy, p=0.95)(Figure 7.5-7). For the Stroop Test, no significant changes were observed in the mean scores for congruent accuracy percentage, congruent reaction time, incongruent reaction time, or interference score after completion of chemotherapy compared to baseline (Table 7.2) (Figure 7.8-12).

7.3 Self-Reported Impact of Cognitive Function on Quality of Life

Using the FACT-Cog, perceived patient self-report of cognitive deficits due to cancer therapy did not change significantly from baseline to end of chemotherapy (Table 7.2). Compared to baseline there was no difference in total score (38.6 ± 14.2 at the baseline vs 40.4 ± 16.2 after completion of chemotherapy, p= 0.77), perceived cognitive impairment (12.7 ± 12.3 at the baseline vs 17.0 ± 18.0 after completion of chemotherapy, p= 0.47), comments from others (1.0 ± 1.9 at the baseline vs 1.1 ± 2.0 after completion of chemotherapy, p=0.88), perceived cognitive abilities (20.1 ±8.1 at the baseline vs 18.6 ± 8.3 after completion of chemotherapy, p= 0.62), or impact on quality of life (4.7 ± 6.3 at the baseline vs 3.7 ± 5.2 after completion of chemotherapy, p= 0.68).
## Table 7.2 Neuropsychological Tests and Self-reported Cognitive Symptoms

<table>
<thead>
<tr>
<th>Tests</th>
<th>Outcome measure</th>
<th>Baseline Mean (SD)</th>
<th>After chemotherapy Mean (SD)</th>
<th>Mean difference</th>
<th>p-value</th>
<th>95 % Confidence interval of mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT-R</td>
<td>TR</td>
<td>49.1 (11.2)</td>
<td>53.3 (8.5)</td>
<td>4.1 (3.10)</td>
<td>0.21</td>
<td>(2.0, 6.3)</td>
</tr>
<tr>
<td></td>
<td>DR</td>
<td>51.9 (12.2)</td>
<td>50.7 (9.91)</td>
<td>-1.2 (3.10)</td>
<td>0.72</td>
<td>(-8.6,6.3)</td>
</tr>
<tr>
<td></td>
<td>RET</td>
<td>47.0 (13.1)</td>
<td>44.4 (12.31)</td>
<td>-2.6 (10.9)</td>
<td>0.56</td>
<td>(-12.7,7.5)</td>
</tr>
<tr>
<td></td>
<td>RDI</td>
<td>49.14 (4.9)</td>
<td>45.3 (13.0)</td>
<td>-3.9 (13.3)</td>
<td>0.47</td>
<td>(-16.1,8.4)</td>
</tr>
<tr>
<td>TMT- A &amp; B</td>
<td>TMT- A</td>
<td>31.3 (12.6)</td>
<td>31.1 (10.9)</td>
<td>-0.2 (14.6)</td>
<td>0.97</td>
<td>(-13.7,13.3)</td>
</tr>
<tr>
<td></td>
<td>TMT- B</td>
<td>63.8 (14.5)</td>
<td>63.9 (26.4)</td>
<td>0.13 (20.72)</td>
<td>0.99</td>
<td>(-19.0,19.3)</td>
</tr>
<tr>
<td></td>
<td>TMT- Difference</td>
<td>32.5 (11.6)</td>
<td>32.9 (18.8)</td>
<td>0.34 (5.1)</td>
<td>0.95</td>
<td>(-12.1,12.8)</td>
</tr>
<tr>
<td>Stroop</td>
<td>Congruent Accuracy %</td>
<td>98.57 (0.03)</td>
<td>99.29 (0.01)</td>
<td>0.72 (2.70)</td>
<td>0.23</td>
<td>(-1.8,0.5)</td>
</tr>
<tr>
<td></td>
<td>Incongruent Accuracy %</td>
<td>97.86 (0.02)</td>
<td>97.86 (0.03)</td>
<td>0</td>
<td>0.31</td>
<td>(-3.0,1)</td>
</tr>
<tr>
<td></td>
<td>Congruent RT</td>
<td>767.35 (111.50)</td>
<td>738 (123.04)</td>
<td>-29.35 (97.89)</td>
<td>0.43</td>
<td>(-119,0.5)</td>
</tr>
<tr>
<td></td>
<td>Incongruent RT</td>
<td>924.40 (207.68)</td>
<td>870.91 (165.78)</td>
<td>-53.49 (116)</td>
<td>0.15</td>
<td>(-160,0.2)</td>
</tr>
<tr>
<td></td>
<td>Interference score</td>
<td>0.19 (0.13)</td>
<td>0.18 (0.09)</td>
<td>-0.01 (0.08)</td>
<td>0.56</td>
<td>(-0.08,0.7)</td>
</tr>
<tr>
<td>FACT-Cog total score</td>
<td>38.60 (14.2)</td>
<td>40.4 (16.2)</td>
<td>1.9 (6.0)</td>
<td>0.77 (13.16,7)</td>
<td>0.47</td>
<td>(9.3,17.9)</td>
</tr>
<tr>
<td></td>
<td>Perceived cognitive impairment</td>
<td>12.7 (12.3)</td>
<td>17.0 (18.0)</td>
<td>4.3 (5.6)</td>
<td>0.47</td>
<td>(9.3,17.9)</td>
</tr>
<tr>
<td></td>
<td>Comments from others</td>
<td>1.0 (1.9)</td>
<td>1.1 (2.0)</td>
<td>0.1 (0.9)</td>
<td>0.88</td>
<td>(-2.0,2.3)</td>
</tr>
<tr>
<td></td>
<td>Perceived cognitive abilities</td>
<td>20.1 (8.1)</td>
<td>18.6 (8.3)</td>
<td>-1.6 (3.0)</td>
<td>0.62</td>
<td>(-8.9,5.8)</td>
</tr>
<tr>
<td></td>
<td>Impact on quality of life</td>
<td>4.7 (6.3)</td>
<td>3.7 (5.2)</td>
<td>-1.0 (2.3)</td>
<td>0.68</td>
<td>(-6.5,4.5)</td>
</tr>
</tbody>
</table>

