EXERCISE DURATION FOR COGNITIVE HEALTH IN BREAST CANCER SURVIVORS

BY

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DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Kinesiology
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2017

Urbana, Illinois

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ABSTRACT

Many breast cancer survivors report deficits in cognitive functioning. Physical activity (PA) has been associated with better processing speed and memory and may prove a useful behavioral modality for improving cognition in breast cancer survivors. The purpose of the present study was to examine the differential duration effects of acute bouts of PA on executive function and processing speed in breast cancer survivors. Breast cancer survivors (N=48, M age=56.02) completed two sessions in counterbalanced order: moderate-intensity treadmill walking and seated rest. Participants were also randomized to one of three time groups: 10 (*n*=15), 20 (*n*=16), or 30 (*n*=17) minutes, signifying the length of time spent walking and resting. Immediately before and after each session, women completed a battery of cognitive tasks. Within- and between-subjects repeated measures analyses of variance revealed several moderately-sized and meaningful three-way (e.g., time by activity by group) interactions. On the flanker task, women were significantly less accurate over time in the resting activity compared with the exercise activity in the 20-minute group (*d* = .75). On single task blocks of the task switching paradigm, women performed significant slower after resting compared with after exercising in both the 10- (*d* = -.96) and 30-minute (*d* = -.52) groups. On the processing speed task, women performed significantly faster after exercising compared with after resting in the 20-minute group (*d* = -.24). Upon collapsing the sample for nonsignificant three-way interactions, two significant time by activity interactions emerged. Specifically, women performed significantly faster on the 2-item Spatial Working Memory task (*d* = -.21) and more accurately on the 3-item Spatial Working Memory task (*d* = .18) after exercise compared with after rest. Notably, these effects were irrespective of time spent exercising and resting. While the optimal length of exercise for providing short-lived cognitive benefits remains unclear, this study offers some initial preliminary evidence for maintained and improved cognitive function after a bout of moderate-intensity aerobic exercise compared with seated rest in breast cancer survivors.

ACKNOWLEDGEMENTS

I sincerely wish there were enough words to fully express my sincere gratitude and appreciation for those who have contributed to my success, both professionally and personally, during my time as a graduate student.

First and foremost, thank you to my advisor, Dr. Edward McAuley, for his unwavering support and guidance. I never imagined when I joined the Exercise Psychology Lab (EPL) as an undergraduate student that I would be embarking on a journey towards not only a fulfilling career far exceeding my expectations, but also exponential personal growth. Eddie, your pursuit of rigorous scientific processes, effortless leadership, encouraging wisdom when all seems lost, and indefatigable humor have molded me into a version of myself I never dreamed possible. I look forward to many years of continued collaboration and friendship.

I would also like to extend a sincere thank-you to my dissertation committee members: Dr. Charles Hillman, Dr. Arthur Kramer, and Dr. Linda Trinh. Your expertise, time, and support throughout my dissertation and graduate studies have been invaluable. It has been an honor to work with and learn from you.

Thank you to the Carle research team, specifically Dr. Kendrith Rowland and Janet Iverson. This project would not have been possible without your tenacity, attention to detail, and voracious pursuit of improved health outcomes after cancer.

My time as a graduate student would have been incomplete without my fellow EPL members: Susan Aguiñaga, Diane Ehlers, Jason Fanning, Susan Houseworth, and Sarah Roberts. Thank you for your constant support during my dissertation and for affording me the type of working environment others can only dream of. I am so thankful to have been surrounded by a

group of intelligent, grounded, and genuine individuals, all of whom I am blessed to have as lifelong friends and colleagues.

Of course, I would like to express my deepest thanks and love to my family. Mom and Dad, thank you for giving me both roots and wings. You have been my champions through life, and I wouldn't be the woman I am today without your countless sacrifices, love, and support. Thank you for being my role models for success in both life and love. Whenever the opportunity arises, I promise I'll always dance. Conor, you are my best friend and brother all rolled into one. Even though you're younger, I will never stop looking up to you. Mumma, thank you for supporting me throughout all my endeavors, even though I still haven't "just taken up sewing" yet. I can only hope to be as rich with wisdom, friendship, and love as you are when I'm your age. Denise, John Sr., and Christine, thank you for supporting and loving me as your own. I'm incredibly thankful and lucky to call you my family.

Lastly, thank you to my fiancé and my rock, John. Thank you for believing in me, encouraging me, and loving me unconditionally in both good times and bad. Every day with you is a day that I become a better version of myself, and I'm beyond blessed to have you as my lifelong partner. Together, we've accomplished the incredible, and I couldn't be more excited for all of life's adventures with you by my side. I am forever thankful for you.

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Chapter I: Introduction

The proposed study addresses an important public health outcome; cognitive dysfunction following treatment for breast cancer. Increases in awareness and early detection combined with advances in medical care have led to a dramatic increase in the 5-year survival rate of breast cancer, which has now climbed to 91% (Siegel, Miller, & Jemal, 2015). Consequently, there are currently over 2.9 million women living with a history of breast cancer in the U.S. alone (National Cancer Institute; SEER Data 2005-2011), a figure that is expected to rise to 4 million by the year 2020 (DeSantis et al., 2014). Breast cancer and its treatment are associated with a host of negative consequences ranging from increased risk of developing comorbid conditions to cancer recurrence (Hewitt, Rowland, & Yancik, 2003).

Following a diagnosis of breast cancer and its subsequent treatment, many women report deficits in cognitive functioning, particularly impairments in a family of cognitive processes that collectively comprise executive function. Executive function reflects a family of top-down mental processes responsible for the selection, scheduling, and coordination of goal-directed behavior, and is comprised of three core processes (e.g. cognitive flexibility, working memory, and inhibition; Miyake et al., 2000; Diamond, 2013), which have been identified as important determinants of long-term survival and quality of life across cancer survivors (Van Harten, van Noort, Warmerdam, Hendricks, & Seidel, 1998; Goodwin, Samet, & Hunt, 1996; Pinto & de Azambuja, 2011). Colloquially referred to as “chemobrain,” this cancer-related cognitive impairment (CRCI) can be defined as the loss of mental acuity associated with cancer and its treatment (Mackenzie, Zuniga, & McAuley, 2015). Evidence suggests impairments in cognitive functioning may persist in up to 35% of breast cancer survivors years after treatment (Koppelmans et al., 2012). It is therefore critical to improve cognitive health and attenuate CRCI in breast cancer survivors; however, it remains unclear if standard treatments alone are effective in protecting against CRCI. Thus, identifying low-cost methods for maintaining, and possibly improving, cognitive function in this cancer cohort is imperative.

Physical activity is a lifestyle behavior that has been consistently associated with improved physical and cognitive health status (Hillman, Erickson, & Kramer, 2008). Physical activity is protective against a host of diseases and has been shown to provide many health benefits to breast cancer survivors, such as decreased fatigue and improved physical functioning and quality of life (Schmitz et al., 2005; Holmes et al., 2005; Speck et al., 2010; Bicego et al., 2009; Mishra et al., 2012), and it has been suggested that physical activity may improve varying cognitive domains in breast cancer survivors (Baumann et al., 2011; Galantino et al., 2012; Zimmer et al., 2016; Hartman et al., 2015). However, while these benefits from physical activity are emerging in the cancer literature, Blanchard and colleagues (2008) concluded that only 37% of breast cancer survivors meet the recommended guidelines for physical activity.

Previous research has suggested that acute bouts of moderate intensity aerobic exercise may provide substantial psychological and physical benefits to breast cancer survivors. Several studies have indicated that an acute bout of exercise decreases state anxiety (Blacklock, Rhodes, Blanchard, & Gaul, 2010; Blanchard et al., 2001). Further, Evans and colleagues (2015) found that the pattern of natural killer cells post-moderate intensity exercise in breast cancer survivors mirrored that of a healthy control group. Whereas this research indicates that acute exercise may provide biological and mental health improvements, it is still unclear as to whether or not these benefits may extend to cognitive functioning. A recent preliminary study found significant improvements in the spatial working memory domain after a 30-minute acute bout of moderate-intensity aerobic exercise compared to a seated rest period in breast cancer survivors, with participants exhibiting reductions in reaction time as well as improvements in accuracy (Awick, Rowland, Kramer, & McAuley, in review). However, there are currently no standardized physical activity recommendations for improving cognitive functioning. Mackenzie and colleagues (2015) have called for further exploration into the dose-response relationship between physical activity, cardiorespiratory fitness, and cognitive functioning in breast cancer survivors given it is still unclear as to the dose or volume of exercise responsible for providing breast cancer survivors with the greatest cognitive benefits.

There is evidence in healthy adults to suggest that acute bouts of exercise of moderate duration may produce greater improvements in cognitive functioning compared to shorter or longer bouts. For example, Chang and colleagues (2015) tested the dose-response relationship between exercise duration and cognition functioning whereby participants engaged in 10, 20, or 45 minutes bouts of exercise on a stationary cycle ergometer, as well as a control condition of seated reading. Upon completion of each bout of either exercise or seated rest, participants completed the Stroop task, a measure of executive function tapping selective attention and cognitive flexibility. The authors found a positive effect for 20 minutes of exercise compared to 10 or 45 minutes, such that participants demonstrated shorter reaction times and higher accuracy, indicating a curvilinear relationship between exercise duration and cognitive functioning, potentially due to an inverted-U effect of exercise (Davey, 1973). Similarly, a meta-analysis conducted by McMorris and colleagues (2011) demonstrated a positive effect for reduced response time on working memory tasks immediately after acute bouts of exercise.

There is further evidence to suggest that the acute exercise duration and cognitive function relationship may be moderated by factors such as cardiorespiratory fitness, physical activity engagement, and type of cognitive task. Cardiorespiratory fitness has been found to significantly moderate the effects of exercise such that lower fit participants demonstrate poorer cognitive performance compared to their higher fit counterparts (Chang, Labban, Gapin, & Etnier, 2012). Mackenzie and colleagues (2016) conducted a case-control study to examine the effects of cardiorespiratory fitness and physical activity levels on working memory in breast cancer survivors. The authors found higher fit women demonstrated greater accuracy on the 1-back task compared to their low fit counterparts. Additionally, greater total physical activity engagement predicted shorter reaction times on the 2-back task in both cancer and disease-free individuals. Similarly, Chaddock-Heyman and colleagues (2015) found higher cardiorespiratory fitness levels were significantly associated with greater hippocampal volume in breast cancer survivors. Specifically, higher fit women displayed comparable hippocampal volumes to non-cancer controls, suggesting that fitness may protect against volumetric decline after cancer treatment. Cognitive task type has also been shown to moderate this relationship such that effects for executive function tasks were much greater than other cognitive measures (e.g., information processing, memory; Chang et al., 2012).

Current physical activity recommendations for cancer survivors mirror the general population public health recommendations of 150 minutes per week of moderate intensity aerobic exercise and avoiding inactivity; however, approximately a third of breast cancer survivors fail to meet these guidelines (Irwin, 2004). In an attempt to increase activity in this cancer cohort, researchers and health behavior theorists suggest survivors accumulate small bouts of activity, specifically 10-minute bouts, throughout the course of a day (Schmitz et al., 2010). If improvements in cognitive functioning are evidenced after 10 minutes of moderate intensity aerobic exercise alone, this would have considerable implications for these specific recommendations in real world settings. However, the literature suggests a longer bout (e.g., 20 minutes) may be necessary (Chang et al., 2015). This discrepancy between prior research and physical activity recommendations warrants further exploration. If indeed 10 minutes of exercise is sufficient to elicit cognitive improvements, researchers would have evidence for recommending a 10-minute bout of activity during the day with the intent of not only working towards satisfying public health recommendations, but also for potentially improving cognitive health.

The purpose of the current study was to examine the effects of varying durations of physical activity on executive function in adult breast cancer survivors in an effort to test whether the acute exercise duration and cognitive function relationship in breast cancer survivors is curvilinear. The specific aims of the proposed research were as follows:

1) To determine if a dose-response relationship exists between exercise duration and cognition (i.e., working memory, cognitive flexibility, and processing speed) in breast cancer survivors. It was hypothesized that the relationship between exercise length and cognitive function improvements would be curvilinear, such that 20 minutes of exercise would provide the largest improvements in cognition (e.g., higher accuracy, shorter reaction time) compared to 10 and 30 minutes. We chose these specific durations to examine the veracity of the physical activity recommendations of not only achieving 30 minutes of moderate intensity aerobic activity a day, but also accumulating smaller 10-minute bouts of aerobic activity throughout the day for improving cognitive functioning in breast cancer survivors.

2) To examine potential moderators of the acute exercise-cognitive function relationship in breast cancer survivors. It was hypothesized that lower grade disease status, longer time since diagnosis, less invasive treatment, higher levels of physical activity and

fitness, greater quality of life, and lower levels of anxiety, depression, and fatigue would be significantly associated with improvements in cognitive function over time within the exercise activity.

Chapter II: Literature Review

The current study examined the relationship between varying durations of moderate intensity aerobic exercise on cognitive functioning in breast cancer survivors. This study is innovative in that it provides information relative to physical activity recommendations for survivors seeking to mitigate cancer-related cognitive impairment. To further underscore the importance and need for such a project, this chapter reviews the following: prevalence of breast cancer, the effects of its treatment, and cognitive functioning; the benefits of physical activity in breast cancer survivors; current physical activity recommendations for cancer survivors; effects of dose-response and acute physical activity for improving cognitive functioning in breast cancer survivors; and potential moderators of the relationship between physical activity and cognition in cancer survivors.

Breast Cancer Prevalence

Breast cancer can be defined as a malignant tumor that originates in the cells of the breast and primarily affects women, although men are still at risk of developing the disease (National Cancer Institute; NCI). While the etiology of breast cancer is still unknown, the NCI has identified a number of risk factors for developing breast cancer, ranging from family history and genetic predisposition to lifestyle behaviors such as obesity and alcohol consumption. The Surveillance, Epidemiology & End Results (SEER) program of the National Cancer Institute has been collecting demographic, epidemiological, and clinical information on cancer survivors since the mid-1970s (DeSantis, Ma, Bryan, & Jemal, 2014) in an attempt to further understand the progression of the disease, incidence trends, and disparities among special populations. As of 2014, it is predicted that 1 in 8 women will develop invasive breast cancer in her lifetime (Siegel, Miller, & Jemal, 2015). In the year 2015 alone, over 230,000 women were diagnosed with invasive breast cancer and more than 40,000 women died from the disease (Siegel et al., 2015). While trends in breast cancer mortality have been consistently declining over the past two decades (Carlson et al., 2009; Siegel et al., 2015), increases in medical technology and heightened awareness have resulted in a steadily increased incidence rate with women living longer after treatment cessation. Specifically, seminal studies of the effects of screening via mammography and palpation found up to a 31% reduction in cancer-related mortality in the screening group compared to the control group (Shapiro, Venet, Strax, Venet, & Roeser, 1982; Tabár et al., 1985). Heightened survival may also be due in part to wider use of systemic therapy in combination with early surgery (Peto, Boreham, Clarke, Davies, & Beral, 2000). Consequently, there are currently over 2.8 million women living with a history of breast cancer in the U.S. alone (National Cancer Institute; SEER Data 2004-2010), a figure that is expected to rise to 4 million by the year 2020 (DeSantis et al., 2014).

Side Effects of Breast Cancer

Treatment for breast cancer is often complex and varied due to the disease's individualized manifestation (National Comprehensive Cancer Network, 2003) and might consist of radiation, chemotherapy, hormonal therapy, endocrine therapy, localized surgery, or any combination of these options (Carlson et al., 2009). While effective in improving survival rates and reducing risk of recurrence and mortality (Abe et al., 2005; Clarke et al., 2005; Vogel et al., 2006), these treatments are not without consequences. The most commonly reported side effects of these therapies include, but are not limited to, fatigue, body image concerns, alopecia, vomiting, nausea, infection, pain, emotional distress, reduced physical functioning, impaired quality of life, and cognitive impairment (Beisecker et al., 1997; Clarke et al., 2005; Coates et al., 1983; Ganz et al., 2004; Lemieux, Maunsell, & Provencher, 2008; Schagen et al., 1999).

Cognitive functioning has emerged as an important determinant of long-term survival in breast cancer survivors (Goodwin, Samet, & Hunt, 1996; Pinto & de Azambuja, 2011; van Harten, van Noort, Warmerdam, Hendricks, & Seidel, 1998), with the consistent association between cognitive dysfunction and cancer treatment garnering increased attention over the past few decades. Often referred to by survivors as “chemo-brain” or “mental fog,” this trouble with memory and/or concentration can be defined as the loss of mental acuity associated with cancer and its subsequent treatment (Mackenzie, Zuniga, & McAuley, 2015). In 1999, the National Coalition for Cancer Survivorship formally recognized cognitive dysfunction as a significant quality of life concern warranting higher priority in clinical cancer research (Ferguson, Riggs, Ahles, & Saykin, 2007). In the years since this formative report, researchers have increased their efforts to investigate the effects of cancer-related treatment on cognitive functioning. As a result, a growing body of evidence has emerged highlighting the relationship between varying forms of cancer treatment and cognitive dysfunction.

A review of the literature in the field of cancer and cognitive change reported that breast cancer survivors report cognitive dysfunction of varying degrees (Ahles, Root, & Ryan, 2012). For example, between 15% and 75% of adult cancer survivors who had previously received chemotherapy treatment have reported some degree of trouble with memory and/or concentration (Vardy & Tannock, 2007). Notably, this finding has been shown to remain constant despite the presence of other cancer-related symptoms, such as anxiety or depression. For example, Brezden and colleagues (2000) stated that breast cancer survivors who received adjuvant chemotherapy demonstrated poorer cognitive functioning compared to healthy controls, a finding independent of mood disturbance. Further discussed in the field of cancer and cognitive impairment is the assumption that exposure to chemotherapy treatment alone is responsible for these cognitive changes. While research has demonstrated that women who received chemotherapy treatment may be over two times more likely to demonstrate impairments in cognitive function (Shilling & Jenkins, 2007), Ahles and colleagues (2012) found that a combination of chemotherapy and endocrine therapy or even endocrine therapy alone may result in breast cancer survivors reporting some level of cognitive dysfunction.

