COGNITIVE AND OCCUPATIONAL FUNCTION IN SURVIVORS OF ADOLESCENT CANCER

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The number of cancer survivors living in the U.S. is dramatically increasing. Cognitive decline is a commonly reported and burdensome symptom of cancer survivors. In addition, many cancer survivors experience difficulty maintaining employment. This dissertation addresses gaps in the literature of cognitive and occupational function of cancer survivors, with particular emphasis on the understudied population of cancer survivors diagnosed as an adolescent or young adult (AYA). For this dissertation, a series of studies were conducted to 1) explore the association between occupation and symptom burden in breast cancer survivors, 2) synthesize the evidence of cognitive outcomes in survivors of AYA cancer, and 3) describe cognitive and occupational function in survivors of adolescent cancer compared to healthy controls.

To address aim one, a secondary analysis of data from early-stage breast cancer survivors explored the relationship between occupation and symptom burden. Breast cancer survivors employed in lower skill level jobs reported greater symptom burden over the first year of anastrozole treatment than women employed at the higher skill level. Survivors employed at lower skill levels had higher levels of fatigue and worse depressive, musculoskeletal, vasomotor, and gastrointestinal symptoms.

To address aim two, an integrative review synthesized the current state of science in terms of cognitive outcomes of those diagnosed with cancer as an AYA. Survivors of AYA cancer tended to experience cognitive difficulties; however, to date, no study has focused exclusively on those diagnosed as an AYA or encompassed the entirety of the AYA age range. Future

studies are needed because cognitive outcomes of survivors of AYA cancer have been largely neglected.

Lastly, a cross-sectional, descriptive comparative study described cognitive and occupational function in survivors of adolescent cancer compared to healthy controls. Survivors of adolescent cancer perceived greater cognitive difficulty than healthy peers, although there were not significant measurable differences in performance on neuropsychological tests. Survivors of adolescent cancer also reported poorer work output than healthy controls.

This dissertation contributes to the growing body of literature pertaining to health and well-being of cancer survivors, in particular cognitive and occupational function, and unique considerations needed for those diagnosed with cancer as an AYA.

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PREFACE

To the cancer survivors and research participants in my study: Thank you for your time and effort in sharing your stories with me and your desire to help future cancer patients and survivors. I hope that I can honor the gift you have given and use the information we learn to help future cancer survivors. Without your participation, this project would not have been possible.

Thank you to my committee chair, Dr. Margaret Rosenzweig for her assistance during my time in the doctoral program and for guiding me as I worked on my dissertation. Thank you also to each of my committee members, Dr. Catherine Bender, Dr. Susan Sereika, and Dr. Jean Tersak. I have learned a great deal from you and am grateful for the guidance and support that each of you have provided. Thank you also to each of the consultants and experts on my F31 grant: Dr. Christopher Ryan, Dr. Ida (Ki) Moore, Dr. Catherine Fiona Macpherson, and Dr. Michael McCue. Finally, a word of thanks to Dr. Bernadine Cimprich who first exposed me to nursing research during my time as an undergraduate at the University of Michigan.

My gratitude goes to all those who have offered encouragement and support for this project and otherwise: to my loving and patient husband, Michael, to my father, Brian, for his unofficial statistical support, and to my peers and classmates who have encouraged and accompanied me on the journey.

Finally, I would like to acknowledge the financial support I received to help make this research study possible: Cognitive Function and Work Productivity in Survivors of Adolescent Cancer (F31NR014958-01), American Cancer Society Doctoral Degree Scholarship in Cancer Nursing (DSCN-14-079-01-SCN), Judith A. Erlen Nursing PhD Student Endowed Research Fund, Margaret E. Wilkes PhD Student Scholarship Award, Bessie Li Sze Oncology Nursing Scholarship, and Interdisciplinary Training of Nurse Scientists in Cancer Survivorship Research (T32NR011972).

1.0 INTRODUCTION

An estimated 14.5 million survivors of cancer currently live in the U.S. (DeSantis et al., 2014) By 2024, the number of cancer survivors is projected to increase dramatically, reaching approximately 19 million cancer survivors. (DeSantis et al., 2014) To better understand cancer survivors' concerns, The Office of Cancer Survivorship of the National Cancer Institute (NCI) stresses the importance of examining understudied populations of cancer survivors, such as adult survivors of adolescent and young adult (AYA) cancer. AYA cancer survivors, defined as those diagnosed with cancer between the ages of 15 to 29 years (worldwide) or 15 to 39 years (United States) (American Cancer Society, 2012; Bleyer, Viny, & Barr, 2006; National Cancer Institute & Lance Armstrong Foundation, 2006), are believed to experience unique challenges related to school, work, and relationships with peers. However, most research and guidelines about treatment recommendations for adult survivors of AYA cancer are based on studies conducted in survivors of childhood cancer. Almost no research has been conducted in adults diagnosed with cancer as adolescents, creating a gap in current knowledge regarding best practices. With more adolescents surviving cancer into adulthood, it is becoming increasingly clear that these individuals encounter significant difficulty in regaining the skills necessary to meet the demands of healthy adult development. Successful reentry into work and school may be impacted by neurocognitive morbidities potentially impacting occupational functioning. (Dieluweit et al., 2011) The ability to work has been shown to improve cancer survivors' quality of life, reduce social isolation, and increase self-esteem. (Nieuwenhuijsen, de Boer, Spelten, Sprangers, & Verbeek, 2009; Spelten, 2002) A recent study reported that survivors of AYA cancer are significantly more likely to experience disability and unemployment than healthy controls (24% vs. 14%) (Tai et al., 2012); however, it is unclear why this disparity exists and what factors may be associated.

The National Institute of Nursing Research (NINR) strategic goals address mitigating the chronic burden of illness (such as cancer) as an important focus in anticipating future challenges and improving patient quality of life. Studying adult survivors of adolescent cancer is important because of the developmentally vulnerable time point in which a cancer diagnosis and treatment are received. While peers are often completing high school education and entering college or the workforce, AYA cancer patients are experiencing treatment that can have devastating consequences. Studies of brain development show that the brain, especially the frontal lobe, continues to mature and develop into the early twenties. (National Institute of Mental Health, 2011) Cancer, cancer treatment, and its effects, such as changes in cognitive function, could impair the typical neurological and behavioral development of the adolescent patient and disrupt the adolescent survivor's long term employment status as they move into adulthood. Studies of childhood (Moore, 2005) and adult cancers (Calvio, Feuerstein, Hansen, & Luff, 2009; Calvio, Peugeot, Bruns, Todd, & Feuerstein, 2010; Kadan-Lottick et al., 2010) indicate disease- and treatment-related cognitive delays, but few systematically include survivors of adolescent cancer.

Disability and unemployment from cognitive impairment can result in lost potential and tremendous personal and societal costs. Yet, the impact of adolescent cancer and its treatment on survivors' cognitive function and occupational function has not been considered. In 2006, the AYA Progress Review Group was assembled by the NCI to address research and cancer care needs for patients in this age group. The progress review group recommends supporting research to improve patient and survivor outcomes and to identify characteristics that distinguish the unique cancer burden for AYA. (National Cancer Institute & Lance Armstrong Foundation, 2006)

The direct contributions of this dissertation project are 1) expanding the understanding of the relationship between occupational skill level and symptom experience in a cohort of breast cancer survivors, 2) providing an overview of current state of the science regarding cognitive function in survivors of adolescent and young adult cancers, and 3) presenting the results of an original research study exploring cognitive and occupational function in adult survivors of adolescent cancer.

Study 1. Maintaining occupational roles for cancer survivors is difficult, indeed; approximately 40% of all cancer survivors never return to work (Spelten, 2002). Of cancer survivors who remain working, up to 13% stop working within 4 years of diagnosis (Taskila & Lindbohm, 2007). Disease and treatment-related symptoms may influence the ability of cancer survivors to return to work, maintain pre-diagnosis levels of work productivity and advance in careers. Few studies have examined the relationship between disease and treatment symptoms and the ability to maintain occupational roles and no studies to date have examined this relationship in postmenopausal women during aromatase inhibitor (AI) therapy for early-stage breast cancer. The purpose of this study is to examine the association of occupation and symptom experience in a cohort of breast cancer survivors. Data for this study came from a secondary analysis of a longitudinal study examining cognitive function in postmenopausal women with early-stage breast cancer receiving aromatase inhibitor (AI) therapy (PI: Bender). This secondary analysis is important to the candidate's program of research because it examined similar concepts of interest, notably occupational roles, and employed similar statistical methods to those planned in the candidate's original research study (Study 3).

Study 2. While there is a growing body of literature suggesting that many cancer survivors may experience cognitive decline after cancer diagnosis and treatment, much less is known about the cognitive outcomes of those diagnosed during the AYA timeframe. Therefore, the second study of this dissertation is an integrative review to summarize and appraise the current state of published literature involving cognitive function in those diagnosed during adolescence and young adulthood. While the review is a distinct study within the dissertation project, it provides a critically important foundation for the candidate's original dissertation research that was conducted in Study 3.

Study 3. In this study, the candidate's original research project is featured. This is a cross-sectional descriptive, comparative study to explore cognitive function and occupational function in adult survivors of adolescent cancer. The specific aims of the study are to 1) describe cognitive function (using objective and self-report measures) and ratings of occupational function among adult survivors of adolescent cancer and 2) explore differences in cognitive function (using objective and self-report measures) and occupational function between adult survivors of adolescent cancer and age- and sex-matched healthy controls.

The evidence obtained in this dissertation will contribute to the growing body of literature pertaining to the health and well-being of cancer survivors, in particular cognitive changes and occupational function. Ultimately, the research conducted through this dissertation is aimed at helping to describe and inform the needs of AYA cancer survivors, a vulnerable, understudied population, and is envisioned as the first step in the development of a program of research examining survivorship concerns of adult survivors of adolescent cancer. Specifically, the knowledge gained from this study could be used to inform the development of behavioral interventions aimed at promoting optimal cognitive and occupational function in survivors of AYA cancer.

The methods (including study design, sample and setting, measures, statistical analysis) for each study are described in detail in the body of each manuscript (see Chapter 3, 4, and 5). Following the three manuscripts, an integrative summary of dissertation findings is provided.

2.0 PRELIMINARY WORK

Prior to entering the PhD program at the University of Pittsburgh School of Nursing, the candidate (Nugent) had interest in better understanding how cancer and treatment during adolescence and young adulthood affected the lifelong health and well-being of these cancer survivors. Several experiences helped the candidate refine her ideas and formulate a research question.

To gain a better understanding of AYA cancers, their treatments, and the unique considerations for this population, the candidate enrolled in a year-long Graduate Certificate program in Adolescent and Young Adult Oncology (one of only two programs offered worldwide) through the University of Melbourne. This was a distance-learning program from which she graduated in December, 2014. The candidate has also attended Survivorship Clinic at Children's Hospital of Pittsburgh of UPMC (under the mentorship of Dr. Jean Tersak) since 2012 to gain a better understanding of survivorship concerns of young adult cancer survivors. These training opportunities gave the candidate exposure to experts in the fields of both AYA Oncology and in survivorship and assisted in the development of her understanding of the unique challenges of this population.

Early on in her studies, a Graduate Student Research (GSR) position with Dr. Paula Sherwood afforded the candidate the opportunity to examine work outcomes in a population of skull base tumor patients. This experience resulted in a data-based paper entitled *Work productivity and neuropsychological function in persons with skull base tumors* and is published in the Journal of Neuro-Oncology Practice. (See Appendix A) The purpose of this investigation was to evaluate the impact of cognitive function on work productivity in persons with skull base tumors prior to resection. Depressive symptoms and cognitive function (including the domains of attention and flexibility, visuospatial ability, and learning and memory) were associated with difficulty meeting work demands and contributed to overall health-related loss of work productivity. This project was influential in defining the candidate's research interest for the dissertation study because it exposed her to the concept of occupational function in cancer survivors. One of the primary tasks of adolescence and young adulthood from a psychosocial perspective is the furthering of education and/or entering the workforce. This project helped to expose the candidate to the concept of both occupational and cognitive function and the potential relationship between the two.

A later GSR position with Dr. Catherine Bender gave the candidate the opportunity to assist in the development of a manuscript pertaining to the complex nature of cognitive function among cancer survivors. This paper is entitled *Cancer and cognitive function: The complexity of the problem* and is published in Seminars in Oncology Nursing (See Appendix C). The purpose of this paper was to describe factors that influence cognitive function in the context of cancer and cancer therapy and to illustrate the complex nature of the problem. The paper describes multiple factors which contribute to changes in cognitive function in this population including demographic, psychological, and physiological factors, the disease itself, disease- and treatment- related symptoms, and the management of those symptoms. Through involvement on this project the candidate gained a greater understanding of the numerous factors impacting cognitive function and assisted her in choosing additional confounders and covariates when conducting her original research study, Study 3 of the dissertation.

2.1 DEMONSTRATION OF ABILITY TO RECRUIT SURVIVORS OF ADOLESCENT CANCER

Through the work on her pilot study, the candidate demonstrated the ability to recruit survivors of adolescent cancer. She applied for and was successfully awarded a grant (University of Pittsburgh School of Nursing Judith Erlen PhD Student Endowed Research Award) to allow her to conduct a pilot study examining psychosocial development and the concepts of posttraumatic stress and posttraumatic growth in survivors of adolescent cancer. (See

Appendix E for IRB Approval Letters) During the course of two years, the candidate was successfully able to recruit 49 patients to her cross-sectional descriptive study and demonstrated that it was feasible to recruit survivors of AYA cancer for her dissertation study through similar means. The findings from the candidate's pilot study were presented through podium presentations at two conferences (2013 Oncology Nursing Society and 2014 Council for the Advancement of Nursing Science). These abstracts can be found in Appendix F and G.

2.2 BSN-TO-PHD MILESTONES

The following table (Table 1) lists the milestones that have been achieved since entrance into the BSN-to-PhD program at the University of Pittsburgh School of Nursing in August 2011. All milestones support the scientific merit of the proposed dissertation study.

Table 1: BSN-to-PhD Program Milestones

Milestone	Date
Interdisciplinary Training of Nurse Scientists in Cancer Survivorship Research (T32NR011972) fellowship appointment	Aug 2011
Judith Erlen PhD Student Endowed Research Award	Aug 2012
Preliminary Examination	May 2013
University of Pittsburgh School of Nursing Bessie Li Sze Memorial Scholarship	Aug 2013
University of Pittsburgh Institutional Review Board Approval for *Cognitive and Occupational Function in Adult Survivors of Adolescent Cancer* (Expedited Review; PRO13100151; Appendix H)	Feb 2014
American Cancer Society Doctoral Degree Scholarship in Cancer Nursing (DSCN-14-079-01-SCN)	July 2014
Cognitive Function and Work Productivity in Survivors of Adolescent Cancer (F31NR014958) Funded by National Institute of Nursing Research	Aug 2014
Completed Graduate Certificate in Adolescent Health and Wellbeing Oncology Stream through the University of Melbourne	Dec 2014
Comprehensive Examination and Overview	May 2015
University of Pittsburgh School of Nursing Margaret E. Wilkes Scholarship Fund Award	July 2015
Attendance at *Clinical and Translational Research Course for PhD Students* offered by the Clinical Center at the National Institute of Health	July 2016

3.0 DISSERTATION MANUSCRIPT #1
THE ASSOCIATION BETWEEN PRE-TREATMENT OCCUPATIONAL SKILL LEVEL AND MOOD AND SYMPTOM BURDERN IN EARLY-STAGE, POSTEMENOPAUSAL BREAST CANCER SURVIVORS DURING THE FIRST YEAR OF ANASTRAZOLE THERAPY

Purpose Previous research has explored occupational activity of breast cancer survivors but has not examined the influence of occupational level on symptoms prospectively. The purpose of this study was to examine the relationship between occupational classification and changes in mood and symptomburden for postmenopausal breast cancer survivors during the first year of anastrozole therapy.

Methods This was an exploratory secondary analysis in 49 postmenopausal women receiving anastrozole therapy for early-stage breast cancer. Participants reported their occupation at baseline and completed self-report questionnaires measuring mood and symptom burden at baseline, 6 months, and 12 months. Occupation was classified according to four major skill levels delineated by the International Standard Classification of Occupations (ISCO).

Results Breast cancer survivors employed at occupational skill levels 1 through 3 reported significantly higher depressive symptoms, fatigue, and total symptoms on average than those employed at ISCO skill level 4. After adjusting for multiple comparisons, this pattern remained for the musculoskeletal, vasomotor, and gastrointestinal symptom subscales.

Conclusions Breast cancer survivors employed at lower skill levels (i.e., ISCO 13) reported poorer mood and greater symptom burden than breast cancer survivors employed at a higher skill level (i.e., ISCO 4). Assessing baseline occupation of occupationally active breast cancer survivors may improve understanding of the association between types of occupations and mood and symptom trajectories and may inform development of interventions to mitigate

symptom severity in order to help breast cancer survivors maintain optimal occupational function and adherence to therapy

The full text of this manuscript can be found in Appendix H as it has been published prior to the submission of this dissertation document.

4.0 DISSERTATION MANUSCRIPT #2
COGNITIVE FUNCTION IN SURVIVORS OF ADOLESCENT AND YOUNG ADULT CANCER: AN INTEGRATIVE REVIEW AND LITERATURE CRITIQUE

Purpose: This integrative review summarizes the current literature pertaining to cognitive outcomes of those diagnosed with cancer as adolescents and young adults (AYA) (ages 15-24) and provides direction for future research.

Methods: PubMed and PsycInfo were searched from inception until March, 2016. All English peer-review studies that included at least one individual diagnosed during the AYA age range and a measurement of cognitive function (either patient perception of neurocognitive testing) were included. All included studies were independently assessed by two investigators.

Results: Of the 646 articles identified, 17 studies were included. Most studies were cross-sectional (62.6%) and measured patient perception of cognitive function without neurocognitive testing (52.9%). Findings across studies varied widely although all generally endorsed some degree of cognitive difficulty in cancer survivors which was influenced by cancer type, treatment received, and age at diagnosis. No study included in the review focused either exclusively on those diagnosed as an AYA or encompassed the entirety of the AYA age range. Common AYA cancers that were particularly underrepresented include carcinoma, melanoma, and germ cell tumors.

Conclusions: Cancer survivors tended to experience cognitive difficulties; however, the heterogeneity of the studies hindered strong conclusions. The current review highlights the paucity of literature in this population. Research is needed to define unique characteristics and neurocognitive outcomes in the AYA population given the disruption of life milestones at a critical time point in development.

Implications for Cancer Survivors: Cancer as an AYA might result in cognitive difficulties; however, more research is needed as current evidence is scarce.

4.1 INTRODUCTION

Cognitive declines with cancer and cancer treatment are seen in 15% to 35% of all cancer survivors, and some studies have reported levels as high as 75% (Ahles, Root, & Ryan, 2012; Asher & Myers, 2015; Janelsins et al., 2011). Although some researchers focus exclusively on the effect of treatment on cognitive function, cognitive difficulties have been observed prior to the initiation of treatment for cancer (Bender et al., 2015; Berman et al., 2014; Pullens, De Vries, & Roukema, 2010; Wefel, Vidrine, et al., 2011). These findings suggest that both treatment for cancer and even cancer itself may influence cognitive function. Cognitive impairment and declines in cognitive function can have long-term negative effects such as poorer quality of life and as well as a major impact on a survivor's education and career plans (Ahles et al., 2012; R. Ferguson & Ahles, 2003; Krull et al., 2012).

Despite earlier theories that brain development was complete during the teenage years, recent research has shown that a tremendous amount of change occurs in the brain during adolescence even up until the early twenties (National Institute of Mental Health, 2011). Specifically, there is a wave of gray matter production which occurs primarily in the frontal lobe (National Institute of Mental Health, 2011). The frontal lobe is associated with numerous domains of cognitive function including psychomotor function, planning, reasoning, judgement, impulse control and memory (Mitrushina, 2005). Since the adolescent and young adult (AYA) brain is at a developmentally critical period, particularly related to development of higher level cognitive function, cancer and cancer treatment at this stage may prove to uniquely affect the brain in survivors of adolescent and young adult cancers. Studies of both childhood and adult cancer survivors indicate cognitive declines in many different domains with cancer and cancer treatment, particularly in attention, concentration, working memory, and executive function (Ahles et al., 2012; Asher & Myers, 2015). However, compared to adults and children with cancer, considerably less is known about how those diagnosed with cancer as an adolescent or young adult (AYA) fare in terms of their cognitive function.

Thus, the purpose of this integrative review was to: 1) summarize the current literature pertaining to cognitive outcomes of those diagnosed with cancer as an AYA between the ages of 15 and 24 years; 2) provide a critique of the literature and its relevance to survivors of AYA cancer; and 3) provide direction for future research. In the context of cancer research, the AYA age range is variable depending on the country of origin ("What Should the Age Range Be for AYA Oncology?," 2011). For example, AYA in the United States is generally considered to be individuals between the ages of 15 to 39 years (National Cancer Institute & Lance Armstrong Foundation, 2006); AYAs in Canada are generally considered to be individuals ages 15 to 29 years (De et al., 2011); AYAs in the United Kingdom are between ages 13 to 24 years (Teenage Cancer Trust, 2014); and, in Australia between ages 15 to 25 years (CanTeen, 2008). For the purpose of this paper, it was decided to use the term AYA to mean individuals ages 15 through 24 years because that range represents the intersection of ranges across the definitions and also captures the important psychological and physiological changes that occur during adolescence and early young adulthood ("What Should the Age Range Be for AYA Oncology?," 2011).

