AN EXPLORATION OF PHYSICAL ACTIVITY IN CANCER SURVIVORSHIP

By

Keith M. Thraen-Borowski

A dissertation submitted in partial fulfillment of

the requirements for the degree of

Doctor of Philosophy

(Kinesiology)

at the

UNIVERSITY OF WISCONSIN-MADISON

2015

Date of final oral examination: 5/14/2015

The dissertation is approved by the following members of the Final Oral Committee:

Lisa H. Colbert, Associate Professor, Kinesiology
Alex K. Adams, Assistant Professor, Family Medicine
Ronald E. Gangnon, Associate Professor, Population Health Sciences & Biostatistics and Medical Informatics
Kelli F. Koltyn, Professor, Kinesiology
Amy Trentham-Dietz, Associate Professor, Population Health Sciences

Acknowledgments

Well, they say it takes a village…and this experience has been no different. If I had to thank every person that has played some role, regardless of how large or small, in helping me to get to this point, I could probably double the length of this already mammoth document. As no one needs that, I would simply like to send a resounding "thank you" to everyone that has offered some assistance to not only this point, but to my academic journey as whole. You know who you are. Still, there are some individuals that I need to mention:

I would like to thank my committee members: Dr. Amy Trentham-Dietz, Dr. Ron Gangnon, Dr. Alex Adams, Dr. Kelli Koltyn and Dr. Lisa Colbert for participating on my dissertation committee. Thank you for your guidance, time, effort, and support throughout this process. I have learned much from you all. I would like to further recognize Dr. Colbert for serving as my advisor, mentor, and committee-chair. Lisa, your guidance, knowledge, support, mentorship, and perhaps above all else, friendship, have been instrumental, not only in this dissertation, but in every step of my academic career at UW. Admittedly, when you left this University, I thought your absence would be detrimental to this project and, at times, even questioned whether I could complete it. Yet, you still made it a priority to get me through, and for that, I am eternally grateful. I will say that, now that this process is coming to a close, I realize that while I so missed your expertise being just down the hall from me while I was toiling away in my office, what I really missed was being able to go and grab a beer with you, because while you are a great professor, you are an even greater human being. Madtown Nutbrown on the terrace has never been the same and I am not sure it ever will. Cheers.

I must also thank Dr. Gary Diffee, who in Lisa's absence played the role of "mentor-in-residence". Gary, thank you for all of your sage advice and for being a great sounding board (usually while over a beverage or two). You are like a real-life Yoda... only way taller. I look forward to teaching you what science actually is in the years to come. Next one is on me, sir.

I would like to also thank my lab mate in the Physical Activity Epidemiology lab, Dr. Keith Gennusso. Keith, you may have been "Jr." in age and time in the lab, but you, sir, are "Sr." when it comes to being a great collaborator, SAS expert, ping pong player, and all around analysis-guru. I have learned a lot from you and am looking forward to learning so much more from you in the future. I can't thank you enough for all of your support the last two years. Further, I would like to thank the Kinesiology Cohesion Committee members for their support, advice and friendship. Specifically, I would like to thank Laura, Jacob, Morgan, Angie and the rest of the Exercise Psychology lab for adopting me and making me an "honorary" lab member when Lisa and Keith left (that lab was getting awfully lonely). You guys are fantastic-thanks for keeping me afloat. Jacob, as you went through every step of this process in time with me, I couldn't imagine trying to do this without your constant insights and positivity. Thank you, my friend, and congrats to you as well.

I would like to thank my friends and family for all of their love, support, and encouragement, not only during this process, but throughout the course of my life. I would especially like to recognize my parents, John and Carol Borowski. Education was a priority in my household growing up, and while I didn’t always understand it then, I am so thankful for it now. To my in-laws, Ray and Judes, thank you for all of your help and well-wishes over the last few years. I couldn’t have done this without you.   A special thank you to everyone who would play or listen to some music with me, share a beverage or two, or simply let me vent while I was in desperate need of a break while trying to finish this dissertation. You are wonderful friends.

Thanks to my son Finn for bringing me immeasurable amounts of love and joy and, above all, for keeping this whole process in perspective for me. It didn’t matter to you how much work or writing I had to do. You just wanted me to read you books, listen to the Ramones or the Beastie Boys with you, and watch you do your “crazy tricks”. It was a great reminder every day about what was really important. I won’t forget. I love you, buddy.