Domains of executive function are among the most commonly reported cognitive impairments reported by cancer survivors and include working memory, cognitive flexibility, and attention (Kesler et al., 2013). Executive function (EF) is a family of top-down processes that manage and control varying cognitive procedures. EF is important for troubleshooting, navigating novel situations, decision making, planning, etc. It is at work most when attempting to override instinctive responses and can be broken down into three main categories: working memory, cognitive flexibility, and inhibition (Diamond, 2013).

Working memory is defined as the act of holding information in memory and working with it to make sense of and manipulate new information. This is important for adapting to new situations, putting plans into action, and considering alternative plans based on previous experiences. However, it should be noted that working memory is different from simply holding information in one's memory. Working memory requires manipulating held information and utilizes a different neural subsystem (D'Esposito, Postle, Ballard, & Lease, 1999). Inhibition can be described as the control of one's behavior, attention, and thoughts in the presence of a strong, overriding extrinsic or intrinsic stimulus. This results in an appropriate rather than impulsive action. Posner & DiGirolamo (1998) describe these impulses that we inhibit as a bottom-up process in which instinct is the driving factor of behavior. Inhibition is crucial in controlling our actions and selecting our behaviors. Cognitive flexibility builds on both working memory and inhibition and involves changing perspective, adjusting to new information as it is presented, then subsequently providing the correct response. It requires inhibiting old information to switch perspectives as well as activating a new perspective using working memory. Cognitive flexibility is associated with creativity and task switching and can be tested through presenting information related to sorting where participants must switch between these sorting variables (Diamond, 2013).

It has also been shown that breast cancer survivors suffer from poorer processing speed following cancer-related treatment. Processing speed operates in combination with executive functioning although it is not a core function. Processing speed can be defined as how quickly an individual views information, processes it, and provides a response, primarily when it comes to performing elementary tasks (Takeuchi et al., 2011).

It is clear that breast cancer survivors undergo a variety of treatments resulting in a host of negative side effects, including cognitive dysfunction. For long-term survival and ultimately improving quality of life throughout these extended years, it has become imperative for clinicians and researchers alike to identify low-cost methods for attenuating health and cognitive decline. Physical activity may be one such method.

Benefits of Physical Activity in Breast Cancer Survivors

Over the past several decades, a considerable body of research has identified the benefits of physical activity across the lifespan for reducing all-cause mortality and a number of other diseases including cardiovascular disease, diabetes, and obesity in the general population (Gregg, Gerzoff, Caspersen, Williamson, & Narayan, 2003; Helmrich, Ragland, Leung, & Paffenbarger, 1991; Kohl, 2001; Lee et al., 2012; Morris & Heady, 1953; A. H. Taylor et al., 2004; Warburton, Nicol, & Bredin, 2006). Physical activity has also emerged as a significant predictor for reduced cancer risk. Seminal reviews of epidemiological research suggest that physical activity, either occupational or leisure, is significantly associated with reduced risk of varying types of cancer, specifically breast and colon (Lee, 2003; Thune & Furberg, 2001; Warburton et al., 2006). Lee (2003) conducted a systematic review of epidemiological studies that revealed a 30-40% and 20-30% reduction in colon and breast cancer, respectively, with increased physical activity. In reviewing case-control and cohort studies, Thune & Furberg (2001) concluded that both leisure and occupational physical activity protected against overall cancer risk, a trend that was consistent across sexes. Dose-response relationships appeared for both colon and breast cancer, such that increased levels of activity were significantly associated with greater reductions in cancer risk.

Physical activity not only reduces cancer risk but also has attendant benefits following a cancer diagnosis. Indeed, physical activity and its benefits transcend primary cancer prevention, where this health behavior has been highlighted as an effective secondary preventive method by providing physical, psychosocial, and cognitive benefits as well as improved survival for those living beyond a diagnosis (Courneya & Friedenreich, 1997; Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005; McNeely et al., 2006; Warburton et al., 2006).

Physical Benefits

Increased levels of physical activity have been associated with improved function, strength, and cardiorespiratory fitness as well as reductions in fatigue and cancer symptoms (Kerry S Courneya et al., 2003; Fong et al., 2012; McNeely et al., 2006; Schmitz et al., 2005; Segal et al., 2001; Speck, Courneya, Mâsse, Duval, & Schmitz, 2010). A systematic review and meta-analysis of 14 randomized controlled trials with 717 breast cancer survivors found evidence for significant improvements in physical functioning (SMD = 0.84, 95% CI 0.36 to 1.32) and cardiorespiratory fitness as the result of increased levels of exercise (McNeely et al., 2006). Segal and colleagues (2001) conducted a randomized controlled trial in 213 stage I and II breast cancer survivors to examine the differences in health outcomes between three groups: usual care, self-directed exercise, and supervised exercise. Physical functioning improved significantly in both exercise conditions compared with the usual care condition ($p=0.04$), and cardiorespiratory fitness was significantly increased in the supervised exercise condition ($p=0.01$). Additionally, there was a significant and clinically meaningful difference between the supervised exercise condition and the usual care group, a finding that illustrates the impact of any physical activity, regardless of setting, on physical functioning in cancer survivors.

Similarly, 53 postmenopausal breast cancer survivors randomized to a 3 times weekly, 15-week cycle ergometer exercise intervention significantly increased peak oxygen consumption compared to a non-trained control group (Courneya et al., 2003). To extend these findings, Courneya and colleagues (2007) conducted another randomized controlled trial in 242 breast cancer survivors to examine the effects of both aerobic and resistance exercise modalities during treatment. As a result, those randomized to the aerobic condition evidenced significantly improved aerobic fitness compared to their usual care counterparts ($p=0.006$). Those randomized to the resistance exercise condition demonstrated greater strength and lean body mass compared to the usual care condition ($p<0.001$ and 0.015, respectively). These findings support the consistent and positive impact of physical activity on physical health outcomes regardless of exercise type.

Fatigue is one of the most frequently reported, intense, and oftentimes debilitating symptoms of cancer and its treatment (Mock et al., 1997). As part of a large systematic review and meta-analysis, McNeely and colleagues (2006) examined the effects of exercise on fatigue levels and found a moderate to large effect size for improvements in this symptom in all 6 studies that included fatigue as a health outcome (SMD 0.46, 95% CI 0.23 to 0.70). Similarly, a randomized controlled trial found significant reductions in fatigue during treatment in those women who exercised at least 90 minutes per week for at least 3 days a week (Mock et al., 2001). These results have been replicated in a home setting as well. Courneya and colleagues (2003) found that cancer survivors randomized to a home-based exercise plus group psychotherapy condition reported significantly reduced fatigue levels (p=0.037, *d*=0.28) compared to individuals in the group psychotherapy only condition. These findings parallel another home-based exercise trial in 119 previously sedentary breast cancer patients (Mock et al., 2005), where women randomized to the moderate-intensity walking program for the duration of their treatment (i.e., adjuvant chemotherapy or radiation) reported significant improvements in fatigue levels at the end of the program compared to those in the usual care group (p=0.03).

Several studies have also highlighted exercise as an effective management tool for physical symptoms that coincide with cancer treatment such as pain and lymphedema (Ahmed, Thomas, Yee, & Schmitz, 2006; Speck et al., 2010). A systematic review of 66 physical activity studies in cancer survivors found a majority indicated significant, positive effects of physical activity interventions on a variety of breast cancer symptoms, including pain and general cancer side effects (Speck et al., 2010). In addition, there was an overall positive effect of a variety of physical activity types (e.g., lifestyle, aerobic, resistance) on lymphedema, such that the condition was not exacerbated by exercise programs (if preexisting) nor was it brought on (if not already present in the body). Similarly, a randomized controlled trial found that a twice-weekly resistance exercise intervention evidenced no changes in arm circumference, self- or clinician-diagnosed lymphedema, or symptoms at the end of the 6 month period (Ahmed et al., 2006).

Psychosocial Benefits

Physical activity also results in numerous psychosocial benefits for breast cancer survivors, including improved quality of life and self-esteem as well as reduced anxiety and depressive symptoms (Blacklock et al., 2010; Courneya et al., 2007; Segar et al., 1998). A randomized controlled trial investigating the effects of a walking exercise intervention compared to a usual care control condition during active treatment found significant improvements in quality of life in the intervention group (Mock et al., 2001). Importantly, among those in the intervention group, women who walked more demonstrated higher levels of quality of life compared to those who walked less. Similarly, another randomized controlled trial conducted by Courneya and colleagues (2003) in 53 postmenopausal breast cancer survivors indicated positive effects of a cycle ergometers exercise intervention on quality of life. Women who were randomized to the intervention group reported significantly higher values of quality of life compared to the control group ($p=0.001$), a finding that was correlated with improvements in peak oxygen consumption. There is also empirical support for improved quality of life for those women meeting physical activity recommendations. Blanchard and colleagues (2004) surveyed 9,105 cancer survivors, of which 2,885 were breast cancer survivors, examining trends in quality of life for those individuals meeting governmental health recommendations for nutrition, smoking habits, and physical activity behavior. Higher levels of physical activity in breast cancer survivors were significantly associated with greater health-related quality of life.

Exercise has also been consistently associated with reductions in anxiety and depressive symptoms. Segar and colleagues (1998) conducted a randomized controlled trial in breast cancer survivors finished with treatment to examine the effects of a 10-week, moderate-intensity aerobic exercise intervention on mental health outcomes. Women in the exercise condition demonstrated significant improvements in both depression and state anxiety scores compared to those in the control group. It's important to note that these findings are also mirrored in breast cancer survivors currently undergoing treatment. A randomized controlled trial conducted in women beginning a 6-week adjuvant radiation therapy regimen examined changes in various health outcomes in a home-based exercise condition compared to usual care (Mock et al., 1997). At the cessation of treatment, those in the exercise group reported significantly reduced anxiety scores. Similar to chronic training effects, acute bouts of aerobic exercise have also been shown to reduce state anxiety in high state anxious breast cancer survivors (Blacklock et al., 2010; Blanchard, Courneya, & Laing, 2001).

Self-esteem is an important determinant of quality of life, and has emerged as a significant outcome of physical activity trials in cancer survivors. A 66-trial meta-analysis of physical activity studies in cancer survivors found a positive and significant impact of physical activity on self-esteem (Speck et al., 2010). Further, Courneya and colleagues (2007) conducted a randomized controlled trial examining the effects of usual care compared to aerobic and resistance exercise conditions, and found both exercise groups demonstrated significantly improved self-esteem compared to the control condition. These findings are similar for both physical and psychosocial health benefits, such that improvements in various health domains are associated with more than one mode of physical activity. Comparatively, Daley and colleagues (2007) found that an 8-week supervised aerobic exercise training and a body conditioning exercise-placebo condition elicited significant improvements in physical self-worth compared to usual care. However, the magnitude of the effect was larger for the aerobic exercise condition than the exercise-placebo condition, indicating that individuals may still need to reach a currently unspecified threshold of physical activity to achieve health improvements.

Interestingly, exercise has also been associated with increased chemotherapy completion rates (Courneya et al., 2007), such that breast cancer survivors currently undergoing adjuvant chemotherapy randomized to the exercise condition adhered more to their chemotherapy regimen compared to those in the control condition. This finding highlights the benefits of physical activity beyond tangible health improvements, such that increased levels of physical activity may be associated with other positive health behaviors (i.e., drug regimens) and consequently, additional health benefits.

Cognitive Benefits

A small but rapidly growing body of evidence has indicated cognitive benefits for cancer survivors as a result of physical activity participation (Campbell et al., 2017; Schaffrath, Oberste, & Zimmer, 2017). For example, a systematic review examining a variety of therapies for improving cognitive functioning in cancer survivors highlighted strength training as a promising method meriting further exploration (Morean, O’Dwyer, & Cherney, 2015). A randomized controlled trial in 101 breast cancer survivors in an exercise condition also demonstrated significant improvements in cognitive performance on an executive function task (Schmidt et al., 2015). Compared to the attentional control group, the relationship favored the exercise group although the between-group difference did not reach significance. While both groups improved in cognitive performance, methodological issues warrant further exploration of this relationship.

Research suggests that similar results to those found after treatment cessation may be elicited across the cancer continuum. For example, Fitzpatrick and colleagues (2012) conducted a longitudinal feasibility study in older adult cancer survivors currently undergoing chemotherapy. As a result, cognitive health significantly improved as physical activity levels increased across time. Additionally, a pilot study assessing changes in health outcomes after a 7 week yoga intervention (Culos-Reed, Carlson, Daroux, & Hately-Aldous, 2006) found that survivors in the yoga group indicated a trend towards improvements in cognitive disorganization ($p<0.10$; Culos-Reed, Carlson, Daroux, & Hately-Aldous, 2006). Similarly, a 12-week randomized controlled trial examining the effects of a resistance training program in breast cancer survivors currently undergoing chemotherapy found improvements in 3 out of 4 cognitive tasks assessed (Baumann et al., 2011). It is important to note that a variety of different exercise modalities (i.e., aerobic, resistance, yoga) have resulted in cognitive functioning improvements in cancer survivors. These findings indicate that physical activity may indeed provide cognitive benefits for cancer survivors, however due to a variety of methodological issues (i.e., weak study design, lack of multiple cognitive functioning measures) further research is warranted before consensus statements can be made.

Survival Rates

It’s important to note the body of work illustrating the impact of physical activity on cancer recurrence, mortality, and survival. Holmes and colleagues (2005) followed approximately 3,000 women in the Nurses’ Cohort Study who developed breast cancer and examined cancer recurrence, mortality, and physical activity levels over an 18 year period. Physical activity exerted a protective effect such that the most active women had a 26-40% reduced risk of cancer recurrence and mortality compared to their least active counterparts.

Similarly, in a prospective study of 933 women in the Health, Eating, Activity, and Lifestyle Study, those who increased their physical activity levels after a breast cancer diagnosis had a 45% reduced risk of death compared to those women who were inactive both before and after diagnosis (Irwin et al., 2008).

These findings also hold true for lifetime physical activity behavior. Friedenreich and colleagues (2009) conducted a cohort study in 1,231 women diagnosed with breast cancer over a 2 year period and followed them for over 8-10 years examining cancer progressions, recurrences, and death. There was a significant reduction in risk of death for those women in the highest quartile of physical activity behavior compared to the lowest quartile, with moderate-intensity physical activity exhibiting the greatest protective effects. Holick and colleagues (2008) found comparative results in a prospective study such that regardless of age, disease stage, and body mass index, women who engaged in greater levels of activity (i.e., ≥21.0 MET-h/wk) had a significantly reduced risk of breast cancer death as well as improved overall survival.

The benefits of physical activity for multiple dimensions of health in breast cancer survivors are unequivocal. However, these benefits are predicated on the fact that breast cancer survivors have knowledge of and will indeed engage in the appropriate amounts of physical activity necessary for achieving these benefits. The next section details physical activity recommendations for the general public and breast cancer survivors, as well as how these guidelines may be lacking in the abundance and specificity necessary for increasing physical activity behavior in breast cancer survivors, thus providing a number of health benefits and improved survival.

Current Physical Activity Recommendations for Breast Cancer Survivors

Physical activity has been identified as a protective behavior for a number of physical and psychological conditions in cancer survivors as well as the general population. In 1995, the Centers for Disease Control and the American Society of Sports Medicine released the first physical activity recommendations to the public to provide a “clear, concise, public health message” that would encourage a largely sedentary society to increase their engagement in physical activity (Haskell et al., 2007). These initial guidelines recommended that individuals achieve 30 minutes a day of moderate-intensity physical activity on most, if not all, days of the week. In the decades since, our scientific knowledge of physical activity and its benefits has only grown, so much so that the World Health Organization (WHO) and the U.S. Department of Health and Human Services (HHS) have expanded upon the initial recommendations and developed more comprehensive guidelines for engaging in physical activity. In 2008, the HHS developed key guidelines for children, healthy adults, and older adults with the goal of providing individuals with a separate guide for recommendations specific to physical activity, given the growth of scientific evidence for physical activity health benefits since the initial 1995 recommendations. In this new set of guidelines, the HHS distinguishes between two different forms of activity: baseline activity and health-enhancing physical activity. “Baseline activity” can be defined as light-intensity activities inherent in daily life, whereas “health-enhancing physical activity,” (i.e., activity beyond that encountered in daily life) when coupled with baseline activity, provides health benefits. These guidelines focus primarily on aerobic exercise, although the HHS recommends that adults engage in at least two days per week of muscle-strengthening exercises to provide additional health benefits. The HHS further delineates four distinct levels of physical activity as can be seen in Table 1.

Physical activity recommendations for cancer survivors mirror those for the general population. Developed by the American Cancer Society (ACS), these recommendations are revisited and updated every 5 years. The most recent physical activity recommendations for cancer survivors were published in 2016 and are closely aligned with those for healthy adults (Runowicz et al., 2016; Panel, 2010); however they provide less comprehensive detail about the potential health benefits. The ACS outlines activity recommendations for both adults and children, but lacks distinction between levels of physical activity as can be seen in Table 2.

There is evidence for the onset of multiple comorbidities after a cancer diagnosis (Demark-Wahnefried, Aziz, Rowland, & Pinto, 2005), which the ACS recognizes as a potential contributing factor for insufficient physical activity. As such, the ACS recommendations include a statement relative to being active. Cancer survivors are encouraged to avoid inactivity by limiting sedentary behaviors such as sitting, lying down, watching TV, or engaging in other screen-time behavior that would limit movement. Additionally, the ACS states that doing some physical activity above usual activity, regardless of one's baseline level of activity, can provide a multitude of health benefits.