4.2 METHODS

A search of the literature was conducted in PubMed and PsycInfo databases from the earliest available date through March 30th, 2016. The keywords of "cancer" or "cancer survivor" were paired with combinations of the terms "cognition", "cognitive function", "neurocognitive", "neuropsychological", and "survivorship". Truncation was used to ensure that both noun and verb forms of each word were captured. Whenever possible, Medical Subject Heading (MeSH) terms were used which serve as a kind of thesaurus and are useful in assisting in the capture of a wider range of relevant literature (U.S. National Library of Medicine, 2015). The search strategy was restricted to publications written in the English language. To be included in the review, articles had to meet strict inclusion and exclusion criteria (Figure 1). Inclusion criteria were: 1) explicitly stating age at diagnosis of sample and inclusion of at least one participant diagnosed with cancer between the ages of 15 and 24; and 2) must include at least one measurement of cognitive function (either patient perception or neurocognitive testing). Exclusion criteria were: 1) animal studies; 2) studies of participants exclusively diagnosed with primary brain tumors; and 3) behavioral intervention studies. Studies examining only participants with primary brain tumors were excluded because there was concern about the confounding influence of brain tumors on cognitive function independent of treatment. Intervention studies were excluded, with the exception of cancer treatment studies (e.g. surgery; radiation; chemotherapy; biologics) since the primary interest is in the effect of cancer and treatment on cognitive outcomes. Each article was screened by two independent reviewers using the inclusion and exclusion criteria set forth. If any discrepancies were encountered, the reviewers discussed and reached an agreement regarding the inclusion of the article. If agreement could not be reached, further consultation was sought from the content experts on the team.

Inclusion Criteria	Exclusion Criteria
• English language • At least 1 patient diagnosed with cancer between the ages of 15 and 24 • Measurement of cognitive function (either patient perception or neurocognitive function)	• Studies including only patients with primary brain tumors • Animal studies • Intervention studies (with the exception of therapeutic studies examining surgery, chemotherapy, radiation, or biologics)

Figure 1: Inclusion and Exclusion Criteria for Integrative Review

4.3 RESULTS

A search of PubMed and PsycInfo databases yielded 641 articles; five additional articles were identified through review of reference lists of identified articles and citation lists of known researchers in the field of cancer and cognitive function (Figure 2). Seventeen articles met the criteria for inclusion in this review (Table 2). The majority of papers were excluded because participants were not within the AYA age range specified for inclusion in this review.

The included research was conducted on three continents: North America, Europe, and Australia. Across all 17 studies, a total of 7,360 cancer survivors are represented. The most common cancer diagnosis represented in the literature based on sample size was leukemia which accounted for 31% of all cases. Eleven (64.7%) of the studies included in the review recruited a convenience sample utilizing a cross-sectional methodology examining cognitive function at only one time point.

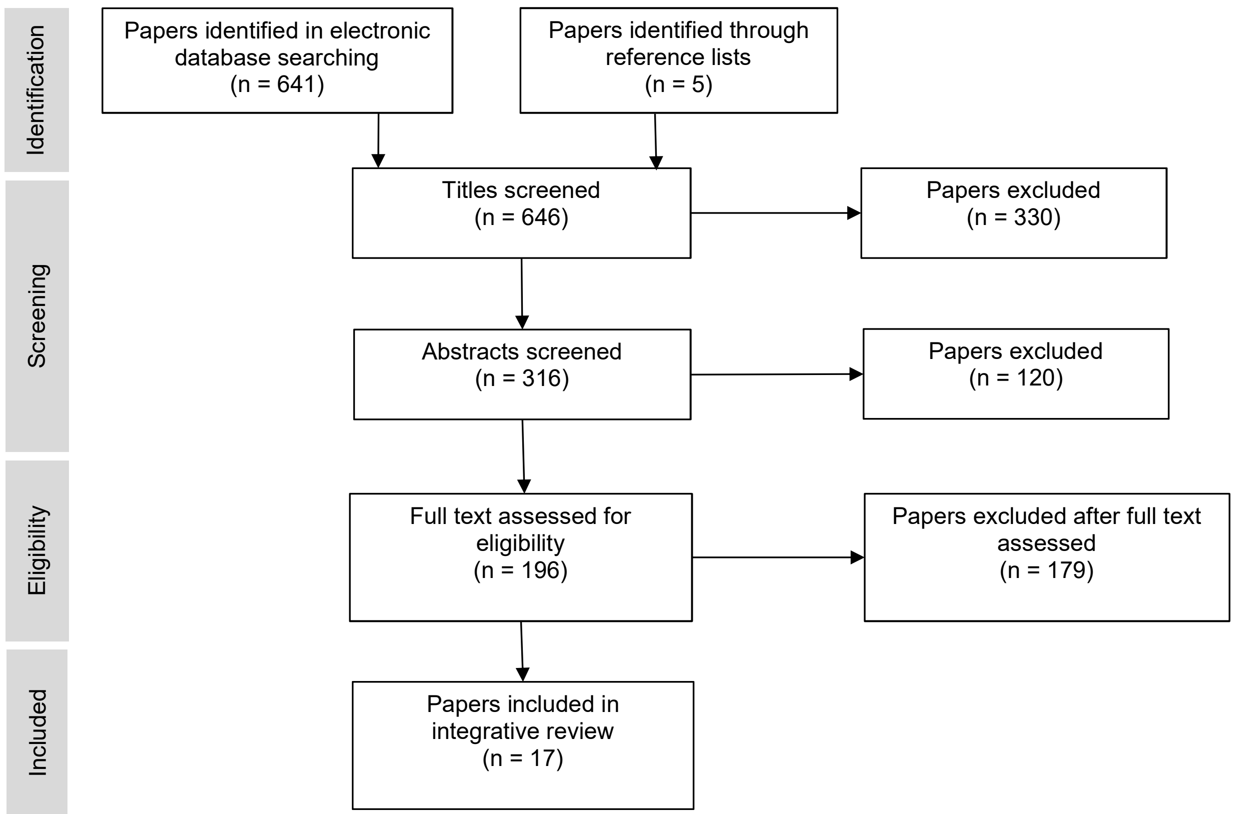


Figure 2: Integrative review study selection algorithm. The 17 studies that fulfilled the inclusion/exclusion criteria were selected from the total of 646 possible articles identified. The process of selecting the 17 articles is displayed.

Four of the studies (Armstrong & Oeffinger, 2013; Krull et al., 2012, 2013; Prasad et al., 2015) included in the review appear to have been taken from the St. Jude Childhood Cancer Survivor Study. While this study is extremely important and comprehensive in terms of measuring longitudinal effects of cancer and treatment in survivors of childhood and adolescent cancer, the individuals represented in these studies may not be unique cases. These four studies included a combined total of 3,159 cancer survivors; it is unclear how many of these are unique cases.

Two methods of measuring cognitive function were used in the identified studies: patient perception and neurocognitive testing. Nine studies (52.9%) used only a measure of patient perception, 6 studies (35.3%) measured cognitive function using a battery of neurocognitive tests, and 2 studies (11.8%) measured both patient perception and neurocognitive function. Of those studies that measured patient perception of cognitive function, each study used either an unvalidated tool or one of five validated questionnaires: the 2-item cognitive functional scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30); the 6-item Cognitive subscale of the Health Utilities Index Mark III (HUI3); the 51-item Functional Assessment of Cancer Therapy- Cognitive (FACT-Cog); the 75-item Behavior Rating Inventory of Executive Function- Adult Version (BRIEF-A), or the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ).

Studies examining patient perception of cognitive function found that cancer survivors reported difficulty in domains of memory, motor, and task completion (Alvarnas et al., 2000; Krull et al., 2012; Prasad et al., 2015). There was a lack of consensus on the trajectory of patient perception of cognitive function over time: some studies reported that patient's perception of cognitive function declined over time (Alvarnas et al., 2000; Hong, Bosco, Bush, & Berry, 2013), one found no change (Bush, Donaldson, Haberman, Dacanay, & Sullivan, 2000), and still others found that cancer survivor's perception of cognitive function improved over time (Kiebert, Jonas, & Middleton, 2003). Factors that were associated with poorer perception of cognitive function included cancer survivors who received particular chemotherapy agents (Dacarbazine) (Kiebert et al., 2003), patients who had undergone a stem cell transplant (Hong et al., 2013), and patients who had a previous cancer diagnosis as compared to those newly diagnosed (Braun, Gupta, & Staren, 2013). Cancer survivors who had been diagnosed with lymphoma or sarcoma reported fewer neurocognitive difficulties than cancer survivors diagnosed with other types of cancers (Prasad et al., 2015). In cross-sectional studies, cancer survivors were more likely to report difficulties with cognitive function than their healthy counterparts (Pogany et al., 2006; Prasad et al., 2015; Tamnes et al., 2015; Wright, Galea, & Barr, 2005).

Eight studies used neurocognitive testing to measure cognitive function. Table 3 lists the various neurocognitive tests that were used to assess each cognitive domain. Across these 8 studies, there were 9 different cognitive domains that study authors reported measuring using various neurocognitive tests: intelligence, executive function, dexterity, psychomotor speed, academic achievement, learning and memory, attention, multi-tasking, and language. On average, each study measuring neurocognitive performance assessed 3 cognitive domains. Minimum number of domains measured was 1 and maximum number of domains measured was 5.

In studies measuring intelligence in cancer survivors, two of three studies found that those who received cranial radiation therapy demonstrated a decline in intelligence over time (Kumar et al., 1995; Nathan et al., 2013), while another study found no change in intelligence from pre- to post-stem cell transplant (Hiniker et al., 2014). In studies that used a broad battery of neurocognitive function, cancer survivors demonstrated impairment in attention, memory, processing speed, fine motor speed, and cognitive fluency as compared to healthy controls or normative data (Armstrong et al., 2013; Hiniker et al., 2014; Krull et al., 2012, 2013). One factor that was found to be associated with poorer cognitive function was higher doses of radiation therapy (Armstrong et al., 2013). Interestingly, two of 6 studies found that a large portion (between 38-46%) of newly diagnosed cancer patients demonstrated cognitive impairment prior to receiving chemotherapy (Hiniker et al., 2014; Wefel, Vidrine, et al., 2011).

To assist in determining relevance of findings to our population of interest, age at diagnosis was recorded across all studies (Figure 3). While each study included at least one individual diagnosed between the ages of 15 and 24 years, only two of the 16 studies included a mean or median age that was within our age range of interest. These studies were reported by Krull, et al (2012), which included Hodgkin's lymphoma survivors, and Prasad, et al (2015), which included individuals diagnosed between the ages of 11 and 21 years. The mean age at diagnosis was 15.1 years and fell at the lower end our age range of interest. Only one study (Pogany et al., 2006) divided the sample into different groups by age at diagnosis, one of which was those diagnosed during 15 and 19 years of age. Still, no study included in our integrative review included either exclusively those diagnosed during the AYA range or encompassed the entirety of the AYA age range.

However, three studies included in our review provide some useful information in terms of cognitive outcomes specifically in those diagnosed with cancer as an AYA. Pogany, et al (2006) measured perception of cognitive function in cancer survivors. While the mean age at diagnosis is well under 15 years, in their analysis the sample was split into 5 different groups based on age at diagnosis and between-group comparisons were made. They found that approximately 30% of patients diagnosed between ages of 0 and 19 years reported cognitive impairment. However, using children diagnosed at less than one year of age as the reference group and adjusting for cancer type, treatment types, gender, and age at survey, patients diagnosed with cancer between the ages of 15 and 19 years were the only age subgroup that had higher odds of reporting cognitive impairment than those diagnosed at less than 1 year of age. This means that those patients diagnosed between 15 and 19 years reported higher rates of impairment, even after controlling for cancer and treatment types.

Prasad, et al (2015) examined perception of cognitive function in patients diagnosed with cancer between the ages of 11 and 21 years. The strength of this study is a very large sample size and many cancer survivors had diagnoses which are particularly relevant to survivors of AYA cancer. This study well represented three of the six most common AYA cancers: sarcoma, leukemia, and lymphoma. This is one of only two studies in our review which included patients who had been diagnosed with sarcomas. Compared to healthy siblings, cancer survivors reported increased difficulties with task efficiency, emotional regulation, and memory. Reported difficulty with task efficiency was associated with unemployment. There were few differences found in perceived cognitive difficulties between those diagnosed at less than 11 years of age and those diagnosed between 11 and 21 years. However, those with a diagnosis of lymphoma and sarcoma were less likely to report perceived cognitive difficulties, than those diagnosed with other types of cancer.

In another study, Krull, et al (2012) conducted both neurocognitive testing and patient perception of cognitive function. The purpose of this study was to determine if patients who had received mantle radiation as treatment for Hodgkin's Lymphoma had decreased cognitive function. The sample size for this study was 62 patients with a mean age at diagnosis of 15.1 years; this was the only study that had a sample mean within our age range of interest. The results of this study found poorer neurocognitive testing in numerous domains: sustained attention (p=.004), attention span (p=.01), memory recall [short-term (p=.001) and long-term (p=.006)], fine motor speed (p¡.001), naming speed (p¡.001), and cognitive fluency (p=.007). Importantly, neurocognitive performance was associated with the survivor's academic and vocational functioning. Survivors reported problems with working memory, task completion, and fatigue on measures of perceived cognitive function. Poorer neurocognitive function was not directly associated with mantle field radiation, although it was associated with cardiac and pulmonary morbidities.

4.4 DISCUSSION

As has been noted in other reviews of cognitive function (Hermelink, 2015; Pullens, Vries, & Roukema, 2010), the findings from the studies included in this review differ vastly. In studies with longitudinal designs, some found that cognitive function declined over the course of cancer treatment, others found it remained unchanged from pre- to post-treatment, and still others found cognitive impairment in cancer patients before treatment had even been initiated. Some of the variability was accounted for by chemotherapy regimen given, receipt of cranial radiation therapy, dose of radiation therapy, or those who had undergone a stem cell transplant. It is worth noting that two of the eight studies that measured neurocognitive function prospectively only assessed intelligence, which is known to be a fairly general measurement of neurocognitive function and is not sensitive to more subtle cognitive changes. Numerous theories have been proposed in an attempt to explain pre-chemotherapy cognitive changes including effects of the cancer or tumor itself, increased oxidative stress, predisposing genetic factors or other mechanisms proposed to be involved in treatment-related cognitive decline (Janelsins, Kesler, Ahles, & Morrow, 2014; Merriman, Von Ah, Miaskowski, & Aouizerat, 2013).

Although each study included in our review included a measure of cognitive function, the difference in approach to measuring this concept (either patient perception or neurocognitive testing) is an important consideration since, although both measurements are informative, they do not generally align well with one another (Cull et al., 1996; Middleton, Denney, Lynch, & Parmenter, 2006). Neurocognitive testing is often considered the "gold standard" in terms of which patients are cognitively impaired. However, the ecological validity of neurocognitive testing is less understood, particularly in terms of how cognitive function may impact an individual's ability to carry out their daily functional activities (Mandy J Bell, Terhorst, & Bender, 2013). Although research in those diagnosed during adolescence and young adulthood is limited, numerous studies in other populations of cancer survivors have found that while cancer survivors may report cognitive difficulty, they still score within the expected range on neurocognitive testing. The reason for this difference is not entirely clear, though research has found that patient perception of cognitive function is related to factors such as depression, anxiety, and fatigue, but is not related to objective performance on neurocognitive testing (Cull et al., 1996; Middleton et al., 2006). To our knowledge, research has not been conducted to explore whether there is a relationship between perceived cognitive function and other downstream effects such as future cognitive decline or whether it is associated with educational and vocational achievement.

Two of the instruments used to measure patient perception of cognitive function are fairly minimal in terms of the number of items: The Cognitive functional scale of the EORTC QLQ-C30 asks one question about memory and another about attention (Fayers et al., 2002); the cognitive subscale of the HUI3 has 6 different items all asking about some aspect of memory. While the other two measures of patient perception of cognitive function, BRIEF-A, FACT-Cog and NCSS-NCQ, are more extensive in terms of the number of items pertaining to cognitive function, only one study used each of these questionnaires. Thus, although patient perception of cognitive function was measured in these studies it is by no means a comprehensive assessment of all domains of cognitive function.

Another important consideration for this age group is the trajectory of cognitive symptoms experienced during cancer treatment and into survivorship. Since the majority of the studies included in our review utilized cross-sectional methodology and did not conduct testing prior to the initiation of treatment, it is difficult to determine the trajectory of cognitive symptoms after cancer and treatment. Research conducted in other populations of cancer survivors have reported short-term cognitive decline that may resolve within a period of time after treatment is completed (Mar Fan et al., 2005; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Many downplay the significance of this short-term cognitive decline as something that will resolve and have minimal long-term impact. However, in comparison to those diagnosed at younger and older ages, even short-term cognitive difficulties in AYA may have devastating long-term effects such as educational and vocational achievement. For instance, children often receive additional support in primary and secondary school if teachers or support staff notice that they are struggling or falling behind. And, adults who have completed higher education or who have obtained a first job have established a career for themselves that, should short-term cognitive difficulties resolve, can return to work following cancer diagnosis and treatment. For those diagnosed during the AYA age, future research is needed to determine if even short-term cognitive effects may impact survivors in achieving long-term goals, particularly in light of their stage of life and developmental status. For example, being diagnosed with cancer during adolescence and experiencing cognitive difficulties (even in the short-term) may impact an individual's ability to enroll in higher education or obtain a job. Delaying or missing these important milestones may have devastating personal and financial long-term consequences for these individuals.

Across the three different continents where much of the research included in our review was conducted, the 6 most common cancers seen in the adolescent and young adult population are lymphoma, leukemia, germ cell tumor, carcinoma, melanoma, and sarcoma (Table 4). These cancers represent about 80% or more of all the cancer diagnoses seen in this age group. However, in our review of the literature, many of the AYA cancers were vastly underrepresented in the literature (Figure 4). In particular, melanoma, carcinoma, and germ cell tumors represent about 40% of all AYA cancer diagnoses; however, these 3 cancer diagnoses only accounted for a combined total of 4% of all the diagnoses represented in the included studies. Thus, findings from the majority of studies included in our review are not appropriately generalized to the wider AYA oncology population.

There are several limitations to acknowledge for this review. First, ideally, only those studies looking primarily at the AYA age range or studies with a mean or median within our ages of interest would have been included in the review. However, the research was so limited in this area that inclusion criteria were expanded to allow for studies with an age range that overlapped our ages of interest so that one or more participants in the study were diagnosed during the AYA age range; thus, for most studies included in the review it is uncertain how many participants in each study were diagnosed during the AYA age range. Second, qualitative research, gray literature such as conference abstracts or dissertations, and literature written in any language other than English were not reviewed, which might have limited the number of studies included in our review and the knowledge in this area. Third, articles which included primary brain tumors were excluded, which limits the generalizability of the findings from this review. Finally, as is true in other literature reviews, our findings might be biased due to the fact that studies with statistically significant results are more likely to be published (Easterbrook, Berlin, Gopalan, & Matthews, 1991; Olson et al., 2002).

4.5 CONCLUSION

Research to date suggests that many cancer survivors report cognitive decline and may experience a decline in neurocognitive function following cancer diagnosis and treatment. However, there is a lack of consensus on the best way to measure cognitive function in AYA patients and it is unclear which domains of cognitive function may be most affected in this age group. While researchers have called for a uniform battery of neurocognitive tests so that results can be compared across studies (Noll et al., 2013; Wefel, Vardy, Ahles, & Schagen, 2011), this age group in particular warrants further thought since the ages represented (15 through 24 years of age) includes individuals who may sometimes be given tests appropriate for childhood and others be given tests appropriate for adults.

Future research is needed to include studies of cognitive function focusing specifically on those diagnosed during the AYA time frame ensuring adequate representation of common AYA cancers. In addition, development of a standard battery of instruments to be used across the entire AYA age range is important in order to compare findings within the group and across studies. Prospective longitudinal studies that include pretherapy cognitive assessments will be important to determine the trajectory of cognitive symptoms over the entire course from cancer diagnosis, through treatment and into survivorship. Finally, it may be valuable to explore implications of cognitive changes (whether short- or long-term) after cancer and treatment in this vulnerable and understudied population such as the more distal outcomes of educational achievement and vocational functioning.