Abbreviations: HVLT-R T, Hopkins Verbal Learning Test-Revised; TR, total recall; DR, delayed recall; RET, percent retained; RDI, retention determination index; TMT, Trail Making Test; FACT-Cog, Functional Assessment of Cancer Therapy-Cognitive Function
Figure 7.1 Total Recall of HVLT-R

Figure 7.2 Delayed Recall of HVLT-R

Figure 7.3 Recognition discrimination Index of HVLT-R

Figure 7.4 Percent Retained of HVLT-R
Figure 7.5 Trail Making Test- A

Figure 7.6 Trail Making Test- B

Figure 7.7 Trail Making Test- Difference
Figure 7.8 Congruent Accuracy of Stroop Test

Figure 7.9 Incongruent Accuracy of Stroop Test

Figure 7.10 Congruent Reaction Time of Stroop Test

Figure 7.11 Incongruent Reaction Time of Stroop Test
7.4 Physical Function, Mobility and Physical Activity Levels

Compared to baseline, no significant change was noted at the end of chemotherapy for 6MWT (608.9 ± 41.1 m at the baseline vs 631.1 ± 25.2 m after completion of chemotherapy, p=0.09) (Figure 7.13), (TUG (4.66 ± 0.62 s at the baseline vs 4.86 ± 0.51 s after completion of chemotherapy, p=0.20) (Figure 7.14), or gait speed (1.74 ± 0.37 m/s at the baseline vs 1.81 ± 0.27 m/s after completion of chemotherapy, p=0.54), (Figure 7.15) (Table 7.3).

There were no significant changes in total occupational, transportation, household, or leisure time physical activity after completion of chemotherapy compared to baseline (Table 7.3). However, the data for the physical activity levels of one participant was considered an outlier due to unreasonably high self-reported hours. This is justified by IPAQ analysis rule to exclude the data where the total sum of all walking, moderate and vigorous time variables is greater than 960 minutes (16 hours) assuming that an average individual spends sleeping eight hours per day (59). There was no significant change in the mean scores of total occupational (9.7 ±23.9 at the baseline vs. 7.2 ±12.5 MET-hrs/week after completion of chemotherapy, p=0.62), transportation (9.3 ± 10.5 at the baseline vs 3.0 ± 2.1 MET-hrs/week, p=0.20), household (12.3± 12.7 at the baseline vs. 19.2 ± 17.8 MET-hrs/week after completion of chemotherapy, p=0.45), and leisure time (31.8 ±37.0 vs 23.6± 17.7 MET-hrs/week after completion of chemotherapy, p= 0.42)
physical activity. Compared to baseline, no significant changes were noted for categorical outcome measures, including total amount of walking (17.6 ± 13.4 at the baseline vs 13.7 ± 12.2 MET-hrs/week after completion of chemotherapy, p = 0.42), moderate-intensity physical activity (16.3 ± 17.6 at the baseline vs. 29.3 ± 52.0 MET-hrs/week after chemotherapy, p = 0.41) or vigorous-intensity physical activity (69.7 ± 116.9 at the baseline vs. 11.4 ± 18.9 MET-hrs/week after completion of chemotherapy, p = 0.24). Compared to baseline, there was also no change in the average hours of sitting time (32.3 ± 22.3 hrs/week at baseline vs. 38.5 ± 12.7 hrs/week after completion of chemotherapy, p = 0.39). In addition, the mean scores of total physical activity levels after completion of chemotherapy (53.0 ± 41.2 MET-hrs/week, p = 0.33) compared to the baseline (63.2 ± 46.6 MET-hrs/week) (Figure 7.16-20), (Table 7.3).
### Table 7.3 Physical Function, Physical Activity and Peripheral Neuropathy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline Mean (SD)</th>
<th>After chemotherapy Mean (SD)</th>
<th>Mean difference (SD)</th>
<th>p-value</th>
<th>95 % Confidence interval of mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Function Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>608.9 (41.1)</td>
<td>631.1 (25.2)</td>
<td>22.2 (11.2)</td>
<td>0.09</td>
<td>(-5.2,2.0)</td>
</tr>
<tr>
<td>TUG (s)</td>
<td>4.66 (0.62)</td>
<td>4.86 (0.51)</td>
<td>0.20 (0.10)</td>
<td>0.20</td>
<td>(-0.1,1.4)</td>
</tr>
<tr>
<td>Gait Speed (m/s)</td>
<td>1.74 (0.37)</td>
<td>1.81 (0.27)</td>
<td>0.10 (0.10)</td>
<td>0.54</td>
<td>(-0.2,0.7)</td>
</tr>
<tr>
<td><strong>Self-reported physical activity IPAQ scores (MET-hrs/week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total PA_ Occupational</td>
<td>9.7 (23.9)</td>
<td>7.2 (12.5)</td>
<td>-2.5 (12.0)</td>
<td>0.62</td>
<td>(-15.2,10.0)</td>
</tr>
<tr>
<td>Total PA_ Transportation</td>
<td>9.3 (10.5)</td>
<td>3.0 (2.1)</td>
<td>-6.3 (10.4)</td>
<td>0.20</td>
<td>(-17.1,4.6)</td>
</tr>
<tr>
<td>Total PA_ Household</td>
<td>12.3 (12.7)</td>
<td>19.2 (17.8)</td>
<td>6.9 (20.7)</td>
<td>0.45</td>
<td>(-14.7,28.7)</td>
</tr>
<tr>
<td>Total PA_ Leisure</td>
<td>31.8 (37.0)</td>
<td>23.6 (17.7)</td>
<td>-8.2 (23.0)</td>
<td>0.42</td>
<td>(-32.4,15.9)</td>
</tr>
<tr>
<td>Total walking</td>
<td>17.6 (13.4)</td>
<td>13.7 (12.2)</td>
<td>-3.9 (10.7)</td>
<td>0.42</td>
<td>(-15.1,7.4)</td>
</tr>
<tr>
<td>Total moderate</td>
<td>16.3 (17.6)</td>
<td>27.9 (23.9)</td>
<td>11.6 (31.8)</td>
<td>0.41</td>
<td>(-21.7,45.0)</td>
</tr>
<tr>
<td>Total vigorous</td>
<td>29.3 (52.0)</td>
<td>11.4 (18.9)</td>
<td>-17.9 (33.2)</td>
<td>0.24</td>
<td>(-52.7,16.9)</td>
</tr>
<tr>
<td>Total PA</td>
<td>63.2 (46.6)</td>
<td>53.0 (41.2)</td>
<td>-10.1 (22.9)</td>
<td>0.33</td>
<td>(-34.2,13.9)</td>
</tr>
<tr>
<td>Total sitting (hrs/week)</td>
<td>32.3 (22.3)</td>
<td>38.5 (12.7)</td>
<td>6.2 (16.2)</td>
<td>0.39</td>
<td>(-10.8, 23.1)</td>
</tr>
<tr>
<td>Average sitting (hrs/week)</td>
<td>4.6 (3.2)</td>
<td>5.5 (1.8)</td>
<td>0.9 (2.31)</td>
<td>0.39</td>
<td>(-1.5,3.3)</td>
</tr>
</tbody>
</table>