It should be noted that information relative to guidance and tips for achieving physical activity recommendations are provided to the general population and include an emphasis on the gradual, slow progression of activity over months as well as detailed examples of how to meet these guidelines (Kushi et al., 2012). Similar information is notably absent in recommendations for cancer survivors, as well as any mention of strength or flexibility guidelines. Furthermore, these recommendations are quite broad in nature even for the general population and lack the tailoring and specificity needed for improving cognitive health. In this same vein, while physical activity benefits specifically for breast cancer survivors are clear and abundant, details about mode, intensity, frequency, and duration of physical activity necessary for eliciting such effects are still equivocal. As such, the scientific community has yet to endorse a specific dosage of physical activity for proving the greatest cognitive benefits in cancer survivors (Mackenzie et al., 2015).

While these recommendations serve as a foundation for increasing physical activity behavior, it is evident that more concrete emphasis on specific physical activity behavior (i.e., mode, intensity, frequency, duration) is warranted. The next section details evidence for emerging doses of physical activity (e.g., dose-response exercise and acute bouts) and their beneficial effects on cognitive functioning in breast cancer.

Dose-Response & Acute Physical Activity in Breast Cancer Survivors

Most of the research in dose-response physical activity in breast cancer survivors lies within the framework of chronic exercise training with findings pointing towards additional health benefits from higher doses of physical activity compared to standard doses alone. For example, a meta-analysis conducted by Brown and colleagues (2012) examining 40 exercise interventions in cancer patients found improvements in mental health in a dose-response fashion such that greater amounts of weekly exercise were significantly associated with reductions in depressive symptoms. Similarly, a randomized controlled trial conducted by Courneya and colleagues (2013) examined differences in quality of life and physical function between three groups: standard aerobic exercise (i.e., 25-30 minutes), higher volume of aerobic exercise (i.e., 50-60 minutes), and a combination of both aerobic and resistance exercise (i.e., 50-60 minutes in combination with resistance exercises). Higher volume of aerobic exercise was not only found to be safe and well-tolerated by breast cancer survivors, but also provided benefits in quality of life and function. While these findings suggest higher doses of physical activity are well-received by breast cancer survivors and may provide additional health benefits than standard doses, there is a paucity of research examining cognitive function as a primary outcome of such dose-response exercise trials. Concurrently, much of this research examines chronic physical activity via longitudinal exercise interventions while simultaneously overlooking the immediate effects of single bouts of activity.

The relationship between acute bouts of physical activity and aspects of cognitive functioning has been well documented in the general population across the lifespan (Chang, Labban, Gapin, & Etnier, 2012; Hwang, 2015; Pontifex, Saliba, Raine, Picchietti, & Hillman, 2013). Acute bouts of moderate-intensity aerobic exercise have demonstrated improved attentional-control as well as scholastic achievement in children (Pontifex et al., 2013). Similarly, Hillman and colleagues (2003) found improved executive function control after a 30-minute bout of aerobic exercise in undergraduate students. This trend appears to remain constant in middle-age as well. For example, research has indicated that a 30-minute aerobic exercise bout elicited shorter reaction time on tasks related to executive function in healthy, middle-aged adults (Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009). Older adults also exhibit similar, if not greater in magnitude, cognitive effects after a single bout of exercise. For example, a meta-analysis of 79 studies examining the effects of acute bouts of exercise on cognitive functioning found a stronger effect for studies in older adults (d=0.18), which was more substantial than the global average effect size for all acute physical activity and cognition studies (d=0.097; Chang et al., 2012). Furthermore, Hogan and colleagues (2013) found that after a moderate-intensity aerobic exercise session, aging individuals significantly improved their performance on a working memory task. These findings may be of great importance when extrapolating this work from the general population to cancer survivors.

One model guiding research on the physical activity-cognition relationship in cancer utilizes an aging perspective. Research has indicated that both breast cancer survivors and older adults may share common brain structure and function (Mackenzie, Zuniga & McAuley, 2015), and it has been hypothesized that cancer and aging exhibit similar underlying biological pathways (Ahles et al., 2012; Edelstein & Bernstein, 2014; Schwartz & Winters-Stone, 2013). For example, brain activation patterns in breast cancer survivors have been shown to be comparable to those seen in healthy, older adults between the ages of 65 and 75 (Cimprich et al., 2010). Notably, the cancer survivors in this specific study had not yet undergone chemotherapy, suggesting that cancer and aging may share common etiologies not attributable to treatment alone. Another theory surrounding the relationship between cancer-related cognitive impairment and aging is that cancer treatment results in an accelerated aging process. Ahles and colleagues (2012) have posited that cancer treatments such as chemotherapy, endocrine therapy, or a combination of the two result in this accelerated brain aging. Mandelblatt and colleagues (2013) have also suggested that cancer-related therapies may trigger the development of a frailty phenotype, often present in older adults. Frailty in and of itself is associated with low cognitive reserve, indicating another potential avenue linking cancer and aging. The similarities between older adults and cancer survivors, paired with an estimated 40% of all new breast cancer diagnoses occurring in women over the age of 65 (DeSantis et al., 2014), suggest that an aging framework may be particularly useful when examining the relationship between cancer, physical activity, and cognition.

A recent pilot study examined the effects of a 30 minute moderate-intensity acute bout of physical activity on spatial working memory and processing speed in breast cancer survivors (Awick et al., in review). Compared to a bout of seated rest, women demonstrated significant reductions in processing speed reaction time and marginally significant greater accuracy on a spatial working memory task after 30 minutes of moderate-intensity (i.e., 40-60% maximal heart rate) treadmill walking. While this project was the first of its kind to evaluate cognitive functioning as an outcome of an acute bout of aerobic exercise in breast cancer survivors, there are several limitations to this project, notably the small sample size and lack of dose-response assessment.

Despite the growing body of evidence for a dose-response relationship between physical activity and cognitive health improvements in individuals of all ages, there remains a surprisingly limited amount of knowledge, specifically in breast cancer survivors, surrounding the cognitive benefits of acute physical activity bouts when examined in a dose-response fashion. As Mackenzie and colleagues (2015) have stated, it is becoming increasingly important for researchers to explore the specific physical activity components necessary for not only improving cognitive functioning, but also for ultimately providing more comprehensive and detailed recommendations to the public. As such, the study herein is the first to date that attempted to examine the dose-response relationship between acute bouts of physical activity and cognitive functioning in breast cancer survivors.

Physical & Psychosocial Moderators/Mediators of the Physical Activity-Cognition Relationship

It is important to highlight a number of other factors that may influence the physical activity-cognition relationship in breast cancer. It is has been suggested that cardiorespiratory fitness, physical activity behavior, and cognitive task type all play a role in moderating the relationship between an acute bout of physical activity and cognitive functioning (Chaddock-Heyman et al., 2015; Chang et al., 2012; Mackenzie et al., 2016). A meta-analysis of 79 studies in healthy individuals examining acute effects of physical activity on cognitive functioning found that participant fitness as well as cognitive task type moderated the results (Y. K. Chang et al., 2012). As such, individuals with high fitness levels demonstrated significant positive effects (i.e., improved performance on cognitive tasks) during an acute bout of activity compared to a negative effect (i.e., poor performance on cognitive tasks) in their low fit counterparts. Also of importance is the variation of cognitive task type utilized in these studies. Effects for tasks measuring executive function domains, attention, and crystallized intelligence did not differ significantly from one another; however all of these tasks were differentially influenced by exercise compared to tasks related to information processing and memory which were not. Interestingly, a meta-analysis by Kramer and Colcombe (2003) in older adults indicated that exercise training improved performance on cognitive function tasks regardless of cognitive task type suggesting that fitness may play a larger role than task type.

When examining the physical activity-cognition relationship in breast cancer survivors, these same factors (e.g., cardiorespiratory fitness, cognitive task type, physical activity) have emerged as moderators and mediators of the relationship. For example, Chaddock-Heyman and colleagues (2015) examined hippocampal volume, an important component of brain health, in breast cancer survivors and age-matched, healthy controls. As a result, cardiorespiratory fitness and hippocampal volume were positively correlated, regardless of disease status. Importantly, higher fit breast cancer survivors showed comparable hippocampal volume to the healthy controls, suggesting that cardiorespiratory fitness may play a critical role in preserving brain health after cancer treatment. Similarly, Cooke and colleagues (2016) examined brain lesion volume, another indicator of brain health, in conjunction with physical activity and memory recall in a sample of 30 breast cancer survivors and 28 age-matched healthy controls. Among breast cancer survivors, women who engaged in more physical activity had smaller lesion volume, and those who had smaller lesion volume also performed better on memory recall tasks (ps both 0.001). Additional analyses indicated that moderate levels of physical activity mediated the impact of lesion volume on memory recall. Another case-control study found that higher levels of physical activity predicted shorter reaction time on working memory tasks in breast cancer survivors (p=0.014; Mackenzie et al., 2016). Further, for both age-matched controls and breast cancer survivors, all women with higher cardiorespiratory fitness levels displayed greater accuracy on a working memory task (p=0.017).

Researchers would do well to also consider other cancer-related and psychosocial factors, such as type of cancer treatment and quality of life, as potential moderators of the exercise-cognition relationship. Courneyna and colleagues (2008) found moderating effects for cancer treatment on health outcomes such breast cancer survivors who received non-taxane chemotherapy, thought to be less toxic and damaging to the body, demonstrated improved muscular strength compared to women who received taxane-based chemotherapy treatments. This finding highlights a potential difference in intervention tolerance among cancer survivors depending on their specific treatment regimen. It is possible that women who received less-toxic treatment suffered fewer side effects as a result and were capable of getting more out of the intervention (i.e., worked at a higher intensity, adhered more). Additionally, Hartman and colleagues (2015) concluded that chemotherapy may have deleterious effects on cognitive functioning in breast cancer survivors. Further, obese survivors performed significantly worse on cognitive tasks compared with their lighter counterparts, suggesting body mass index (BMI) may also influence cognitive functioning after breast cancer. As cognitive function has been identified as an important determinant of long-term survival and quality of life after cancer (Van Harten, van Noort, Warmerdam, Hendricks, & Seidel, 1998; Goodwin, Samet, & Hunt, 1996; Pinto & de Azambuja, 2011), it will also be important to examine how an acute bout of exercise may influence cognition independent of quality of life scores. Future researchers would benefit from examining differences in the strength of the exercise-cognition relationship based on the presence of these other factors. This would allow for the design and implementation of exercise programs for targeting specific subgroups of cancer survivors to provide the greatest cognitive health benefits possible.

A closer examination of these moderators and mediators in the context of specific dosages of physical activity is warranted. Specifically, future researchers should distinguish the independent role of acute bouts of physical activity from cancer-related factors, fitness, physical activity participation, quality of life, and psychosocial factors. In doing so, public health recommendations may be tailored to target specific subgroups (i.e., lower fit, less active individuals) for promoting improved cognitive health.

Summary

There has been an extensive effort towards attenuating cancer-related cognitive impairment in breast cancer survivors. Physical activity has emerged as a key factor in mitigating health declines as well as promoting improved cognitive functioning, with preliminary evidence suggesting that acute bouts of moderate-intensity physical activity may elicit improvements in cognitive performance in breast cancer survivors. Moreover, physical activity is a low-cost, lifestyle behavior that a majority of survivors are physically capable of performing. The present study built on this foundation to determine whether a specific duration of physical activity had the capacity to elicit significant improvements in cognitive functioning in breast cancer survivors.

Chapter III: Methods

Participants

Recruitment, randomization, and all testing procedures were conducted on a rolling basis between September, 2016 and February, 2017. Two primary sources of recruitment were used in the current study. First, oncologists and research staff at Carle Foundation Hospital informed patients about the current project. These referrals were facilitated by providing physicians with study design information (e.g., inclusion/exclusion criteria, outcome measures) and verbal communication. When an oncologist approached a patient about the study and the patient indicated interest in participation, the oncologist provided the patient with a study flyer. The patient then had the option to either call the study coordinator or allow the oncologist to provide the study coordinator with her contact information. Additionally, participants from a data-base of breast cancer survivors who had requested notification of future exercise research studies were contacted. Other methods of recruitment included email, social network, websites and listserve announcements. All advertisements included contact information for the research team.

Of the women who were able to recall their advertising source (*n* = 114), oncologists at Carle made contact with most of the women (*n* = 92), followed by data-base participants (*n* = 22). Potential participants for telephone screening were identified by self-disclosing contact information in response to advertising. Upon initial contact with study staff, potential participants underwent a prescreening process via telephone. This telephone screening also included the Telephone Interview for Cognitive Status-Modified (TICS-M; de Jager, Budge, & Clarke, 2003) to assess baseline cognitive status before inclusion into the study; however, scores were not exclusionary. The study coordinator made a maximum of three attempts to reach patients for screening to minimize the potential for perceived harassment.

Overall, 48 eligible participants completed all testing requirements, representing 75% of the initial recruitment goal. Of these participants, all 48 completed their three appointments, 46 returned accelerometers with sufficient data for analyses, 47 completed the online psychosocial questionnaires, and 44 returned completed health histories. Detailed flow through the study can be seen in Figure 1.

Inclusion/Exclusion Criteria

As most breast cancer diagnoses occur in adult women, individuals eligible for the current study were female and over the age of 18 with a past diagnosis of breast cancer (stages 0-III). In addition, individuals were no longer undergoing primary treatment and English speaking. Participants were required to provide their personal physician's medical clearance for them to be involved in the study. Participants also reported having memory and/or concentration problems after breast cancer diagnosis/treatment. Full inclusion/exclusion details are outlined in Table 3.

Experimental Design & Study Sequence

The current project utilized a repeated measures, within- and between-subjects experimental design to examine the acute effects of varying doses of physical activity (i.e., 10, 20, or 30 minutes) on cognitive functioning in breast cancer survivors. Once participants passed prescreening, they were sent a hyperlink to access the initial online portion of the study. This hyperlink instructed them to set a password that they then used, with a unique username, to access the following: online informed consent, online physician's release form, and online questionnaires. These questionnaires were designed to assess quality of life, anxiety, depression, cognitive perceptions, and fatigue. Participants were then scheduled for their first appointment consisting of an informational meeting, in-person informed consent procedures, baseline cognitive task battery, and submaximal walking treadmill fitness test. The second and third appointments were scheduled at the end of this appointment and were counterbalanced to prevent learning effects of the cognitive tasks. One of these two appointments consisted of aerobic exercise and the other of seated, quiet rest. Duration of both the exercise and rest sessions was decided randomly (e.g., 10, 20, or 30 minutes) using block randomization after prescreening was passed. Both appointments included cognitive tasks at the beginning and end of each session. Participants had all tests explained to them in detail at the beginning of each appointment and had the opportunity to ask questions and address concerns before beginning. No two participants completed testing in the same room in an attempt to control for additional stimuli that may have affected the results. All assessments were completed at Freer Hall on the University of Illinois at Urbana-Champaign campus where the Exercise Psychology Laboratory is located. In addition to the online questionnaires and these three appointments, participants also wore an accelerometer for 7 days.

Procedures

First Appointment & Fitness Test

The first appointment consisted of a brief orientation, one round of the cognitive tasks, and a submaximal exercise test to predict aerobic capacity via a walking treadmill test. After orientation and the informed consent process, participants completed a full battery of cognitive tasks assessing several domains of executive function (cognitive flexibility, spatial working memory, and attention/inhibition) and processing speed in a quiet, distraction-free room. All instructions for the cognitive tasks were presented for participants to read, and accuracy feedback was given during practice rounds only. A trained staff member was present in the room during these practices to answer any questions or concerns and troubleshoot comprehension and/or computer difficulties. The staff member then exited the room before the actual trial began. This baseline assessment was beneficial in that it habituated participants to the tasks to mitigate practice and learning effects at the following two appointments.

Upon completion of the cognitive tasks, participants were measured for their height and weight and fitted with a heart rate monitor. The fitness test followed a modified Naughton protocol such that increases in workload (e.g., changes in treadmill speed, elevation, or both) occurred every two minutes. During these two minute “stages,” heart rate, blood pressure, and rating of perceived exertion were measured. The goal of the test was to reach 85% of participants’ age-predicted maximum heart rates. Upon completion of this appointment, participants were given their accelerometer, scheduled for their final two sessions, and paid $20.

Aerobic Exercise Session

The aerobic exercise session consisted of two rounds of cognitive tasks and either 10, 20 or 30 minutes spent walking on a treadmill, depending on group allocation. Upon arrival, participants completed the same battery of cognitive tasks as their baseline appointment. After the first round of cognitive tasks, individuals were fitted with a heart rate monitor and given detailed instructions and safety cues about the aerobic session. Participants were instructed to walk at a moderate pace for their respective duration. Thus, treadmill speed was self-selected by both the participant (to ensure comfort) and exercise specialist (to ensure appropriate intensity: 60% of their age-predicted maximal heart rate). To account for varying heart rates that may have prevented participants from achieving the target heart rate (e.g., use of beta blocker medications), participants also maintained a rating of perceived exertion between 8 and 12 (Borg, 1998). This session was supervised by a trained exercise specialist and began and ended with a 2-minute warm up and cool down period, respectively. The warm up period assisted in increasing participants’ heart rates to ensure that most of the exercise session was indeed conducted at 60% intensity. Talking was kept to a minimum to prevent the potential confounding influence of social interaction between participants and exercise leader. Heart rate, blood pressure, and rating of perceived exertion were measured before, after, and during the session as needed to maintain safety. Upon completion of the cool down, participants removed the heart rate monitor and returned to the same quiet room to complete the same battery of cognitive tasks as before, but without the practice rounds to ensure that potential acute effects were captured during the assessment rather than practice in the event of effect decay. Participants were paid $20 for this appointment.