Table 2: Summary of articles included in integrative review

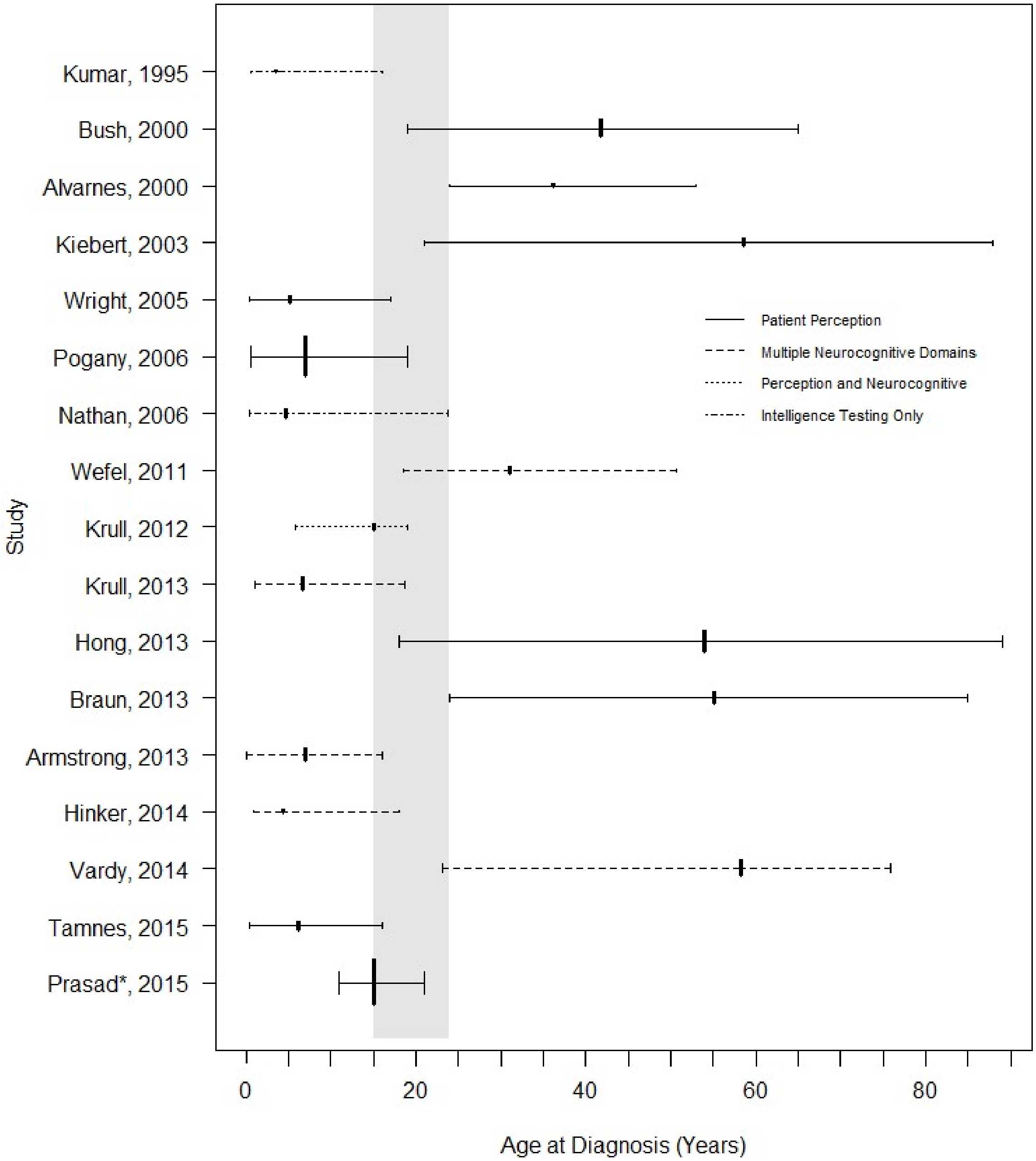
Study, Year (Location)	Study Design	Patient Group ± Controls (N)	Age at Diagnosis (years)	Age at testing (years)	Domains of cognitive function assessed	Results	Cancers Represented
Kumar, 1995 (USA)	Longitudinal (prior to CSI, 12 and 24 months)	10	Range: 0.6-16.6 Median: 3.5	1.8-17	Intelligence	Nine of 10 survivors treated with Chemo and CSI for CNS relapse demonstrated no decline in intelligence. One patient had frank IQ decline.	ALL
Bush, 2000 (USA)	prospective longitudinal (1,2,3,4 yrs post-BMT)	Yr 1: 407-411 Yr 2: 216-217 Yr 3: 115-117 Yr 4: 31-35	Range: 19-65 Mean: 41.8	20-66	Patient perception	Perceived cognitive functioning remained stable throughout the follow-up period.	Leukemia, NHL, Breast, Other
Alvarnas, 2000 (USA)	cross-sectional	15	Range: 24-53 Mean: 36.2	24-54	Patient perception	Survivors reported decline in neurocognitive function including memory and motor deficits.	NHL
Kiebert, 2003 (UK)	prospective longitudinal RCT (1, 12, 24 wks)	TMZ: 50 DTIC: 31	Range: 21-88 Mean: 58.6	21-88	Patient perception	Over time, cognitive scores improved for TMZ group, but remained unchanged for the DTIC group.	Melanoma
Wright, 2005 (Canada)	cross-sectional	Survivors: 99 HC: 89	Range: 0.3-17 Mean: 5.2	5.1-31.5	Patient perception	Significant differences in perceived cognition between survivors and healthy controls.	ALL
Nathan, 2006 (USA)	Prospective longitudinal (0, 12, 24 mos)	126	Range: 0.3-23.8 Median: 4.7	0.3-23.8	Intelligence	Survivors treated with CRT had poorer verbal IQ neurocognitive performance over time, while those treated without CRT improved.	ALL
Pogany, 2006 (Canada)	cross-sectional	Survivors: 2079 HC: 2365	Range: <1-19 Median: 7	5-37	Patient Perception	Reports of impairment in dexterity and impaired cognition were more likely in survivors than their peers.	Leukemia, Lymphoma, CNS/SNS, Retinoblastoma, Renal, Hepatic, Bone, Sarcoma, Germ Cell, Carcinomas
Wefel, 2011 (USA)	cross-sectional	69	Range: 18.5 - 50.7 Mean: 31.0	18.5 – 50.7	Attention; Psychomotor Speed; Language; Learning/memory; Executive Function; Motor	Compared to normative data, approximately 46% of sample was considered neurocognitively impaired before beginning adjuvant chemo.	NSGCT testicular cancer
Krull, 2012 (USA)	cross-sectional	62	Range: 5.9-19.0 Mean: 15.1	34.4 - 55.4	Intelligence; Attention; Memory; Processing speed; Executive Function; Patient perception	Compared to normative data, survivors showed declines in attention, memory, fine-motor speed, and cognitive fluency. Survivors self-reported problems with working memory, task completion, and fatigue.	HL
Braun, 2013 (USA)	cross-sectional	new DX: 127 previous DX: 59	Range: 24-85 Mean: 55.1	24-85	Patient perception	New DX group tended to have higher perceived cognitive function than those with previous DX	Pancreatic
Krull, 2013 (USA)	cross-sectional	243	Range: 1.0-18.7 Mean: 6.6	Unreported	General intelligence; Processing speed; Memory; Attention; Parent-reported	Survivors had significantly elevated rates of impairment on measures of sustained attention. Parents also reported elevated rates of attention problems.	ALL
Hong, 2013 (USA)	prospective longitudinal (before/during treatment)	SCT: 191 Med/Rad: 436	Range: 18-89 Mean: 53.9	18-89	Patient perception	Decline in cognitive function found in both groups between Time 1 and Time 2; SCT (medium effect) and MED/RAD (small effect).	Breast; GI; GU; Gyn; Head and Neck; Leukemia; Lung; Lymphoma; Myeloma; Other
Armstrong, 2013 (USA)	cross-sectional	18 GyRT: 127 24 GyRT: 138	Range: 0-16 Mean: 6.9	Mean: 37.1	Memory; Cognitive status; Intelligence	Those who received 24 GyRT had increased impairment in memory and reduced cognitive status, but not the 18GyRT group suggesting a CRT dose-response effect.	ALL
Hiniker, 2014 (USA)	prospective longitudinal (pre-SCT, ~4.4 years post-SCT)	16	Range: 0.9-18 Mean: 5	4.4-21.2	Intelligence; Academic achievement; Working Memory; Motor	No change in IQ from pre- to post- SCT; 38% of survivors showed deficiencies in processing speed and/or working memory.	ALL
Vardy, 2014 (Canada, Australia)	cross-sectional	Local CRC: 291 Met CRC: 66 HC: 72	Range: 23.1-75.9 Mean: 58.3	Unreported	Processing speed; Learning/memory; Attention	CRC patients exhibited cognitive impairment in ≥2 domains compared to HC. No significant differences between Local CRC and Met CRC.	Colorectal cancer
Tamnes, 2015 (Norway)	cross-sectional	Survivors: 125 HC: 130	Range: 0.3-16 Mean: 6.2	18.6-46.5	Patient perception	ALL survivors reported significantly more problems in executive function than HCs.	ALL
Prasad, 2015 (USA)	Cross-sectional	DX ages 11-21: 2589 DX age < 11: 3603 Siblings: 390	Range: <6-21	15 - >35	Patient Perception	Compared to siblings AeYA reported more difficulty with task efficiency, emotional regulation, and memory. Those diagnosed with lymphoma or sarcoma during AeYA were at decreased risk for self-reporting neurocognitive problems.	Leukemia, CNS, HL, NHL, Sarcoma

Abbreviations: BMT bone marrow transplant; NHL non-hodgkin's lymphoma; NP neuropsychological; ALL acute lymphoblastic leukemia; CRT cranial radiation therapy; RCT randomized clinical trial; SCT stem cell transplant; TMZ temozolomide; DTIC dacarbazine; HC healthy controls; CNS Central Nervous System; SNS Sympathetic Nervous System; NSGCT nonseminomatous germ cell tumors; HL Hodgkin's Lymphoma; CSI craniospinal irradiation; Med/Rad medical or radiation oncology treatment; GI Gastrointestinal; GU genitourinary; Gyn Gynecologic; CRC colorectal cancer; AeYA adolescent and early young adulthood

Table 3: Tests used to measure various cognitive domains across studies

Cognitive Domain	**Neuropsychological Tests Used**
Intelligence	WISC-IV WAIS-R Wechsler Abbreviated Scale of Intelligence Brief Cognitive Status Exam
Executive Function	Trail Making Test Part B Controlled Oral Word Test WAIS-III Digit Span Backward
Psychomotor Speed	WAIS-R Digit Symbol Trailmaking Test Part A
Dexterity	Grooved Pegboard
Attention, Processing Speed, Working Memory	Grooved Pegboard Stroop Color-Word Test Conners' Continuous Performance Test-II (CPT-II) WAIS-III Digit Symbol Trail Making Test Part A and B WISC-III or WAIS-III Processing speed index WISC-III or WAIS-III Freedom from distractibility index Trail Making Test Part A WAIS-R Digit Span WAIS-III Letter-Number Sequencing WAIS-III Digit Span Forward WMS-III Digit Span WMS-III Spatial Span Cambridge Neuropsychological Test Automated Battery (CANTAB)
Learning & Memory	Hopkins Verbal Learning Test (HVLT) Hopkins Verbal Learning Test-Revised (HVLT-R) Brief Visuospatial Memory Test-Revised (BVMT-R) Cambridge Neuropsychological Test Automated Battery (CANTAB) Wide Range Assessment of Memory and Learning (WRAML2) Wechsler Memory Scale
Language Skills	MAE Controlled Oral Word Association
Multi-Tasking	Six Elements Test
Academic Achievement	Woodcock Johnson Tests of Academic Achievement (WJ-III)
Patient Reported	European Organization for Research & Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Health Utilities Index Mark III (HUI3) Functional Assessment of Cancer Therapy- Cognitive (FACT-Cog) Behavior Rating Inventory of Executive Function- Adult Version (BRIEF-A) CCSS Neurocognitive Questionnaire (CCSS-NCQ)
Parent-reported Attention	Conners' Parent Rating Scale

WISC-IV = Wechsler Intelligence Scale for Children – Fourth Edition
WAIS-R = Wechsler Adult Intelligence Scale-Revised
WAIS-III = Wechsler Adult Intelligence Scale – Third edition
WMS-III = Wechsler Memory Scale – Third edition
MAE = Multilingual Aphasia Examination
CCSS = Childhood Cancer Survivor Study



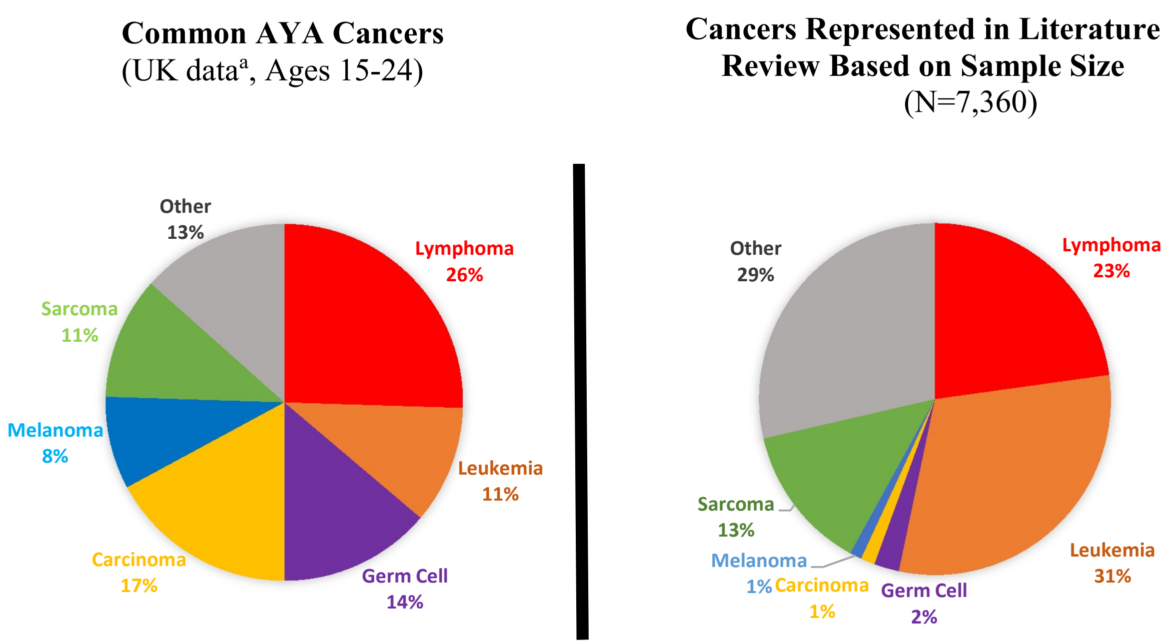
*Estimation of mean based on age groupings and sample size. No measure of central tendency reported in this study.

Figure 3: Sample Age Mean and Range for Included Studies Examining Cognitive Function. The ages of interest are highlighted in gray (ages 15- 24). Each line represents one study. The endpoints of the line indicate the range of age at diagnosis for that particular study. The hash mark in the middle of each line represent the mean or median of the sample, with the height of the hash mark relative to sample size with larger hash marks indicating a larger sample.

Table 4: Distribution of common AYA cancers across the world

	United States[a] (15-19 y.o.)	United Kingdom[b] (15-24 y.o.)	Australia[c] (15-29 y.o.)
Lymphoma	20.7%	25.5%	15.3%
Leukemia	13.8%	10.7%	6.2%
Germ cell	12.3%	13.8%	13.9%
Carcinoma	19.6%	17.1%	25.3%
Melanoma		8.4%	25.6%
Sarcoma	13%	11.1%	6.3%
TOTAL	79.4%	86.6%	92.6%

[a](National Cancer Institute, 2015)
[b](Birch et al., 2002)
[c](Australian Institute of Health and Welfare, 2011)



[a](Teenage Cancer Trust, 2014)

Figure 4: Comparison of Common AYA Cancers to Those Represented in Integrative Review

5.0 DISSERTATION MANUSCRIPT #3 COGNITIVE AND OCCUPATIONAL FUNCTION IN SURVIVORS OF ADOLESCENT AND YOUNG ADULT CANCER

5.1 INTRODUCTION

Adolescents with cancer are greatly understudied, particularly in terms of their survivorship needs. Studying adult survivors of adolescent cancer is tremendously important because of the developmentally vulnerable time point in which these individuals receive a cancer diagnosis and treatment. The healthy peers of adolescent survivors are often completing their high school education and entering college or the workforce, while adolescents with cancer are undergoing treatment for disease and miss important life milestones (Bellizzi et al., 2012; D'Agostino, Penney, & Zebrack, 2011). Studies of brain development show that the brain, especially the frontal lobe, continues to mature and develop into the early twenties (National Institute of Mental Health, 2011). Cancer and its treatment could affect the typical neurological and behavioral development of the adolescent patient with cancer and disrupt the adolescent survivor's long term employment status as they move into adulthood.

Despite earlier theories that brain development was complete during the teenage years, recent research has shown that a tremendous amount of change occurs in the brain during adolescence even into the early twenties (Dahl, 2004). This is an important consideration since middle and late adolescence is defined as ages 15-21 years (Erikson, 1950; Marshall & Tanner, 1974; Nelson et al., 2004). New technologies have allowed in-depth research on the timing and effects of brain development and have altered long-held assumptions about the timing of brain maturation. A report released by the National Institute of Mental Health in 2011 outlines several changes that occur in the brain during adolescent development, including a surprising finding that the amount of gray matter is highest during adolescence (National Institute of Mental Health, 2011). The adolescent brain experiences a wave of gray matter production specifically in the frontal lobe. The frontal lobe is associated with several domains of cognitive function including psychomotor function, planning, reasoning, judgment, impulse control and memory. However, there is a lack of research examining the cognitive changes experienced by adolescents diagnosed with cancer during this vulnerable time of brain development.

Previous studies of adult survivors of adolescent and young adult (AYA) cancer have described rates of employment (Dieluweit et al., 2011; Parsons et al., 2012; Tai et al., 2012). Results of the studies varied, however they generally indicate some level of reduction in employment status in survivors of AYA cancer compared to healthy controls. Yet, no study to date has explored occupational function. Occupational function is much more than whether or not an individual is employed. Occupational function addresses the physical, mental, and social health, basic competence and occupational virtues that are required by an individual to perform some form of work (Tengland, 2011). Thus, exploring occupational function will yield much richer information than simply whether or not an individual is employed including more information about how they are able to function in occupational roles.

Studies examining the relationship between occupational function (Calvio et al., 2009, 2010; Feuerstein, Hansen, Calvio, Johnson, & Ronquillo, 2007; Hansen, Feuerstein, Calvio, & Olsen, 2008) and cognitive function in other populations of cancer survivors have been conducted. A study of breast cancer survivors revealed that the strongest predictors of work limitations are difficulties in the cognitive domains of memory and executive function (Calvio et al., 2010). Similarly, a study of brain tumor survivors found that work limitations were most significantly predicted by memory, executive function, and attention deficits (Calvio et al., 2009). In addition, a study of adult survivors of childhood non-central nervous system cancers showed that impaired task efficiency, organization, memory, and behavioral regulation were all significantly associated with lack of employment as an adult (Kadan-Lottick et al., 2010). The frontal lobe is involved in numerous domains of cognitive function including memory and executive function and dysfunction in this part of the brain is associated with work limitations in other populations of cancer survivors (Calvio et al., 2009, 2010;

Kadan-Lottick et al., 2010). However, research has not been conducted to explore these relationships specifically in those diagnosed with cancer as an adolescent.

The aims of this exploratory study are to: 1) describe cognitive function (using objective and self-report measures) and self-reported ratings of occupational function among adult survivors of adolescent cancer; and 2) explore differences in cognitive function and occupational function between adult survivors of adolescent cancer and age- and sex-matched healthy controls. This study is innovative because it is the first to examine cognitive function and occupational function in adults who were diagnosed and treated for cancer as adolescents. Since adolescence is such a developmentally-rich time period, elucidating the potential disruption of a cancer diagnosis and its treatment may lead to better understanding of cognitive and occupational outcomes associated with adolescent cancer. Clearly articulating the unique features of the young adult survivor of adolescent cancer experience, including cognitive function and occupational function, will inform and provide direction for the planning and implementation of interventions to improve survivor outcomes related to the work experience.

5.2 METHODS

In this study, a descriptive, comparative design was employed to describe cognitive function and occupational function among adult survivors of adolescent cancer and explore group differences between adolescent cancer survivors and age- and sex-matched healthy controls at a single time point. The study was approved by the University of Pittsburgh Institutional Review Board. Informed consent was obtained for all participants in the study. For this study, cancer survivors were recruited from February, 2015 until May, 2016 from the Children's Hospital of Pittsburgh of UPMC outpatient oncology clinic. Eligible cancer survivors who agreed to take part in the study were asked to refer a "healthy friend/sibling" of the same sex and within 2 years of their age to serve as a control, although this was not a required component of participating in the study. All testing occurred at a single visit, often occurring before or after a regularly scheduled check-up at the outpatient clinic.

5.3 PARTICIPANTS

Inclusion and exclusion criteria. Inclusion criteria for survivors of adolescent cancer are: 1) cancer diagnosis between the ages of 15 and 21 years (middle or late adolescence); 2) currently between the ages of 18 and 39 years; 3) two years or more since active treatment for disease; and 4) able to speak English. Exclusion criteria for cancer survivors are: 1) diagnosis of neurological condition or mental impairment prior to cancer diagnosis; and 2) under the age of 18 years. Healthy controls met the same inclusion and exclusion criteria except that they had no history of cancer. In addition, healthy controls were frequency matched to the cancer survivors, being of the same sex and within two years of the survivor's age. Some of the cancer survivors that were recruited to the study stated that they did not have a healthy friend or sibling to ask to participate in the study. In this case, they were included in the study without a healthy control.

5.4 MEASURES

Cognitive function of participants was measured objectively with a battery of neuropsychological tests appropriate for adolescents and young adults between the ages of 18 and 39 years. The participants were also asked to complete measures of anxiety, depressive symptoms, perception of cognitive function, and questions about their work and occupational function in daily life. Altogether participants completed 15 measures: 10 neuropsychological tests, 1 measure of patient perception of cognitive function, 2 measures of occupational function, and 2 instruments to measure confounding factors.

Demographic and clinical characteristics. All participants completed a demographic questionnaire which collected information about race, marital status, education, and employment. Clinical characteristics including medical history and current medications were collected; these were verified through use of medical records for the group of cancer survivors. *The Intensity of Treatment Rating (ITR-3.0) Scale* (Kazak et al., 2012) is used to classify the intensity of pediatric cancer therapy according to treatment modality and stage/risk level for the patient. The ITR assigns an intensity level based on strict and comprehensive criteria from 1 (minimally intensive) to 4 (most intensive) by extracting diagnosis, stage, and treatment data from a patient's medical record. The ITR-3.0 is a reliable and valid instrument (Kazak et al., 2012) that facilitates classification of complex diagnoses and treatment regimens and allows for comparisons to be made across intensity groups (Children's Oncology Group, 2008). Thus, ITR-3.0 is an appropriate instrument for use in this study population and has been previously used in research studies of AYA cancer patients (Parsons et al., 2012).

Neuropsychological Tests. A battery of 10 neuropsychological tests assessing a broad range of cognitive domains was used in the study. The tests were selected for their demonstrated reliability, validity, and sensitivity to cognitive function, as well as their relevance to cognitive development in adolescents and young adults. The tests described below are routinely evaluated in a neuropsychological examination of adolescents.

Digit Vigilance (DV) Test (*Lafayette Clinical Repeatable Neuropsychological Test Battery*, 1989) is used as a measure of capacity for sustained attention and visual discrimination on a repetitious task. Participants are asked to scan 2 pages of numbers and asked to cross out every appearance of a specified target number as quickly and accurately as they can. Score is the amount of time needed to complete the task with higher scores indicating poorer function.

Digit Symbol Substitution (DSS) Test (Wechsler, 1981) is used to assess one's capacity for sustained, focused concentration and directed visual shifting and is largely unaffected by memory or learning. Participants are given a coding key in which numbers are paired with a unique symbol. For the task, participants are instructed to draw the symbol corresponding to each number as shown in the key as quickly as they can. Score is the number of symbols completed correctly in a given amount of time with higher scores indicating better function.

Grooved Peg Board Test (GPBT) (Lafayette Instrument Company, 2002) assesses dexterity and psychomotor functioning. The board consists of 25 randomly placed holes and 25 pegs with a key along one side. Pegs must be rotated to match the hole before they can be inserted. Scoring for this test is the amount of time it takes to insert all pegs into the holes successfully.