Last, but certainly not least, I would like to thank my partner, wife, best friend, and overall partner-in-crime, Irene, for being the most incredible person I have ever known. I could not have done any of this without your love, support, friendship, and patience. Frankly, I can’t believe they aren’t giving you one of these damn degrees, as I feel as though some days you might deserve it more than me! You really are the best. I love you. Can’t wait for the next chapter….

§

I would like to dedicate this project to all of the cancer survivors that I have known, admired, and loved over the years. And to those of you still fighting, you got this

(I’m looking at you, Hammer!). I specifically want to acknowledge the survivors that volunteered their time and knowledge to this dissertation project. Please know that we will keep working hard for you and with you. To those that we have lost in the process of this project, I am so fortunate and thankful to have been part of your journey. You were a true inspiration to us all and will be missed.

Unfortunately, there are just too many individuals to name that have passed from this dreadful disease. We all know of someone (if not many individuals) that has touched our lives and have lost their battle with this illness. Again, this work is dedicated to you. As a great deal of this work focused on lung cancer survivorship, I would specifically like to mention a great man who passed from this disease. Doc, you were a wonderful man. Your kindness, generosity, warmth, and laughter was a gift to our family, our friends, and this community, and for that, I cannot thank you enough. We miss you. I promise to think of you every time we’re “Pickin’ a bouquet of dogwood flowers….”.

Table of Contents

Chapter I: Introduction

Cancer continues to affect an extensive number of lives in this country. With over one and a half million new cancer cases diagnosed each year [1], it has been estimated that half of all men and one third of all women in the United States (US) will be diagnosed with cancer in their lifetime [2]. As such, cancer incidence remains a substantial public health problem. Fortunately, advances in screening and improved treatments have led to a recent trend towards longer survival [3]. In fact, about 66% of people diagnosed with cancer are expected to live at least five years after diagnosis [4]. As a result, the cancer survivor population has grown exponentially in the last few decades, with over 4% of the total US population now having been diagnosed with cancer [4]. Currently, there are over 13 million individuals with a history of cancer alive today [1]. As the US population continues to age, these numbers will inevitably climb. However, cancer survivorship will continue to not only grow in number of total survivors, but also in length of survival. As of 2007, 4.7 million people who had been diagnosed with cancer have lived with the disease for over 10 years, while over one million people have lived with the disease for over 25 years [3]. In response to this growing population, a greater understanding of these individuals is needed.

Physical activity (PA) is a behavior that has been examined in relation to cancer in the past few decades. In this short time, an impressive body of literature has been accumulated. Early studies were focused on the relationships between a physically active lifestyle and the risk of incident cancers. With over one hundred epidemiological studies dedicated to evaluating the role of PA with the risk of colon and breast cancer, we now know that active individuals can expect up to a 30%-40% reduction and 20%-30% reduction, respectively, in risk compared to their inactive peers [5]. While there is considerably less work dedicated to other cancer types when compared with that of colon and breast cancer, there have still been greater than one hundred epidemiological studies devoted to PA and cancer risk of other types of cancers, and these findings have been generally positive [5]. Lagging behind, however, have been studies of the role of PA in cancer survivors. Early studies were small, uncontrolled trials looking at the effects of exercise on components of fitness, and some treatment-related symptoms [6]. More recently, larger epidemiologic studies have been published examining the role of PA in survival, with data suggesting that exercise may extend survival for those diagnosed with breast and colon cancer [7-10]. Even more recently, larger randomized studies are being done to look at the role of PA in cancer survivors, with various biomarkers and symptoms being examined [11, 12]. Through this work, there has been consistent evidence that PA is safe during and after cancer treatment and that improvement can be made concerning aerobic fitness, muscular strength, and fatigue in breast, prostate, and hematologic cancer survivors [13]. Given the number of cancer survivors and the improvements in survival, the impact of PA on their day to day lives is of great interest. One important consideration is their health-related quality of life (HQOL).

While the improvement in cancer survivorship has certainly been welcomed, research has documented that these survivors may face many physical, emotional, social and financial challenges associated with their disease and related treatments [14]. These complications can detrimentally affect one's prognosis and HQOL[14-16]. HQOL, commonly defined as the extent to which one's usual or expected physical and emotional well-being is affected by a medical condition or its treatment [17], has become a focus of many researchers as the HQOL of cancer survivors may differ greatly from that of the general public and those with other chronic diseases. As such, it is necessary to better understand the challenges associated with HQOL and their influence on cancer survivorship, along with ways to ameliorate these complications whenever possible.