Resting Session

The resting session was very similar to the aerobic exercise session sequentially, but instead of exercising in between rounds of cognitive tasks, participants sat quietly in a distraction-free room for their respective duration (e.g., 10, 20 or 30 minutes). Upon arrival, participants completed the same battery of cognitive tasks with practice rounds. Afterwards, they were fitted with a heart rate monitor and instructed to sit quietly without working on anything (i.e., reading, talking, writing) and were asked to remain awake. Participants had the option to watch a television show. Heart rate, blood pressure, and rating of perceived exertion were measured before, during, and after this session to ensure that participants were indeed physiologically rested. After this resting period, participants removed the heart rate monitor and completed the same battery of cognitive tasks as before, but without the practice rounds. Participants were paid $20 for this appointment.

Measures

Cardiorespiratory Fitness

Cardiorespiratory fitness level was predicted in this study by submaximal exercise testing using the modified Naughton submaximal test protocol. This type of submaximal test has been recommended by the American College of Sports Medicine (ACSM) for older adults as well as cancer survivors (ACSM’s Guidelines for Exercise Testing and Prescription, 2013). This test began with a 5-minute resting period during which the details of the test were explained to the seated participant. Once this 5-minute period was complete, resting physiological measures (e.g., heart rate, blood pressure, rating of perceived exertion) were collected. The test then operated in two minute stages during which heart rate, blood pressure, and rating of perceived exertion were assessed. The treadmill increased in workload every two minutes through changes in speed, elevation, or both to make the test progressively more difficult. Once participants reached 85% of their age-predicted maximum heart rate [(220-age)*0.85], they completed that terminal two-minute stage and then completed a three-minute cooldown of slower walking with no elevation. The test ended with a two-minute period of seated rest after the cooldown where heart rate, blood pressure, and rating of perceived exertion were continuously monitored for safety. In the event participants were on beta-blocker medication, a rating of perceived exertion ≥17 was used as a proxy for 85% maximum heart rate. Predicted cardiorespiratory fitness (e.g., VO2 max) was calculated using MET values at the terminal stage (Balady et al., 2000; Wasserman et al., 1987).

Cognitive Function Measures

Task Switching. The task switching paradigm was used to assess cognitive flexibility. This assessment is a computer based cognitive task that requires participants to switch between sets based on the background color presented (Schneider & Logan, 2005). In the center of a black screen, a box appeared up with a number inside of it. If the background of the box was BLUE, participants had to indicate if the number was higher or lower than 5. If the background was PINK, participants had to indicate if the number was odd or even. Participants completed two single task blocks (1 block of high/low and 1 block of odd/even) of 30 trials each with preceding practice rounds that included accuracy feedback. The third round was a mixed task block that combined both the BLUE and PINK backgrounds chosen randomly for 180 trials, again with a preceding practice with accuracy feedback. Participants indicated their choices using keys on a keyboard ("z" for *odd/low* or "/" for *high/even*). Stimuli were presented on the screen for a duration of 2000 milliseconds (ms). Variables from this paradigm include reaction time and accuracy for the single task blocks and mixed task block. Within the single task blocks, there were two primary outcome variables: accuracy and reaction time. Averaged accuracy and reaction time were calculated from the single task blocks where participants were not required to switch between different sets. Within the mixed task block, there were several primary outcome variables: accuracy and reaction time for both switch trials and repeat trials. When the preceding trial presented a different task, it was a switch trial, compared with when the preceding trial presented the same task, it was a repeat trial. Another outcome variable used from this task was switch cost, defined as the difference in reaction times between switch and stay trials. Higher switch cost is thought to be indicative of poorer cognitive control.

Spatial Working Memory. The spatial working memory task is a computer based cognitive assessment that requires participants to focus on a cross in the middle of a white screen. 2, 3, or 4 black dots appeared on the screen for a duration of 500 ms before disappearing. A red dot then appeared for 2000 ms. Participants were asked to indicate whether or not the location of the red dot matched one of the previous black dots locations using keys on a keyboard (“X” for *no match* or “M” for *match*). Participants completed a practice round of 12 trials with accuracy feedback. The final round consisted of 120 trials without feedback. Outcome variables from this task were accuracy and reaction time for all three factors corresponding with the number of dots presented on the screen (e.g., 2-item, 3-item, 4-item).

Flanker. The flanker task is designed to measure attention/inhibition. It is computer based and, similar to the spatial working memory task, requires participants to focus on a cross in the middle of a black screen (Eriksen & Eriksen, 1974). Five arrows flashed on the screen for a duration of 125 ms before disappearing. The interstimulus interval was jittered between 1000, 1250, 1500, and 1750 ms to prevent participants from getting into a rhythm of responding. Participants were asked to indicate whether the middle arrow was pointing to the left or right using keys on the keyboard (“X” for *left* or “M” for *right*). There were two separate conditions within this task: congruent and incongruent. A congruent condition is defined as all five arrows pointed in the same direction, compared with an incongruent condition when the arrows pointed in different directions. Outcome variables were accuracy and reaction time for both the congruent and incongruent factors. An additional outcome variable was interference cost, defined as the difference in reaction time between incongruent and congruent trials. Higher interference cost is thought to be indicative of poorer cognitive control.

Letter Comparison. The letter comparison measure was used to assess processing speed. The letter comparison measure is a paper-pencil based cognitive task that requires participants to determine whether two strings of letters are the same or different (Salthouse, 1996). Participants were presented with two sheets of paper with several strings of letters, each separated by a line (Ex: YSTX **____** YSTX). Participants marked an “S” on the line if the string of letters was the same, or a “D” if they were different. Participants were informed of the importance of working through the items in order from top to bottom of the page without skipping around as quickly and as accurately as possible. Instructions were presented on the first page as well as a 3-item practice to ensure familiarity before beginning the actual test. Outcome variables from this task were averaged accuracy and reaction time across the two pages.

Physical Activity

Physical activity was assessed using Actigraph accelerometers (Actigraph, Pensacola, FL: model GT1M or GT3X). Participants were instructed to wear the accelerometer on their non-dominant hip for 7 consecutive days during waking hours and record the time worn on a log sheet. Data retained for analyses met a wear time validation criteria of ≥ 10 hours of wear time per day for at least 3 valid days when scored with an interruption period of 60 minutes (Troiano et al., 2008). These data were then downloaded as activity counts, which represent raw accelerations summed over a specific epoch length (e.g., 1 second) and subsequently processed into activity intensities in ActiLife software package (Version 6; Actigraph, Pensacola, FL) using adult-specific intensity (counts/min) cut-points as follows: sedentary (<100 counts/minute), light (100-759 counts/minute), moderate (1952-5724 counts/minute), vigorous (5725-9498 counts/minute), and very vigorous (≥9499 counts/ minute; Freedson, Melanson & Sirard, 1998). Cut points were then summed to create a measure of time spent within each intensity category. Estimated average daily minutes spent in each intensity category were calculated by dividing the number of minutes spent in each category by the total number of valid days worn per participant.

Psychosocial Measures

Functional Assessment of Cancer Therapy – Fatigue (Fact-F). The FACT-Fatigue is a 13-item subscale questionnaire from the FACT-General designed to measure fatigue after cancer. Participants were asked to indicate the frequency with which they experienced several statements on a Likert scale from 0, “not at all,” to 4, “very much.” An example item of the FACT-F is “I have trouble starting things because I am tired.” Negatively-worded items were recoded and summed for a total score. Higher scores on this scale are indicative of lower levels of fatigue.

Hospital Anxiety & Depression Scale (HADS). The HADS is used to measure anxiety and depression in general medical patients (Snaith, 2003). Participants were asked to indicate the frequency with which they experienced several statements on a 14-item Likert scale ranging from 1, “most of the time” to 4, “not at all.” An example of the HADS is “Worrying thoughts go through my mind.” While this questionnaire does not provide a total score, it yields two subscales: anxiety and depression. Higher scores are indicative of greater anxiety and depressive symptoms.

Functional Assessment of Cancer Therapy – Breast (FACT-B). This questionnaire is designed to measure quality of life in breast cancer survivors specifically (Brady et al., 1997). Similar to the FACT-Fatigue, the FACT-Breast includes cancer specific questions in additional to the FACT-General. Subscales from this measure are as follows: physical well-being, social well-being, emotional well-being, functional well-being, and additional concerns. Participants were asked to indicate the frequency with which they experience and agree with several statements. Items are scored on a Likert scale ranging from 0, “not at all,” to 4, “very much.” An example item from the FACT-B is “My family has accepted my illness.” Higher scores for each subscale are indicative of greater quality of life with respect to each category.

Functional Assessment of Cancer Therapy – Cognition (FACT-Cog). The FACT-Cog is designed to assess cognitive impairment across the cancer continuum. There are several subscales of the FACT-Cog: perceived cognitive impairments, comments from others, perceived cognitive abilities, and impact on quality of life. Participants were asked to indicate the frequency with which they experienced several statements on a Likert scale ranging from 0, "not at all," to 4, "very much." An example from the FACT-Cog is "I have had to work harder than usual to keep track of what I was doing." Higher scores of these subscales are indicative of greater quality of life with respect to each different category of cognitive perceptions.

Data Analysis

All analyses were conducted in SPSS (Version 24; IBM Corp. Armonk, NY). Initially, descriptive statistics were used to assess normality as well as calculate means and standard deviations. Initial linear regression analyses were used to identify potential covariates (i.e., age, education, time since diagnosis) of changes in cognitive function from pre- to post-exercise. Cohen's d effect sizes were also calculated. Defined as the standardized difference between treatment and comparison group means (Cohen, 1988), effect sizes are independent of sample size and thus are better indicators of group differences than traditional *p* values (Sullivan & Feinn, 2012).

Specific Aim 1

The primary aim of this project was to determine whether there were differential effects of exercise duration on cognitive function. As all participants received different durations of both resting and aerobic activity, we approached the analysis in a systematic fashion. First, we conducted a two (time; pre-post) by two (activity; rest, exercise) by three (group; 10, 20, 30 minute) repeated measures analysis of variance (RM-ANOVA) to determine if changes in cognitive function over time between exercise and rest differed as a function of the length of the activity. If the three-way interaction between time, activity, and group was significant and/or meaningful, we decomposed the interaction to explore time by activity interactions within each of the three groups. Given that the purpose of this project was to gauge the size of the effects of exercise and rest on cognitive function over time, we considered three-way interactions with a moderate effect size or above (i.e., partial eta squared ≥ .07). If the three-way interaction was nonsignificant with a negligible effect size, we collapsed the groups and conducted two (time; pre-post) by two (activity; rest, exercise) RM-ANOVAs in the full sample. It was hypothesized that for moderately-sized or larger three-way interactions, the effect would be driven by a significant time and activity interaction favoring exercise within the 20-minute group, such that the effects of exercise compared with rest over time would be more robust than those in the 10- and 30-minute groups. For nonsignificant three way interactions, we hypothesized that the time by activity interactions in the full sample would still be significant and/or meaningful favoring improvements in cognitive function after exercise compared with rest.

Specific Aim 2

In this aim, we examined potential cancer-related and lifestyle factors associated with improved cognitive function after exercise. We opted to use bivariate correlations in lieu of linear regression analyses given the small sample sizes within each group and large number of potential moderators. For this same reason, we included all variables with a p value ≤ .10 to discuss marginally significant associations. Change scores were created for each cognitive outcome variable from pre- to post-exercise with post-exercise cognitive outcome variables being subtracted from pre-exercise cognitive outcome variables. These change scores were then entered into the bivariate correlation analysis. As we aimed to explore potential moderators of acute exercise’s influence on cognition, only change scores for moderate to large effects were analyzed. Potential moderators of the exercise-cognition relationship were also included in the correlation model: BMI, fitness, all physical activity variables, anxiety, depression, all subscales of the FACT-B (i.e., physical well-being, emotional well-being, general total score, etc.), all subscales of the FACT-Cog (i.e., perceived cognitive impairments), total FACT-Fatigue score, disease stage, time since treatment, and type of treatment. It was hypothesized that fitness and physical activity would be significantly correlated with change in cognition such that higher fitness and greater physical activity engagement would be associated with improved accuracy and decreased reaction time after exercise. Additionally, we hypothesized that greater quality of life, lower levels of fatigue, and fewer perceived cognitive impairments would be correlated with improved accuracy and decreased reaction time after exercise. Lastly, we hypothesized that lower disease stage and longer time since cancer treatment would be significantly correlated with decreased reaction time and improved accuracy after exercise.

Quality Control & Data Checking

All raw data were de-identified apart from study ID number provided for each participant and are currently maintained in the Exercise Psychology Lab at Freer Hall in locked cabinets. Only research personnel are able to identify a participant by his/her study ID number unless otherwise requested by state or federal law. Informed consents as well as medical histories are kept in a secured, locked filing cabinet. The identity key is kept separate from the rest of the data.

Data were checked immediately in the presence of the research participant if possible for clarity and completeness at time of collection. For data provided by mail, follow-up telephone calls to clarify missing data were made. If necessary, incomplete or ambiguous results were corrected with follow-up telephone calls and/or additional appointments with research staff. Data were coded and double entered directly on a computer by graduate students. Once files were created, frequency distributions for the measures were examined to check for missing information and out-of-range values. System files were then created once all errors in the raw data were corrected.

Chapter IV: Results

Participant Characteristics

Participant characteristics can be seen in Table 4. Briefly, women in the current study (M_{age} = 56.02 ±10.99) were married (70.8%), Caucasian (85.4%), employed full-time (43.8%), highly educated (70.8%), and earning at least $75,000 per year (52.1%).

Specific Aim 1: Differential Exercise Duration Effects on Cognitive Functioning

Task Switching

Single Task Block

Linear regression analyses did not indicate any significant covariates of change in the single task block over time in the exercise activity. RM-ANOVAs revealed a significant time effect for both accuracy and reaction time (*p*s < .01) such that women were more accurate but slower over time across activities. There was also a significant time by activity interaction for reaction time (*p* = .001) driven by significantly longer reaction time in the resting activity over time. Three-way analyses revealed a moderately-sized three-way interaction for reaction time [$F(2,44)=11.87$, P =.21, η^2 = .07], which was then decomposed within groups. This examination revealed a significant time by activity interaction in the 10-minute group [$F(1,13)=13.56$, P =.003, η^2 = .51] and a marginally significant time by activity interaction in the 30-minute group [$F(1,16)=3.19$, P =.09, η^2 = .17]. Specifically, women performed significantly slower after rest compared with after exercise in the 10- (*d* = -.96) and 30-minute (*d* = -.52) groups. The time by activity interaction in the 20-minute group mirrored this same trend of longer reaction time after rest, but the interaction was nonsignificant with a small effect (*p* = .44, *d* = -.23).

The three-way interaction between time, activity, and group for accuracy on the single task block was nonsignificant with a negligible effect size (p = .87, η^2 = .01), therefore groups were collapsed for subsequent analysis. As such, the two-way (i.e., time by activity) interaction in the full sample was nonsignificant (p = .56, d = .09). Means (SE) and effect sizes for the single task block variables can be seen in Table 5.

Mixed Block – Switch Trials

Again, linear regression analyses revealed no significant covariates of change in either accuracy or reaction time on the switch trials of the mixed block. RM-ANOVAs revealed significant time effects for both accuracy and reaction time (ps < .02) such that women performed more accurately and faster over time. Analyses revealed a moderately sized effect for the three-way interaction of time, activity, and group on switch trial accuracy [$F(2,44)$=1.60, P =.21, η^2 = .07]. Further exploring this moderate three-way interaction revealed no significant or meaningful time by activity interactions within the 10-, 20-, or 30-minute groups (ps > .17, ds < .17).

The three-way interaction for reaction time was nonsignificant with a negligible effect size (p = .84, η^2 = .01). Groups were then collapsed for further analysis of switch trial reaction time in the full sample. The two-way RM-ANOVA revealed a nonsignificant and negligible time by activity interaction (p = .31, d = -.15). Means (SE) and effect sizes for the switch trial variables can be found in Table 6.

Mixed Block – Repeat Trials

Linear regression analyses indicated that education was significantly associated with change in accuracy over time in the exercise activity and was therefore added as a covariate to the accuracy model. Three-way repeated measures ANOVAs revealed a significant time effect for reaction time on the repeat trials (p = .004), again with women performing faster over time. There was also a significant time by group interaction for accuracy (p = .04) which was driven by significant increases in accuracy over time in both the 10- and 30-minute conditions (ps < .03). Analyses did not reveal significant three-way interactions for either accuracy (p = .83, η^2 = .01) or reaction time (p = .64, η^2 = .02), therefore groups were subsequently collapsed. Two-way RM-ANOVAs in the full sample revealed nonsignificant time by activity interactions for both accuracy (p = .08, d = .03) and reaction time (p = .73, d = .05). Means (SE) and effect sizes for the repeat trials are depicted in Table 7.

Switch Cost

Linear regression analyses revealed no significant predictors of change in switch cost over time in the exercise activity. RM-ANOVAs revealed a significant time effect for switch cost (p <.001), such that women significantly reduced their cost of switching over time. The three-way interaction between time, activity, and group was nonsignificant (p = .89, η^2 = .01), and thus further two-way RM-ANOVAs were conducted in the full sample. Analyses in the full sample revealed a nonsignificant two-way interaction between time and activity for switch cost (p = .51, d = .10). Switch cost Means (SE) and effect size can be seen in Table 8.

Spatial Working Memory

Initial analyses including task item (e.g., 2-, 3-, and 4-item components) as a within-subjects factor indicated a nonsignificant 4-way interaction, thus 3-way repeated measures analyses of variance were conducted separately for each task item.