Stroop Color and Word Test (Golden & Freshwater, 1978) is a measure of executive function and cognitive inhibition. The test consists of three trials measuring the relative speed of one's ability to read the names of colors (Word), naming colors (Color), and naming colors from words of colors printed with an incongruently colored ink (Color-Word). The Stroop interference score is the difference between the Color-Word score and the predicted Color-Word Score based on performance on the Color and Word tests. Higher scores on the Stroop interference score indicate better function.

Verbal Fluency Test (Spreen & Benton, 1977) is a subtest of the Neurosensory Center Comprehensive Examination for Aphasia. The test requires participants to say as many words as possible in 1 minute that begin with the letters F, A, and S (alternating). One point is given for each unique word spoken by the participant. To successfully retrieve words, the verbal fluency test requires control of executive function over cognitive processes including selective attention, mental set shifting, internal response generation, and self-monitoring. Higher scores indicate better functioning.

Trail Making Test (TMT) A and B (Reitan, 1955) consists of 25 circles distributed across a sheet of paper for each test. In Test A, the circles are numbered from 1-25 and the participant is asked to draw lines connecting the numbers in ascending order. In Test B, the circles include both numbers (1-13) and letters (A-L). Similar to Test A, the participant is asked to connect the circles in ascending order, but with the additional task of alternating between letters and numbers (i.e., 1-A-2-B-3-C, etc.). Participants are instructed to draw lines connecting the circles in order as quickly as possible. The TMT tests assess executive function, mental flexibility and attention. Scores on the TMT are the amount of time taken to complete the task with higher scores indicating poorer function.

Wechsler Memory Scale (Wechsler, 2009) is designed to measure a variety of aspects of memory. For this test the participant is read a short story and asked to recall details from the story. There is also a delayed recall component that occurs 20-30 minutes after the immediate recall. The score is the total number of items recalled correctly with higher scores indicating better function.

Letter Number Sequencing Test (Wechsler, 2008) is part of the Wechsler Intelligence Scale and is a measure of working memory, the ability to simultaneously organize and recall stimuli of different and similar types. In the Letter Number Sequencing Test, the examiner presents combinations of letters and numbers from 2 to 9. The participant must first repeat the numbers in the sequence in ascending order, then the letters in alphabetical order. Score is the number of sequences recalled correctly with higher scores indicating better function.

Rey-Osterrieth Complex Figure Test (ROCF) (Rey & Osterrieth, 1993) assesses visual perceptual, skills, spatial organization, constructional ability, and visual memory (immediate and delayed recall). Participants are instructed to carefully copy a figure and then, without prior warning, to redraw the figure immediately after the figure is removed and again in, approximately 30 minutes later (delayed recall). Score is based on the number of items correctly drawn and placed with higher scores indicating better function.

Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) is primarily used to assess perseveration and abstract thinking in individuals, but is also considered a measure of executive function because of its sensitivity to frontal lobe dysfunction. Administration of the WCST requires use of a deck of stimulus cards. The cards can be matched by number (1/ 2/ 3/ 4), color (red/ green/ blue/ yellow), or shape (circle/ square/ star/ cross). The participant is shown four stimulus cards at a time and then is asked to match a card from the deck to one of the stimulus cards, but is not instructed on what rule to match the cards. The participant will be told "correct" or incorrect" depending on whether they guess the rule correctly or not. Scoring is based on the number of cards matched correctly, but also yields a perseveration score from the number of "incorrect" guesses which would have been "correct" based on the previous rule.

Perceived cognitive function. Patients Assessment of Own Functioning Inventory (PAOFI) (Chelune, Heaton, & Lehman, 1986) is a self-report measure of cognitive difficulties which has shown correlation with changes in neuropsychological functioning in samples of cancer patients (Bender et al., 2006, 2008; Pullens, Vries, et al., 2010) and has been shown to be a reliable and valid instrument (Bell, Terhorst, & Bender, 2013). The PAOFI assesses perceptions of performance in five different domains of cognitive functioning: memory, executive function, language, orientation, and sensorimotor ability. Higher scores on the PAOFI indicate poorer perceived cognitive function.

Anxiety, Fatigue and Depression. Depressive symptoms were measured with the full

20-item *Center for Epidemiological Studies-Depression Scale-Revised [CESD-R]* (Radloff, 1977) which has shown good reliability and validity in a sample of cancer patients (Hann, Winter, & Jacobsen, 1999). Anxiety and fatigue were measured by the *Profile of Mood States-Short Form [POMS-SF]* (Curran, Andrykowski, & Studts, 1995) Tension-Anxiety subscale and Fatigue-Inertia subscale, respectively. The POMS-SF has also demonstrated good reliability and validity (Curran et al., 1995).

Occupational Function. The *Work Limitations Questionnaire (WLQ)* (Lerner et al., 2001) is a 25-item self-report measure of work functioning. The WLQ has shown reliability and validity for use among several different jobs and chronic health condition groups including those with cancer (Gordon et al., 2011). The WLQ yields four subscale scores when a respondent was limited in performing a specific dimension of their job (Time, Physical, Mental and Interpersonal, and Output) and a total score. Higher scores indicate poorer function.

Missing Data. In the case of missing item responses on multi-item questionnaires, unless instructed otherwise by the instrument developer, as long as 80% of items for each subscale and total score were completed by the participant, we calculated the mean item response from the available item responses to impute values for the missing items and obtain subscale and total scores. In the event that less than 80% (or the developer specified amount) of items had been answered for a particular subscale or sum score, no score was calculated.

5.5 DATA ANALYSIS

Data were first screened for any anomalies (i.e., outliers, normality, multicollinearity, etc.) by group using descriptive and exploratory analyses. Group-specific standard descriptive statistics, consistent with a variable's level of measurement and observed distribution, were calculated. We performed comparative analyses to explore whether there were any differences on demographic or clinical characteristics between those cancer survivors who were able to refer a healthy control and those unable to refer a healthy control. We also explored whether there were differences on demographic characteristics between the survivors of adolescent cancer and healthy control groups. Tests to look for between group differences included independent sample t-tests for interval and ratio variables (e.g., age, years of education, age at diagnosis, time since treatment, depressive symptoms, level of fatigue, and intensity of treatment rating) and chi-square tests of independence or Fisher's exact test if sparse cells for nominal variables (sex, race, marital status, clinically significant anxiety symptoms, and cancer diagnosis). Given the sample size of the study, nonparametric testing using the Mann-Whitney U-test for interval and ratio scaled variables was used in cases of nonnormality or if outliers were present.

For aim 1, simple descriptive statistics including means and standard deviations were calculated for each subscale and total score in both the adolescent cancer survivor and healthy control groups. The confidence interval of the mean (95%) was calculated and reported for the survivor of adolescent cancer group. For aim 2, given the small sample size we focused on the estimation of effect sizes with confidence intervals rather than hypothesis testing. Additionally, one-way multivariate analysis of variance (MANOVA) with test-specific independent samples t-tests were conducted for cognitive and occupational function between the survivor and healthy control groups. Effect sizes as the standardized mean difference (Cohen's *d*) with 95% confidence intervals were calculated for each neuropsychological test, subscale, and total score. Interpretation of effect sizes of Cohen's *d* were guided by general ranges put forth in the field of neuropsychology where an effect size of 0.20-0.49 is considered a small effect, 0.50-0.79 is considered a medium effect, and 0.80 and greater is considered a large effect (Zakzanis, 2001). Separate MANOVA's were performed for the sets of tests for each domain of cognitive function (attention, memory, and executive function), except for the domain of psychomotor speed where an independent t-test was used since there was only one primary score for this domain. Additionally, we explored the correlation of perceived cognitive function with depressive symptoms, anxiety, and fatigue using Spearman's rho since these factors have been shown to be correlated to perceived cognitive function in other populations of cancer survivors (Merriman et al., 2015; Vardy, Wefel, Ahles, Tannock, & Schagen, 2008), yet has not been explored in survivors of adolescent cancer. Assumptions of MANOVA (independence of observations, homogeneity of group variance-covariance matrices, no multicollinearity among dependent variables, multivariate normality, and linear relationship between pairs of dependent variables with each level of categorical independent variable, and no univariate or multivariate outliers) (Nimon, 2012) and independent t-test (i.e., normality, linearity, sphericity, and homogeneity of regression slopes) (Pallant, 2013) were met for dependent variables in the model. There were no univariate outliers in our study, but there was one multivariate outlier, a cancer survivor who demonstrated an unusual pattern in performance on neuropsychological measures of attention. Analyses were performed with and without this individual. The analyses which included the multivariate outlier did not change the conclusions drawn, thus we opted to use the entire sample in our analysis.

5.6 RESULTS

Statistically significant between group differences were not found in regards to cancer survivors who were able to refer a healthy control and those unable to refer a health control with respect to demographic factors and disease and treatment characteristics. Thus, we opted to use the entire sample for our study. Demographic and clinical characteristics of the sample are shown in Table 5. Twenty-three cancer survivors and fourteen healthy controls were included in our analysis. Fifty-nine percent ($n = 14$) of the survivors included in our study were able to identify a healthy age- and gender-matched friend to serve as a healthy control. Cancer survivors were approximately 23 years of age and had some (14.7 mean years) college education. The majority of participants were Caucasian ($n = 21$, 91.3%), male ($n = 16$, 69.6%), and had never married ($n = 20$, 87,0%). The mean age at diagnosis for the survivor group was 17.4 years and cancer treatment lasted about 1 year, on average. The most common cancer diagnosis was Hodgkin's Lymphoma ($n = 10$, 43.4%). There were no differences between the cancer survivor and healthy control groups except for levels of anxiety. Cancer survivors had significantly higher anxiety scores than the healthy controls ($p = .049$); however, the mean level of anxiety reported by survivors was still within the normal range based on population normative data. Since research has shown that self-reports of anxiety symptoms in the absence of clinically significant anxiety is not known to affect cognitive performance (Waldstein, Ryan, Jennings, Muldoon, & Manuck, 1997), level of anxiety was recoded as a dichotomous variable (clinically significant anxiety or not clinically significant anxiety). There were no differences in the number of people in each group reporting clinically significant levels of anxiety (t-score greater than or equal to 60) (Curran et al., 1995), $p = 0.275$. Thus, anxiety was not included as a covariate in the model.

Table 5: Baseline characteristics of survivors of adolescent cancer and healthy control groups

Characteristic	**Survivors of AYA Cancer *n*=23**	**Healthy Control *n*=14**	**Test Statistic**	***p*-value**
	Mean ± *SD* Median (IQR)	Mean ± *SD* Median (IQR)		
Age (years)	23.8 ± 4.0	22.9 ± 3.8	t=0.64	.526
	22.6 (5.0)	21.7 (3.1)	U_{MW}=133.0	.394
Education (years)	14.7 ± 2.4	14.7 ± 2.5	t=0.03	.976
	15.0 (5.0)	14.0 (4.0)	U_{MW}=152.5	.793
Disease and Treatment Factors				
Age at Diagnosis (years)	17.4 ± 1.9	NA	--	--
Length of Treatment (years)	1.2 ± 1.4	NA	--	--
Mood				
Depressive Symptoms	11.7 ± 11.9	9.5 ± 8.9	t=0.62	.538
	7.0 (14.0)	7.1 (13.0)	U_{MW}=149.0	.722
Anxiety (T score)	48.9 ± 11.5	41.7 ± 7.5	t=2.04	.049
	49.0 (20.0)	39.5 (9.0)	U_{MW}=98.0	.049
Fatigue (T score)	46.3 ± 10.2	43.3 ± 6.7	t=0.94	.354
	44.0 (19.0)	42.0 (9.0)	U_{MW}=135.5	.429
	Percent (n)	Percent (n)		
Sex (Male)	69.6 (16)	64.3 (9)	--	1.000^{FE}
Marital Status (Never Married)	87.0 (20)	85.7 (12)	--	1.000^{FE}
Race (Caucasian)	91.3 (21)	85.7 (12)	--	0.625^{FE}
Hispanic Descent (No)	95.7 (22)	78.6 (11)	--	0.142^{FE}
Identified a Healthy Control (Yes)	60.8 (14)	NA	--	--
Cancer Diagnosis				
Acute Lymphoblastic Leukemia	17.4 (4)	NA	--	--
Acute Myelocytic Leukemia	4.3 (1)	NA	--	--
Osteosarcoma	8.7 (2)	NA	--	--
Chondrosarcoma	4.3 (1)	NA	--	--
Ewing's Sarcoma	8.7 (2)	NA	--	--
Germ Cell Tumor	8.7 (2)	NA	--	--
Hodgkin's Lymphoma	43.4 (10)	NA	--	--
Non-Hodgkin's Lymphoma	4.3 (1)	NA	--	--

SD Standard Deviation, *IQR* Interquartile Range, *MW* Mann Whitney U Test; NA Not Applicable; *FE* Fisher's Exact

The results for the comparisons between survivors of AYA cancer and healthy controls for cognitive function are summarized in Table 6. Although no statistically significant differences were found based on multivariate and univariate analysis of variance, effects that were seen suggest poorer cognitive function in cancer survivors than in healthy controls. In addition, effect size calculation indicated several cognitive domains demonstrating small or medium sized effects for one or more neuropsychological tests or subscale scores. The effect size for the digit vigilance test ($d = 0.396$) and the Stroop interference score ($d = -0.226$) fell into Cohen's (1988) range for a small effect. Small or medium effect sizes were found for all perceived cognitive function subscales except the sensory perceptual domain. Total perceived cognitive function scores for cancer survivors also exhibited a small to medium effect ($d = 0.441$) indicating that survivors of adolescent cancer ($M = 32.78$, $SD = 23.02$) reported greater difficulty with overall cognitive functioning as compared to healthy controls ($M = 23.71$, $SD = 15.54$). A follow-up analysis found that, for both cancer survivors and healthy controls, poorer perceived cognitive function in each subscale (except the Use of Hands) and total perceived cognitive function were correlated to increases in level of depressive symptoms, anxiety and fatigue and were found to be significant at the .05 level.

The results for the comparisons between survivors of AYA cancer and healthy controls for occupational function are summarized in Table 7. For work limitations, no statistically significant differences were found for participants who were working comparing between survivors of adolescent cancer and healthy controls. Effect size estimation, however, revealed a small to medium effect in reported work output ($d = 0.430$) indicating that survivors of adolescent cancer ($M = 21.66$, $SD = 29.98$) who were working reported worse work output than healthy controls ($M = 10.71$, $SD = 14.92$) who were working.

Finally, the correlations between perceived cognitive function and depressive symptoms, anxiety, and fatigue can be found in Table 8. We conducted a follow-up analysis and found that, for both cancer survivors and healthy controls, poorer perceived cognitive function in each subscale (except the Use of Hands) and total perceived cognitive function were correlated to increases in level of depressive symptoms, anxiety and fatigue and were found to be significant at the .05 level.

5.7 DISCUSSION

The purpose of this study was to describe cognitive and occupational function in survivors of adolescent cancer and explore differences in cognitive and occupational function between survivors of adolescent cancer and healthy controls. We did not find statistically significant differences in cognitive or occupational function between cancer survivors and healthy controls. However, we did detect two small effect sizes for neuropsychological performance and several small and medium effect sizes in perceived cognitive function. Finally, we found a small to medium effect size in reported work output in the cancer survivor group.

While statistically significant differences between survivors of adolescent cancer and healthy controls were not found, this may have been due, in part, to a limited sample size, or the inability of the chosen neuropsychological measurements to detect subtler cognitive differences between groups. Effect size measurements of neuropsychological tests using Cohen's d, suggest that survivors of adolescent cancer may experience difficulty in some aspects of memory and executive function. Furthermore, the digit vigilance test and Stroop test may be sensitive tests in detecting between group differences in survivors of adolescent cancer and healthy controls. This is consistent with findings from other studies which suggest that both the digit vigilance and Stroop tests demonstrate excellent sensitivity to more subtle changes in cognitive function. The Stroop test has been found to be sensitive in detecting prefrontal dysfunction (Homack & Riccio, 2004) and the Digit Vigilance Test demonstrates excellent sensitivity in detecting frontal lobe dysfunction (Lafayette Clinical Repeatable Neuropsychological Test Battery, 1989). However, it must be restated that this is the first study designed to explicitly measure cognitive function in survivors of adolescent cancer and thus we are unable to directly to compare with other studies findings in this population.

Survivors of adolescent cancer reported greater perceived cognitive difficulty including poorer memory, language and communication skills, higher level cognitive and intellectual function, and total perceived cognitive function than their gender- and age-matched healthy counterparts. These findings are consistent with others who have found that cancer survivors report poorer perceived cognitive function than healthy controls even in the absence of worse neuropsychological function (Mehnert et al., 2007; J. L. Vardy et al., 2008). Similar to other research in perceived cognitive function in cancer survivors, we found an association between perceived cognitive function and levels of anxiety, depressive symptoms, and fatigue (Merriman et al., 2015; J. L. Vardy et al., 2008). However, it is uncertain whether symptoms of anxiety, depression, and fatigue contribute to poorer perceived cognitive function or whether they may be the result of subtle cognitive difficulties that may go undetected in measures of neuropsychological function.

It has been theorized that greater perceived cognitive difficulty may relate to compensatory mechanisms in the brain even in the absence of impaired neuropsychological function (Reuter-Lorenz & Cimprich, 2013; Von Ah & Tallman, 2015). For instance, research using functional MRI's (fMRI's) in other populations of cancer survivors have shown that although neuropsychological performance may not be impaired, the alterations in activation patterns in the brain suggest a compensatory mechanism whereby greater effort and mental processes are required to perform similarly to heathy controls (Cimprich et al., 2010; R. J. Ferguson, McDonald, Saykin, & Ahles, 2007; McDonald, Conroy, Ahles, West, & Saykin, 2012). Future research is needed to investigate whether or not perceived cognitive difficulties may align with mechanisms of compensation in the brain and whether or not the deficits align with education or work outcomes.

Survivors of adolescent cancer in our sample were not less likely to be employed or work part-time than their healthy counterparts; however, survivors of adolescent cancer did report reduced work quality and quantity as compared to healthy controls (Lerner et al., 2001). While numerous studies have examined the concept of "return to work" following cancer diagnosis, survivors of adolescent cancer warrant further investigation since these individuals often are not employed at the time of cancer diagnosis and treatment. For survivors of adolescent cancer, there is the additional factor of pursuing higher education or training and establishing a career and entering the workforce after cancer diagnosis and treatment. To our knowledge, the concept of assisting survivors of adolescent cancer in entering the workforce has not been previously explored. Whether cancer survivors only perceive reduced work output or in fact have reduced quantity and quality of work should be further explored since this may have great impact on their ability to maintain employment and could have vast financial implications for this population. Future research will be important to explore factors that contribute to poorer work output with consideration to both qualitative and quantitative methods. Investigation into how to best support this vulnerable population in achieving professional goals and optimal occupational functioning is of particular importance given their life stage.

5.7.1 Strengths and Limitations

There are several limitations to acknowledge in our study. First, this study used a cross-sectional design so we were unable to examine whether there were changes in cognitive function over time. Future studies should include a longitudinal design to permit examination of changes in cognitive function including a testing performed pre-treatment. Second, our limited and unequal sample sizes did not provide adequate power to focus on hypothesis testing and may have contributed to the lack of statistically significant differences observed. The small sample sizes also prevented more complex analyses including adequate power to investigate the relationship between cognitive and occupational function. Third, the neuropsychological measures used in this study did not provide a comprehensive assessment of all domains of cognitive function and may not have been sensitive to subtle differences between groups. The neuropsychological battery was limited to 10 tests assessing four domains of cognitive function so as to limit subject burden and fatigue. However, a more extensive neuropsychological battery may have detected statistically significant differences between the groups that we were unable to detect.

The strengths of this study include the use of a neuropsychological battery specifically chosen to measure aspects of cognitive function that are developing during adolescence. Our sample was composed exclusively of individuals diagnosed with cancer during adolescence and included a matched control group of healthy individuals. To our knowledge, this is the first study specifically designed to explore cognitive function in survivors of adolescent cancer.

5.7.2 Conclusions

Findings suggest that survivors of adolescent cancer may or may not exhibit poorer performance on objective measures of cognitive function. However, survivors of adolescent cancer consistently report poorer perceived cognitive function than their healthy counterparts. In addition, there were no statistically significant differences in the rate or level of employment between adolescent cancer survivors and healthy controls, however adolescent cancer survivors reported more difficulty with work output compared to their healthy counterparts. Future, longitudinal studies are needed that include a larger sample of survivors of AYA cancer to elucidate who is at risk for cognitive difficulties and difficulty with work output. Clearly understanding the cognitive and occupational problems associated with disease and treatment will inform development of interventions to assist survivors in achieving optimal functioning.