Legend: *, n=6 (1 participant removed due to values outside possible ranges)
Abbreviations: MET-hrs/week, Metabolic Equivalent of Task- hours per week; 6-MWT, 6-minute walk test; TUG, timed up and go; IPAQ, International Physical Activity Questionnaire; PA, Physical activity
Figure 7.13 6-Minute Walk Test

Figure 7.14 Timed Up and Go

Figure 7.15 Gait Speed

Figure 7.16 Total Physical Activity_ Occupational
Figure 7.17 Total Physical Activity_ Transportation

Figure 7.18 Total Physical Activity_ Total Domestic

Figure 7.19 Total Physical Activity_ Total Leisure-time

Figure 7.20 Total Physical Activity_ Average Sitting/ Day
7.5 Feasibility of Obtaining Prospective Cognitive and Physical Function Measures

Out of the 20 colon cancer patients approached by the BCCA oncologists, 17 patients were referred for screening for this study in order to assess their eligibility and willingness to commit to this prospective study. Of the 17 referrals received, seven patients were enrolled and 10 patients were not enrolled. For those not enrolled, one patient was ineligible due to refusal of the receipt of chemotherapy and one participant was ineligible due to receipt of chemotherapy before being screened. The eight additional patients were uninterested in enrollment due to inability to commit, as well as, concern with regarding to commuting to the study site for the study visits. Thus, the enrollment rate for this study recruitment was 35%. The referring oncologist confronted difficulties referring colon cancer patients to the study due to the English-speaking eligibility criteria; the reason being that Vancouver’s multi-ethnic population consists of large diverse Asian and Chinese-speaking communities. Thus, this was one of the barriers during the recruitment, which lead to the small sample size.

7.6 Chemotherapy Induced Peripheral Neuropathy

Using the self-reported Patient Neurotoxicity Questionnaire (PNQ), more patients reported moderate (n =2, 29%), moderate to severe (n=1, 14%) sensory, or severe neuropathy symptoms (i.e., grade C, D, or E) (n=1, 14%) after completion of chemotherapy compared to baseline (p=0.46) (Table 7.4). For motor neuropathy symptoms, three patients did not self-report any motor symptoms (43%), whereas two patients (29%) reported mild motor symptoms at baseline. Thus, after completion of chemotherapy, more patients reported moderate to severe (n
=2, 29 %) or severe symptoms (n=1, 14%) (i.e. grade C, D, or E) while, none self reported motor neuropathy symptoms at baseline (p=0.85) (Figure 7. 21-22), (Table 7.4).

| Table 7.4 Distribution of Patient Neurotoxicity Questionnaire (PNQ) Scores |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                              | Baseline                   | After chemotherapy          |                             |
| PNQ sensory a (oxaliplatin)  | PNP Symptoms n (%)         | No PNP Symptoms n (%)       | PNP Symptoms n (%)         |
|                              | A                           | 1(14%)                      | 6 (86%)                    | 7 (100%)                   |
|                              | B                           | 2(29%)                      | 5 (71%)                    | 1(14%)                     |
|                              | C                           | 1(14%)                      | 6 (86%)                    | 2(29%)                     |
|                              | D                           | 0                           | 7 (100 %)                  | 1(14%)                     |
|                              | E                           | 0                           | 7 (100 %)                  | 0                           |
| p=0.46                      | p=0.98                      |                             |                             |
| PNQ motor a (oxaliplatin)    |                              |                             |                             |
|                              | A                           | 3(43%)                      | 4 (57%)                    | 2(29%)                     |
|                              | B                           | 2(29%)                      | 5 (71%)                    | 1(14%)                     |
|                              | C                           | 0                           | 7 (100 %)                  | 2(29%)                     |
|                              | D                           | 0                           | 7 (100%)                   | 1(14%)                     |
|                              | E                           | 0                           | 7 (100 %)                  | 0                           |
| p=0.85                      | p=0.96                      |                             |                             |