2-item factor

Linear regression analyses indicated age was significantly associated with changes in accuracy and reaction time on the 2-item factor and was thus added as a covariate to all models. Three-way RM-ANOVAs revealed a significant time effect for both accuracy and reaction time (*p*s < .02) such that women were significantly more accurate and faster over time. There was also a marginally significant time by group interaction (*p* = .06). Pairwise comparisons indicated that women in the 10-minute group had significantly lower accuracy scores than women in both the 20- and 30-minute groups (*p*s < .05). For reaction time, a significant time by activity interaction emerged (*p* = .04). Specifically, women in both activities performed significantly faster over time (*p*s < .04), however women in the exercise activity had a two-fold shorter response time compared with those in the rest activity. Analyses revealed no significant or meaningful three-way interactions for either accuracy (*p* = .84, η^2 = .01) or reaction time (*p* =.60, η^2 = .02), therefore groups were collapsed. Two-way RM-ANOVAs in the full sample revealed a nonsignificant time by activity interaction for accuracy (*p* = .12, *d* = -.15). However, a significant time by activity interaction emerged for reaction time [F(1,45)=4.81, *P*=.03, η^2 = .10], such that women performed significantly faster on the 2-item factor after exercise compared with after rest (*d* = -.21), regardless of group placement (i.e., time spent exercising/resting). Means (SE) and effect sizes for the 2-item factor can be seen in Table 9.

3-item factor

Again, linear regression analyses highlighted age as a significant predictor of changes in accuracy and reaction time on the Spatial Working Memory 3-item factor and was therefore added to the models as a covariate. Three-way RM-ANOVAs revealed a significant activity effect for accuracy on the 3-item factor (*p* = .01) as well as marginally significant time (*p* = .09) and time by activity (*p* = .08) effects. However, pairwise comparisons suggested that the two activities did not significantly differ at either time point (*p*s > .49) nor did either activity significantly change in accuracy over time (*p*s > .32). There was also a significant time effect for reaction time on the 3-item factor (*p* = .001) such that women performed significantly faster over time. Analyses revealed nonsignificant three-way interactions for both accuracy (*p* = .71, η^2 = .02) and reaction time (*p* = .66, η^2 = .02), therefore groups were collapsed for subsequent analyses. Two-way RM-ANOVAs in the full sample revealed a marginally significant time by activity interaction on accuracy [F(1,44)=3.54, *P*=.07, η^2 = .07], such that women in the current study improved their accuracy scores after exercise compared with after rest (*d* = .18) regardless of how long they spent exercising and resting. There was no significant two-way interaction between time and activity for 3-item reaction time (*p* = .26, *d* = .04). 3-item factor Means (SE) and effect sizes can be seen in Table 10.

4-item factor

Linear regression analyses indicated time since diagnosis significantly predicted changes in reaction time on the 4-item Spatial Working Memory factor after exercise and was therefore added to the reaction time models. Three-way RM-ANOVAs revealed a significant time effect for reaction time (*p* = .01) with women performing significantly faster over time. Both three-way interactions between time, activity, and condition were nonsignificant with negligible effect sizes for accuracy (*p* = .30, η^2 = .05) and reaction time (*p* = .84, η^2 = .01), therefore groups were collapsed. Two-way RM-ANOVAs in the full sample evidenced a nonsignificant time by activity interaction on accuracy (*p* = .20, *d* = .19). Similarly for reaction time, the interaction between time and activity in the full sample was nonsignificant (*p* = .60, *d* = .13). Means (SE) and effect sizes for the 4-item factor can be seen in Table 11.

Flanker

Initial analyses including task item (e.g., congruent and incongruent) as a within-subjects factor indicated a nonsignificant 4-way interaction, thus 3-way repeated measures analyses of variance were conducted separately for each task item.

Congruent factor

Linear regression analyses indicated age and education level were significantly related to changes in reaction time for the congruent factor and were thus entered into the appropriate RM-ANOVA. Three-way analyses revealed nonsignificant and negligible effect sizes for both accuracy (p = .65, η^2 = .02) and reaction time (p = .54, η^2 = .03) on the congruent Flanker task. After collapsing groups across the sample, two-way RM-ANOVAs revealed a nonsignificant interaction between time and activity on accuracy (p = .72, d = .06) of the congruent factor as well as reaction time (p = .63, d = .02). Means (SE) and effect sizes for the congruent factor can be seen in Table 12.

Incongruent factor

Linear regression analyses did not indicate any significant predictors in changes in accuracy or reaction time on the incongruent Flanker task after exercise. Three-way RM-ANOVAs revealed a significant time effect for reaction time (p = .001) such that women performed significantly slower over time. Analyses also revealed a marginally significant three-way interaction between time, activity, and group on incongruent Flanker accuracy [$F(2,42)=2.57$, P =.09, η^2 = .11]. Decomposing this interaction within groups revealed no significant interactions between time and activity (ps > .20), however the large effect size in the 20-minute group (d = .75) suggests that the interaction between time and activity in this group is meaningful and important. Specifically, women in the 20-minute group demonstrated longer reaction time after rest compared with no changes after exercise.

The three-way interaction for reaction time was nonsignificant with a negligible effect size (p = .51, η^2 = .03), therefore groups were collapsed. Two-way RM-ANOVAs in the full sample revealed a nonsignificant time by activity interaction for reaction time (p = .71, d = .07). Incongruent factor means (SE) and effect sizes are displayed in Table 13.

Interference Cost

Linear regression analyses did not reveal significant predictors of change in reaction time interference cost after exercise. Three-way RM-ANOVAs did not reveal a significant or meaningful interaction between time, activity, and group on interference cost (p = .67, η^2 = .02), therefore groups were collapsed across the sample. Subsequent two-way RM-ANOVAs did not reveal a significant or meaningful time by activity interaction (p = .53, d = .09). Means (SE) and effect size for interference cost can be seen in Table 14.

Processing Speed

Linear regression analyses did not reveal any significant covariates for processing speed accuracy or reaction time. Three-way RM-ANOVAs revealed significant time effects for both accuracy and reaction time on the processing speed task (ps < .04). In addition, there was a significant time by activity interaction for reaction time [$F(1,47)=5.84$, P =.02, η^2 = .11], such that women performed significantly faster after exercise compared with after rest. Analyses also revealed a moderately-sized three-way interaction for reaction time [$F(2,45)=1.60$, P =.21, η^2 = .07]. Upon decomposing this interaction within groups, no significant or meaningful time by activity interactions emerged in either the 10- or 30-minute groups (ps > .20, ds < -.10).

However, there was a significant time by activity interaction in the 20-minute group [$F(1,15)=6.43$, $P=.04$, $\eta^2 = .26$], such that women in the exercise activity significantly reduced their reaction time over time compared with women in the resting activity ($d = -.24$).

The three-way interaction between time, activity, and group was nonsignificant for accuracy with a negligible effect size ($p = .41$, $\eta^2 = .04$), therefore groups were collapsed. Two-way RM-ANOVAs for accuracy in the full sample revealed a nonsignificant interaction between time and activity ($p = .52$, $d = .07$). Processing speed means (SE) and effect sizes are displayed in Table 15.

Specific Aim 2: Moderating Variables

Full cancer-related characteristics, and means and standard deviations for physiological measures and psychosocial questionnaires can be found in Tables 16-18. Generally, participants underwent radiation (64.6%) or chemotherapy (66.7%) treatment for cancer and had a disease stage ≥ Stage 2 (56.2%). Overall, participants were on average overweight ($M = 28.95 \pm 6.39$ BMI) and low fit ($M = 23.33 \pm 4.74$ ml/kg), however were meeting physical activity guidelines (54.3% ≥ 30 min/day MVPA; $M = 37.41 \pm 20.66$ min/day MVPA). The outcomes that met our moderate effect size criteria for analysis ($d \geq .50$; Cohen, 1977) were reaction time on the single task block of the task switching paradigm in the 10- and 30-minute groups and accuracy on the incongruent factor of the flanker task in the 20-minute group. A full correlation matrix depicting all correlations with at least marginal significance can be seen in Table 19.

Task Switching Single Task Block Reaction Time – 10 minute group (d = -.96).

Bivariate correlations did not reveal any significant associations between change in reaction time on the single task block and any of the predicted moderators. However, several marginally significant relationships emerged. Disease stage, radiation treatment, FACT-Cog Perceptions of Cognitive Abilities subscale, and FACT-Cog Comments from Others subscale were all marginally associated with changes in reaction time on the single task block after exercise. Specifically, increased reaction time (e.g., slower performance) was marginally associated with higher disease stage, past radiation treatment, and higher quality of life regarding perceived cognitive abilities and comments from others.

Task Switching Single Task Block Reaction Time – 30 minute group (d = -.52).

Bivariate correlations did not reveal any significant or marginally significant associations between single task block reaction time after exercise and potential moderators within the 30 minute group.

Flanker Incongruent Accuracy – 20 minute group (d = .75).

Bivariate correlations suggested significant relationships between change in incongruent flanker accuracy and months since chemotherapy and average daily MVPA. Specifically, decreased accuracy after exercise was associated with more recent chemotherapy treatment and lower levels of average daily MVPA. Marginally significant associations were also present between decreased incongruent flanker accuracy and fewer months of radiation therapy and lower levels of average daily light PA.

Summary

Regarding the primary aim of the project, there was a moderately-sized three-way interaction for reaction time on the single task block in the task switching paradigm. Further decomposition of this interaction revealed significantly longer reaction times (i.e., slower performance) after rest compared with after exercise in both the 10- (*d* = -.96) and 30-minute (*d*

= -.52) groups. Additionally, a moderately-sized and marginally significant three-way interaction for accuracy on the incongruent factor of the flanker task emerged, which was driven by decreased accuracy over time in the resting activity compared with the exercise activity within the 20-minute group (*d* = .75). Lastly, there was a meaningful three-way interaction on processing speed reaction time driven by a significant time by activity interaction in the 20-minute group such that women shortened their reaction time (e.g., performed faster) after exercise compared with after rest (*d* = -.24).

Aside from these effects, there did not appear to be other significant or meaningful differences in how exercise influenced cognitive function over time compared with rest as a function of the length of time spent exercising/resting. In other words, none of the time groups significantly differed from one another with respect to how exercise and rest differentially influenced cognitive functioning over time. However, when collapsing the groups, two time by activity interactions in the full sample emerged for faster reaction time and improved accuracy on the 2-item and 3-item factors of the spatial working memory task, respectively (*d*s > .18), regardless of time spent exercising and resting.

With respect to the secondary aim, several cancer-related, psychosocial, and physical activity variables were marginally significantly and significantly associated with changes in cognitive function over time in the exercise activity. Specifically, poorer performance was associated with higher disease stage, past treatment for longer periods of time, greater quality of life, and lower levels of physical activity. The next section further discusses the implications of these findings.

Chapter V: Discussion

The present study was designed to determine if the effects of exercise versus rest over time on cognitive function in breast cancer survivors differed as a function of time spent exercising. This study is the first, to our knowledge, to examine the potential dose-response relationship of acute exercise duration on cognition in cancer survivors. Women in the current project completed an exercise and resting session with a battery of cognitive tasks immediately before and after each activity bout. To determine the effects of varying exercise durations, women were also randomized to one of three time groups (i.e., 10, 20, or 30 minutes), signifying the length of time spent exercising and resting. Regarding the primary aim of the study, there were several meaningful three-way interactions between time, activity, and group, suggesting that the length of time spent either exercising or resting is important for changes in cognition over time in this cancer cohort. Notably, the effect sizes for these interactions ranged from small to large in magnitude suggesting the differential effects of exercise and rest over time may have meaningful and important contributions for not only attenuating cognitive declines, but also improving some domains of cognition, after breast cancer. Additionally, when analyses were conducted in the full sample, women evidenced improvements on a working memory task after exercise regardless of group placement, suggesting that for certain domains of cognition some exercise is better than none. Regarding the secondary aim, there were several interesting correlations that may inform the development of future interventions in cancer survivors for improved cognitive health. Specifically, regular physical activity levels, treatment history, time since diagnosis, and quality of life emerged as potentially important factors in the relationship between acute exercise and cognition. Although these findings only partially support the primary hypothesis, we believe this study provides preliminary evidence for the selective influence of both physical activity and rest on cognitive functioning in breast cancer survivors.

Analyses revealed a meaningful three-way interaction between time, activity, and group for single block reaction time of the Task Switch. When decomposing this interaction within groups, there were significant and marginally significant time by activity interactions and large and moderate effects within the 10-minute (*d* = -.96) and 30-minute (*d* = -.52) groups, respectively. Interestingly, these effects were driven by significantly longer reaction time (e.g., slower performance) after rest rather than shorter reaction time (e.g., faster performance) after exercise. These findings contrast past work demonstrating significantly shortened reaction time after acute bouts of moderate-intensity exercise (McMorris & Hale, 2012; McMorris et al., 2008, Tomporowski et al., 2003), suggesting that acute exercise simply may not provide enough stimulus to influence this domain of cognition in breast cancer survivors. Instead, these results suggest that rather than exercise being the agent of cognitive change, there may have been a key component of the resting activity that contributed to slower performance. Given that 89.7% of the current sample opted to watch television during their resting sessions, it is possible that screen time in the present study resulted in negative cognitive performance. Indeed, there is a growing body of evidence highlighting the negative influence of television viewing on varying domains of cognition across the lifespan (Armstrong & Greenberg, 1990; Landhuis et al., 2007; Takeuchi et al., 2013), suggesting that while exercise did not contribute to improved cognitive performance in breast cancer survivors, it still may be a more appropriate choice than television viewing for maintaining cognitive processes in the short-term. Future research should explore the use of different control groups for acute exercise in breast cancer survivors, specifically rest with no television.

Interestingly, there were significant time effects for both accuracy and reaction time in the single task block such that women in both activities performed slower, but more accurately, over time. Thus, it is possible that the women engaged in a speed-accuracy tradeoff, sacrificing speed for accuracy. This phenomenon has been of interest to cognitive scientists for over 40 years, specifically in the field of acute exercise and cognition. Several studies have discussed the inherent differences between the motoric responses of cognitive tasks utilized and their underlying biological processes. For example, Yanagisawa (2009) argued that if decreases in P3 latency (indicative of increased speed of classification of a stimulus on the event-related potential waveform) accompanied decreases in response time, then these changes are likely due to increased arousal as a result of exercise. However, if P3 latency remains unchanged but reaction time decreases, then it is possible that the participant began motor preparation and made a response selection before fully comprehending and classifying the stimulus. Interestingly, as this example shows, most of theoretical arguments for speed-accuracy tradeoffs contend that individuals sacrifice accuracy for increased speed. However, if women in the current study did indeed engage in such a tradeoff, it was in the opposite direction thus preserving accuracy scores and simultaneously sacrificing reaction time. This may be due to the demographic makeup of the present sample. Salthouse (1979) found a greater bias towards accuracy in older subjects compared with younger ones. Given that almost half of the current sample was aged 60 or older (45.8%), age may have played a role in accuracy preservation. Additionally, breast cancer survivors are, for the most part, highly motivated towards research engagement and thus may have worked towards preserving accuracy scores in an attempt to provide "good results" for the research team. Further research should attempt to examine how this specific cancer cohort engages in research to disentangle population-specific differences on cognitive performance.

However, we are unable to definitively state that women in the current study purposefully engaged in a speed-accuracy tradeoff without additional neuroelectric measures for assessing event-related potentials and P3 amplitudes and latencies. Future research should include such assessments to determine if moderate-intensity exercise contributes to changes in both behavioral response time as well as neuroelectric components of the brain.

Notably, the effect sizes for these interactions ranged from moderate (*d* = -.52) to large (*d* = -.96), suggesting that the interaction between exercise and rest over time is important and meaningful for future practice in this cancer cohort. Interestingly, the 10-minute group had the largest effect between exercise and rest over time (*d* = -.96) compared with the 20- and 30-minute groups. This may be due to such a short period of time between cognitive task batteries. Women may have felt like they did not receive much of a "break" between cognitive task batteries and were simply fatigued, dreading a repeat of the cognitive battery so soon after the first one. In keeping with this theory, women in the 30-minute group may have felt the resting session was too long and were therefore bored which may then have contributed to poor cognitive performance. These effects may also be due to the differential brain activation in exercise and resting activities. Specifically, women who exercised for 10 minutes moved to a different room and were engaged in goal-oriented behavior during the exercise activity, while women who rested remained in the same room for 10 minutes and their minds were allowed to wander. It is then possible that during the resting activity the default mode network (DMN) of the brain was activated. Over the past decade, a considerable body of work has examined the DMN and its activation during wakeful rest (Raichle et al., 2007; Buckner, Andrews-Hanna, & Schacter, 2008). Activation of the DMN is associated with internally-directed thoughts, passive rest, and mind wandering and thus deactivates other areas of the brain associated with goal- or task-oriented behavior. While the DMN was likely activated during all resting sessions, it is possible that 10 minutes was not enough time for women in the resting activity to finish their internally-directed thoughts which when coupled with their fatigue subsequently slowed performance on the second cognitive battery. More work is certainly warranted to further explore the detrimental influence of rest on this domain of cognitive function and what underlying pathways may be driving these decrements.

Of further interest is the lack of meaningful interactions in the mixed task block. Quesnel and colleagues (2009) have suggested that only retrieval capacity of already stored information may be impaired after treatment for breast cancer. This aligns with the current findings such that participants only demonstrated significant differences between exercise and rest over time on the single task block. This task block did not tap into the cognitive flexibility domain of executive function as it did not require participants to switch between sets; they were simply asked to respond to a number based on well-known and widespread classifications already stored in their memory (i.e., high/low and odd/even). It will be important to further determine if indeed breast cancer survivors only suffer impairments in retrieval or simple processing speed rather than cognitive flexibility, as the current findings suggest, to not only better tailor interventions and programs aimed at improving cognitive health after cancer, but also to improve our knowledge of cancer-related cognitive impairment.