Table 6: Cognitive function in survivors of adolescent cancer compared to healthy controls

Test	Cancer Survivors Mean ± SD [95% C.I.] n=23	Healthy Controls Mean ± SD n=14	Test statistic p-value	Cohen's *d* [95% C.I.]
Attention			F_{MV} = 0.671 p = .518	
Digit Vigilance (sec)†	409.13 ± 100.72 [365.58, 452.69]	370.91 ± 88.95	F_{UV} = 1.365 p = .251	d = 0.396* [-0.28, 1.07]
Digit Symbol, 90-sec total (number correct)	80.52 ± 14.54 [74.24, 86.81]	82.79 ± 15.85	F_{UV} = 0.197 p = .660	d = -0.151 [-0.82, 0.51]
Memory			F_{MV} = 0.343 p = .883	
Letter Number Sequencing (number correct)	11.26 ± 3.19 [9.88, 12.64]	11.07 ± 3.22	F_{UV} = 0.199 p = .658	d = 0.059 [-0.61, 0.72]
Rey Figure, Immediate (scaled score)	22.48 ± 6.47 [19.68, 25.27]	21.64 ± 6.68	F_{UV} = 0.564 p =.564	d = 0.128 [-0.54, 0.79]
Rey Figure, Delayed (scaled score)	22.09 ± 6.63 [19.22, 24.95]	20.82 ± 6.50	F_{UV} = 0.639 p = .429	d = 0.193 [-0.47, 0.86]
Stories B & C, Immediate (no. correct)	25.61 ± 5.71 [23.14, 28.08]	25.64 ± 5.34	F_{UV} = 0.013 p = .909	d = -0.005 [-0.670, 0.659]
Stories B & C, Delayed (number correct)	22.70 ± 5.64 [20.25, 25.14]	23.46 ± 5.09	F_{UV} = 0.164 p = .688	d = -0.140 [-0.80, 0.53]
Executive Function			F_{MV} = 0.163 p = .956	
Stroop Interference (scaled score)	3.96 ± 8.08 [0.46, 7.45]	5.86 ± 8.97	F_{UV} = 0.443 p = .510	d = -0.226* [-0.89, 0.44]
Trail Making, Part B (seconds)†	69.21 ± 23.13 [59.21, 79.22]	71.50 ± 31.81	F_{UV} = 0.064 p = .802	d = -0.086 [-0.75, 0.58]
Verbal Fluency, FAS (number correct)	37.70 ± 11.54 [32.70, 42.69]	38.50 ± 11.23	F_{UV} = 0.043 p = .837	d = -0.070 [-0.73, 0.59]
Wisconsin Card Sorting Test Perseverative Errors (number of errors)†	9.09 ± 5.52 [6.70, 11.47]	9.86 ± 7.12	F_{UV} = 0.136 p = .715	d = -0.125 [-0.79, 0.54]
Psychomotor Speed				
Grooved Pegboard, Dominant hand (seconds)†	69.93 ± 17.39 [62.41, 77.45]	67.33 ± 14.62	t = 0.461 p = .648	d = 0.158 [-0.51, 0.82]
Patient Perception			F_{MV} = 1.514 p = .215	
Memory†	14.96 ± 9.35 [10.91, 19.00]	10.00 ± 6.04	F_{UV} = 4.191 p = .048	d = 0.599** [-0.08, 1.28]
Language and Communication†	7.91 ± 5.57 [5.51, 10.32]	4.85 ± 4.06	F_{UV} = 3.020 p = .091	d = 0.605** [-0.07, 1.28]
Use of Hands†	1.00 ± 1.31 [0.43, 1.57]	1.79 ± 1.53	F_{UV} = 1.695 p = .202	d = -0.566** [-1.24, 0.11]
Sensory Perceptual†	1.22 ± 1.86 [0.41, 2.02]	1.29 ± 2.02	F_{UV} =0.233 p = .632	d = -0.036 [-0.70, 0.63]
Higher Level Cognitive and Intellectual Function†	7.70 ± 7.42 [4.49, 10.90]	5.79 ± 6.55	F_{UV} = 1.894 p = .178	d = 0.269* [-0.40, 0.94]
Total†	32.78 ± 23.02 [22.83, 42.74]	23.71 ± 15.54	t = 1.301 p = .202	d = 0.441* [-0.23, 1.11]

C.I. Confidence Interval
† Higher scores indicate poorer performance.
F_{MV} = Multivariate F statistic
F_{UV} = Univariate F statistic
*Small effect size
**Medium effect size

Table 7: Occupational function in survivors of adolescent cancer compared to healthy controls

Occupational Factors	Cancer Survivors n (%) n=23	Healthy Controls n (%) n=14		
Work Status				
Full-time student, not working	4 (17.4%)	3 (21.4%)		
Student and part-time work	5 (21.7%)	4 (28.6%)		
Student and full-time work	1 (4.3%)	0 (0.0%)		
Part-time work only	3 (13.0%)	0 (0.0%)		
Full-time work only	10 (43.4%)	7 (50%)		
	Mean ± SD n=19 [95% C.I.]	**Mean ± SD n=11**	**Test Statistic p-value**	**Cohen's *d* [95% C.I.]**
Aspects of Occupational Function in participants who are employed			F_{MV} = 1.877 p = .147	
Time	21.31 ± 31.04 [7.35, 35.27]	21.36 ± 20.50	F_{UV} = 0.240 p = 0.628	d = -0.002 [-0.74, 0.74]
Physical	8.03 ± 11.88[a] [2.54, 13.52]	13.03 ± 20.91	F_{UV} = 0.680 p = .417	d = -0.316 [-1.07, 0.44]
Mental-Interpersonal	24.43 ± 27.93 [11.87, 36.99]	22.70 ± 17.33	F_{UV}=0.101 p =.753	d = 0.070 [-0.67, 0.81]
Output	20.53 ± 28.91 [7.53, 33.53]	11.36 ± 15.67	F_{UV} = 0.384 p = .541	d = 0.367* [-0.38, 1.12]
Total	4.50 ± 5.28[a] [2.13, 6.87]	4.67 ± 4.34	t = -0.090 p = .929	d = -0.034 [-0.78, 0.72]

C.I. Confidence Interval
F_{MV} = Multivariate F statistic
F_{UV} = Univariate F statistic
*Small effect size
[a]n=18

Table 8: Correlation between perceived cognitive function and depressive symptoms, anxiety, and fatigue

PAOFI Score	**Depressive symptoms (*n*=36)**	**Anxiety (*n*=36)**	**Fatigue (*n*=36)**
Memory			
Spearman's rho	.528	.378	.339
p	.001	.023	.043
Language & Communication			
Spearman's rho	.652	.437	.413
p	<.001	.008	.012
Use of Hands			
Spearman's rho	.315	.293	.200
p	.062	.083	.242
Sensory Perceptual			
Spearman's rho	.574	.510	.384
p	<.001	.001	.021
Higher level Cognitive and Intellectual Function			
Spearman's rho	.769	.509	.456
p	<.001	.002	.005
Total			
Spearman's rho	.727	.513	.480
p	<.001	.001	.003

PAOFI = Patient Assessment of Own Functioning Inventory

6.0 SUMMARY OF DISSERTATION FINDINGS

This dissertation project consists of 3 complementary studies to address several gaps in the scientific literature on cognitive and occupational function in cancer survivors. Findings are documented in the following three manuscripts:

Manuscript #1: The association between pre-treatment occupational skill level and mood and symptom burden in early-stage, postmenopausal breast cancer survivors during the first year of anastrozole therapy;

Manuscript #2: Cognitive function in survivors of adolescent and young adult cancer: An integrative review and literature critique; and

Manuscript #3: Cognitive and occupational function in survivors of adolescent cancer.

Although each of these three manuscripts had a distinct purpose, viewing the studies together reveals several themes. **First, this dissertation explored the relationship between cancer and occupational function.** Occupational factors are an important consideration in cancer survivors both during treatment and in long-term survivors. Understanding the occupation in which cancer survivors are employed at diagnosis may help to predict the trajectory of symptom burden over time. This association was explored in manuscript 1, which revealed that breast cancer survivors employed at lower skill levels experienced greater overall symptom burden as well as significantly worse musculoskeletal, vasomotor, and gastrointestinal symptoms than those employed at the higher skill level. Findings of manuscript 3 suggest that survivors of adolescent cancer reported poorer work output than their healthy counterparts without a history of cancer. Taken together, these findings affirm that assessing occupational factors of cancer survivors may have implications for both symptom management as well as occupational counseling to assist cancer survivors in finding and maintaining employment.

This dissertation also explored the relationship between cancer and cognitive function, with particular emphasis on the paucity of research that has been done in those diagnosed during adolescent and young adulthood. The integrative review (manuscript 2) demonstrated that while a good deal of work has been done to explore cognitive function in cancer survivors more broadly, very little research has been done to explore cognitive function in those diagnosed during adolescence and young adulthood. No study to date has focused exclusively on measuring cognitive outcomes in survivors of adolescent cancer. To our knowledge, this dissertation contains the first study conducted to explore cognitive function specifically in those diagnosed during adolescence (manuscript 3). We found that survivors of adolescent cancer perceived poorer cognitive function than their peers without a history of cancer, however we found no significant measurable differences in objective measures of neuropsychological function. However, our sample size was small and future studies are needed to examine the cognitive outcomes in this group of vulnerable cancer survivors.

In conclusion, this dissertation provides an overview of the relationship between work and cancer and cognitive function and cancer, with particular emphasis on the population of cancer survivors diagnosed during adolescence and young adulthood. **Knowledge obtained from this dissertation work suggests future research studies are needed. In particular,**

1. Exploration of the relationship between cognitive function and occupational function in cancer survivors.
2. Descriptive studies using a larger sample and longitudinal study design are needed to explore cognitive function in survivors of adolescent and young adult cancer.
3. Descriptive studies are needed to explore correlates of perceived cognitive function such as association with compensatory mechanisms in the brain, even in the absence of altered performance on neuropsychological tests.
4. Future intervention research to promote optimal occupational function in cancer survivors should test theory-driven strategies to assist cancer survivors in finding and maintaining employment. While many studies have focused on the concept of "return-to-work" in cancer survivors, particular considerations are needed to meet the unique needs

of cancer survivors who have not yet entered the work force when confronted with a cancer diagnosis.

APPENDIX A

PRELIMINARY WORK MANUSCRIPT #1: WORK PRODUCTIVITY AND NEUROPSYCHOLOGICAL FUNCTION IN PERSONS WITH SKULL BASE TUMORS

The version of record Nugent BD, Weimer J, Choi CJ, et al. Work productivity and neuropsychological function in persons with skull base tumors. Neuro-Oncology Practice 2014;1(3):106-113. doi:10.1093/nop/npu015 is available online at: http://nop.oxfordjournals.org/cgi/content/full/npu015?ijkey=egewQicYRUErDZR&keytype=ref

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Work productivity and neuropsychological function in persons with skull base tumors

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Background. Skull base tumors comprise many common benign brain tumors. Treatment has advanced, allowing many survivors to return to work. However, literature is limited about the neuropsychological status of these patients prior to treatment. Literature pertaining to the relationship between neuropsychological functioning and occupational ability prior to surgical intervention is even more limited. The purpose of this analysis was to evaluate the impact of neuropsychological function on work productivity in persons with skull base tumors prior to resection.

Methods. Neuropsychological function and work productivity were assessed in adults newly diagnosed with skull base tumors ($n = 45$) prior to surgical intervention. Univariate analyses identified potential predictors of work limitations; variables with $P < .10$ were analyzed using multivariate regression analyses controlled for age, sex, tumor type, and education.

Results. Poorer mental attention and flexibility (MF) and higher depressive symptoms (DS) were significantly associated with poor time management at work (MF: $\beta = -0.59$, $P = .01$; DS: $\beta = 3.42$, $P < .01$; $R^2 = 0.54$). Difficulty meeting physical work demands was significantly associated with poorer visuospatial ability (VA) and higher depressive symptoms (VA: $\beta = -3.30$, $P = .05$; DS: $\beta = 2.29$, $P < .01$; $R^2 = 0.29$). Lower learning and memory scores (LM) and higher depressive symptoms were significantly associated with difficulty meeting mental-interpersonal work demands (LM: $\beta = -3.39$, $P = .04$; DS: $\beta = 3.25$, $P < .01$; $R^2 = 0.47$) and overall health-related loss of work productivity (LM: $\beta = -0.72$, $P = .05$; DS: $\beta = 0.659$, $P < .001$; $R^2 = 0.43$).

Conclusion. Domains of neuropsychological function that predicted work productivity were identified. Future research should examine neuropsychological function, depressive symptoms, and work productivity across the care trajectory from diagnosis through long-term survivorship.

Keywords: cognitive function, neuropsychological function, occupational function, skull base tumors, work ability.

Since the 1970s, the incidence of benign brain tumors has been on the rise, due in part to improved technology and ability to detect neoplasms.[1,2] According to the Central Brain Tumor Registry of the United States [CBTRUS], ~142 000 new cases of benign intracranial tumors are diagnosed each year; 48% of all intracranial tumors are benign.[1] While there are several different types of benign brain tumors, some of the most common are skull base tumors including adenomas, meningiomas, and Rathke cleft cysts.[3–7] The skull base includes the bones that form the bottom of the head and the back of the eye socket.

The focus in brain tumors has centered on the diagnosis and treatment of malignant tumors. There has been growing recognition, however, that benign intracranial tumors, including skull base tumors, can impose significant societal costs related to medical care, case fatality, and lost productivity.[1] In contrast to most other brain and nervous system tumors, the diagnosis of a skull base tumor does not automatically qualify an individual for disability under the United States Social Security Act[8] and thus may not allow the individual to quit work or qualify for disability. Yet, even benign brain tumors have the ability to cause altered physical and neuropsychological function.[9–12] However, the manner in which these alterations affect a person's ability to fulfill normal obligations, such as meeting occupational demands, is unknown. This potential for work disruption in particular has

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significant societal and personal implications that are not known. The purpose of this analysis was to examine the relationship between neuropsychological function and work productivity in individuals with a skull base tumor prior to any treatment or resection.

Background

Many skull base tumors are considered to be benign. If the tumor does not grow, is seemingly asymptomatic, or produces only minimal symptoms, the recommended treatment may be to continue careful monitoring (watchful waiting) in an attempt to avoid overly aggressive treatment that may expose the patient to more risk than the expected benefit.[13,14] The risk/benefit of nonsurgical management of skull base tumors is limited, especially as it impacts daily activities. However, Van Nieuwenhuizen, et al[12] found that patients with low-grade meningiomas undergoing the watchful waiting approach had lower psychomotor speed and working memory capacity.

One of the main difficulties in assessing the impact of symptoms on persons' lives is that alterations in neuropsychological function and the accompanying symptoms are common but often "silent" because they can be quite subtle and develop gradually. Alterations in neuropsychological function may not be as readily recognized as physical dysfunction, yet it can still have a large impact on patients' ability to continue societal, familial, and occupational roles. Research has shown an association between impaired neuropsychological function and poor work performance and employability in other patient populations.[15–18]

There is sparse literature regarding the impact of neuropsychological function on occupational obligations in persons with any type of primary brain tumor. Teixidor, et al[19] found preoperatively that patients with a tumor in the language center of the brain scored lower than normal on most measures of verbal working memory. Another study examined patients with tumors in the frontal or temporal lobe and found that more than 90% of their sample displayed impairment in at least one area of cognition.[11] These studies examined the impact of malignant brain tumors preoperatively and their effect on neuropsychological functioning, yet altered neuropsychological functioning and its effect on occupational functioning is not reported; thus, the tumor's impact on productivity and quality of life is less well known. Alterations in neuropsychological functioning in patients with skull base brain tumors could affect their job performance and employment status. The purpose of this analysis was to determine neuropsychological functioning of patients with skull base tumors and examine its relation to patients' perceptions of work limitations and their ability to fulfill occupational demands.

Materials and Methods

Data for this interim analysis were obtained from a large prospective longitudinal study examining outcomes of patients scheduled to undergo endoscopic assisted microneurosurgery or the use of the expanded endonasal approach for brain tumor resection. Inclusion criteria were recent diagnosis (within 1 month) with a midline brain tumor as determined by MRI, aged 18 years or older, and ability to read and speak English. Patients with a previous history of surgery for brain tumor removal and/or who had a tumor located in the region of the foramen magnum were excluded from the larger parent study. For this analysis, data were gathered from participants diagnosed via surgical pathology with any benign skull base lesion, including pituitary adenomas, meningiomas, and Rathke cleft cysts.

Following Institutional Review Board approval, participants were recruited through the neurosurgery clinic at a Level 1 trauma center, which serves as a major referral source for western Pennsylvania, northern West Virginia, and eastern Ohio. Eligible participants were identified by clinic staff, and permission was obtained by the staff for research personnel to approach the participant. A member of the research team completed a screening enrollment form, explained the study, and obtained written consent. Data were collected via in-person assessments 1–2 days prior to surgical intervention.

Measures

Depressive Symptoms

Study participants completed the Center for Epidemiological Studies - Depression (CESD)-10,[20] a widely used, validated, and reliable instrument, especially for studies focusing on depressive symptoms in nonpsychiatric populations. Total CES-D-10 scores range from 0–30, with higher scores indicating higher levels of depressive symptoms.

Profile of Mood States-Short Form (POMS-SF)

The Tension/Anxiety subscale of the POMS-SF[21] was administered to assess anxiety. The internal consistency rating for the POMS-SF is 0.76–0.95. The correlation between the subscales and the total score in POMS and POMS-SF was calculated as 0.84. The shortened anxiety subscale of the POMS-SF scores range from 0–20, with higher scores indicating higher levels of anxiety.

Work Functioning

The purpose of the analysis was not to discern the impact of neuropsychological function on return to work but rather to evaluate person's limitations in performing specific tasks within a job. Neuropsychological dysfunction is often a "hidden" limitation, one that may not be readily apparent. However, the ability to perform tasks on the job is heavily dependent upon neuropsychological function, and thus work limitations are a more sensitive indicator of an employee's ability to be productive. Participants completed the Work Limitations Questionnaire (WLQ),[22] a 25-item self-report measure of work functioning. The WLQ has shown reliability and validity for use among several different job and chronic health condition groups. Reliability of the WLQ subscales is good, with Cronbach alphas ranging from 0.88 to 0.9. The validity of the WLQ is well established in the literature and ranges from 0.53 to 0.83. The WLQ questionnaire yields 4 subscale scores and a total score. Each WLQ subscale score reflects the percentage of time in the past 2 weeks that the respondent was limited in performing a specific dimension of his or her job (Time, Physical, Mental/ Interpersonal, and Output). The Time Management subscale addresses difficulty meeting a job's time and scheduling demands. The Physical Demands subscale refers to an individual's ability to perform job tasks that involve bodily strength, movement, endurance, coordination, and flexibility. The Mental/Interpersonal domain of the WLQ assesses both the difficulty performing cognitive job tasks or tasks involving the processing of sensory information as well as the problems a person encounters while interacting with people on the job. The Output subscale refers to difficulty meeting demands for quantity, quality, and timeliness of completed work. The WLQ Productivity Loss Score is based on a weighted sum of the 4 subscale scores and indicates the percentage decrement in work output due to health problems. The WLQ Productivity Loss Score expresses the estimated percent differences in output compared with employees who do not have health-related work limitations.

Neuropsychological Assessment

The reliability and validity of each of the neuropsychological tests administered have been well established in the literature. Several domains of neuropsychological function were assessed: learning and memory, attention and mental flexibility, executive function, psychomotor/speed, and language.

Learning and Memory

Auditory Verbal Learning Test

Administration of the Auditory Verbal Learning Test (AVLT)[23] includes 5 successive presentations of a list of 15 common words followed by free recall on each trial, an interference trial (presentation and recall of a list of 15 different words), postinterference recall of the words from the original list, and a delayed (30 min) recall. The AVLT test is used to assess immediate and delayed verbal learning and memory, memory acquisition, and retention.

Rey-Osterrieth Figure Test

The Rey-Osterrieth Figure Test (ROCF)[24] assesses visual perceptual, skills, spatial organization, constructional ability, and visual memory (immediate and delayed recall). Participants are instructed to carefully copy a figure and then to redraw the figure immediately after the figure is removed and again in ∼30 minutes (delayed recall).

Wechsler Memory Scale III, Logical Memory Subtest

With the Wechsler Memory Scale III (WMS-III), Logical Memory Subtest (LM I-II),[25] participants are read 2 short stories out loud and asked to retell the stories from memory immediately and after a 30 minute delay. Story A is read only once, whereas Story B is read twice. Participants are credited for each correctly recalled detail (maximum of 25) and for general themes (maximum Story A = 7, Story B = 8). The WMS-III assesses verbal learning and memory (short- and long-term), logical memory, and retention.

Attention and Mental Flexibility

Wechsler Adult Intelligence Scale III, Digit Symbol Coding Subtest

In the Digit Symbol Coding Subtest,[26] participants are presented with a key of symbols paired with numbers under which is a series of rows with randomly ordered numbers. Using the key, participants are instructed to draw the corresponding symbol under each number as fast as they can. The score is determined by the number of symbols correctly drawn within the 120 second time limit. This test assesses psychomotor response speed, visuomotor coordination, and attention.

Trail Making Test

Both Trail Making Tests (TMT A and B)[27] consist of 25 circles distributed across a sheet of paper. In Test A, circles are numbered from 1 to 25, and the participant is asked to draw lines connecting the numbers in ascending order. In Test B, the circles include both numbers (1–13) and letters (A-L). Similar to Test A, the participant is asked to connect the circles in ascending order, but with the additional task of alternating between letters and numbers (ie, 1-A-2-B-3-C, etc.). Participants are instructed to draw lines connecting the circles in order as quickly as possible for each test without lifting the pencil from the paper. The TMT scores reflect the total number of seconds it took to complete each trial. The TMT tests assess executive function, mental flexibility, and attention.

Executive Function

Stroop Color Word Test

With the Stroop Color Word Test,[28] participants are given a booklet with the colors blue, red, or green listed in random order in 5 columns of 20 colors. They are asked to read the colors out loud, going down each column as fast as they can. The test consists of 3 trials measuring the relative speed of a person's ability to read the names of colors (W), naming colors (C), and naming colors from words of colors printed with an incongruently colored ink. The Stroop Color Word Test is scored by reporting the number of colors read in 45 seconds for each trial and assesses executive functioning through inhibition and cognitive flexibility through interference.

Psychomotor/Speed

Grooved Peg Board Test

The Grooved Peg Board Test (GPT)[29] uses a metal board with rows of slotted holes angled in different directions. The task is to insert 25 metal pegs with ridges on the sides into each hole in sequential order. Participants are asked to do the first trial with their dominant hand, and then repeat the task with their non-dominant hand. The score is based on the time it takes to fill in all the holes and the number of pegs dropped for each trial; higher scores indicate poorer function. The Grooved Peg Board Test evaluates psychomotor speed, fine motor control, and visual-motor coordination.

Language

Controlled Oral Word Association Test F, A, S and Animal Naming

In the Controlled Oral Word Association Test (COWAT) F, A, S, and Animal Naming[30] test of verbal fluency, participants are instructed to orally generate as many words as they can, beginning with the letters F, A, and S, as well as name as many animals as they can in 60 seconds for each trial. The COWAT assesses executive function, auditory attention, short-term memory, cognitive flexibility, and vocabulary. The score is generated based on the total number of words produced in each trial.

Estimated General Intelligence

North American Adult Reading Test

The North American Adult Reading Test (NAART-R)[31] requires participants to read and pronounce a list of 61 irregularly spelled words (eg, debt, gauge, leviathan). It provides an excellent estimate of premorbid verbal intelligence, which has been shown to be resistant to the effects of acquired brain damage.