Within the context of HQOL, there are many gaps in our understanding regarding the role of PA in cancer survivorship. As with other health outcomes, studies of minority populations, including Native Americans (NA), are rare[18-20]. Additionally, breast cancer survivors have been studied more than any other survivor population [5, 6, 14]. In many ways, this is a much different population than that of other cancer survivors. Lung cancer is currently the second most commonly diagnosed cancer in men and women [4], yet only a handful of studies have looked at the role of PA in lung cancer survivors. Finally, a most interesting area that has not yet been examined is the role of PA in informal caregivers of cancer survivors. This dissertation will address these three gaps, which will be outlined briefly here.

Native Americans

We know that not all populations suffer from the challenges associated with survivorship equally. When discussing the many potential health challenges that face the US in the future, a large area of consideration is that of health disparities. Health disparities, defined as the differences in health outcomes between groups that reflect social inequalities [21], are an area of concern for many health researchers. Since 1946, the Centers for Disease Control and Prevention have monitored the challenges of the nation's health, with particular focus on reducing the health gaps between the least and most vulnerable populations [22]. Health outcomes evaluated among these populations include illness, injury, risk behaviors, use of preventative health services, exposure to health hazards, and premature death. While researchers have begun to make substantial progress in both improving health outcomes and reducing disparities in the US, many differences among racial/ethnic, economic, and other social groups still exist [19, 21-24]. One of the groups most affected by these disparities is NA [20, 22, 25]. It has been said that the health of NA may be considered as poor as, if not worse than, the health of any other group in the US [18]. There have been well documented health disparities that exist between this population and that of the general US population, including significantly higher rates of diabetes, mental health disorders, cardiovascular disease, obesity, and cancer [20, 22, 25-32]. While cancer incidence rates have been decreasing in whites and most ethnic minorities over the last decade, research has shown that these rates have been failing to decrease among NA living in the US [33]. While advances are clearly needed to improve NA cancer prevention in this group, it is important to note that NA cancer survivors face many challenges associated with survival specific to their ethnicity [25, 34-37]. These challenges may detrimentally affect the HQOL in this population, further driving inequality in health outcomes of NA as compared to other populations. Unfortunately, though PA may help to improve HQOL in this group, information on the use of PA to improve cancer-related health outcomes specific to NA cancer survivors is greatly lacking. As prognosis and HQOL may be worse in this population than that of the general population and other ethnic minorities, PA may be a successful treatment modality.

Lung Cancer Survivors

While PA is increasingly becoming recognized as an important component of survivorship across cancer types, most of the literature available on PA affecting symptoms, various biomarkers, and the declines in HQOL found in cancer survivors focuses specifically on breast cancer survivors [5, 6, 14]. While encouraging, it is important to recognize that each cancer type brings with it its own set of challenges. As such, it is essential to investigate survivors of other cancer types to elucidate the challenges of cancer-specific diagnosis and treatments. Research examining the role of PA in individuals diagnosed with lung cancer is in its infancy when compared to other major cancer sites [5]. Lung cancer survivors face serious complications, both physical and mental, specific to their cancer. Unfortunately, there are few studies evaluating PA in this population. The current evidence does, however, suggest that, as in other malignancy types, exercise may be a safe and feasible adjunct treatment option for operable lung cancer patients, both before and after resection [13].

As peak oxygen consumption is a strong predictor for post-surgical complications in lung cancer patients, including fatigue, diminished HQOL, and reductions in physical function, and as chronic aerobic exercise has been widely established as the most effective method to improve peak oxygen consumption, this has become an interesting area of research in this population as of late [38]. Findings from this work suggest that exercise training programs can improve exercise capacity in both pre- and post-operative patients. While these results are encouraging, most of the studies conducted have been pilot studies, utilizing small, convenience-sample designs. Well-controlled trials in this area are needed.

The relationship between HQOL and PA has begun to be evaluated in this population. PA has been shown to be associated with various HQOL constructs, both before and after treatment [13, 39-45]. The majority of work evaluating these relationships, however, has been either observational in nature or case series. There have been three well-controlled trials conducted and though findings are encouraging, the variability in the exercise interventions and measures of HQOL used make drawing conclusions difficult [46-48]. Well-designed RCTs utilizing exercise interventions that mimic PA recommendations and using validated measures of HQOL specifically designed for lung cancer survivors in order to better understand the burden experienced by these survivors are clearly needed.