There was also a marginally significant and moderately-sized time by activity by group interaction on accuracy on the incongruent flanker factor, suggesting there were differences in how exercise and rest differentially influenced this cognitive domain based on the length of time spent exercising and resting. Upon decomposing this 3-way interaction further, there were no significant time by activity interactions within any of the three groups. However, there was a large effect within the 20-minute group (*d* = .75) such that, similar to the single task block, women did not demonstrate significant improvements in accuracy after exercise, but rather performed less accurately after rest. Past research examining the effects of acute aerobic exercise on accuracy is equivocal as some studies have found improvements in accuracy 30 minutes after exercise cessation (Joyce et al., 2009), others no change (McMorris & Graydon, 1996), and a recent meta-analysis has even suggested that exercise may result in small to moderate detrimental effects on accuracy (McMorris et al., 2011). It is therefore possible that for this specific cancer cohort, while exercise may not improve attention accuracy, it works to attenuate declines that may normally occur throughout the day after seated rest. This effect may also be due to a ceiling effect as women in the 20-minute group in the exercise activity scored a mean 97% on the task before and after exercise. While we attempted to avoid such an effect through the use of an interstimulus interval jitter and short stimulus presentation duration, it is quite possible that there was simply no room for significant improvements after the exercise session thus making this maintenance effect important.

More importantly, the large effect between exercise and rest over time (*d* = .75) was evidenced within the 20-minute group. This finding is in line with several theories that have hypothesized an inverted-U effect of exercise, such that moderate arousal/activation results in optimal performance (Yerkes & Dodson, 1908; Davey, 1973; Arcelin et al., 1997; McMorris & Hale, 2012). While the large effect of this interaction suggests that 20 minutes of exercise compared with rest is meaningful for maintaining selective attention in breast cancer survivors, this effect was driven by significant declines in accuracy after rest. Similar to task switching, there may have been a component of the resting session that contributed to poorer performance. It has been argued that accuracy scores on tasks such as the flanker are typically in place only to keep participants honest and fully processing the task at hand (McMorris & Hale, 2012). Therefore, while 20 minutes of moderate-intensity exercise arguably maintained such comprehension and is therefore still a better choice than resting, more work is warranted to explore the influence of acute exercise on attention in breast cancer survivors.

Finally, there was one moderately-sized and meaningful three-way interaction for Processing speed reaction time that was driven by a significant time by activity interaction in the 20-minute group. Specifically, women in this group significantly shortened their reaction time after exercise compared with after rest (*d* = -.24). While the Cohen's D effect size is smaller than other relationships in the current study, the partial eta squared effect size for this 2-way interaction in the 20-minute group was quite large (η^2 = .26), a discrepancy that is likely due to greater variation in this task. Taken together with the significance of the interaction, we believe this to be a meaningful effect worth discussing. As such, this finding aligns with past research demonstrating significant reductions in reaction time after acute bouts of moderate-intensity exercise. This result also contributes to and expands upon the inverted-U hypothesis (Yerkes & Dodson, 1908; Davey, 1973), such that exercise duration may follow a similar bell curve as intensity on the x-axis such that a moderate length of exercise produces the most optimal results on speed of processing (Ludyga et al., 2016).

This three-way interaction is the only one in the present study driven by significant improvements over time by the exercise activity compared with the resting activity, suggesting that this domain of cognitive function may be positively influenced by exercise in breast cancer survivors. While not a domain of executive function, processing speed has been shown to work alongside higher order processes and is also one of the most reported cognitive deficits by cancer survivors (Takeuchi et al., 2011; Kopplemans et al., 2012; Wefel et al., 2011). Taken together with the current findings, it is possible that physical activity and processing speed share similar biological pathways by which exercise may exert more robust effects on this cognitive domain. As such, future research is warranted to explore the role of acute exercise, specifically 20 minutes, for improving processing speed after cancer.

It is also worth discussing meaningful time by activity interactions in the full sample when analyses indicated no significant differences between the three different time groups. For reaction time on the 2-item factor of the spatial working memory task, women in the current study performed significantly faster after exercise. On the 3-item factor, women were significantly more accurate after exercise. Importantly, these interactions were irrespective of the amount of time spent exercising or resting. These findings are generally in agreement with the literature highlighting the positive influence of acute exercise on improved reaction time on working memory tasks specifically (McMorris et al., 2011). Improvements in accuracy after exercise regardless of time spent walking is also an encouraging finding that contributes to the equivocal acute exercise-cognitive accuracy literature. Similar to processing speed, the partial eta squared effect sizes for these interactions ($\eta^2 > .07$) were moderately sized with smaller Cohen's D effects ($d = .18$), likely due to larger standard deviations on this specific task. Future research should explore the inter-individual differences on such tasks to further determine what role individual differences and underlying latent profiles may play in the meaningfulness of this interaction.

Overall, findings from the present study suggest that exercise's influence on cognition in breast cancer survivors is selective by length of time spent exercising and resting, accuracy or reaction time, and cognitive task type. There were only a few meaningful three-way interactions between time, activity, and group; however, the magnitudes of these effects were primarily moderate or large in size suggesting that each interaction is meaningful and important for future practice. When examined separately, each effect carries weight, but when taken together fail to paint a patently clear picture for the dose-response effects of acute exercise on cognition in cancer. There was a notable difference in the groups influenced by rest and exercise over time in the current study, seemingly dependent on cognitive domain. The 10- and 30-minute groups performed significantly slower on the single task block after rest whereas the 20-minute group performed less accurately on the flanker incongruent factor after rest but faster on the processing speed task after exercise. Further, spatial working memory accuracy and reaction time were improved after exercise regardless of group placement. While this discrepancy may align with the documented differential effect of exercise on accuracy and reaction time (McMorris et al., 2011), it certainly does not follow any of the theoretical discussions surrounding acute exercise's influence on cognitive function.

There are several plausible explanations for the findings reported herein that warrant further discussion. The first of these is increased levels of boredom during the cognitive task assessment, which may have served to mask potential exercise effects. While objective neuropsychological tests are common in many research fields, participants often find them unengaging and effortful (D'Angiulli & LeBeau, 2002; Healy et al., 2004; Lumsden et al., 2016). DeRight and Jorgensen (2014) found that if participants are bored by such cognitive assessments, data quality is more likely to be negatively impacted, subsequently producing noise and suboptimal performance. Specifically, in this study's design, we were asking women to complete two full batteries of cognitive testing in one day, something that anecdotally displeased participants. Future research should investigate the influence of boredom during cognitive testing and explore whether adding certain game-like features, as proposed by Lumsden (2016), to standard neuropsychological tests may help prevent participants from “checking out” during such testing. However, it will be important to ensure that these features don’t create extra “load” and consequently poor performance. Qualitative feedback following such novel testing should be assessed to further explore perceived boredom or fatigue during neuropsychological testing.

Another potential explanation for the equivocal findings reported herein may be due to the repeated measures cognitive task protocol used in the present study. McMorris and Hale (2012) explored the potential moderating effect of counterbalancing or randomizing cognitive tasks within a battery and found surprisingly larger effect sizes for reaction time when this method was employed rather than a standard pre- and post-exercise protocol: an unexpected finding given the logical assumption that greater learning effects would take place using a pre- and post-protocol. The authors further discussed exercise anticipation when performing the cognitive task immediately pre-exercise, which may have contributed to increased levels of stress. Thus, participants may have been performing above their normal “rest” or control levels subsequently masking any true effect of exercise on cognition. Indeed, other studies have found increases in concentrations of plasma catecholamines in anticipation of immediate exercise (Mason et al., 1973). Therefore, our use of a pre- and post-cognitive testing protocol may have tempered additional exercise effects. We opted to use this protocol in an attempt to avoid wash out effects due to cognitive decay after exercise given our smaller sample size. However, future studies with larger samples should employ a counterbalanced cognitive testing protocol to determine if indeed there were effects of exercise lost to pre-exercise stress in the current study. Heightened pre-exercise stress may also be combated through blinding the women to which session they would be performing until immediately after the cognitive battery is completed. As such, the women will be told at the beginning of the study that they will have a 50% chance of exercising at each session. Of course, women should be briefed as to the true protocol at the end of the study, but this procedure would prevent the use of process of elimination as to what activity would be performed as women progress throughout the study.

There is also evidence suggesting that baseline expectations of exercise may mediate the influence of an acute bout of exercise on a number of psychological and physiological outcomes. Specifically, Mothes and colleagues (2016) found that individuals with more positive habitual exercise expectations demonstrated improvements in psychological (e.g., anxiety) and physiological (e.g., blood pressure, alpha waveform power) factors after an acute bout of exercise. However, breast cancer survivors have demonstrated mixed to poor expectations for the capacity of exercise to improve long-term negative effects of treatment *despite* being motivated to engage in exercise (Hirschey et al., 2016). These findings may have implications for the impact that future physical activity interventions have on cognitive health for breast cancer survivors. Specifically, future research might determine the extent to which targeting and/or manipulating these physical activity outcome expectations may work to improve cognitive function in acute settings. If indeed such expectations result in better cognitive outcomes, when added together these sessions may produce overall better health benefits in the context of long-term physical activity interventions.

We would be remiss in not addressing a likely explanation for the mixed findings herein; an acute bout of moderate-intensity exercise may not be robust enough to significantly and meaningfully improve cancer-related cognitive impairment after breast cancer. Rather, this specific population may need chronic exercise training to elicit larger cognitive benefits. It is also possible that breast cancer survivors suffer impairments in aspects of cognitive function that we do not fully understand, and subsequently fail to test. Several researchers have explored the interrelatedness of executive control processes due to their differing definitions yet many similarities. Redick and Engles (2006) explored the prediction of attention by working memory and Diamond (2013) has discussed how cognitive flexibility may simply be an extension of working memory and inhibition. Miyake and colleagues (2000) went one step further and conducted structural equation modeling to identify the diversity and unity of these processes. The model fit was best when each domain was independent yet freely loading on one another. However, when the correlations were set to zero (i.e., indicating completely separate factors) the model no longer fit the data. These findings highlight both unity and diversity among these control processes; although they are indeed independent constructs, they share similar characteristics and thus may share neural pathways. Therefore, it will be important for future researchers to identify which specific cognitive processes are indeed impaired after cancer. It is possible that there is only one pathway impaired that we are partially targeting through these cognitive batteries, but we are still failing to fully capture the entire domain. Garnering a better understanding of cancer-related cognitive impairment will then allow researchers to more effectively test the effects of lifestyle behaviors, such as exercise, on cognition.

It is also possible that the discrepancies between perceptions of cognitive impairment and objectively-measured cognitive function via neuropsychological measures contribute to these findings. A recent review in this field has suggested that subjective cognitive dysfunction and objective cognitive dysfunction are indeed uncorrelated in cancer survivors (Pullens et al., 2010). However, the authors noted that subjective cognitive dysfunction remains an important determinant of quality of life in breast cancer survivors and may actually be more significantly associated with high levels of fatigue and psychological distress. Valentine and Meyers (2001) have similarly called for further research to disentangle the complex relationship between cognitive function and psychological factors such as depression and fatigue to determine their inter-relatedness. However, the present sample was relative high functioning and active, potentially masking effects that may be larger in magnitude in more diseased, low active survivors. Indeed, most of the women in the current study scored ≥ 21 on the TICS-M during prescreening (89.6%), suggesting that the sample may not have been, on average, truly cognitively impaired. It will be important for future work to not only determine which psychosocial factors may benefit the most from exercise, but also how acute exercise may contribute to subjective and objective cognitive impairment in more clinically-impaired survivors (i.e., depressed, sedentary).

Secondary analyses revealed several interesting relationships between potential moderators that contribute to such knowledge of cancer-related cognitive impairment and exercise. While cardiorespiratory fitness did not emerge as significantly correlated to change in cognition, several cancer-related, physical activity, and cognitive perception variables *were* associated with change in objectively-measured cognitive function after exercise. Specifically, higher disease stage and no radiation treatment were marginally associated with slower performance on the single task block exercise (*p*s < .09), and shorter length of time since chemotherapy and fewer months of radiation were related to decreased accuracy on the incongruent factor of the flanker task (*p*s < .06). Taken together, these findings suggest that more advanced cancer may indeed negatively influence acute exercise's influence on reaction time. Additionally, it seems that being further out from cancer treatment, specifically chemotherapy, may be more beneficial for accuracy. This finding is encouraging in that it suggests that even if women may suffer short term detrimental cognitive effects of chemotherapy, these impairments may diminish over time. Future work should explore the underlying mechanisms of the relationship between acute exercise and cognition in breast cancer survivors to determine chemotherapy's individual role in cancer-related cognitive impairment. Interestingly, *not* having received radiation treatment was associated with slower cognitive performance. It will be important to further explore the interaction between exercise and radiation treatment to determine if there are shared underlying pathways thus making exercise a more robust mode of improving cognition in those who underwent radiation therapy compared with those who did not.

The significant associations between lower levels of average daily light and moderate-to-vigorous physical activity and poorer cognitive performance partially support our hypothesis that higher levels of physical activity may work to positively moderate the relationship between acute exercise and cognitive function. This finding is promising such that by engaging in a positive lifestyle behavior (i.e., physical activity), cancer survivors may attenuate declines in cognitive function and position themselves to cognitively benefit more from an acute bout of moderate-intensity exercise. Even more interesting is the association between higher levels of perceived cognitive abilities and comments from others on the FACT-Cog questionnaire with slower reaction time after exercise. In concert with the literature demonstrating differences between objective and subjective cognitive impairment, it will be important for future researchers to determine how such cognitive perceptions are related to, and may subsequently influence, objective measures of cognition after cancer.

Strengths

There are several strengths worth noting in the present study. First, the current study is the first of its kind in that it explored the potential dose-response relationship of exercise duration on the influence of cognitive function over time in breast cancer survivors. This project is novel through its contribution to the not only the acute exercise-cognitive literature, but also to the field of exercise oncology. Second, the cognitive tasks employed are objective, well-validated and reliable measures of cognitive function across the lifespan. However, more work should be conducted to validate such measures in cancer populations specifically. Third, physical activity was measured using accelerometry, an objective, reliable method for capturing such data. Finally, all cognitive protocols and exercise and resting activities were employed by a trained exercise specialist to ensure standardized testing with minimal confounding variables.

Limitations

Of course, there are limitations to the current project. The present study had a small sample size (i.e., < 20 subjects per group) and was comprised of primarily white, highly educated women, therefore findings may not be generalizable across all breast cancer survivors. These findings are relevant to only four tasks measuring four domains of cognitive function. Future research examining the effect of acute exercise on other, or even the same, domains should use a variety of tasks to ensure that the full effects of exercise on cognition are captured and not lost to task specificity. Additionally, it remains unclear how long differential effects between exercise and rest over time on cognitive function may persist beyond the end of an exercise bout. Future research should include a follow-up cognitive assessment to determine if indeed effects persist, or alternatively, decay after a certain period of time. More research is warranted to replicate and extend the findings reported herein to provide greater insight into the relationship between acute physical activity and cognition in cancer survivors.

Conclusions

This study offers some initial preliminary evidence for cognitive function maintenance and improvements after a bout of moderate-intensity aerobic exercise compared with seated rest in breast cancer survivors. However, the optimal length of exercise for providing such cognitive benefits is still unclear. While more work is certainly needed to understand the specific domains of cognition most heavily impaired by cancer and its treatment, it’s evident that exercise may still be a better alternative than rest in this cancer cohort and the present findings suggest that even some exercise is better than none. Given the meaningful effect sizes in the current study, the next steps should be to demonstrate the efficacy of the current study in a larger sample of heterogeneous breast cancer survivors. Specifically, future research should utilize a wider variety of cognitive tasks as well as psychological measures (e.g., cognitive perceptions, anxiety, depression, fatigue) pre- and post-exercise to better understand the differences between subjective and objective cancer-related cognitive impairment. As the population continues to age and more women are diagnosed with breast cancer, it will become increasingly important to understand and prevent the deleterious health effects associated with cancer treatment. The “chemo brain” phenomenon and cognitive dysfunction in breast cancer survivors still remains largely misunderstood; however, the results from the present study offer preliminary evidence for the positive relationship between exercise and cognition.