Analysis

There was a sample size calculation performed for the larger parent study; however, this pilot analysis used a subset of the larger study. Descriptive analyses were conducted to explore the frequency and distribution of the independent and dependent variables. To examine relationships between sociodemographic characteristics, estimated general intelligence, mood, neuropsychological domains, and work limitations in each WLQ subscale and total sum score, 2-tail *t* tests and Pearson correlations were conducted. Variables that reached statistical significance of $P < .10$ were included as potential predictor variables in the multiple linear regression model. Separate backward multiple linear regression analyses were conducted for each WLQ subscale and total sum score to model the impact of neuropsychological function on work productivity, controlling for general intelligence, depression, and anxiety scores. All analyses were performed using SPSS version 19.

Table 1. *Sociodemographic* characteristics of sample ($n = 45$)

Characteristic	Mean (SD) or *n* (%)
Years of education	15.05 (2.75)
Age (years)	43.4 (13.17)
Tumor volume(cc)*	4.27 (7.16)
Sex	
Male	17 (37.8%)
Female	28 (62.2%)
Race	
White	36 (87.8%)
Black	4 (9.8%)
Hispanic	1 (2.4%)
Tumor type	
Adenoma	32 (71.1%)
Meningioma	7 (15.6%)
Rathke's cleft cyst	6 (13.3%)
Job classification	
Managers	5 (11.1%)
Professionals	9 (20.0%)
Technicians and associate professionals	5 (11.1%)
Clerical support workers	9 (20.0%)
Service and sales workers	7 (15.6%)
Skilled agricultural, forestry, and fishery workers	1 (2.2%)
Craft and related-trades workers	4 (8.9%)
Plant and machine operators	2 (4.4%)
Elementary occupations	1 (2.2%)
Unemployed**	2 (4.4%)

*Resultafter removing one outlier.
**The participantquit work immediately before an expanded endonasal approach procedure.

Results

Approximately 75% of the patients approached agreed to participate in this study. A total of 45 participants were included in this analysis (see Table 1). Almost all participants had more than one symptom complaint prior to resection. More than 60% of participants reported headaches ($n = 27$), and more than 30% reported visual disturbances ($n = 14$). Other reported symptoms included endocrinopathies (acromegaly, Cushing's syndrome, and dysmenorrhea), sexual dysfunction (decreased libido, erectile dysfunction, and infertility), and mood disturbances (anxiety and depression). The majority of participants were white females with an average age of 43.1 years (SD = 13.17). The average number of years of formal education was 15.05, equivalent to some college education. Seventy-one percent of all participants' tumors were classified as adenomas with an average tumor volume of 4.27 cc. Categorizing participants' jobs according to the International Standard Classification of Occupations revealed that participants were most likely to be professionals or clerical support workers (40%, $n = 18$).[26]

Descriptive statistics for participants' performance on preoperative neuropsychological tests are reported in Table 2 as compared with mean and standard deviations found in population normative data.[25,32] Sample mean scores on neuropsychological tests were within one standard deviation of population normative values; thus, it was assumed that the sample's overall neuropsychological status did not significantly differ from that of the general population.

Descriptive statistics for participants' perception of work limitations (as measured by the WLQ questionnaire) can be found in Table 3. Overall, participants with skull base tumors reported the highest dysfunction in the time management subscale. The percentage of time in the past 2 weeks that participants were limited in performing time management skills was 27.09%. Difficulty meeting mental/interpersonal demands presented the second highest level of dysfunction in work functioning for participants, followed by difficulty meeting physical demands, and finally, difficulty meeting output demands. Calculations of total percent health-related work productivity loss yielded a mean productivity loss of 6.15% in participants with a skull base tumor.

Table 4 contains the results of the multiple linear regression analyses examining the relationship between domains of neuropsychological function and work limitations. The first subscale of the WLQ was time management. Greater difficulties with time management were predicted by poorer mental attention and flexibility ($\beta = -0.59$, $P = .01$) as measured by the Digit Symbol Coding task and higher depressive symptoms ($\beta = 3.42$, $P < .01$) as measured by the CES-D (total model $R^2 = 0.55$, $P < .01$).

Table 2. Comparison of sample neuropsychological test scores to normative data

Cognitive Domain	Neuropsychological Test	Expected Score (SD)*	Sample Mean (SD)
Verbal learning	AVLT learning slope (V-I)	5.8 (1.7)	**5.6** (1.5)
	Logical Memory learning slope (WMS-III)	5.0 (3.0)	**5.2** (2.7)
Verbal memory	AVLT delayed recall	10.2 (2.8)	**8.3** (2.6)
	Logical Memory total unit delayed recall (WMS-III)	24.0 (11.0)	**26.4** (7.1)
Logical memory	Logical Memory total theme delayed recall (WMS-III)	11.0 (3.0)	**12.1** (2.5)
Spatial organization	ROCF copy	34.4 (2.3)	**34.0** (2.2)
Constructional ability	ROCF recall	23.6 (6.9)	**20.0** (5.6)
Visual memory	ROCF delayed recall	23.1 (6.7)	**19.6** (4.9)
Executive function	TMT B time	64.6 (22.3)	**59.9** (17.7)
	Stroop color/word T-score	50 (10)	**47.0** (8.8)
Verbal fluency	COWAT total FAS	45.1 (11.2)	**39.0** (11.0)
	COWAT animal naming	23.0 (4.7)	**19.0** (5.7)
Psychomotor processing speed and visual-motor coordination	Digit Symbol Coding	75.0 (3.0)	**74.5** (16.6)
	GPT nondominant hand	72.9 (15.3)	**84.3** (23.6)

Abbreviations: AVLT, Auditory Verbal Learning Test; COWAT, Controlled Oral Word Association Test; GPT, Grooved Peg Test; ROCF, Rey-Osterrieth Figure Test; TMT, Trail Making Tests; WMS, Wechsler Memory Scale.
*Expected scores were obtained from the Wechsler Memory Scale: Third Edition Manual[25] and the Handbook of normative data for neuropsychological assessment.[32]

Table 3. Percent decrement in work functioning

Work domain	*n*	Mean (SD)
Time	45	27.09 (25.84)
Physical	42	25.07 (24.89)
Mental/Interpersonal	45	26.02 (27.54)
Output	44	19.79 (25.18)
Total	41	6.15 (5.89)

Difficulty meeting the physical demands of work was predicted by poorer visuospatial ability ($\beta = -3.30$ $P = .05$) as measured by the Rey Figure Copy task and higher depressive symptoms ($\beta = 2.29$, $P < .01$) (total model $R^2 = 0.29$, $P < .01$). Problems meeting the mental/interpersonal demands of work were associated with poorer verbal learning and memory ($\beta = -3.394$, $P = .04$) as measured the AVLT delay and higher depressive symptoms ($\beta = 3.246$, $P < .01$) (total model $R^2 = 0.47$, $P < .01$).

There were no significant associations between difficulty meeting output demands and performance on any neuropsychological measures that were administered.

The total percent of health-related loss of work productivity was calculated by a weighted summing of the 4 subscales of the WLQ (Time, Physical, Mental/Interpersonal, and Output). Lower learning and memory scores, specifically lower scores on AVLT learning delay test, significantly predicted total work productivity loss ($\beta = -0.72$, $P = .05$). Higher reports of depressive symptoms were also associated with greater loss of work productivity ($\beta = .66$, $P < .01$) (total model $R^2 = 0.43$, $P < .01$).

Discussion

Findings from this study revealed that certain neuropsychological tests may predict work limitations in patients with skull base tumors. It is worth noting that, although the sample mean was similar to that of the general population, slight individual differences could not be detected given the small sample size. A multivariate regression analysis revealed that neuropsychological tests were found to predict occupational functioning despite the overwhelming majority of persons included in this study who scored within published population normative values. Difficulties with tasks of mental attention and flexibility and learning and memory, as well as visuospatial dysfunction and higher depressive symptoms, were significantly associated with difficulty in one or more subscales of work life.

Subscales of work life represent various aspects of work productivity. Time management indicates the ability to handle scheduling, organizing, and prioritizing tasks to accomplish a goal. Measuring physical demands provides insight into whether a person is able to coordinate movement and has the strength and endurance to accomplish a task. Lower scores on the mental/interpersonal demands subscale indicate that a person has deficits in cognitively processing information and working with others in the occupational setting to accomplish a task. Finally, limitations in the output demands subscale indicate that a person's productivity is at risk, either from decreased quantity and/or quality of work. Neuropsychological functions that affect these areas of occupational productivity are described in the following sections.

Specifically, the Digit Symbol Coding Test (a measure of attention and mental flexibility) was useful for predicting difficulty with time management at work. Poorer performance on the Rey

Table 4. Neuropsychological predictors of work limitations

Domain	Test	β	SE	P
Time		$R^2 = 0.55$; Model $P < .01$		
	Digit Symbol Coding	−0.59	0.22	.01
	Depression (CES-D)	3.42	0.63	<.01
Physical		$R^2 = 0.29$; Model $P < .01$		
	Rey Figure Copy	−3.30	1.63	.05
	Depression (CES-D)	2.29	0.65	<.01
Mental/ Interpersonal		$R^2 = 0.47$; Model $P < .01$		
	AVLT learning delay	−3.39	1.56	.04
	Depression (CES-D)	3.25	0.68	<.01
Output*		$R^2 = 0.07$; Model $P = .10$		
	–	–	–	–
Total Work Loss		$R^2 = 0.43$; model $P < .01$		
	AVLT learning delay	−0.72	0.35	.05
	Depression (CES-D)	0.66	0.16	<.01

Abbreviations: AVLT, Auditory Verbal Learning Test; CES-D, Center for Epidemiological Studies – Depression.
*No neuropsychological tests were found to significantly predict difficulty in the Output domain of work functioning.

Figure Copy task, a measure of visuospatial ability, was a predictor for difficulties managing the physical demands associated with work. Poorer performance on the AVLT learning delay test predicted difficulty meeting the mental and interpersonal demands of work. As other studies have shown,[33,34] reports of greater number of depressive symptoms were highly correlated with difficulties meeting the time management, physical, and mental/interpersonal demands of work as well as the overall percent of health-related work productivity loss.

The Digit Symbol Coding test was developed to assess attention and mental flexibility under time pressure. The time management subscale of occupational functioning includes the ability to meet demands for quantity, quality, and timeliness of work completed; thus, it is not surprising that the results of this study found the Digit Symbol Coding test to be a predictor of time management in an occupational setting. The Rey Figure Copy Task is a test used to assess visuospatial ability and motor functioning. In this study, the Rey Figure Copy Task was found to be a predictor of difficulties meeting the physical demands of a person's occupation. The results of this study, which found that the AVLT predicted ability to meet mental/interpersonal demands, have been shown in other studies,[33,34] although in different populations such as patients who had experienced a traumatic brain injury and patients with primary brain tumors. In relation to interpersonal demands, a study of patients with traumatic brain injury reported that the AVLT predicted difficulty with social adaptation.[33] The association between AVLT and mental, or cognitive, impairment was also found in a study examining patients with primary brain tumors prior to intervention.[34] Consistent with findings from other studies, neuropsychological tests that assess visuospatial ability and psychomotor skills may be useful for predicting work dysfunction.

Previous studies have been conducted examining the influence of depression on work productivity. These studies, however, relied on the classification of patients as "depressed" or "nondepressed." The current study correlated their measure of self-reported depressive symptoms on the CES-D, although interestingly, very few of these patients actually met the criteria for being at risk for clinical depression. Past research in patients with pituitary adenomas has shown that these individuals have a higher incidence of mood disorders, including depression, than the general population.[35–37] Examining the scatter plot of CES-D scores, as it correlates with occupational difficulty (Fig. 1), revealed that many of the participants with skull base tumors showed decrements in neuropsychological functioning and difficulty completing occupational tasks beginning with a CES-D score of 10.

The clinical implications of this study include recognizing that patients with skull base tumors have the potential to experience altered neuropsychological function that may limit their ability to meet the demands of their occupation in one or more areas of work life. It is worth noting that 95% of participants remained employed ($n = 34$) and that 5% ($n = 2$) quit work immediately prior to surgery. Thus, although individuals may remain employed, assessment of individuals may be important to detect underperformance in particular areas of work functioning.

The potential for work limitations may be predictable using the individual's performance on specific neuropsychological tests. Specifically, difficulty on tests of attention and mental flexibility, learning and memory, visuospatial ability, and scoring higher than a 10 on the CES-D may indicate that the individual is more likely to experience work limitations. Careful screening of patients with skull base tumors may be able to help better identify those patients who are at particular risk for work limitations in order to intervene and ameliorate the distress or limitations they experience.

This study has shown that higher levels of depressive symptoms are consistently correlated with a decline in the ability to meet occupational demands. Brief screening tools for depressive symptoms are already implemented in many physician practices. Clinicians should recognize that the presence of depressive symptoms may predict occupational difficulties and should be prepared to discuss this with patients. Patients who undergo neuropsychological testing and exhibit difficulty in the visuospatial, attention

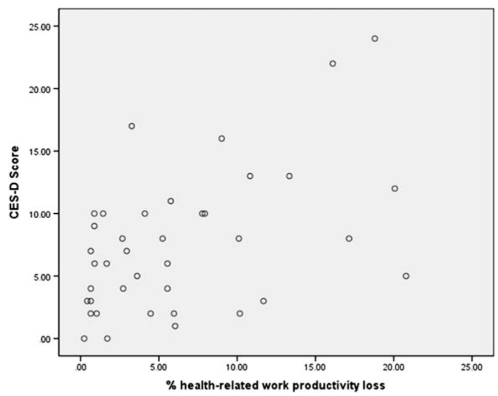

Fig. 1. Percent of health-related work productivity loss as a function of CES-D score. A scatterplot was generated to visualize each participant's percent of health-related work productivity loss as measured on the WLQ (X-axis) as a function of individual CES-D scores, which are a measure of depressive symptomatology (Y-axis). There appears to be a trend towards increased percent of work-productivity loss with higher levels of depressive symptoms.

and mental flexibility, or learning and memory domains should also be screened for difficulty meeting occupational demands. Any patients experiencing occupational dysfunction should then be referred for supportive or rehabilitative services in order to maintain the highest level of functioning possible.

The research implications of this study include recognizing that even mild reporting of depressive symptoms on the CES-D may help to identify patients at risk for difficulty meeting occupational demands. Findings from this study also raise questions as to whether or not patients with benign skull base tumors are able to maintain optimal occupational functioning. Further research should follow these patients longitudinally to assess the relationships between changes in neuropsychological and occupational functioning over time.

Limitations

The sample size was relatively small and largely homogenous in terms of race. A more diverse population may help verify whether these findings hold true for racially diverse groups and for all ages. This study also lacked a control group, so it is unclear how individuals with skull base tumors might differ in comparison with a group of healthy controls without a symptomatic skull base tumor. Patients' work status is self-reported, as is their functioning at work. Thus, patients' perceptions of their occupational functioning may differ significantly from their employers' perceptions or from objective measures of occupational functioning. Finally, a larger sample may help to detect any differences in occupational or neuropsychological dysfunction related to tumor type.

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APPENDIX B

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APPENDIX C

PRELIMINARY WORK MANUSCRIPT #2: CANCER AND COGNITIVE CHANGES THE COMPLEXITY OF THE PROBLEM

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Cancer and Cognitive Changes: The Complexity of the Problem

Catherine M. Bender and Bethany D. Thelen

Objectives: *To describe the factors that influence cognitive function in the context of cancer and cancer therapy, and to illustrate the complex nature of the problem.*

Data Sources: *Peer-reviewed literature.*

Conclusion: *Multiple factors contribute to changes in cognitive function in this population, including demographic, psychological, and physiological factors, the disease itself, disease- and treatment-related symptoms, and the management of those symptoms.*

Implications for Nursing Practice: *Nurses' recognition of the multiple factors that may influence cognitive function in patients with cancer should guide appropriate patient assessment. Appreciation of the complex basis of the changes in cognitive function in patients with cancer can provide direction for the appropriate management of the problem.*

Key Words: *Cognitive function, cancer, cancer therapy, symptoms, depression*

COGNITIVE function is a higher order mental process that involves the capacity to process information, necessitating integrated action of numerous areas of the brain.[1] Cognitive function encompasses multiple domains including attention, learning and memory, executive function, psychomotor efficiency, mental flexibility, visuospatial ability, and language. These domains are highly interrelated so that impairment in one domain can have a deleterious effect on the function of other cognitive domains. Cognitive function is assessed objectively with batteries of neuropsychological measures that provide domain-specific information. Perceived cognitive function also can be assessed with self-report measures. Demographic characteristics such as age, gender, and

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years of education, as well as psychological factors including anxiety and depression, influence cognitive function in adults. In addition, changes in hormone levels that normally occur over the course of one's life, as well as medications taken to manage other health problems such as hypertension, also may influence cognitive function.[2]

Abundant evidence exists for changes in cognitive function in patients with cancer.[3-7] Most patients with cancer do not meet criteria for impairments in cognitive function[8]; rather, they experience more subtle deterioration in function that can impact daily functioning and quality of life.[3] Multiple factors contribute to changes in cognitive function experienced by patients with cancer including: demographic, psychological, and physiological factors, cancer therapy, the disease itself, disease- and treatment-related symptoms, and the management of those symptoms (Table 1).[9] The purpose of this article is to discuss the factors that influence cognitive function in the context of cancer and cancer therapy to illustrate the complex nature of this problem. The physiological bases for this problem are described elsewhere.[10]

Factors Influencing Cognitive Function

Demographic Factors

In general, higher levels of cognitive function are associated with greater years of education and higher general intelligence in adults.[11] Declines in cognitive function are associated with advancing age.[11] Differences in cognitive function also may be based on gender. Gender differences in the level of functioning of specific domains of cognitive function include female superiority in verbal fluency and articulation, perceptual speed and accuracy, and fine distal motor movements.[11] Male superiority has been demonstrated in spatial rotation and manipulation and mathematical reasoning.[12] These differences may be a consequence of the influences of the prenatal hormonal environment on neuronal connectivity.[13,14] No gender differences exist for general intelligence.[15] Several factors that increase the risk for deterioration in cognitive function include advancing age, lower IQ, a history of neurological or psychiatric illness or developmental disorders, a history of substance abuse, and prior cancer therapy.[16]

Psychological Factors

Depression and anxiety are related to poorer cognitive function in adults.[17] Individuals who meet formal diagnostic criteria for depression and anxiety are at risk for cognitive impairment, particularly with advancing age.[18] Prevalence of major depressive disorder is estimated to be approximately 11% in patients with cancer, as compared with 5% in the general population, although rates may vary depending on cancer type.[19] The prevalence of anxiety disorders in cancer patients is 9.8%.[20] However, symptomatology without meeting the Diagnostic and Statistical Manual of Mental Disorder (DSM IV) criteria for depression and anxiety is not associated with cognitive impairment but may be related to the perceived cognitive problems reported by patients with cancer.[21,22]

Cancer Therapy- and Cancer-Related Factors

Nearly all types of therapy for cancer have been associated with deterioration in cognitive function in patients with cancer, including both systemic

TABLE 1.
Factors that Influence Cognitive Function in Patients with Cancer

Demographic	Psychological	Cancer therapy and cancer-related factors	Disease- and treatment-related symptoms
Years of education	Depression	Systemic therapies (ie, chemotherapy, hormonal therapy, biotherapy)	Anemia
General intelligence	Anxiety	Local therapies (ie, radiation therapy and surgery)	Fatigue
Age		Dose and duration of therapy	Pain
Gender		Concurrent therapies	Sleep disturbances
History of:		Direct delivery to central nervous system	
Neuropsychological disorder			
Psychiatric illness			
Developmental disorders			
Substance abuse			
Prior cancer therapy			

(chemotherapy, hormonal therapy, and biotherapy) and local (radiation therapy and surgery) treatments. The risk for decline in cognitive function with cancer therapy increases with higher doses of therapy, longer duration of therapy, concurrent chemoradiation or chemotherapy administered after radiation to the brain, and therapy delivered directly to the central nervous system.[16] Existing evidence also suggests that priming patients with information about the potential for decline in cognitive function with therapy is associated with greater likelihood of self-reporting such problems.[23]

Deterioration in cognitive function has been associated with chemotherapy in multiple populations of adults with cancer,[3,24,25] including women with breast[3,6,24] and ovarian cancer,[26] men with testicular cancer,[27] and adults with non-small cell lung cancer[28] and primary malignant brain tumors.[29] Cognitive domains found to deteriorate with chemotherapy include attention, learning and memory, psychomotor efficiency, and executive function.[30] Hormonal therapy also has been associated with deterioration in cognitive function in both men and women. In women with breast cancer receiving hormonal therapy, deficits in verbal[4,31-34] and visual memory,[4,32,35] psychomotor speed,[33-36] visuospatial ability,[32,35] and executive functioning[35,36] have been reported. Deteriorations in attention, learning and memory, executive functioning, and visuospatial ability also have been observed with androgen deprivation therapy in men with prostate cancer.[37-40] Although less well-documented, deterioration in cognitive function also has been associated with biotherapy agents such as interferon therapy.[41,42]

Radiation therapy administered to the brain has been associated with cognitive dysfunction in both adults and children. Most of this research has involved patients with primary malignant brain tumors, but these relationships also have been documented in patients with metastatic brain lesions from primary breast and non-small cell lung cancers, and from cancer of the head and neck. Deterioration in learning and memory, executive functioning, psychomotor efficiency, and verbal ability have been associated with radiation therapy.[43-46]

Surgery and anesthesia may contribute to poorer cognitive function in women with breast cancer. Of the few investigations of cognitive function related to cancer surgery, Cimprich found poorer "capacity to direct attention" in women with breast cancer 15 days after breast-conserving surgery or mastectomy.[47] Poorer capacity to direct attention was associated with greater extent of breast cancer surgery and older age, particularly in women ages 65 to 79 years.[47] Poorer post-surgery cognitive function in non-cancer populations is predicted by older age,[48] use of general anesthesia,[49] and poorer physical status, according to the American Society of Anesthesiologists.[48,50] More research is needed to examine the effect of surgery and anesthesia on cognitive function in patients with cancer. This need is particularly relevant because some patients with cancer exhibit poorer cognitive function before the initiation of systemic cancer therapy.