Legend: a PNQ scale ranges from A (no neuropathy) to E (severe neuropathy)
Abbreviations: PNQ, Patient Neurotoxicity Questionnaire, PNP, Peripheral Neuropathy

Figure 7.21 Patient Neurotoxicity Questionnaire (Sensory)
7.7 Health-Related Quality of Life and Psychosocial Outcomes

Health related quality of life did not change significantly from baseline to end of chemotherapy, as measured by the EORTC-QLQ-C29 (Table 7.5). There was a trend toward lower social/family well-being (22.7 ±5.7 at the baseline vs 21.6 ±6.4 after completion of chemotherapy, p=0.08) noted using the FACT that did not reach statistical significance, and there was no difference in fatigue levels using the FACT-fatigue sub scale (11.7 ± 10.5 at the baseline vs 18.4 ±17.3 after completion of chemotherapy, p=0.78) or total FACT-F score (75.6 ± 17.2 at the baseline vs 70.6 ± 19.2 after completion of chemotherapy, p=0.21). No change was observed in depression (10.1 ± 4.1 at the baseline vs 10.4 ± 3.6 after completion of chemotherapy, p=0.77); however, there was a significant decrease in anxiety after chemotherapy that was noted using the STPI (23.3 ± 4.2 at the baseline vs 19.0 ± 4.0 after completion of chemotherapy, p=0.03). Due to the small sample size and lack of change in the main outcomes, a secondary analysis adjusting for the observed change in anxiety was not completed.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline Mean (SD)</th>
<th>After chemotherapy Mean (SD)</th>
<th>Mean difference (SD)</th>
<th>p-value</th>
<th>95 % Confidence interval of mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC QLQ-C29</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body image</td>
<td>84.1 (18.0)</td>
<td>79.4 (14.9)</td>
<td>-4.8 (6.8)</td>
<td>0.51</td>
<td>(-21.4, 11.9)</td>
</tr>
<tr>
<td>Weight</td>
<td>90.5 (31.7)</td>
<td>71.4 (23.0)</td>
<td>-19.0 (16.0)</td>
<td>0.28</td>
<td>(-58.3, 20.2)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>66.7 (33.3)</td>
<td>57.1 (16.3)</td>
<td>-9.52 (15.8)</td>
<td>0.57</td>
<td>(-48.2, 29.1)</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>19.0 (17.8)</td>
<td>11.9 (15.9)</td>
<td>-7.1 (9.5)</td>
<td>0.48</td>
<td>(-30.4, 16.2)</td>
</tr>
<tr>
<td>Blood or mucus in stool</td>
<td>0 (0)</td>
<td>9.5 (18.9)</td>
<td>9.5 (7.1)</td>
<td>0.23</td>
<td>(-8.0, 27.0)</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>45.2 (40.5)</td>
<td>33.3 (21.5)</td>
<td>-11.9 (10.7)</td>
<td>0.31</td>
<td>(-38.2, 14.4)</td>
</tr>
<tr>
<td>FACIT-F total score</td>
<td>75.6 (17.2)</td>
<td>70.6 (19.2)</td>
<td>-5.0 (3.6)</td>
<td>0.21</td>
<td>(-13.8, 3.8)</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>9.0 (8.8)</td>
<td>6.4 (5.9)</td>
<td>-2.6 (2.8)</td>
<td>0.40</td>
<td>(-9.4, 4.3)</td>
</tr>
<tr>
<td>Social/family Well-being</td>
<td>22.7 (5.7)</td>
<td>21.6 (6.4)</td>
<td>-1.1 (1.5)</td>
<td>0.08</td>
<td>(-2.5, 0.2)</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>6.1 (2.0)</td>
<td>5.4 (2.6)</td>
<td>-0.7 (1.5)</td>
<td>0.64</td>
<td>(-4.3, 2.9)</td>
</tr>
<tr>
<td>Functional well-being</td>
<td>19.3 (5.5)</td>
<td>19.9 (6.8)</td>
<td>0.6 (2.4)</td>
<td>0.82</td>
<td>(-5.3, 6.4)</td>
</tr>
<tr>
<td>Fatigue subscale</td>
<td>11.7 (10.5)</td>
<td>18.4 (17.3)</td>
<td>6.7 (4.0)</td>
<td>0.78</td>
<td>(-10.9, 8.6)</td>
</tr>
<tr>
<td><strong>STPI</strong></td>
<td>23.3 (4.2)</td>
<td>19.0 (4.0)</td>
<td>-4.3 (1.6)</td>
<td>0.03*</td>
<td>(0.4, 8.1)</td>
</tr>
<tr>
<td><strong>CES-D</strong></td>
<td>10.1 (4.1)</td>
<td>10.4 (3.6)</td>
<td>0.3 (0.90)</td>
<td>0.77</td>
<td>(-2.6, 2.0)</td>
</tr>
</tbody>
</table>

P-values at $\alpha \leq 0.05$ are denoted with an asterisk (*)
Abbreviations: EORTC QLQ-C29, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Colon; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; STPI, State-Trait Personality Inventory; CES-D, Center for Epidemiological Studies Depression Scale
7.8 Discussion

This is the first prospective longitudinal study to simultaneously examine the effect of chemotherapy on cognitive function, physical function and physical activity levels in newly diagnosed individuals receiving adjuvant chemotherapy for colon cancer.