Chapter VI: Figures & Tables

Figure 1. Detailed flow of participants through the study

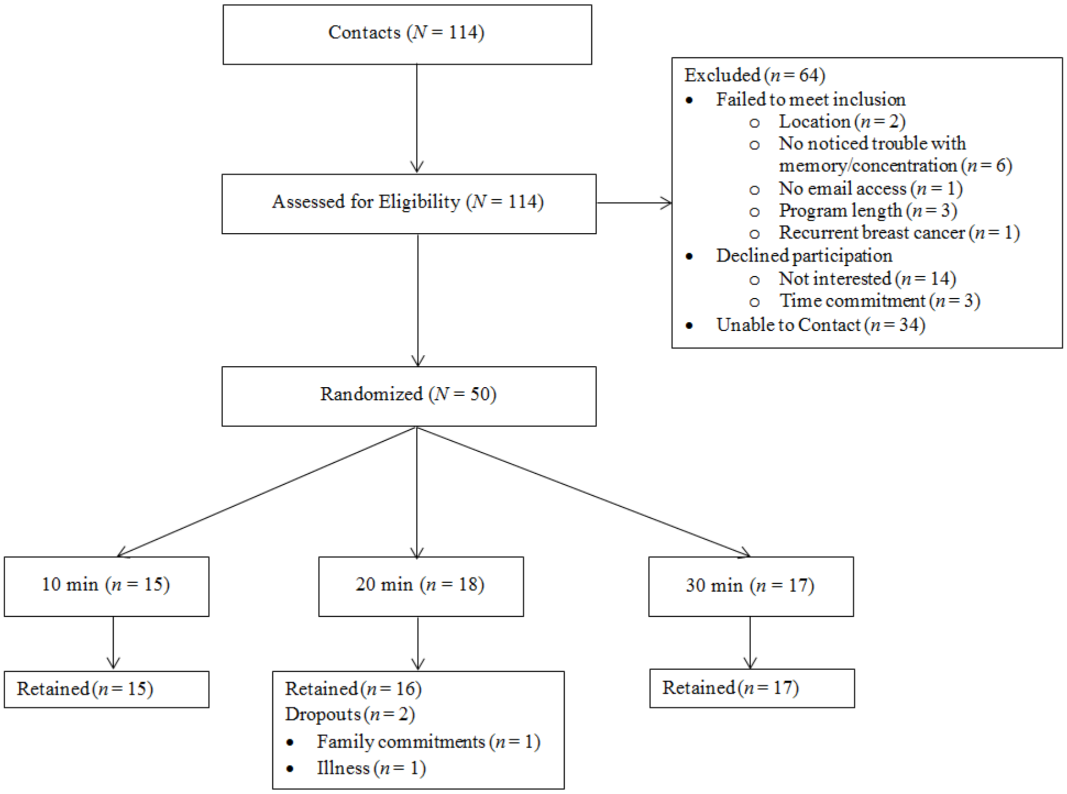

Table 1. Physical activity levels, adapted from HHS Physical Activity Guidelines, 2008

Levels of Physical Activity	**Range of Moderate-Intensity Minutes a Week**	**Summary of Overall Health Benefits**	**Comments**
Inactive	No activity beyond baseline	None	Being inactive is unhealthy.
Low	Activity beyond baseline but fewer than 150 minutes a week	Some	Low levels of activity are clearly preferable to an inactive lifestyle
Medium	150 minutes to 30 minutes a week or the equivalent amount, 75 minutes, of vigorous-intensity exercise	Substantial	Activity at the high end of this range has additional and more extensive health benefits than activity at the low end.
High	More than 300 minutes a week	Additional	Current science does not allow researchers to identify an upper limit of activity above which there are no additional health benefits.

Table 2. Physical activity recommendations, adapted from ACS guidelines on nutrition and physical activity for cancer prevention, 2012.

	Range of Moderate-Intensity Minutes a Week
Adults	Get at least 150 minutes a week, or 75 minutes of vigorous intensity (or a combination of both) – preferably spread throughout the week
Children	Get at least 1 hour of moderate or vigorous intensity activity each day, with vigorous activity at least 3 days a week

Table 3. Full inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
Over 18 years of age	Younger than 18 years of age
Breast cancer survivors who have completed primary treatment	Females who have never received a breast cancer diagnosis OR if they have received a breast cancer diagnosis and are still undergoing primary treatment (surgery, chemotherapy, radiation, etc.)
Female	Male
No past diagnosis of metastatic, stage IV, or recurrent breast cancer	Past diagnosis of metastatic, stage IV, or recurrent breast cancer
Reported trouble with memory or concentration	No reported trouble with memory or concentration
English fluency	Inability to communicate effectively in English
Personal physician’s examination and/or consent to participate in testing	Non-consent of physician
No history of dementia or organic brain syndrome	History of dementia or organic brain syndrome
Not pregnant	Pregnant
Able to walk unassisted	Unable to walk unassisted
Not currently enrolled in or participating in another exercise study	Currently enrolled in or participating in another exercise study
No diagnosed color blindness	Diagnosed with color blindness
No health reasons that may prevent ability to exercise	Other health reasons that may prevent ability to exercise
Available to attend three visits to the Exercise Psychology Lab	Unavailable to attend three visits to the Exercise Psychology Lab

Table 4. Participant demographic characteristics

Variable	**Mean(SD)/Frequency(%)**
Age	56.02(10.99)
Married	34(70.8)
Employed Full-Time	21(43.8)
Race	
Caucasian	41(85.4)
African American	5(10.4)
Biracial	2(4.2)
≥ College Graduate	34(70.8)
Earning ≥$75,000/year	25(52.1)

Table 5. Means (SE) for Task Switching Single Task Block

Measure	**Pre**	**Post**	***d***
Accuracy			
Overall			
Exercise	.95(.02)	.98(.01)	0.09
Rest	.96(.01)	.98(.00)	
Reaction Time			
10 minutes			
Exercise	754.49(33.37)	791.60(41.13)	-0.96
Rest	775.64(39.35)	944.20(47.19)	
20 minutes			
Exercise	702.10(20.76)	736.10(33.66)	-0.23
Rest	782.38(47.42)	850.70(34.83)	
30 minutes			
Exercise	700.71(15.61)	746.90(36.11)	-0.52
Rest	785.14(37.77)	893.13(44.71)	

Table 6. Means (SE) for Task Switching Mixed Switch Average

Measure	**Pre**	**Post**	***d***
Accuracy			
10 minutes			
Exercise	.94(.03)	.95(.03)	-0.17
Rest	.92(.03)	.95(.02)	
20 minutes			
Exercise	.94(.02)	.96(.01)	0.17
Rest	.94(.02)	.94(.02)	
30 minutes			
Exercise	.97(.01)	.98(.01)	-0.16
Rest	.96(.02)	.97(.01)	
Reaction Time			
Overall			
Exercise	1161.88(23.39)	1089.71(23.54)	-0.15
Rest	1139.53(25.91)	1087.09(26.51)	

Table 7. Means (SE) for Task Switching Mixed Stay Average

Measure	**Pre**	**Post**	***d***
Accuracy			
Overall			
Exercise	.95(.01)	.96(.01)	0.03
Rest	.95(.01)	.96(.01)	
Reaction Time			
Overall			
Exercise	980.08(15.83)	956.42(18.34)	0.05
Rest	986.71(21.89)	957.63(21.03)	

Table 8. Means (SE) for Task Switching Switch Cost

Measure	**Pre**	**Post**	***d***
Overall			
Exercise	199.46(16.19)	169.74(14.39)	0.10
Rest	194.50(15.18)	154.38(14.64)	

Table 9. Means (SE) for SPWM 2-item

Measure	**Pre**	**Post**	***d***
Accuracy			
Overall			
Exercise	.90(.01)	.90(.01)	-0.15
Rest	.90(.01)	.91(.01)	
Reaction Time			
Overall			
Exercise	841.40(20.40)	805.76(21.06)	-0.21
Rest	817.77(19.69)	799.74(18.32)	

Table 10. Means (SE) for SPWM 3-item

Measure	**Pre**	**Post**	***d***
Accuracy			
Overall			
Exercise	.86(.01)	.87(.01)	0.18
Rest	.86(.01)	.86(.02)	
Reaction Time			
Overall			
Exercise	885.43(18.33)	864.28(21.67)	0.04
Rest	875.42(19.42)	860.09(20.53)	

Table 11. Means (SE) for SPWM 4-item

Measure	**Pre**	**Post**	***d***
Accuracy			
Overall			
Exercise	.85(.01)	.84(.02)	-0.19
Rest	.82(.02)	.84(.01)	
Reaction Time			
Overall			
Exercise	921.64(18.33)	905.65(20.19)	0.13
Rest	925.60(19.75)	893.62(20.58)	

Table 12. Means (SE) for Flanker Congruent

Measure	**Pre**	**Post**	***d***
Accuracy			
Overall			
Exercise	.98(.01)	.98(.01)	0.06
Rest	.98(.01)	.97(.01)	
Reaction Time			
Overall			
Exercise	554.57(10.19)	572.07(12.16)	0.02
Rest	561.68(13.72)	577.39(15.41)	

Table 13. Means (SE) for Flanker Incongruent

Measure	**Pre**	**Post**	***d***
Accuracy			
10 minutes			
Exercise	.97(.01)	.95(.02)	-0.33
Rest	.93(.03)	.94(.03)	
20 minutes			
Exercise	.97(.01)	.97(.01)	0.75
Rest	.98(.01)	.96(.01)	
30 minutes			
Exercise	.97(.01)	.96(.01)	-0.02
Rest	.96(.01)	.95(.01)	
Reaction Time			
Overall			
Exercise	630.97(11.33)	651.13(14.12)	0.07
Rest	641.10(16.35)	658.59(15.36)	

Table 14. Means (SE) for Flanker Interference Cost

Measure	**Pre**	**Post**	***d***
Overall			
Exercise	84.24(9.14)	82.30(6.79)	0.09
Rest	84.57(8.27)	77.19(8.71)	

Table 15. Means (SE) for Processing Speed

Measure	**Pre**	**Post**	***d***
Accuracy			
Overall			
Exercise	.94(.01)	.95(.01)	0.07
Rest	.95(.01)	.96(.01)	
Reaction Time			
10 minutes			
Exercise	69.30(4.19)	67.87(4.33)	-0.01
Rest	70.26(4.95)	69.03(4.96)	
20 minutes			
Exercise	61.31(3.21)	57.96(3.31)	-0.24
Rest	60.14(3.23)	59.94(3.50)	
30 minutes			
Exercise	59.41(4.31)	55.88(4.07)	-0.08
Rest	58.74(4.49)	56.67(4.09)	

Table 16. Breast-cancer specific participant characteristics

Variable	**Frequency(%)**
Disease Stage	
< Stage 2	19(39.6)
≥ Stage 2	27(56.2)
Unknown	2(4.2)
Estrogen Receptor Positive	35(72.9)
Received chemotherapy	32(66.7)
≥ 3 years since chemotherapy	19(59.4)
Received radiation	31(64.6)
≥ 3 years since radiation	19(61.3)
Underwent surgery	43(89.6)

Table 17. Physiological characteristics

Variable	**Mean(SD)**
BMI	28.95(6.39)
Predicted VO2 Max	23.33(4.74)
Total MVPA	257.70(145.87)
Average Daily MVPA	37.41(20.66)

Table 18. Psychosocial characteristics

Variable	**Mean(SD)**
HADS	
Anxiety	5.51(3.57)
Depression	5.45(4.43)
FACT-B	
PWB	22.54(3.93)
SWB	20.89(5.13)
EWB	19.82(3.33)
FWB	20.67(5.26)
Gen Total Score	83.93(13.62)
Add Concerns	24.39(4.77)
Total Scale Score	108.31(16.21)
FACT-Fatigue	
Total Scale Score	39.00(9.89)
FACT-Cog	
Perceived Cog Impairments	42.43(12.47)
Impact of Perceptions on QOL	10.65(3.65)
Comments from Others	14.16(2.63)
Perceived Cog Abilities	14.24(5.16)

PWB=Physical Well-Being, SWB=Social Well-Being, EWB=Emotional Well-Being, FWB=Functional Well-Being, QOL=Quality of Life

Table 19. Bivariate correlation matrix of potential moderating variables

Variable	**Single Task Block RT 10-min**		**Single Task Block RT 30-min**		**Incongruent ACC Flanker 20-min**	
	R	*p*	R	*p*	R	*p*
Breast cancer stage	-0.473	0.088	*ns*	*ns*	*ns*	*ns*
Received radiation only	0.522	0.082	*ns*	*ns*	*ns*	*ns*
Months since chemotherapy	*ns*	*ns*	*ns*	*ns*	-0.603	0.050*
Months of radiation	*ns*	*ns*	*ns*	*ns*	-0.616	0.058
Average Daily Light PA	*ns*	*ns*	*ns*	*ns*	-0.429	0.097
Average Daily MVPA	*ns*	*ns*	*ns*	*ns*	-0.537	0.032*
FACT-Cog: Perceived cognitive abilities	-0.496	0.071	*ns*	*ns*	*ns*	*ns*
FACT-Cog: Comments from others	-0.506	0.065	*ns*	*ns*	*ns*	*ns*

*significant at *p* = .05

References:

Abe, O., Abe, R., Enomoto, K., Kikuchi, K., Koyama, H., Masuda, H., … Houghton, J. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, *365*(9472), 1687–717. http://doi.org/10.1016/S0140-6736(05)66544-0

Ahles, T. A., Root, J. C., & Ryan, E. L. (2012). Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *30*(30), 3675–86. http://doi.org/10.1200/JCO.2012.43.0116

Ahmed, R. L., Thomas, W., Yee, D., & Schmitz, K. H. (2006). Randomized controlled trial of weight training and lymphedema in breast cancer survivors. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *24*(18), 2765–72. http://doi.org/10.1200/JCO.2005.03.6749

Baumann, F. T., Drosselmeyer, N., Leskaroski, A., Knicker, A., Krakowski-Roosen, H., Zopf, E. M., & Bloch, W. (2011). 12-week resistance training with breast cancer patients during chemotherapy: effects on cognitive abilities. *Breast Care*, *6*(2), 142–143. http://doi.org/10.1159/000327505

Beisecker, A., Cook, M. R., Ashworth, J., Hayes, J., Brecheisen, M., Helmig, L., … Selenke, D. (1997). Side effects of adjuvant chemotherapy: perceptions of node-negative breast cancer patients. *Psycho-Oncology*, *6*(2), 85–93. http://doi.org/10.1002/(SICI)1099-1611(199706)6:2<85::AID-PON247>3.0.CO;2-T

Blacklock, R., Rhodes, R., Blanchard, C., & Gaul, C. (2010). Effects of exercise intensity and self-efficacy on state anxiety with breast cancer survivors. *Oncology Nursing Forum*, *37*(2), 206–212. http://doi.org/10.1188/10.ONF.206-212

Blanchard, C. M., Courneya, K. S., & Stein, K. (2008). Cancer survivors’ adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society’s SCS-II. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *26*(13), 2198–204. http://doi.org/10.1200/JCO.2007.14.6217

Blanchard, C. M., Stein, K. D., Baker, F., Dent, M. F., Denniston, M. M., Courneya, K. S., & Nehl, E. (2004). Association between current lifestyle behaviors and health-related quality of life in breast, colorectal, and prostate cancer survivors. *Psychology & Health*, *19*(1), 1–13. http://doi.org/10.1080/08870440310001606507

Brady, M. J., Cella, D. F., Mo, F., Bonomi, A. E., Tulsky, D. S., Lloyd, S. R., … Shiomoto, G. (1997). Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *15*(3), 974–86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9060536

Breast cancer Clinical Practice Guidelines in Oncology. (2003). *Journal of the National Comprehensive Cancer Network : JNCCN*, *1*(2), 148–88. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19768876

Brezden, C. B., Phillips, K.-A., Abdolell, M., Bunston, T., & Tannock, I. F. (2000). Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J. Clin. Oncol.*, *18*(14), 2695–2701. Retrieved from http://jco.ascopubs.org/content/18/14/2695.short

Brown, J. C., Huedo-Medina, T. B., Pescatello, L. S., Ryan, S. M., Pescatello, S. M., Moker, E., … Johnson, B. T. (2012). The efficacy of exercise in reducing depressive symptoms among cancer survivors: a meta-analysis. *PloS One*, *7*(1), e30955. http://doi.org/10.1371/journal.pone.0030955

Carlson, R. W., Allred, D. C., Anderson, B. O., Burstein, H. J., Carter, W. B., Edge, S. B., … Wolff, A. C. (2009). Breast cancer. Clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network : JNCCN*, *7*(2), 122–92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19200416

Chaddock-Heyman, L., Mackenzie, M. J., Zuniga, K., Cooke, G. E., Awick, E., Roberts, S., … Kramer, A. F. (2015). Higher cardiorespiratory fitness levels are associated with greater hippocampal volume in breast cancer survivors. *Frontiers in Human Neuroscience*, *9*, 465. http://doi.org/10.3389/fnhum.2015.00465

Chang, Y.-K., Chu, C.-H., Wang, C.-C., Wang, Y.-C., Song, T.-F., Tsai, C.-L., & Etnier, J. L. (2015). Dose-response relation between exercise duration and cognition. *Medicine and Science in Sports and Exercise*, *47*(1), 159–65. http://doi.org/10.1249/MSS.0000000000000383

Chang, Y. K., Labban, J. D., Gapin, J. I., & Etnier, J. L. (2012). The effects of acute exercise on cognitive performance: a meta-analysis. *Brain Research*, *1453*, 87–101. http://doi.org/10.1016/j.brainres.2012.02.068

Cimprich, B., Reuter-Lorenz, P., Nelson, J., Clark, P. M., Therrien, B., Normolle, D., … Welsh, R. C. (2010). Prechemotherapy alterations in brain function in women with breast cancer. *Journal of Clinical and Experimental Neuropsychology*, *32*(3), 324–31. http://doi.org/10.1080/13803390903032537

Clarke, M., Collins, R., Darby, S., Davies, C., Elphinstone, P., Evans, V., … Wang, Y. (2005). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet (London, England)*, *366*(9503), 2087–106. http://doi.org/10.1016/S0140-6736(05)67887-7

CM, B., KS, C., & D, L. (n.d.). Effects of acute exercise on state anxiety in breast cancer survivors. *Oncology Nursing Forum*, *28*(10), 1617–1621. Retrieved from http://europepmc.org/abstract/med/11759309

Coates, A., Abraham, S., Kaye, S. B., Sowerbutts, T., Frewin, C., Fox, R. M., & Tattersall, M. H. N. (1983). On the receiving end—patient perception of the side-effects of cancer chemotherapy. *European Journal of Cancer and Clinical Oncology*, *19*(2), 203–208. http://doi.org/10.1016/0277-5379(83)90418-2

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A Meta-Analytic study. *Psychological Science*, *14*(2), 125–130. http://doi.org/10.1111/1467-9280.t01-1-01430

Cooke, G. E., Wetter, N. C., Banducci, S. E., Mackenzie, M. J., Zuniga, K. E., Awick, E. A., … Kramer, A. F. (2016). Moderate physical activity mediates the association between white matter lesion volume and memory recall in breast cancer survivors. *PloS One*, *11*(2), e0149552. http://doi.org/10.1371/journal.pone.0149552