While physiological biomarkers have recently been a common outcome variable in PA studies due to their prognostic significance with several types of cancers [11], work describing this relationship in lung cancer survivors is severely lacking. Markers of chronic inflammation, considered to play a role in pathogenesis and treatment in the cancer population [49-51], and of oxidative DNA damage, which may play a major role in carcinogenesis [52], are commonly studied. Researchers have begun to evaluate the relationship between PA and these outcomes, yet among lung cancer survivors there is only one study evaluating markers of inflammation, and to date, there are no studies evaluating oxidative DNA damage [53].

Informal Caregivers of Cancer Survivors

Interestingly, when discussing the burden and challenges associated with cancer survivorship, we now know that cancer becomes an entire family's concern rather than being solely the problem of the individual being diagnosed with the disease [54, 55]. Care of cancer patients carried out by friends or family members, including treatment-related symptom management, treatment monitoring, emotional, financial, and spiritual support, along with assistance with personal and instrumental care, can lead to a number of challenges experienced by these informal caregivers [54-59]. Common problems associated with this informal caregiving include conflict in social roles, restriction of activities, strain in family relationships, psychological distress, and diminished physical health [56, 60], all of which could lead to a decreased HQOL [54-56, 61, 62]. Given the burdens on the healthcare system, the number of chronically-ill patients, and our aging population, the number of informal caregivers is increasing drastically such that it is beginning to be recognized as a major public health concern [63]. While advances in research have been made regarding our understanding of the informal caregiver of cancer survivors, very little work has been dedicated towards evaluating the use of behavioral interventions to reduce HQOL complications and there are no controlled trials evaluating the use of PA in these caregivers. A greater understanding of ways to improve the HQOL of caregivers of cancer survivors is essential, both to optimize HQOL in the caregiver, as well as to enhance the efficacy of caregiving. As such, the use of PA as a potential treatment to improve HQOL in these individuals should be considered.

Summary

Quality research has been done to further our understanding of the role of PA as a potential therapeutic modality to better health outcomes of cancer survivors. Yet, there are clearly gaps in our understanding that need to be addressed. Therefore, the goal of the following proposed research to help fill these gaps is three-fold: 1) to explore the relationship between PA and HQOL in a national sample of NA cancer survivors, 2) to evaluate the role of an exercise intervention in improving both prognostic and HQOL measures in a sample of lung cancer survivors, and 3) to evaluate the role of an exercise intervention to improve the HQOL of a cohort of informal caregivers of lung cancer survivors.

These populations have been selected for numerous reasons. Our understanding of health disparities in cancer survivors has suggested that NA have significantly poorer cancer outcomes when compared to other populations, including HQOL [20, 22, 25-32]. Yet, there is very little research on this topic specific to NA cancer survivors, with only two studies dedicated to HQOL in this population. Further, there have been no studies to date evaluating the association between PA and HQOL in this population. As this may be a potentially successful treatment option in this population, this area of study is needed.

It is well known that lung cancer is an important public health problem because of its high incidence, rapid progression, and poor outcome [3, 4, 64-71]**.** Thus, measuring biomarkers and HQOL in this population have become important endpoints in studies of lung cancer survivorship. However, few studies have evaluated exercise as a therapeutic modality to improve these endpoints in lung cancer patients, even though this is a cancer site in which it is likely that patients may reap benefits by increasing their PA. As there are many potential differences between lung cancer survivors and other cancer survivor populations, work specific to this group is needed.

Regarding caregivers of cancer survivors, there is a growing body of literature describing the challenges, and associated HQOL [54-56, 61, 62], of these individuals, but by comparison, little work has been done to evaluate potential interventions to mediate these challenges. Despite the potential benefits, few behavioral interventions to enhance caregivers' HQOL have been developed [56]. Of the few interventions that have been tested, most emphasize, problem-solving skills, and psychological counseling [72]. Currently, there have been very few studies evaluating PA to improve health outcomes in caregivers in general and none in caregivers of cancer survivors.

SPECIFIC AIMS

Physical Activity and Health-Related Quality of Life in Native American Cancer Survivors

Statement of Purpose

The primary purpose of this study is to examine the relationships between PA and HQOL in a group of NA cancer survivors. Specifically, we will attempt to examine the association between PA and various HQOL constructs, including physical and mental health.