7.8.1 Assessment of Cognitive Function

No significant changes were observed for the neuropsychological test scores after completion of chemotherapy compared to baseline. However, due to the small sample size, it would be more comprehensive and meaningful to analyze individual data as opposed to the mean scores of the outcome measures. Using the HVLT-R, a test of verbal learning and memory, there was a non-significant decrease in delayed recall, percent retained, and the recognition discrimination index from baseline to end of chemotherapy. Therefore, there was a non-significant decrease in the ability to complete a delayed recall of the total words after the three learning trials along with the ability to retain the word list and discriminate between words included on the list and distractors.

In the test of visual attention and task switching, using the TMT, there was no difference from baseline to end of chemotherapy. The normative values for the TMT A (31.72 ±10.14 s) and –B (68.74 ±21.02 s) have been reported for a healthy population with age range of 55-59 years old and education level of more than 12 years. Thus, our results for the TMT A and –B are consistent with the healthy population whose age range and education level is similar to our study population (99).

In the test of selective attention and processing speed, using the Stroop Test, there was no difference from baseline to end of chemotherapy. There was a non-significant change in the mean scores for the congruent and incongruent reaction time after completion of chemotherapy.
compared to baseline, as well as a decrease in interference scores. Previous studies have assessed chemotherapy-associated cognitive function using the Stroop Test among the breast cancer population. Consistent with our finding, in a prospective longitudinal study of 71 breast cancer survivors, Jansen et al. reported no significant difference after completion of chemotherapy in standardized T scores based on age and education (100).

While objective neuropsychological tests are deemed to be the most appropriate approach to monitoring cognitive function, several self-report outcome measures have also been developed (95). The FACT-Cog is a self-report measured used to assess the “real-world” impact of chemotherapy-induced cognitive impairment (101). A prospective study in 220 breast cancer survivors published in 2014 was the first to report the minimal clinically important difference for the FACT-Cog, and provided an estimate of 6.9–10.6 points. The study administered the FACT-Cog at baseline and 3-months later, and validated the FACT-Cog with the EORTC-QiQ-C-30 cognitive function scale. The results of our current study noted only a non-significant 1.9-point change in total FACT-Cog total score, which does not meet this minimal clinically important difference cutoff (102). Thus, we can conclude that, from the patients’ perspective, no significant cognitive complaints were noted.

To date, there has been one published longitudinal study on cognitive function in colon cancer. Andreis et al. examined cognitive function in 57 consecutive colorectal cancer patients going onto receive FOLFOX chemotherapy at baseline, end of chemotherapy and 6-months post-treatment (19). This study used similar outcome measures as those in our study; testing visuospatial memory (Clock Drawing Test), information processing speed (Rey Complex Figure, Trail Making Test -A and –B, verbal memory (Rey Auditory Verbal Learning Test), emotional distress (Psychological Distress Inventory), anxiety (State and Trait Anxiety Inventory), and depression
(Beck Depression Inventory). No significant effect of FOLFOX was reported for the aforementioned cognitive assessments (19). Our findings are consistent with those of Andreis et al. and suggest that FOLFOX chemotherapy treatment for colon cancer may not influence cognitive function. Interestingly, no correlation was found between the total dose of oxaliplatin and cognitive function. This reveals that no changes were found in cognitive function as a result of oxaliplatin, although previous studies have postulated the detrimental effect of oxapliplatin on the neuronal voltage-gated sodium channels, which are present in the central as well as peripheral nervous system (103).

The absence of significant difference at the 6-month compared to baseline in our study could reflect the non-existence of cognitive dysfunction among this population or other methodological issues, such as patient baseline characteristics or cognitive function tests selected that failed to adequately capture potential changes. A 2005 meta-analysis reported lower mean scores on neuropsychological tests among breast cancer patients who had received chemotherapy, compared to either normative population or those with baseline measures (3). However, use of normative data as a comparison fails to account for changes over time within an individual, which could be examined using a prospective study design. In 2004, the first prospective longitudinal study utilized comprehensive neuropsychological evaluation and revealed the evidence for the association of chemotherapy and cognitive function among non-metastatic breast cancer patients (2). In a recent prospective longitudinal study of women with breast cancer, 71% of those with cognitive dysfunction at one-year follow-up from the baseline, showed continuous cognitive decline after cessation of the treatment (1). Evaluation of cognitive function in longitudinal prospective studies, using a variety of neuropsychological tests, suggests the rate of cognitive impairment in controlled studies ranges from 16% to 50% (101).
Our study examined specific domains of cognitive function that are suggested to be most affected by chemotherapy (3,4), specifically visuospatial skill, attention, delayed memory, and motor function in breast cancer patients (100). We employed the chosen neuropsychological tests based on their validity and reliability as well as the recommendations of ICCTF. The ICCTF strives to optimize and harmonizing the cognitive tests used to assess cognitive function studies in cancer patients (4).

Patient characteristics, including anxiety and depression, which are common psychosocial complaints with a cancer diagnosis and treatment, may also impact cognitive function. It has been proposed that in addition to chemotherapy-associated cognitive function, cancer-associated factors such as anxiety, depression, or comorbid medical conditions contribute to the reported cognitive dysfunction. A meta-analysis by Anderson-Hanley et al. reported that 12 out of the 29 included studies controlled for the impact of potential variables (e.g., age, type of treatment, fatigue, mood, anxiety); 11 out of those 12 studies found that the measured variables did not account for any changes in cognitive decline (104). Although we found a significant decrease in anxiety after chemotherapy in our study, no significant changes were noted in the scores for fatigue, depression, and health-related quality of life factors.