Results from several longitudinal studies of cognitive function associated with cancer therapy that included pretreatment assessments revealed that some adults with cancer have poorer cognitive function before the initiation of systemic adjuvant therapy compared with healthy individuals.[7,8,24,51] Poorer pretreatment cognitive function has been observed in patients with breast,[8,24] prostate,[51] and lung cancer.[52] Several factors may contribute to pretreatment changes in cognitive function, including psychological (depression or anxiety), persistent effects of general anesthesia following primary surgery, and disease-related factors such as extent of disease. Factors that increase one's risk for the development of cancer, such as low-efficiency efflux pumps, deficits in DNA repair mechanisms and/or a deregulated immune response also may contribute to changes in cognitive function that are present before the initiation of therapy.[53] Moreover, the capacity to repair DNA and protect against oxidative stress is variable in the general population and this variability may inform the differences in cognitive function noted in women with breast cancer.[53]

Disease- and Treatment-Related Symptoms

A variety of symptoms related to cancer and cancer-treatment may be associated with poorer cognitive function. Strategies to manage these symptoms, particularly pharmacologic management, also may influence cognitive function in patients with cancer. Disease- and treatment-related symptoms such as anemia, fatigue, and pain illustrate this association.

Anemia can damage any tissue or organ and cognitive dysfunction and neurological injury have been reported in cases of severe anemia, indicating that the brain is susceptible to anemia-induced injury.[54] More than 30% of patients with cancer experience anemia with a greater incidence in certain types of cancer treatments and progressive disease. [55] The causes of anemia include infiltration of bone marrow by malignant cells, altered hemoglobin production related to radiation or chemotherapy treatments, iron deficiency, or low endogenous erythropoietin levels.[56] Cancer and treatment-related risk factors especially associated with anemia include certain tumor types, myelosuppressive chemotherapy or radiation therapy, platinum-based chemotherapies, and low hemoglobin levels before initiation of treatment.[56]

Thirty-six percent of colorectal cancer patients reported cognitive problems before initiation of chemotherapy, and 52% of these patients reported experiencing fatigue.[57] Cella et al[58] reported that anemic patients with cancer reported significantly higher levels of fatigue than non-anemic patients with the disease who, in turn, reported significantly higher levels of fatigue than the non-cancer population. Thus, although anemia is a factor that may contribute to high levels of fatigue, it is not the only factor that contributes to the development of this symptom. Other factors related to the incidence and severity of fatigue in patients with cancer include body mass index, clinical stage, menopausal status, duration of endocrine therapy, physical activity, and diet.[59]

Pain frequently accompanies cancer, particularly in advanced disease, as well as specific cancer therapies. Results from a meta-analysis showed that greater than 50% of patients with cancer (across disease types and stages) reported experiencing pain.[60] A review by Moriarty et al[61] revealed that individuals experiencing pain showed poorer cognitive functioning in the domains of attention, learning and memory, processing speed, and executive functioning compared with those not experiencing pain. While the mechanistic relationship of pain and cognitive function is unclear, some have suggested brain morphologic or electrophysiological alterations may mediate this relationship.[61] In addition, use of some analgesic agents is associated with poorer cognitive function in patients with cancer.[61]

Sleep disturbances are commonly experienced by cancer survivors.[62] Increasing age, irregular sleep/wake schedules, depression, anxiety, symptoms (ie, pain, fatigue, nausea and vomiting), changes in hormone and cytokine secretion, cancer therapies, and medications such as analgesics, antidepressants, antiemetics, anxiolytics, and corticosteroids contribute to sleep disturbances in patients with cancer. Disease-related factors also may play a role in disrupting sleep through altered circadian rhythms and the HPA axis regulatory processes before therapy.[63] In the general population, deteriorations in cognitive function are associated with sleep disturbances; experimental studies have revealed that sleep disruption impairs psychomotor vigilance and learning and memory.[64-66] Results from a study of adult survivors of childhood cancer showed that even many years after diagnosis and therapy, survivors are significantly more likely than siblings to report poor sleep quality and score poorer on neurocognitive functioning tests.[67]

Conclusion

More research is needed to explicate the complex bases for the changes in cognitive function experienced by patients with cancer. Some have suggested that the term "chemobrain" leads health care providers to underestimate the complex nature of this problem[68] and may limit the scope of their assessment of the potential factors that may influence changes in cognitive function in patients with cancer. Nurses must appreciate the multiple factors that influence cognitive function in patients with cancer to guide the assessment and management of the problem.

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APPENDIX E

IRB APPROVAL LETTERS FOR PILOT STUDY (PRO12050659)

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Bethany Thelen

From: Christopher Ryan, PhD, Vice Chair

Date: 7/24/2012

IRB#: PRO12050659

Subject: Psychosocial Development of Survivors of Adolescent Cancer

---

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under: 45 CFR 46.110.(5)(7).

The IRB has determined the level of risk to be minimal.

Approval Date: 7/23/2012
Expiration Date: 7/22/2013

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

University of Pittsburgh
Institutional Review Board
3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To:	Bethany Thelen
From:	Christopher Ryan, PhD, Vice Chair
Date:	6/11/2013
IRB#:	REN13060059 / PRO12050659
Subject:	Psychosocial Development of Survivors of Adolescent Cancer

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under: 45 CFR 46.110.(5)(7).

Please note the following information:

Approval Date:	6/11/2013
Expiration Date:	6/10/2014

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

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Memorandum

To:	Bethany Thelen
From:	Christopher Ryan, PhD, Vice Chair
Date:	5/1/2014
IRB#:	REN14040270 / PRO12050659
Subject:	Psychosocial Development of Survivors of Adolescent Cancer

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under: 45 CFR 46.110.(5).

Please note the following information:

Approval Date:	5/1/2014
Expiration Date:	4/30/2015

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The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

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Memorandum

To:	Bethany Nugent
From:	IRB Office
Date:	2/24/2015
IRB#:	REN15020056 / PRO12050659
Subject:	Psychosocial Development of Survivors of Adolescent Cancer

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:
45 CFR 46.110.(5)
45 CFR 46.110.(7)

Please note the following information:

Approval Date:	2/24/2015
Expiration Date:	2/23/2018

This approval is for analysis of data only.

This study meets the criteria for an extended approval period of three years. In the event that any type of federal funding is obtained during this interval, a modification must be submitted immediately so the IRB can reassess the approval period.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX F

ABSTRACT PRESENTED AS PODIUM PRESENTATION AT ONCOLOGY NURSING SOCIETY (ONS) CONFERECE 2013

Perception of Trauma in Young Adult Survivors of Adolescent Cancer: A Pilot Study

Bethany Thelen, BSN, RN[1] Jean M. Tersak, MD[2], and Margaret Rosenzweig PhD, CRNP-C, AOCN[1]

[1]University of Pittsburgh School of Nursing
[2]Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center

Objective: Describe the perception of trauma (Posttraumatic Stress and Posttraumatic Growth) in young adult survivors of adolescent cancer.

Significance & Purpose: Studies have reported higher levels of posttraumatic stress (PTS) in cancer survivors than healthy controls while others, however, have reported the occurrence of posttraumatic growth (PTG). Traditionally it has been assumed that the experience was either negative (PTS) or positive (PTG) and not able to occur concurrently. Thus, the purpose of this pilot study was to examine young adult survivors of adolescent cancer's perception of cancer as trauma.

Methods & Analysis: A cross-sectional descriptive pilot study is underway to explore young adult survivors of cancer's perception of cancer as trauma. Survivors of adolescent cancer are recruited from a large pediatric hospital's outpatient Hematology/Oncology clinic. Participants must be diagnosed with cancer between the ages of 15 and 21, are two or more years after completion of cancer therapy, and have no evidence of disease recurrence. PTS is assessed using the reliable and valid Posttraumatic CheckList- Civilian Version (PCL-C) and PTG using the Posttraumatic Growth Inventory (PTGI). Descriptive statistics were conducted to characterize the incidence of PTS and PTG in this sample, and means, standard deviations, and scatterplots will be reported on the complete sample.

Findings & Interpretations: To date, 4 subjects of planned sample of 10 have been enrolled. Symptoms of PTSD (M=29.50, SD=8.69) were reported in addition to areas of PTG (M=68.50, SD=7.37). The most commonly reported PTS symptom is persistent avoidance (M= 12.00, SD=3.16). The most commonly reported areas of PTG are Relating to Others (M=26.75, SD=1.71) and Appreciation for Life (M=11.00, SD=2.16).

Discussion & Implications: Early preliminary data indicates the presence of PTS as well as areas of PTG suggesting that the two may co-occur. The cancer experience may trigger perceptions of personal growth, even with concurrent reports of distress associated with the cancer experience. We project a sample size of 10 participants to be included and presented in the analysis. This pilot study will provide critical information to design larger studies examining PTS and PTG in survivors of adolescent cancer. Advancing the knowledge of developmentally appropriate psychosocial care in this subpopulation of survivors warrants further attention in the literature.

APPENDIX G

ABSTRACT PRESENTED AS PODIUM PRESENTATION AT COUNCIL FOR THE ADVANCEMENT OF NURSING SCIENCE (CANS) IN 2014

Posttraumatic Responses in Young Adult Survivors of Adolescent Cancer: A Pilot Study

Bethany Thelen, BSN, RN[1] Jean M. Tersak, MD[2], Aimee Costello, RN, MSN, PPCNP-BC[2] and Margaret Rosenzweig PhD, CRNP-C, AOCN[1]

[1]University of Pittsburgh School of Nursing
[2]Children's Hospital of Pittsburgh of UPMC

Aims: High levels of posttraumatic stress (PTS) or posttraumatic growth (PTG) are reported in cancer survivors, though incidence and contributing factors have not been explored. Specific cancer types may influence this experience. This study aims to: 1) Describe incidence of Posttraumatic Stress and Posttraumatic Growth in young adult survivors of adolescent cancer; and 2) Explore differences in levels of Posttraumatic Stress and Posttraumatic Growth between survivors of leukemia versus lymphoma.

Methods: A cross-sectional descriptive pilot study was conducted. Participants (N=12) were diagnosed with leukemia (n=5) or lymphoma (n=7) between ages 15 and 21, were 2+ years after completion of therapy, without recurrence. PTS was assessed using the Posttraumatic CheckList- Civilian Version (PCL-C) and PTG using the Posttraumatic Growth Inventory (PTGI). Analysis included descriptive statistics and an independent samples t-test.

Results: Symptoms of PTS (M=25.25, SD=9.78) and PTG (M=55.67, SD=25.50) were reported. Adult survivors of leukemia reported significantly greater Avoidant PTS symptoms (t(10)=1.48, p=.043), Hyper-arousal PTS symptoms (t(10)=1.30, p<.001), and overall levels of PTS (t(10)=1.25, p=.012) than did survivors of lymphoma.

Conclusions: Findings suggest PTS and PTG may co-occur in young adult survivors of adolescent cancer. Moreover, survivors of leukemia experienced significantly more Avoidant and Hyper-arousal symptoms of PTS, as well as total levels of PTS than survivors of lymphoma. Larger studies examining PTS and PTG in survivors of adolescent cancer are needed to elucidate potential predictors, including disease, treatment, and aspects of the cancer experience, and develop interventions which would maximize PTG and minimize PTS.

APPENDIX H

DISSERTATION MANUSCRIPT #1
THE ASSOCIATION BETWEEN PRE-TREATMENT OCCUPATIONAL SKILL LEVEL AND MOOD AND SYMPTOM BURDERN IN EARLY-STAGE, POSTEMENOPAUSAL BREAST CANCER SURVIVORS DURING THE FIRST YEAR OF ANASTRAZOLE THERAPY

Support Care Cancer
DOI 10.1007/s00520-016-3161-y

ORIGINAL ARTICLE

The association between pre-treatment occupational skill level and mood and symptom burden in early-stage, postmenopausal breast cancer survivors during the first year of anastrozole therapy

Bethany D. Nugent[1] · Susan M. Sereika[1] · Margaret Rosenzweig[1] · Michael McCue[2] · John D. Merriman[1] · Catherine M. Bender[1]

Received: 4 November 2015 / Accepted: 7 March 2016

Abstract
Purpose Previous research has explored occupational activity of breast cancer survivors but has not examined the influence of occupational level on symptoms prospectively. The purpose of this study was to examine the relationship between occupational classification and changes in mood and symptom burden for postmenopausal breast cancer survivors during the first year of anastrozole therapy.
Methods This was an exploratory secondary analysis in 49 postmenopausal women receiving anastrozole therapy for early-stage breast cancer. Participants reported their occupation at baseline and completed self-report questionnaires measuring mood and symptom burden at baseline, 6 months, and 12 months. Occupation was classified according to four major skill levels delineated by the International Standard Classification of Occupations (ISCO).
Results Breast cancer survivors employed at occupational skill levels 1 through 3 reported significantly higher depressive symptoms, fatigue, and total symptoms on average than those employed at ISCO skill level 4. After adjusting for multiple comparisons, this pattern remained for the musculoskeletal, vasomotor, and gastrointestinal symptom subscales.
Conclusions Breast cancer survivors employed at lower skill levels (i.e., ISCO 1–3) reported poorer mood and greater symptom burden than breast cancer survivors employed at a higher skill level (i.e., ISCO 4). Assessing baseline occupation of occupationally active breast cancer survivors may improve understanding of the association between types of occupations and mood and symptom trajectories and may inform development of interventions to mitigate symptom severity in order to help breast cancer survivors maintain optimal occupational function and adherence to therapy.

Keywords Occupational skill · Employment · Cognitive function · Breast cancer survivors · Anastrozole therapy

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2 School of Health & Rehabilitation Sciences, University of Pittsburgh, 4028 Forbes Tower, Pittsburgh, PA 15260, USA

Introduction

Returning to and sustaining employment for cancer survivors is challenging indeed; approximately 40 % of all cancer survivors never return to work [1]. Of cancer survivors who remain working, up to 13 % stop working within 4 years of diagnosis [2]. Three main categories of factors influence cancer survivors' ability to return to work and maintain pre-diagnosis occupational roles: disease- and treatment-related factors (e.g., cancer site, disease stage, treatment, symptoms), work-related factors (e.g., workload, job demands, social climate, employer support), and person-related factors (e.g., age, gender, education level) [1, 3, 4]. Disease- and treatment-related symptoms may influence the ability of cancer survivors to return to work, maintain pre-diagnosis levels of work productivity, and advance in careers. Disability and unemployment in cancer survivors result in lost potential and tremendous personal and societal costs. Few studies have examined the relationship between disease and treatment symptoms and the ability to maintain occupational roles, and no studies to date have examined this relationship in postmenopausal women during aromatase inhibitor (AI) therapy for early-

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stage breast cancer. Understanding the relationship between work-related factors and symptoms is crucial in preventing work disability, maintaining occupational roles, and achieving career potential.

Annually, over 100,000 postmenopausal women in the USA are diagnosed with estrogen receptor-positive breast cancer, the most common breast cancer diagnosis [5]. This type of cancer is commonly treated with AI, an endocrine therapy prescribed after initial surgery and taken daily for 5 or more years; since AI are taken orally and often without concurrent chemotherapy, many maintain occupational roles during treatment. Thus, breast cancer survivors receiving AI are an ideal cohort to study when examining factors that may influence the symptom experience and maintenance of occupational roles throughout active cancer treatment.

Aromatase inhibitors have side effects including changes in mood, cognitive complaints, dyspareunia, diarrhea, gynecological complaints, hot flashes, arthralgia, and musculoskeletal difficulties including osteopenia and fractures [6–8]. These symptoms are not usually severe enough to be dose-limiting but may be bothersome and affect employment. In the general population, mood disorders (e.g., anxiety, depression) are a major cause of loss in work productivity [9]. Fatigue is an independent predictor of a cancer survivors' ability to return to work [4]. The relationship between disease- and treatment-related symptoms and women's occupational role may depend on each woman's day-to-day activities. The International Standardized Classification of Occupations (ISCO) has grouped occupations into four skill levels based on the general physical and cognitive requirements associated with occupational role [10].

Work-related factors are complex and multifactorial. However, evaluation of job classification and the accompanying tasks involved is an important step in clearly understanding which cancer survivors may have greatest difficulty in maintaining occupational roles. Studies examining employment rarely take into consideration how cancer and its treatment may interfere with a survivor's ability to perform certain job tasks. One study examining job tasks in men with prostate cancer found increased difficulty in maintaining occupational roles particularly when the jobs involved highly physical tasks [11]. Difficulty concentrating and learning new things were also associated with maintenance of occupational roles [11].

Previous studies of breast cancer survivors who maintained occupational roles found that they experienced greater age-adjusted work limitations than non-cancer controls; moreover, these limitations were predicted by fatigue level [12] and patient-reported cognitive limitations at work [13]. No study prospectively examined the role of symptoms in maintenance of occupational roles for breast cancer survivors. This study's aims were to (1) examine differences in changes in mood (depressive symptoms and anxiety) for breast cancer survivors during the first year of AI therapy between occupational classifications (skill level 4 versus skill levels 1–3) before therapy and (2) examine differences in changes in reported symptom burden during the first year of AI therapy between those employed at skill level 4 and those employed at lower skill levels (skill levels 1–3) before therapy.

Methods

This study was part of a larger longitudinal study, approved by the University of Pittsburgh Institutional Review Board, and examines cognitive function in postmenopausal women with early-stage breast cancer receiving AI therapy (R01 CA107408). Informed consent was obtained from all individual participants included in the study. Recruitment occurred between 2005 and 2012 through the University of Pittsburgh Cancer Institute Magee Women's Breast Cancer Program. The parent study assessed cognitive function at baseline (pre-AI therapy) and at 6 and 12 months after therapy initiation. Data for the current study are drawn from the baseline, 6-month, and 12-month assessments.

Participants

Parent study inclusion criteria were women who were postmenopausal with breast cancer stages I–IIIa, post-surgery, age ≤75 years, able to speak and read English, educated for ≥8 years, without history of neurological illness or previous cancer (except non-melanoma skin cancer), not currently receiving hormone replacement therapy, and not hospitalized for psychiatric illness within 2 years. The subset of women considered for inclusion in this secondary analysis received AI without chemotherapy ($n = 158$) and had completed symptom questionnaires at baseline (i.e., pre-AI therapy) and at 6 and 12 months post-AI initiation. They also reported at baseline that they were currently employed outside the home. After applying these criteria, 49 women were included in our analysis.

Instruments

Demographic and clinical characteristics

Participants completed a demographic questionnaire at baseline, which assessed age, race, marital status, education, employment, and occupation. Clinical characteristics were collected and verified using medical records.

Occupational classification

Participants reported their occupation on a baseline demographic questionnaire, which was re-coded using the ISCO [14] skill level, which formed fewer, more homogenous groups in terms of the tasks/skills required. This allowed for simpler and meaningful comparisons across skill groupings. The ISCO has four distinct occupational skill levels.

Skill level 1. Skill level 1 [14] occupations typically involve performance of simple and routine physical or manual tasks and may require physical strength and/or endurance. Some skill level 1 jobs require basic literacy or numeracy, but this is not a major component of the work. Examples of skill level 1 occupations include cleaners, freight handlers, garden laborers, and kitchen assistants.

Skill level 2. Skill level 2 [14] occupations typically involve performance of tasks such as operating machinery/equipment, driving vehicles, maintenance of electrical and mechanical equipment, and manipulation, ordering, and storage of information. Many skill level 2 occupations require relatively advanced literacy and numeracy, good interpersonal communication, and a high level of dexterity. Examples of skill level 2 occupations include butchers, bus drivers, secretaries, clerks, sales assistants, police officers, hairdressers, electricians, and mechanics.

Skill level 3. Skill level 3 [14] occupations typically involve performance of complex technical and practical tasks using extensive factual, technical, and procedural knowledge in a specialized field. Skill level 3 occupations generally require a high level of literacy and numeracy and well-developed communication skills, including the ability to understand complex written material, prepare reports, and communicate with distressed individuals. Examples of skill level 3 occupations include managers, laboratory technicians, legal secretaries, commercial sales representatives, and computer technicians.

Skill level 4. Skill level 4 occupations typically involve performance of tasks requiring complex problem solving and decision-making based on extensive theoretical and factual knowledge in a specialized field. Occupations at skill level 4 generally require advanced literacy and numeracy and excellent communication skills, including the ability to understand complex written material and communicate complex ideas in writing and orally. Examples of skill level 4 occupations include sales managers, engineers, secondary education teachers, doctors, nurses, and computer system analysts.

For this analysis, skill levels 1 to 3 were considered as one group due to sample distribution and compared to skill level 4. Higher skill levels involve greater complexity and range of tasks. Skill level 4 occupations typically necessitate, at minimum, a bachelor's degree, while lower skill level occupations often require an associate's degree, vocational training, or high school education. Individuals with at least bachelor's degrees generally have occupations requiring higher skill level [10]; thus, women in occupational roles that require skill level 4 may experience different difficulties than breast cancer survivors in lower skill level occupations, given the complexity required to maintain these occupational roles.

Depressive symptoms

Symptoms of depression were assessed using the Beck Depression Inventory-II (BDI-II) [15], a 21-item Likert scale questionnaire measuring affective and somatic depressive symptoms. Total scores range from 0 to 63, with higher scores indicating greater depressive symptoms. The BDI-II has high internal consistency (Cronbach's alpha = 0.91) [16] and 1-week test-retest reliability (Pearson's $r = 0.93$) [15], indicating that it is not overly sensitive to daily mood variations.

Anxiety

Anxiety symptoms were measured using the Profile of Mood States-Short Form (POMS-SF) tension-anxiety subscale, which has good internal consistency (Cronbach's alpha = 0.80) and product moment correlation (Pearson's $r = 0.85$) in a sample of breast cancer patients [17]. The tension-anxiety subscale consists of nine items with total subscale scores ranging from 0 to 36, with higher scores indicating greater anxiety.

Fatigue

Fatigue was measured using the POMS-SF fatigue-inertia subscale, which has been used to measure fatigue in cancer patients with excellent internal consistency (Cronbach's alpha = 0.89) [17], 48-h test-retest reliability (Pearson's $r = 0.74$), and construct validity demonstrated through interinstrument correlational analysis with other subscales of the POMS-SF explaining 83 % of the variance in responses [18]. The fatigue-inertia subscale consists of seven items with total subscale scores ranging from 0 to 28, with higher scores indicating greater fatigue.