Specific Aims

The proposed study will analyze data on PA and HQOL in a nationwide sample of NA cancer survivors to address the following specific aims:

Specific Aim 1: To examine the association between physical activity and HQOL in a population of Native American cancer survivors from across the country.

Hypothesis 1: Engaging in the recommended amounts of physical activity (150 min/week of moderate-vigorous intensity) will be positively associated with HQOL in NA cancer survivors.

Rationale: Meeting PA guidelines has been shown to improve both physical and mental health and functioning in a host of populations including ethnic minorities, those with chronic diseases and cancer survivors. As physical health, mental health, and function are the main constructs of HQOL, it is likely that participating in 150 min/week of moderate intensity exercise will be associated with HQOL.

Specific Aim 2: To examine the association of PA and HQOL across various intensities and types of physical activity.

Hypothesis 2a: Greater amounts of both light intensity and moderate-vigorous intensity PA will be independently associated with higher HQOL; however, the association with moderate-vigorous PA will be stronger.

Hypothesis 2b: Participation in greater amounts of planned exercise will be associated with higher HQOL; however, participation in greater amounts of other types of PA, independent of participation in planned exercise, will also be associated with higher HQOL.

Rationale: There are significant gains to be made in health by incorporating PA into a previously sedentary lifestyle. Studies have shown that those who perform planned moderate-vigorous exercise may have the best health outcomes, yet the greatest gains in health-related benefits may be in those individuals who perform some PA, even light intensity activity, versus those individuals who do not perform any PA. While perhaps not achieving the same benefit as those in the highest intensity category, the benefit of doing light intensity PA as opposed to none may be worthwhile. Studies also show that those individuals who perform any type of PA achieve gains in health-related benefits when compared to those individuals who did not perform any PA. While possibly not attaining the same health benefits as those performing planned exercise, there may be significant improvements in health in this population by simply participating in any type of PA.

The proposed study can beneficially add to the existing research on HQOL in cancer survivors, as there are currently no studies evaluating the relationship between PA and HQOL in NA cancer survivors. If PA is shown to be associated with improved HQOL measures specific to that of NA cancer survivors, new treatment interventions for this population may be introduced.

Impacts of Exercise on Prognostic Biomarkers and Health-Related Quality of Life in Lung Cancer Patients

Statement of Purpose

The primary purpose of this study is to determine how exercise in a population of lung cancer survivors can alter various health outcomes in this population. Specifically, we will examine the effect of an exercise intervention consistent with current PA guidelines on biomarkers of prognosis, exercise capacity, and HQOL.

Specific Aims

The proposed randomized, controlled trial of exercise will examine biomarkers of prognosis, exercise capacity and HQOL in a sample of lung cancer patients to address the following specific aims:

Specific Aim 1: To determine the effect of an eight-week exercise intervention on biomarkers of inflammation and oxidative stress, exercise capacity, and HQOL in lung cancer patients.

Hypothesis 1a: The intervention will lower systemic levels of inflammation as indicated by serum C-Reactive protein, Interleukin (IL)-1β, IL-6, and TNF-α.

Hypothesis 1b: The intervention will decrease oxidative damage as indicated by serum 8-hydroxy-2'-deoxyguanosine (8-OHdG).

Hypothesis 1c: The intervention will improve exercise capacity as indicated by an increase in gate speed on the Long Distance Corridor Walk (LDCW) test.

Hypothesis 1d: The intervention will improve physical and functional well-being scores on the FACT-L.

Rationale: Previous work has shown exercise to be beneficial to health in a number of populations, including those with chronic disease and specific cancer survivor populations. Specifically, exercise interventions consisting of moderate-intensity exercise and resistive training have demonstrated improvements in levels of systemic inflammation and oxidative stress, increases in exercise capacity, and improvements in the components of HQOL, including physical and mental health and functioning, in breast, colorectal and prostate cancer survivors. As these health factors can influence cancer risk, morbidities, and prognosis in lung cancer survivors, this population may also benefit greatly from participating in this type of exercise program.