Finally, type and dose of chemotherapy treatment may impact the prevalence of cognitive changes (15). However, we found no effect of chemotherapy dose on the neuropsychological outcomes in our study. In addition, a change in menopausal status, common with chemotherapy for breast cancer (14,27), did not occur in the women in our study who were all pre-menopausal at baseline and remained so during the study. Therefore, a change in estrogen levels, which is commonly linked to cognitive changes with breast cancer (14), likely did not have an impact in our study.
7.8.2 Chemotherapy-Associated Physical Function and Functional Mobility

There were no significant changes observed from baseline to end of chemotherapy for 6MWT, TUG, and gait speed. For the 6MWT, participants completed a mean distance of 609 metres at baseline and 631 metres at end of chemotherapy. To provide context for these results, a small study with the aim of validating 6MWT among cancer population reported a mean distance of 622±87 metres among 47 cancer patients who underwent chemotherapy/radiation treatment for breast and colorectal cancer, but the distance covered by 13 colorectal cancer patients was 586±83 metres (51). Our results for the baseline and after chemotherapy 6MWT were consistent with the colorectal cancer patients in the validation study, who had a mean age of 61±10 years old. Interestingly, from the same study, the off-treatment group (patients who recently finished their cancer treatment or who had a therapy intermission) walked a mean of 569±60 m, which was lower than those who were chemotherapy/radiation (606±98 m) (51). The prognostic value of 6MWT has also been reported among newly diagnosed advanced non-small cell lung cancer patients (mean age of 62 ±10 years old) after assessment at baseline, pre-chemotherapy test, and after two cycles of chemotherapy. Inconsistent with our study, significant declines in 6MWT distance were observed and it was concluded that a baseline 6MWT less than 400 metres could identify patients with advanced non-small cell lung cancer patients at high risk for developing functional decline. This inconsistency is likely due to the more advanced cancer stage, poorer prognosis and additional treatment complications seen with non-small cell lung cancer (105).

Population normative data for the 6MWT have been published for healthy adults. Among 96 community dwelling adults (60-69 years old), the maximum mean distance covered in
six minutes has been shown to be 572 metres and 538 metres in male and female, respectively. In a study, which aimed to establish a reference equation for the 6MWT, a mean distance of 576 metres and 494 metres was reported respectively in 117 healthy males and 173 females aged 40 to 80 years old (106). Although many confounding variables warrant consideration when comparing our sample with the reported normative values, the reported norm values are consistent with the results observed in our population. The slightly higher values for the 6MWT results in our population could be attributed to a younger mean age of our sample as well as the differences in baseline physical fitness and activity levels.

As a validated test for the assessment of physical function, 6MWT has been shown safe and clinically feasible among cancer patients and healthy elderly adults. However, it might not be as sensitive enough to detect physical deficits attributed to peripheral neuropathy or chemotherapy treatment specifically among colon cancer patients who have reasonable functional capacity. However, compared to other objective and subjective tests assessing exercise capacity or physical function measures, 6MWT poses lower burden on patients and is a feasible test to include in clinical-based research. The learning effect or familiarization with the walking course has been reported, however, differences in test-retests reliability have been reported as small. The learning effect issues was not seen as sufficient to warrant adding a second testing visit, which was a burden to participants at a time when they had many demands on time related to starting chemotherapy.

Functional mobility was measured by the TUG test and gait speed test. Despite a slight increase in TUG score after completion of chemotherapy, which indicated a decrease in functional mobility, this was not statistically significant. The lack of statistical significance could be due to the small sample size or a lack of difference in the population. A meta-analysis
by Bohannon et.al has reported a mean TUG score of 8.1 seconds (95% CI: 7.1-9.0) among individuals aged 60-69 years old. However, our study population, with the mean age of 53, had a lower mean TUG score(107). To date, TUG has not been utilized for the assessment of physical function and balance among colon cancer population undergoing chemotherapy treatment. Thus, we would not be able to compare our results with any other existing literature.

No change in gait speed was noted following completion of chemotherapy in our study. To date gait speed related to chemotherapy treatment has not been reported in studies looking at physical function in cancer patients. The exception is a single case study report by Hile et al. (45)of an 81-year-old woman receiving neurotoxic chemotherapy after curative mastectomy for breast cancer which reported that gait speed declined from a baseline of 1.2 m/s to 0.74 m/s after 3 months of chemotherapy, along with significant sensory peripheral neuropathy symptoms, which could have contributed to the gait speed decline. Our findings were inconsistent with the findings of Hile et.al. (45). It is warranted to consider the age group when comparing the gait speed scores across different population since it has been shown that older populations without known pathology have slower gait speeds than young adults (54). The published normative value for individuals without any known impairments with a similar age range to the patients in our study, namely an age range of 54-58 years old, is an average gait speed of 1.39 m/s for comfortable walking speeds and 2.01 m/s for fast walking speeds (107). Our results are consistent with the above.

The assessment of physical function and functional mobility using objective validated tests is vital among cancer patients undergoing chemotherapy treatment. Before the establishment of any interventions or physical function rehabilitation, the prognosis of any functional deficits must be considered among individuals who are undergoing chemotherapy
treatment. Overall, the non-significant changes observed after completion of chemotherapy compared to baseline, suggests that physical function and function mobility were maintained in our sample of colon cancer patients. This may be due to lack of change or inability of the outcome measures used to capture any declines that may be present. However, given the mean age of our sample, which represents a relatively young population of colorectal cancer survivors, we suggest that measures of functional mobility, such as the TUG and gait speed, could be of value in future studies to examine change in functional mobility in colon cancer patients, especially given that colon cancer is more common in individuals over age 60 years (18).