Symptom experience

Symptom burden was measured using the 42-item Breast Cancer Prevention Trial (BCPT) checklist [19, 20], which measures symptoms during breast cancer treatment [20]. There are eight subscales, each representing a clinically relevant cluster of symptoms, cognitive, musculoskeletal, vasomotor, nausea, vaginal, sexual, bladder, and body image. Total scores on the BCPT range from 0 (no symptoms) to 168 (extremely bothersome symptoms). The BCPT subscales demonstrated adequate internal consistency (Cronbach's alpha greater than 0.70), except the gastrointestinal symptoms (Cronbach's alpha = 0.624), dyspareunia (Cronbach's alpha = 0.618), weight problems (Cronbach's alpha = 0.616), and gynecological symptoms (Cronbach's alpha = 0.557). To be included in the analysis, women had to have answered at least 80 % of the items that made up each score.

Data analysis

Standard descriptive statistics and frequency distributions were generated to characterize the total sample as well as the two skill level groups. We assessed for differences in demographic and clinical characteristics between the skill level groups using two-sample *t* tests for continuous variables and Fisher's exact tests for categorical variables. To test the aims of the study, we used a repeated measures multivariate analysis of covariance (RM-MANCOVA). The assumptions for homogeneity of group variance-covariance matrices were not satisfied for age and years of education. The assumptions of normality of residuals were met for all independent variables in our model except for years of education, but RM-MANCOVA is robust against violations of normality. To improve the distribution of residuals, we considered the applications of the square root and log base 10 transformations to the data. Analyses using transformed data did not change the conclusions drawn; thus, we reported results from untransformed data in their original scaling.

We conducted a RM-MANCOVA to examine relationships between occupational skill level and mood (i.e., scores for BDI-II, POMS tension-anxiety subscale) at baseline, 6 months, and 12 months, after controlling for years of education as a covariate in the model since this was significantly different between the skill level groupings. We examined polynomial contrasts and added a covariate, age, for the analysis of depressive symptoms [21]. Assumptions of the RM-MANCOVA method (i.e., normality, linearity, sphericity, homogeneity of regression slopes, and reliable measurement of the covariate) [22] were met for dependent variables in the model. To protect against inflation of type I error when looking at multiple dependent variables, we first examined the results of multivariate tests, and only if the multivariate test was statistically significant did we proceed to look at results of the univariate tests to see which variables, more specifically, demonstrated statistical significance. For aim 2, we used a RM-MANCOVA to examine changes over time in reported symptom burden overall as well as by specific symptom domains by those employed at skill level 4 and those employed at skill levels 1–3. Partial eta-square values were calculated as a measure of effect size for group mean differences. Two-sided hypothesis testing was conducted at the 0.05 significance level using IBM® SPSS® Statistics, version 22.0 (IBM Corp., Armonk, NY).

Results

Participant characteristics

Table 1 summarizes participant characteristics by skill level grouping. Approximately 59 % of the samples were employed

Table 1 Demographic and clinical characteristics at baseline by occupational group (n = 49)

Characteristic	Skill levels 1–3, n = 20 (40.8 %)	Skill level 4, n = 29 (59.2 %)	Test statistics	p value
	Mean (SD)	Mean (SD)		
Age (years)	59.2 (1.7)	58.2 (0.8)	t = 0.54	0.631
Education (years)	13.0 (0.4)	17.0 (0.6)	t = 5.18	<.001
Weeks since diagnosis (n = 48)	8.9 (0.8)	8.6 (0.8)	t = 0.23	.815
Weeks since first surgery	5.0 (0.5)	5.1 (0.6)	t = 0.14	.888
	Percent (n)	Percent (n)		
Married or partnered (yes)	45.0 (9)	72.4 (21)	–	.075[a]
White (yes)	100.0 (20)	100.0 (29)	–	1.000[a]
Natural menopause (yes)	70.0 (14)	86.2 (25)	–	.133[a]
HRT-ever (yes)	50.0 (10)	51.7 (15)	–	.568[a]
Mastectomy (versus BCS) (n = 47)	10.5 (2)	17.9 (5)	–	.685[a]
Radiation therapy (yes) (n = 46)	84.2 (16)	92.6 (25)	–	.635[a]
Stage of disease				
I	90.0 (18)	89.7 (26)	–	.486[a]
IIa	10.0 (2)	3.4 (1)	–	–
IIb	0.0 (0)	6.9 (2)	–	–

SD standard deviation, *HRT* hormone replacement therapy, *BCS* breast-conserving surgery

[a] Fisher's exact test

at skill level 4, while the rest were employed at skill levels 1 through 3. As expected, women employed in occupations at skill level 4 had significantly more education ($p < .001$) than women employed in lower skill level occupations. Thus, years of education was included as a covariate in our model. No other significant differences between occupational skill groups were found.

Occupational skill level and mood

RM-MANCOVA examining the relationship between subjects' skill level group and their mood at baseline, 6 months, and 12 months after beginning AI therapy showed a main effect of group on mood, $F(2,45) = 4.86$, $p = .01$, partial $\eta^2 = 0.178$. Compared to individuals employed at skill level 4, those employed at the lower skill levels reported significantly higher anxiety and depressive symptoms on average. The levels of anxiety ($p = .46$) and depressive symptoms ($p = .17$) did not significantly vary over time. Analysis revealed significant differences in the level of depressive symptoms between lower skill levels and skill level 4 over the first year of AI therapy, $F(1,47) = 4.29$, $p = .04$, partial $\eta^2 = 0.09$ (Fig. 1), but no significant differences for anxiety (see Table 2).

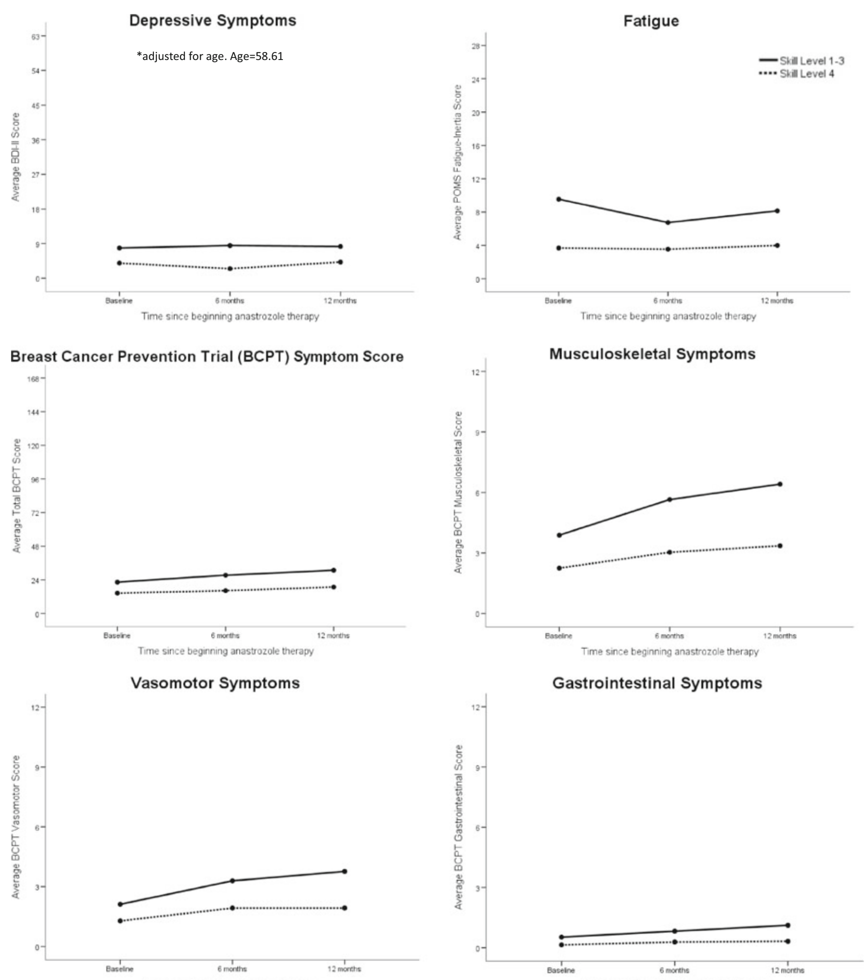

Fig. 1 Trajectory of treatment-related symptoms in the first year of anastrozole therapy

Table 2 Occupational skill level and mood over time

Mood	Skill levels 1–3, n = 20 (40.8 %)	Skill level 4, n = 29 (59.2 %)	Test statistics	p value
	Mean (SD)	Mean (SD)		
Depressive symptoms				
Baseline	7.9 (8.4)	3.9 (2.7)	$F_{Group}(1,46) = 8.91$	.005
6 months	8.5 (9.4)	2.5 (2.3)	$F_{Time}(2,92) = 0.68$	.512
12 months	8.3 (9.9)	4.2 (4.3)	$F_{Group \times Time}(2,92) = 1.83$	.166
Anxiety				
Baseline	8.0 (6.1)	6.6 (3.6)	$F_{Group}(1,46) = 2.77$	.103
6 months	8.2 (7.4)	5.4 (3.6)	$F_{Time}(2,92) = 0.72$	.487
12 months	7.0 (7.6)	5.1 (4.8)	$F_{Group \times Time}(2,92) = 0.79$	.456

SD standard deviation

Occupational skill level and symptom experience

Total BCPT symptom scores and fatigue levels demonstrated a time effect, $F(2,94) = 17.0$, $p < .001$, partial $\eta^2 = 0.266$, and group effect, $F(2,94) = 4.9$, $p = .009$, partial $\eta^2 = 0.095$. The univariate tests for time, however, showed that only total BCPT had a significant time effect, $p < .001$, partial $\eta^2 = 0.181$ (see Table 3). The test of between-subject effects showed that there are significant between group differences for both fatigue, $p = .009$, $\eta^2 = 0.169$, and total BCPT, $p = .023$, partial $\eta^2 = 0.105$ (see Fig. 1). More specifically, those at skill levels 1 through 3 reported significantly higher levels of fatigue and total symptom scores and this pattern persisted over the 1-year time period.

When exploring differences between the two occupational skill levels and the specific symptom domains of the BCPT over time using RM-MANCOVA, we found a significant time effect, $F(16,28) = 3.4$, $p = .002$, partial $\eta^2 = 0.661$, and group effect, $F(8,36) = 2.9$, $p = .014$, partial $\eta^2 = 0.390$. As summarized in Table 3, univariate tests revealed that musculoskeletal symptoms ($p < .001$), vasomotor symptoms ($p = .001$), dyspareunia ($p < .001$), bladder problems ($p = .017$), and weight concerns ($p = .011$) worsened over the 1-year study time frame. The test of between-subject effects showed that those employed at skill levels 1 through 3 reported significantly more severe musculoskeletal ($p = .005$), vasomotor ($p = .028$), and gastrointestinal ($p = .010$) symptoms than those employed at skill level 4 (see Fig. 1). Though results were not statistically significant for each of the other BCPT subscales, it is worth noting that mean symptom burden scores for skill levels 1 through 3 were consistently higher across all three time points for cognitive complaints, musculoskeletal symptoms, vasomotor symptoms, gastrointestinal symptoms, bladder control, and weight concerns.

Discussion

This study suggests that occupational skill level is associated with mood and symptom burden in women receiving AI therapy for breast cancer, with a small effect size. In this longitudinal, observational study, women employed at skill levels 1 through 3 reported higher anxiety and depressive symptoms than those employed at the higher skill level (4). Women at lower skill levels also reported higher levels of symptom burden associated with AI therapy including fatigue, musculoskeletal complaints, vasomotor symptoms, gastrointestinal problems, and total symptom burden. From baseline through the first year of therapy, symptom burden related to AI therapy worsened for both skill level groupings. However, women in the lower skill level grouping reported more severe symptom burden than those employed at the higher level in six (cognitive complaints, musculoskeletal symptoms, vasomotor symptoms, gastrointestinal symptoms, bladder control, and weight concerns) out of eight symptom subscales on the BCPT at each of the three time points measured in the study (baseline, 6 months, and 12 months).

Findings suggest that women employed at lower skill levels may be more bothered by symptoms during the first year of AI therapy, which might be related to lower skill levels typically involving high levels of physicality. It is also possible that women employed at lower skill levels may not have as comprehensive a benefit package or receive accommodations as easily as women employed at the highest skill level. With fewer benefits, those employed at lower skill levels may not be eligible for paid time off to attend appointments to adequately address symptoms or may not have employers as willing to implement workplace accommodations, which may contribute to poorer mood and more bothersome symptoms [23–26]. Future research should investigate why breast cancer survivors employed at lower skill levels reported more bothersome symptoms than those employed at skill level 4. Future work should develop interventions to mitigate symptom burden for women beginning AI therapy who wish to maintain their occupational roles.

Results of this study may inform future studies of mood and symptom experience in women receiving AI for early-stage breast cancer. This study suggests a proxy variable to help predict which breast cancer survivors may experience more severe symptoms and difficulty maintaining occupational roles

Table 3 Occupational skill level and symptom burden over time

Symptom	Skill levels 1–3	Skill level 4	Test statistics	*p* value
	Mean (SD)	Mean (SD)		
	n = 20 (40.8 %)	*n* = 29 (59.2 %)		
Fatigue				
Baseline	9.6 (8.8)	3.7 (3.2)	$F_{Group}(1,47) = 9.56$	<.001
6 months	6.8 (6.0)	3.6 (3.7)	$F_{Time}(2,94) = 1.95$	.009
12 months	8.2 (8.9)	4.0 (3.5)	$F_{Group \times Time}(2,94) = 9.56$	.003
Total BCPT				
Baseline	22.4 (20.1)	14.5 (8.5)	$F_{Group}(1,47) = 5.54$	.023
6 months	27.3 (22.3)	16.3 (10.0)	$F_{Time}(2,94) = 10.42$	<.001
12 months	30.9 (23.9)	18.9 (11.3)	$F_{Group \times Time}(2,94) = 1.18$	.311
	n = 17 (37.8 %)	*n* = 28 (62.2 %)		
Cognitive				
Baseline	2.1 (3.0)	1.5 (1.5)	$F_{Group}(1,43) = 1.08$	.304
6 months	2.2 (2.6)	1.3 (1.7)	$F_{Time}(1.6,69.4) = 0.19$	.784
12 months	2.1 (2.4)	1.8 (1.8)	$F_{Group \times Time}(1.6,69.4) = 0.83$	.418
Musculoskeletal				
Baseline	3.9 (3.2)	2.3 (2.3)	$F_{Group}(1,43) = 8.91$	.005
6 months	5.6 (4.2)	3.0 (2.7)	$F_{Time}(2,86) = 8.39$	<.001
12 months	6.4 (4.3)	3.4 (2.8)	$F_{Group \times Time}(2,86) = 1.28$	.285
Vasomotor				
Baseline	2.1 (2.8)	1.3 (1.2)	$F_{Group}(1,43) = 5.19$	.028
6 months	3.3 (3.0)	1.9 (1.7)	$F_{Time}(2,86) = 7.90$	.001
12 months	3.8 (3.5)	1.9 (1.4)	$F_{Group \times Time}(2,86) = 1.36$	.261
Gastrointestinal				
Baseline	0.5 (1.1)	0.1 (0.4)	$F_{Group}(1,43) = 7.18$	.010
6 months	0.8 (1.0)	0.3 (0.8)	$F_{Time}(1.7,72.8) = 2.73$	.080
12 months	1.1 (1.7)	0.3 (0.8)	$F_{Group \times Time}(2,86) = 0.79$	.437
Dyspareunia				
Baseline	0.4 (0.8)	1.4 (2.1)	$F_{Group}(1,43) = 3.44$	.071
6 months	1.0 (2.0)	2.1 (2.4)	$F_{Time}(1.6,69.3) = 10.44$	<.001
12 months	1.4 (1.9)	2.4 (2.3)	$F_{Group \times Time}(2,94) = 0.00$	1.0
Bladder control				
Baseline	1.1 (1.9)	0.5 (0.7)	$F_{Group}(1,43) = 3.02$	.090
6 months	1.4 (2.1)	0.6 (1.0)	$F_{Time}(1.6,68.1) = 4.78$	.017
12 months	1.8 (2.5)	0.8 (1.5)	$F_{Group \times Time}(1.6,68.1) = 1.07$	.336
Weight concerns				
Baseline	1.9 (2.4)	1.3 (1.4)	$F_{Group}(1,43) = 1.68$	.202
6 months	2.4 (2.2)	1.5 (1.8)	$F_{Time}(2,86) = 4.8$	.011
12 months	2.6 (2.4)	2.0 (1.8)	$F_{Group \times Time}(2,86) = 0.32$	.725
Gynecological				
Baseline	0.2 (0.6)	0.3 (0.5)	$F_{Group}(1,43) = 0.02$	.904
6 months	0.4 (0.6)	0.4 (0.8)	$F_{Time}(2,86) = 0.40$	.675
12 months	0.4 (0.7)	0.3 (0.7)	$F_{Group \times Time}(2,86) = 0.02$	.942

SD standard deviation, *BCPT* Breast Cancer Prevention Trial Symptom Checklist

from diagnosis through early treatment and survivorship. Many clinics routinely screen for symptom severity at office visits, but it is often unclear how the trajectory of mood and symptoms in a patient will develop over time. This study suggests that assessment of the woman's occupation at baseline may help predict the severity of symptoms throughout the first year of treatment. Knowing the likely course of symptom severity before treatment provides a window of opportunity to counsel the woman about what she may experience, as well as the opportunity to develop and implement interventions which can prevent or treat these symptoms early, before they interfere with the ability to maintain an occupational role. It would be incorrect to assume that cancer survivors who remain employed during and after treatment have less severe symptoms and that their symptoms do not increase in severity over time. This knowledge is important because other studies have found that severity of symptoms predict poor adherence to treatment [27, 28] and who will remain employed [12, 24, 29].

Studies of cancer survivors found that physical symptoms, depression, and fatigue were associated with ability to return to work [4]. Receiving advice from a healthcare provider about returning to work improves cancer survivors' ability to maintain employment [24, 30]. Given that our study found significant associations between occupational skill level and both depression and symptom burden, the development of interventions aimed at assisting women, particularly those employed at the lower occupational skill levels, may mitigate the severity of symptoms experienced and assist them in maintaining occupational roles.

Study limitations

The current study has several limitations that are relevant to data interpretation. First, this study is a secondary analysis of a larger study collecting longitudinal data of breast cancer survivors' cognitive function. The occupational skill level groups were formed post hoc and additional, unmeasured confounding variables may have been associated with skill level. Skill level was classified based on participant's job title at baseline. For our analyses, we assumed that the occupation reported at baseline remained unchanged over the first year of AI therapy. Therefore, we could not evaluate relationships between symptom burden and ability to return to work or stay employed. Additionally, due to our limited sample size, we were unable to examine the relationships between symptoms and working full time or part time. While the relationships between occupational classification and physical and psychological symptoms were statistically significant, the effect sizes were small. Future studies should examine the clinical significance of these relationships.

Future research should incorporate more sophisticated instruments of occupational classification and work function, which may yield a richer picture of occupation and the tasks involved. These instruments may also assess other important factors known to affect cancer survivors' employment status, including the workplace and employer adaptations [2, 24]. Lastly, given the small sample size and the distribution of occupational skill level, future research with a larger sample size and more diverse occupational skill level classifications should be conducted to confirm findings in this exploratory study.

Conclusion

Despite these limitations, this study offers a unique perspective on the association between occupational skill level and the symptom burden of postmenopausal women receiving AI therapy for breast cancer. This study highlights the importance of considering the occupation of cancer survivors when assessing the symptom experience and predicting the degree of bother associated with symptoms during the first year of therapy. Future research with a larger, more diverse sample is needed to assess occupational skill level based on more specific ISCO occupational classification and to examine what work tasks and aspects of the work environment are most associated with mood and symptom severity. Including as a part of routine clinical care whether or not a breast cancer patient is employed and, if so, whether she is planning to continue working may add to the ability to examine symptoms in the context of a woman's occupation. Clinicians working with cancer survivors might consider asking about occupational function and difficulties to gain perspective on what aspects are most difficult. Finally, it will be important to expand the findings from our study to other cancer populations and ultimately formulate efficacious interventions to reduce symptom severity and assist survivors in maintaining occupational roles for as long as possible.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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APPENDIX I

PERMISSION LETTER FOR DISSERTATION MANUSCRIPT #1

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Introduction
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APPENDIX J

IRB APPROVAL LETTERS FOR DISSERTATION STUDY (PRO13100151)

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Bethany Thelen
From: Sue Beers, Vice Chair
Date: 2/23/2014
IRB#: PRO13100151
Subject: Cognitive and Occupational Function in Adult Survivors of Adolescent Cancer

---

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:
45 CFR 46.110.(5) clinical data
45 CFR 46.110.(7) characteristics/behaviors

The IRB has approved the waiver for the requirement to obtain a written informed consent.

The risk level designation is Minimal Risk.
Approval Date: 2/23/2014
Expiration Date: 2/22/2015

The following documents were approved by the IRB:
Recruitment letter (version 1) consent forms

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Ground Level
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Bethany Nugent

From: IRB Office

Date: 1/16/2015

IRB#: MOD13100151-02 / PRO13100151

Subject: Cognitive and Occupational Function in Adult Survivors of Adolescent Cancer

---

The University of Pittsburgh Institutional Review Board reviewed and approved the requested modifications by expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110.

Modification Approval Date:	1/16/2015
Expiration Date:	1/8/2016

The following documents were approved by the IRB:
Recruitment letter (version 1) consent forms

For studies being conducted in UPMC facilities, no clinical activities that are impacted by the modifications can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

University of Pittsburgh
Institutional Review Board
3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
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http://www.irb.pitt.edu

Memorandum

To: Bethany Nugent
From: IRB Office
Date: 11/2/2015
IRB#: REN15100226 / PRO13100151
Subject: Cognitive and Occupational Function in Adult Survivors of Adolescent Cancer

---

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:

45 CFR 46.110.(5)
45 CFR 46.110.(7)

Please note the following information:

Approval Date:	11/2/2015
Expiration Date:	11/1/2016

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

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