The proposed study can to add to the growing body of literature regarding the use of exercise in cancer survivors. As there is currently a lack of information evaluating the relationships between exercise and these health outcomes in lung cancer survivors, this study will add to our knowledge of the effects of exercise as a therapeutic modality in the cancer survivor. If the intervention studied is shown to be associated with these improved health outcomes in lung cancer survivors, new therapies for this population may be established.

Impacts of Exercise on HQOL in Informal Caregivers of Lung Cancer Patients

Statement of Purpose

The primary purpose of this study is to determine how exercise can alter HQOL in a population of informal caregivers of lung cancer survivors. Specifically, we will attempt to examine the role of an exercise intervention consistent with current PA guidelines on various HQOL constructs, including physical and mental health.

Specific Aims

The proposed randomized, controlled trial of exercise will examine HQOL in a sample of informal caregivers of lung cancer patients to address the following specific aims:

Specific Aim 1: To determine the effect of an eight-week exercise intervention on HQOL in informal caregivers of lung cancer patients.

Hypothesis 1a: The intervention will improve HQOL scores on the SF-36.

Rationale: Caregivers face many health challenges as a result of providing care to cancer survivors, including increased levels of stress, diminished physical health, strain in marital and family relationships, depressive symptoms, and poor mental health. All of these health challenges can have a detrimental effect on an individual's HQOL. As exercise interventions have been shown to provide a myriad of health benefits, including improvements in HQOL and associated constructs in numerous populations, this group could potentially benefit from this type of intervention.

The proposed study can add to the literature on limiting HQOL concerns in informal caregivers, specifically those of cancer survivors, as the relationship between PA and HQOL has not currently been evaluated in this population. As a result, this study will broaden our knowledge on potential therapeutic modalities in this group. If the intervention studied is shown to be successful, this may be a potential avenue for informal caregivers to improve HQOL in the future.

Section Summary- Through the work proposed in these aims, we will further our understanding of the role that PA may play in cancer survivorship. First, we will be able to identify ways in which PA could help to reduce health disparities through evaluating PA practices in NA cancer survivors and their relationship with HQOL outcomes. We will also be able to evaluate individual components of PA practices, such as type, intensity, and amount of activity and the role that they might play on HQOL. This information could be used in designing future interventions specifically for this population. Second, we will be able to identify if exercise may be a relevant component in the treatment and management of lung cancer. Improvements in prognostic biomarkers, exercise capacity, and HQOL would help direct future work addressing the long-term outcomes in lung cancer survivors. Finally, we will be able to ascertain the potential role of exercise in stress management and HQOL in individuals providing support and care to survivors. Information derived from this study can help to shape future interventions to assure the continued or improved health of those supporting cancer survivors.

Chapter II: Literature Review

Study 1: Physical Activity and Health Related-Quality of Life in Native American Cancer Survivors

Prevalence/Incidence

There are about 5.2 million Native Americans (NA) living in the US today, making up approximately 1.7% of the total US population [73]. Comprising roughly 560 federally-recognized tribal nations [73, 74], NA (which refers to both American Indian and Alaska Natives [20]) have a unique and distinctive political status in the US as compared to other racial and ethnic minority groups: they are citizens of sovereign “domestic, dependent” tribal nations [75]. This is important as NA remain entangled in the policies and practices of the U.S. government [76]. Specifically, through a series of treaties, the US has recognized a moral obligation to provide health care for NA communities through the branch of the U.S. Public Health Service known as the Indian Health Service (HIS) [74, 75, 77]. Unfortunately, this care has never been funded at a level comparable to that of other Americans [78, 79], creating growing disparities between NA and other US populations.

Despite the recent commitment by congress to appropriate funds to help deliver better health care services for NA [77], this population still continues to suffer disproportionately from a variety of illness and disease [20, 22, 31]. These well documented disparities include significantly higher rates of diabetes, mental health disorders, cardiovascular disease, pneumonia, influenza, tobacco use, obesity, and cancer [20, 22, 31]. NA are over 770 percent more likely to die from alcoholism and 420 percent more likely to die from diabetes than any other population in America, including other minority populations [20]. Further, NA have higher mortality rates due to chronic liver disease than do non-Hispanic whites [22]. NA have a life expectancy rate nearly five years lower than the rest of the US population [22]. Despite medical advances that have helped to decrease morbidity and mortality rates, the health of NA lags significantly behind the majority of the US population. In fact, the health of NA may be considered as poor as, if not worse than, the health of any other group in the US [18].