Although our results for the physical activity levels did not reach significant levels, compared to baseline, the means scores of physical activity levels decreased and the total sitting time and the average time spent sitting were increased after completion of chemotherapy. There have been several recent reviews that reported on self-reported physical activity levels on colon cancer survivors (108-111). Through assessment of physical activity participation using the Exercise & Quality of Life Questionnaire, Chung et al. have reported the reduction of strenuous intensity physical activity participation during treatment for colorectal cancer, followed by significantly higher physical activity participation after completion of chemotherapy compared to pre-diagnosis state (11). Unlike the study by Chung et al., total walking, moderate, and vigorous physical activity levels of our study population had a non-significant decline (11). According to Speed-Andrews et al., a survey of colorectal cancer patients found that based on the 2008 Physical Activity Guidelines for Americans (150 minutes per week of moderate-intensity aerobic activity), only 33% of colorectal cancer survivors met these physical activity guidelines and approximately 50% of them were sedentary (112). Similarly, according to a survey by
McGowan et al., less than 23.0 % of colorectal cancer survivors participated in a sport in the past month (113).

These studies are helpful in understanding the physical activity levels of colorectal cancer after diagnosis. However, these studies have not reported the physical activity levels before and after chemotherapy treatment. Thus, our study adds to the sparse literature on the impact of chemotherapy, and potential associated changes in physical function or functional mobility, on physical activity levels from pre-chemotherapy to completion of chemotherapy. Based on well-conducted studies, the World Health Organization has recommended adults aged 18- 64 years old, irrespective of gender, ethnicity, or income level, should engage at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or at least 75 minutes of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity (114).

7.8.3 The Relationship Between Chemotherapy-Associated Cognitive Dysfunction and Peripheral Neuropathy

After chemotherapy, the severity of sensory grades reported by the patients increased. In addition, the number patients who reported no sensory (grade A) or mild sensory (grade B) symptoms decreased compared to baseline. The same trend was observed for motor peripheral neuropathy, with the exception of no change in number of patients reporting severe motor peripheral neuropathy (grade E) after completion of chemotherapy. Thus, more patients reported moderate (grade C) and moderate to severe (grade D) for both sensory and motor symptoms. Grade C and D have been reported to correspond with neuromotor and neurosensory symptoms which interfere with patient’s activities of daily living (73).
An increase in sensory and motor symptoms of peripheral neuropathy could be a rationale for the decline in the parameters of physical activity levels seen in the study and could reflect the interference of these symptoms with activities of daily livings. The PNQ has been deemed suitable for physician’s decision-making concerning postponing the treatment, modifying the dose, and discontinuing treatment. Since it is justified that the grades correspond to the presence of neurosensory or neuromotor symptoms, the non-significant decline in physical activity observed in our study could be related to the increased reported symptoms of sensory and motor peripheral neuropathy (71). It has been reported that the PNQ adequately assesses symptoms’ severity, as well as, the degree of functional impairment in patients experiencing chemotherapy induced peripheral neuropathy. Although the decline in physical activity levels in our study was not statistically significant, this is a novel result indicating that the peripheral neuropathy affecting activities of daily livings may influence the physical activity of cancer patients during treatment. However, to date, no solid conclusion has been formed as to the effect of chemotherapy-induced peripheral neuropathy on physical function and physical activity.

7.8.4 The Effect of Cancer and Chemotherapy-Associated Factors on Psychosocial Factors and Health-Related Quality of Life

Several factors are reported to potentially cause cancer patients to be at higher risk of developing cognitive dysfunction include increasing age, anxiety, depression, and fatigue. These factors can also impact quality of life, which is reported to decrease during chemotherapy treatment (115-119).

Fatigue is a common side effect of cancer treatment (102,116,117). However, there was no difference in fatigue levels from baseline to end of chemotherapy in our study. The results for
the fatigue level in our study revealed consistency with seven prospective longitudinal studies, which evaluated the change in fatigue levels. None of these studies have reported significant increases in fatigue levels with chemotherapy treatment (19,42,120-124).

Depression is reported to also be part of the cancer experience. However, our results for the depression scores are consistent with the results of eight other prospective longitudinal studies that have examined the changes in cognitive function with chemotherapy treatment for breast cancer. These studies have reported no significant difference in depression scores from baseline to following treatment in breast cancer patients, and no association with cognitive function (2,42,121,122,124-128). However, the studies have used a variety of different questionnaires for the assessment of depression. On the other hand, our study results are inconsistent with the single prospective study of cognitive function in colon cancer patients with chemotherapy that reported significant improvement in depression symptoms at the end of chemotherapy as well as 6 months after treatment (19).

Inconsistent with six other prospective longitudinal studies that evaluated chemotherapy-associated cognitive function from baseline to following treatment in breast cancer patients, and included a measure of anxiety; we found a significant decrease in anxiety (2,121,122,124,126,128). This significant decrease in the mean anxiety score after completion of chemotherapy may reflect intensified anxiety levels at the time of the diagnosis and related to having to make treatment decisions and schedule chemotherapy sessions. The improvement noted in our study may be explained by the psychological or psychosocial adjustments that occur during the period of cancer treatments (19). Our results for the anxiety mean scores are consistent with the single prospective study that examined cognitive function related to
chemotherapy treatment for colon cancer, which also used the same questionnaire (State-Trait Anxiety Inventory) (19).

No change in quality of life was noted in our study. Interestingly, consistent with our study, Van Dam et al., used EORTC QLQ-C30 quality-of-life questionnaire and did not report any significant difference in the scores for quality of life measures, among those who did not receive chemotherapy, low, and high dose adjuvant chemotherapy for breast cancer treatment (129). A cross-sectional study by Schag et al., reported on the quality of life measures in a disease-free sample of lung, colon, and prostate cancer survivors. Overall, colon cancer survivors revealed a pattern of improvement overtime; this fits with our results where we have noted a non-significant improvement after completion of chemotherapy.