Courneya, K. S., & Friedenreich, C. M. (1997). Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. *The Journal of Alternative and Complementary Medicine*, *3*(3), 215–226. http://doi.org/10.1089/acm.1997.3.215

Courneya, K. S., Mackey, J. R., Bell, G. J., Jones, L. W., Field, C. J., & Fairey, A. S. (2003). Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *21*(9), 1660–8. http://doi.org/10.1200/JCO.2003.04.093

Courneya, K. S., Segal, R. J., Mackey, J. R., Gelmon, K., Reid, R. D., Friedenreich, C. M., … McKenzie, D. C. (2007). Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *Journal of Clinical Oncology*, *25*(28), 4396–4404. http://doi.org/10.1200/JCO.2006.08.2024

Culos-Reed, S. N., Carlson, L. E., Daroux, L. M., & Hately-Aldous, S. (2006). A pilot study of yoga for breast cancer survivors: physical and psychological benefits. *Psycho-Oncology*, *15*(10), 891–7. http://doi.org/10.1002/pon.1021

D’Esposito, M., Postle, B. R., Ballard, D., & Lease, J. (1999). Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain and Cognition*, *41*(1), 66–86. http://doi.org/10.1006/brcg.1999.1096

Daley, A. J., Crank, H., Saxton, J. M., Mutrie, N., Coleman, R., & Roalfe, A. (2007). Randomized trial of exercise therapy in women treated for breast cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *25*(13), 1713–21. http://doi.org/10.1200/JCO.2006.09.5083

de Jager, C. A., Budge, M. M., & Clarke, R. (2003). Utility of TICS-M for the assessment of cognitive function in older adults. *International Journal of Geriatric Psychiatry*, *18*(4), 318–24. http://doi.org/10.1002/gps.830

Demark-Wahnefried, W., Aziz, N. M., Rowland, J. H., & Pinto, B. M. (2005). Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *23*(24), 5814–30. http://doi.org/10.1200/JCO.2005.01.230

DeSantis, C., Ma, J., Bryan, L., & Jemal, A. Breast cancer statistics, 2013. *CA: A Cancer Journal for Clinicians*, *64*(1), 52–62. http://doi.org/10.3322/caac.21203

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*, 135–68. http://doi.org/10.1146/annurev-psych-113011-143750

Edelstein, K., & Bernstein, L. J. (2014). Cognitive dysfunction after chemotherapy for breast cancer. *Journal of the International Neuropsychological Society*, *20*(4), 351–356. http://doi.org/10.1017/S1355617714000149

Evans, E. S., Hackney, A. C., McMurray, R. G., Randell, S. H., Muss, H. B., Deal, A. M., & Battaglini, C. L. (2015). Impact of acute intermittent exercise on natural killer cells in breast cancer survivors. *Integrative Cancer Therapies*, *14*(5), 436–45. http://doi.org/10.1177/1534735415580681

Fitzpatrick, T. R., Edgar, L., & Holcroft, C. (2012). Assessing the relationship between physical fitness activities, cognitive health, and quality of life among older cancer survivors. *Journal of Psychosocial Oncology*, *30*(5), 556–72. http://doi.org/10.1080/07347332.2012.703768

Fong, D. Y. T., Ho, J. W. C., Hui, B. P. H., Lee, A. M., Macfarlane, D. J., Leung, S. S. K., … Cheng, K. (2012). Physical activity for cancer survivors: meta-analysis of randomised controlled trials. *BMJ (Clinical Research Ed.)*, *344*(jan30_5), e70. http://doi.org/10.1136/bmj.e70

Friedenreich, C. M., Gregory, J., Kopciuk, K. A., Mackey, J. R., & Courneya, K. S. (2009). Prospective cohort study of lifetime physical activity and breast cancer survival. *International Journal of Cancer. Journal International Du Cancer*, *124*(8), 1954–62. http://doi.org/10.1002/ijc.24155

Galantino, M. Lou, Greene, L., Daniels, L., Dooley, B., Muscatello, L., & O'Donnell, L. Longitudinal impact of yoga on chemotherapy-related cognitive impairment and quality of life in women with early stage breast cancer: a case series. *Explore (New York, N.Y.)*, *8*(2), 127–35. http://doi.org/10.1016/j.explore.2011.12.001

Ganz, P. A., Kwan, L., Stanton, A. L., Krupnick, J. L., Rowland, J. H., Meyerowitz, B. E., … Belin, T. R. (2004). Quality of life at the end of primary treatment of breast cancer: first results from the moving beyond cancer randomized trial. *JNCI Journal of the National Cancer Institute*, *96*(5), 376–387. http://doi.org/10.1093/jnci/djh060

Goodwin, J. S., Samet, J. M., & Hunt, W. C. (1996). Determinants of survival in older cancer patients. *Journal of the National Cancer Institute*, *88*(15), 1031–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8683633

Gregg, E. W., Gerzoff, R. B., Caspersen, C. J., Williamson, D. F., & Narayan, K. M. V. (2003). Relationship of walking to mortality among US adults with diabetes. *Archives of Internal Medicine*, *163*(12), 1440–7. http://doi.org/10.1001/archinte.163.12.1440

Haskell, W., Lee, I.-M., Pate, R., Powell, K., Blair, S., Franklin, B., … Bauman, A. (2007). Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. Retrieved from http://scholarcommons.sc.edu/sph_physical_activity_public_health_facpub/119

Helmrich, S. P., Ragland, D. R., Leung, R. W., & Paffenbarger, R. S. (1991). Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *The New England Journal of Medicine*, *325*(3), 147–52. http://doi.org/10.1056/NEJM199107183250302

Hewitt, M., Rowland, J. H., & Yancik, R. (2003). Cancer survivors in the United States: age, health, and disability. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*(1), 82–91. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12560417

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nature Reviews. Neuroscience*, *9*(1), 58–65. http://doi.org/10.1038/nrn2298

Hillman, C. H., Snook, E. M., & Jerome, G. J. (2003). Acute cardiovascular exercise and executive control function. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, *48*(3), 307–14. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12798990

Holick, C. N., Newcomb, P. A., Trentham-Dietz, A., Titus-Ernstoff, L., Bersch, A. J., Stampfer, M. J., … Willett, W. C. (2008). Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *17*(2), 379–86. http://doi.org/10.1158/1055-9965.EPI-07-0771

Holmes, M. D., Chen, W. Y., Feskanich, D., Kroenke, C. H., & Colditz, G. A. (2005). Physical activity and survival after breast cancer diagnosis. *JAMA*, *293*(20), 2479–86. http://doi.org/10.1001/jama.293.20.2479

Hwang, J. (2015, September 4). Physical activity, vascular risk and cognitive performance in young adults. Retrieved from https://repositories.lib.utexas.edu/handle/2152/30930

Irwin, M. L., Smith, A. W., McTiernan, A., Ballard-Barbash, R., Cronin, K., Gilliland, F. D., … Bernstein, L. (2008). Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *26*(24), 3958–64. http://doi.org/10.1200/JCO.2007.15.9822

Kesler, S., Hadi Hosseini, S. M., Heckler, C., Janelsins, M., Palesh, O., Mustian, K., & Morrow, G. (2013). Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. *Clinical Breast Cancer*, *13*(4), 299–306. http://doi.org/10.1016/j.clbc.2013.02.004

Kohl, H. W. (2001). Physical activity and cardiovascular disease: evidence for a dose response. *Medicine and Science in Sports and Exercise*, *33*(Supplement), S472–S483. http://doi.org/10.1097/00005768-200106001-00017

Koppelmans, V., Breteler, M. M. B., Boogerd, W., Seynaeve, C., Gundy, C., & Schagen, S. B. (2012). Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *30*(10), 1080–6. http://doi.org/10.1200/JCO.2011.37.0189

Kushi, L. H., Doyle, C., McCullough, M., Rock, C. L., Demark-Wahnefried, W., Bandera, E. V, … Gansler, T. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA: A Cancer Journal for Clinicians*, *62*(1), 30–67. http://doi.org/10.3322/caac.20140

Lee, I.-M. (2003). Physical activity and cancer prevention--data from epidemiologic studies. *Medicine and Science in Sports and Exercise*, *35*(11), 1823–7. http://doi.org/10.1249/01.MSS.0000093620.27893.23

Lee, I.-M., Shiroma, E. J., Lobelo, F., Puska, P., Blair, S. N., & Katzmarzyk, P. T. (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*, *380*(9838), 219–29. http://doi.org/10.1016/S0140-6736(12)61031-9

Lemieux, J., Maunsell, E., & Provencher, L. (2008). Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review. *Psycho-Oncology*, *17*(4), 317–28. http://doi.org/10.1002/pon.1245

Mackenzie, M. J., Zuniga, K. E., & McAuley, E. (2015). Cognitive impairment in breast cancer survivors: the protective role of physical activity, cardiorespiratory fitness, and exercise training. *In Exercise-Cognition Interaction: Neuroscience Perspectives* (pp. 399-419). Elsevier Inc.. DOI: 10.1016/B978-0-12-800778-5.00019-0

Mackenzie, M. J., Zuniga, K. E., Raine, L. B., Awick, E. A., Hillman, C. H., Kramer, A. F., & McAuley, E. (2016). Associations between physical fitness indices and working memory in breast cancer survivors and age-matched controls. *Journal of Women's Health (2002)*, *25*(1), 99–108. http://doi.org/10.1089/jwh.2015.5246

Mandelblatt, J. S., Hurria, A., McDonald, B. C., Saykin, A. J., Stern, R. A., VanMeter, J. W., … Ahles, T. (2013). Cognitive effects of cancer and its treatments at the intersection of aging: what do we know; what do we need to know? *Seminars in Oncology*, *40*(6), 709–25. http://doi.org/10.1053/j.seminoncol.2013.09.006

McMorris, T., Sproule, J., Turner, A., & Hale, B. J. (2011). Acute, intermediate intensity exercise, and speed and accuracy in working memory tasks: a meta-analytical comparison of effects. *Physiology & Behavior*, *102*(3–4), 421–8. http://doi.org/10.1016/j.physbeh.2010.12.007

McNeely, M. L., Campbell, K. L., Rowe, B. H., Klassen, T. P., Mackey, J. R., & Courneya, K. S. (2006). Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ : Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *175*(1), 34–41. http://doi.org/10.1503/cmaj.051073

Mock, V., Dow, K. H., Meares, C. J., Grimm, P. M., Dienemann, J. A., Haisfield-Wolfe, M. E., … Gage, I. (1997). Effects of exercise on fatigue, physical functioning, and emotional distress during radiation therapy for breast cancer. *Oncology Nursing Forum*, *24*(6), 991–1000. Retrieved from http://europepmc.org/abstract/med/9243585

Mock, V., Pickett, M., Ropka, M. E., Lin, E. M., Stewart, K. J., Rhodes, V. A., … McCorkle, R. (2001). Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Practice*, *9*(3), 119–127. http://doi.org/10.1046/j.1523-5394.2001.009003119.x

Morean, D. F., O'Dwyer, L., & Cherney, L. R. (2015). Therapies for cognitive deficits associated with chemotherapy for breast cancer: a systematic review of objective outcomes. *Archives of Physical Medicine and Rehabilitation*, *96*(10), 1880–97. http://doi.org/10.1016/j.apmr.2015.05.012

Morris, J. N., & Heady, J. A. (1953). Mortality in relation to the physical activity of work: a preliminary note on experience in middle age. *British Journal of Industrial Medicine*, *10*(4), 245–54. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1037497&tool=pmcentrez&rendertype=abstract

Peto, R., Boreham, J., Clarke, M., Davies, C., & Beral, V. (2000). UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet (London, England)*, *355*(9217), 1822. http://doi.org/10.1016/S0140-6736(00)02277-7

Pinto, A. C., & de Azambuja, E. (2011). Improving quality of life after breast cancer: dealing with symptoms. *Maturitas*, *70*(4), 343–8. http://doi.org/10.1016/j.maturitas.2011.09.008

Pontifex, M. B., Hillman, C. H., Fernhall, B., Thompson, K. M., & Valentini, T. A. (2009). The effect of acute aerobic and resistance exercise on working memory. *Medicine and Science in Sports and Exercise*, *41*(4), 927–34. http://doi.org/10.1249/MSS.0b013e3181907d69

Pontifex, M. B., Saliba, B. J., Raine, L. B., Picchietti, D. L., & Hillman, C. H. (2013). Exercise improves behavioral, neurocognitive, and scholastic performance in children with attention-deficit/hyperactivity disorder. *The Journal of Pediatrics*, *162*(3), 543–51. http://doi.org/10.1016/j.jpeds.2012.08.036

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8759042

Schagen, S. B., van Dam, F. S., Muller, M. J., Boogerd, W., Lindeboom, J., & Bruning, P. F. (1999). Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer*, *85*(3), 640–50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10091737

Schmidt, M. E., Wiskemann, J., Armbrust, P., Schneeweiss, A., Ulrich, C. M., & Steindorf, K. (2015). Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: A randomized controlled trial. *International Journal of Cancer. Journal International Du Cancer*, *137*(2), 471–80. http://doi.org/10.1002/ijc.29383

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvao, D. A., Pinto, B. M., … American College of Sports Medicine. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine & Science in Sports & Exercise*, *42*(7), 1409–1426. http://doi.org/10.1249/MSS.0b013e3181e0c112

Schmitz, K. H., Holtzman, J., Courneya, K. S., Mâsse, L. C., Duval, S., & Kane, R. (2005). Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology*, *14*(7), 1588–95. http://doi.org/10.1158/1055-9965.EPI-04-0703

Schneider, D. W., & Logan, G. D. (2005). Modeling task switching without switching tasks: a short-term priming account of explicitly cued performance. *Journal of Experimental Psychology. General*, *134*(3), 343–67. http://doi.org/10.1037/0096-3445.134.3.343

Segal, R., Evans, W., Johnson, D., Smith, J., Colletta, S., Gayton, J., … Reid, R. (2001). Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *19*(3), 657–65. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11157015

Segar, M. L., Katch, V. L., Roth, R. S., Garcia, A. W., Portner, T. I., Glickman, S. G., … Wilkins, E. G. The effect of aerobic exercise on self-esteem and depressive and anxiety symptoms among breast cancer survivors. *Oncology Nursing Forum*, *25*(1), 107–13. Retrieved from http://europepmc.org/abstract/med/9460778

Shapiro, S., Venet, W., Strax, P., Venet, L., & Roeser, R. (1982). Ten- to fourteen-year effect of screening on breast cancer mortality. *J Natl Cancer Inst*, *69*(2), 349–355. http://doi.org/10.1093/jnci/69.2.349

Shilling, V., & Jenkins, V. (2007). Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. *European Journal of Oncology Nursing : The Official Journal of European Oncology Nursing Society*, *11*(1), 6–15. http://doi.org/10.1016/j.ejon.2006.02.005

Siegel, R. L., Miller, K. D., & Jemal, A. (2015). Cancer statistics, 2015. *CA: A Cancer Journal for Clinicians*, *65*(1), 5–29. http://doi.org/10.3322/caac.21254

Snaith, R. P. (2003). The Hospital Anxiety And Depression Scale. *Health and Quality of Life Outcomes*, *1*, 29. http://doi.org/10.1186/1477-7525-1-29

Speck, R. M., Courneya, K. S., Mâsse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Journal of Cancer Survivorship : Research and Practice*, *4*(2), 87–100. http://doi.org/10.1007/s11764-009-0110-5

Tabár, L., Gad, A., Holmberg, L. ., Ljungquist, U., Fagerberg, C. J. ., Baldetorp, L., … Pettersson, F. (1985). Reduction in mortality from breast cancer after mass screening with mammography. *The Lancet*, *325*(8433), 829–832. http://doi.org/10.1016/S0140-6736(85)92204-4

Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., Nouchi, R., & Kawashima, R. (2011). Effects of training of processing speed on neural systems. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(34), 12139–48. http://doi.org/10.1523/JNEUROSCI.2948-11.2011

Taylor, A. H., Cable, N. T., Faulkner, G., Hillsdon, M., Narici, M., & Van Der Bij, A. K. (2004). Physical activity and older adults: a review of health benefits and the effectiveness of interventions. *Journal of Sports Sciences*, *22*(8), 703–25. http://doi.org/10.1080/02640410410001712421

Thune, I., & Furberg, A. S. (2001). Physical activity and cancer risk: dose-response and cancer, all sites and site-specific. *Medicine and Science in Sports and Exercise*, *33*(6 Suppl), S530-50–10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11427781

Troiano, R. P., Berrigan, D., Dodd, K. W., Mâsse, L. C., Tilert, T., & McDowell, M. (2008). Physical activity in the United States measured by accelerometer. *Medicine and Science in Sports and Exercise*, *40*(1), 181–8. http://doi.org/10.1249/mss.0b013e31815a51b3

van Harten, W. H., van Noort, O., Warmerdam, R., Hendricks, H., & Seidel, E. (1998). Assessment of rehabilitation needs in cancer patients. *International Journal of Rehabilitation Research. Internationale Zeitschrift Für Rehabilitationsforschung. Revue Internationale de Recherches de Réadaptation*, *21*(3), 247–57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9812254

Vardy, J., & Tannock, I. (2007). Cognitive function after chemotherapy in adults with solid tumours. *Critical Reviews in Oncology/hematology*, *63*(3), 183–202. http://doi.org/10.1016/j.critrevonc.2007.06.001

Vogel, V. G., Costantino, J. P., Wickerham, D. L., Cronin, W. M., Cecchini, R. S., Atkins, J. N., … Wolmark, N. (2006). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*, *295*(23), 2727–41. http://doi.org/10.1001/jama.295.23.joc60074

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. D. (2006). Health benefits of physical activity: the evidence. *CMAJ : Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, *174*(6), 801–9. http://doi.org/10.1503/cmaj.051351