### 7.8.5 The Effect of Dose and Disease Stage on Cognitive Function, Physical Function and Physical Activity

Since all of the subjects had the same stage of colon cancer (stage III) and therefore similar treatment regimes, no conclusion can be drawn with regards to the prediction of cognitive and physical function in terms of the severity of disease stage or treatment dose.

### 7.8.6 The Link Between Chemotherapy-Associated Cognitive Dysfunction and Physical Dysfunction and Physical Inactivity

It is still not clear whether the chemotherapy-associated cognitive dysfunction and the physical and psychosocial factors associated with receiving chemotherapy treatment lead to lower physical activity or if physical inactivity worsens the chemotherapy–associated cognitive dysfunction. Based on the literature linking physical activity levels and improved cognition in
older adults, there could be a vicious cycle between cognitive function, physical activity and physical function in cancer patients. It is crucial to investigate whether physical activity levels may impact a reduction in the risk of developing cancer-associated cognitive dysfunction or improvements in cognitive function following treatment. Furthermore, more research is needed into the impact of chemotherapy and the physical side effects, particularly peripheral neuropathy, on functional mobility, which could in turn alter ability to engage in physical activity. Alternatively, the reduction in physical activity commonly seen with treatment could be an underlying factor for potential changes in physical function and functional mobility. It remains to be elucidated whether decreased physical activity levels and increased average sitting time would impact the chemotherapy-associated cognitive dysfunction, and how physical activity, physical function and mobility are linked in this population.

7.8.7 Significance

To date, the majority of prospective studies examining cognitive function or physical function have been done in women undergoing treatment for breast cancer. Thus, research is needed to determine if colon cancer patients are at risk of experiencing a reduction in cognitive function, physical function or functional mobility with chemotherapy and to better understand the time course of these potential changes. This pilot study will serve as the foundation for generating hypotheses and identifying targets for proposing intervention strategies to help colon cancer patients to cope with the side effects of cancer treatment and to provide clinicians with information to identify the patients in need of rehabilitation services.

The association of cognition with functional mobility is an emerging area of research, and has not been examined to date in colon cancer patients. In the future, a larger prospective study may be considered to investigate cognitive and mobility dysfunctions in colon cancer patients,
including a wider range of cancer stage and patient age. The novel contribution of this study is that it adds to the sparse literature on the chemotherapy-associated physical and functional deficits, assessed by objective tests, in colon cancer patients.

7.8.8 Limitations

There are several limitations to the current study. First, there are limitations to using neuropsychological tests for the assessment of chemotherapy-associated cognitive dysfunction. There is on-going research into the most appropriate objective tests to capture chemotherapy-associated cognitive dysfunction. While the ICCTF has provided a suggested test battery, which was used in the study, future research may provide more insight into the most sensitive and appropriate tests. Normative HVLT-R raw scores have been reported for the total recall, percent retention, and recognition discrimination index among healthy population with the age range of 55 – 69 years old(130). Since these scores have not been standardized to T- scores based on age, we were not able to compare them with our results. In addition, it has been shown that significant practice effects limit the Stroop’s potential for detecting better executive functioning among healthy adults (131,132).

Second, patient characteristics may influence the occurrence of decline in cognitive or physical function. Individuals with high cognitive abilities before diagnosis may still score well in the normal clinical relevant ranges after chemotherapy despite experiencing chemotherapy-associated cognitive decline. The inter-subject variability in daily fatigue levels and possibility of emotional distress due to self-perceived cognitive and physical dysfunctions may also negatively impact neuropsychological test scores, as well as performance during the functional mobility testing.
Third, the age category of our sample may not be representative of patients diagnosed with colon cancer, as the mean age of cancer diagnosis is 68 and 72 among men and women, respectively. The age of our sample may be influenced by the lack of willingness of older adults to travel to testing visits. Finally, the sparse literature on the chemotherapy-associated physical function and functional mobility in colon cancer survivors using and objective validated tests has made it difficult to compare our results with other studies.

7.8.9 Future Directions

It would be beneficial if subsequent studies included the assessment of control subjects, who are colon cancer patients not receiving chemotherapy treatment or healthy controls. This would provide insight into the impact of chemotherapy versus other treatment-related factors on cognitive and physical function findings. It remains to be elucidated why cognitive changes have been fairly consistently report in women receiving treatment for breast cancer, while our findings and those of Andreis et al. (19) report no evidence of cognitive changes in individuals receiving treatment for colon cancer.

Furthermore, more research is needed to understand the relationship between neuropsychological test scores, physical activity levels and physical function in all cancer survivors. Emerging studies have reported association of gait speed scores with cognitive processing speed and executive function among older adults. It has been reported that decline in gait speed among older adults is a reflection of lower attention/executive function (133,134), or memory function (133,135). In addition, studies have suggested that cognitive-processing speed (136); executive and memory deficits in older adults can be predicted by a slow gait speed (137).
Thus, it has been noted that slower gait speed is associated with the cognitive processes related to prefrontal lobe function such as attention and executive function (134-138).

7.9 Conclusions

Using a pilot longitudinal study design, definitive statements could not be made with regards to the changes in cognitive function, physical function, and physical activity with FOLFOX chemotherapy treatment for colon cancer, due to our small sample size. Compared to baseline, no significant changes were noted for the neuropsychological test scores from baseline to completion of chemotherapy. Furthermore, from baseline to the end of chemotherapy, physical activity levels, physical function and functional mobility did not change significantly. This study provided preliminary insights into the chemotherapy-associated cognitive dysfunction, physical function, and physical activity levels of colon cancer patients, and has identified future avenues for research.
Bibliography


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