Cancer Rates in Native Americans

While NA generally have lower cancer rates than do non-Hispanic whites, disparities in this area still exist. Cancer incidence rates have been decreasing in whites and certain ethnic minorities, yet research has shown that these rates have not decreased among NA living in the United States [80]. Cancer is the leading cause of death for NA women [81] and NA cancer survivors have the poorest five-year survival rate when compared with both non-Hispanic whites and other minority, poor, and medically underserved populations [27, 82]. This is especially true for breast [26], colon [83], and cervical cancer survivors [19]. NA are more than twice as likely to have, and die from, liver cancer than non-Hispanic Whites [84]. NA women are 40% more likely to have kidney/renal or pelvis cancer as non-Hispanic White women and they have the highest cervical cancer mortality rate of any population in the US [84]. NA are also 1.6 times as likely to have, and nearly twice as likely to die from, stomach cancer as non-Hispanic whites [29]. The most common types of cancer in NA males are prostate, lung and colon, whereas the most common for NA women are breast, lung, and colon [85]. When compared to non-Hispanic whites, NA have the highest percentage of distant stage lung, breast, prostate and colorectal cancers[19, 86].

Impact/Burden of Survivorship

Advances are clearly needed to improve cancer survivorship in this population, but cancer survivors of all backgrounds face many challenges associated with survival. Generally speaking, cancer survivors are at greater risk for both recurrence of disease and for developing secondary cancers than that of the general population [87]. This could in part be due to the effects of treatment associated with cancer, unhealthy lifestyle behaviors typically seen in chronically diseased patients, underlying genetics, or the risk factors that helped to contribute to the initial cancer [2]. Cancer diagnosis and treatments can also create physical, emotional, social and financial challenges for the survivor. These complications have all had a significant impact on the health and quality of life of cancer survivors [3]. Unfortunately, in NA cancer survivors, there is very little data regarding cancer-associated morbidity issues [88], including HQOL, further muddying the picture of survivorship in this population. As such, a greater understanding of the NA cancer survivor is needed.

Health Related Quality of Life (HQOL) in Cancer Survivors

The World Health Organization (WHO) has defined health as a state of complete physical, mental, and social well-being, not simply an absence of disease [89]. HQOL is one of the constructs related to overall health, and though used frequently in the literature, there is no single agreed upon standard definition [2]; however, the term is synonymous with an individual's assessment of his or her own general well-being. HQOL can also be considered the extent to which one's usual or expected physical and emotional well-being is affected by a medical condition or its treatment [17].

Traditionally, medical and health-related research has focused on "hard" clinical outcomes (e.g. mortality rates, measurable changes in physiologic biomarkers, prevalence/incidence of disease, cost of healthcare, etc.), typically benefiting our understanding of "quantity of life". Yet, the perspective of the patient is one that is necessary as it may improve our understanding of how cancer and its respective treatments can influence patients' livelihood [90]. As cancer diagnosis and treatment are likely to have an effect on HQOL [91], research of this kind is necessary. While various treatment options may increase survival rates, if the treatment is unfavorable to a patient's HQOL, it can be argued that the treatment may be neither practical nor worthwhile. Information gained from HQOL research can help to monitor current therapeutic interventions while shaping future interventions. This research can also be used to measure the efficacy and cost-effectiveness of certain interventions to improve patient coping strategies, and help to shape public health policy [92].

As a result of this line of thinking, researchers have shifted to embrace these patient perspective outcomes, and HQOL research in the cancer survivor population has grown substantially [93]. In fact, The American Society of Clinical Oncology has gone so far as to introduce guidelines for HQOL assessment [94], and the FDA has recently outlined HQOL as an important endpoint for development and approval of new cancer treatment medication therapies [95].

HQOL is a multidimensional concept. Within the two larger domains of physical and mental health, there are many different constructs related to HQOL, including, but not limited to, fatigue, general health and bodily pain [96]. As cancer survivors are at greater risk for detriments to both physical and mental functioning [97], it is imperative to review these outcomes as they pertain to the patient's overall QOL.

Physical Health in Cancer Survivors

Cancer survivors face many physical challenges. According to national survey data, cancer survivors have higher levels of physical disability than those in the general population [98], including limitations in activities of daily living (ADL) such as eating, grooming, bathing, and chores as well as physical function declines in activities such as walking, standing or climbing stairs. In fact, while older cancer survivors suffer losses in all health domains, their losses are the most profound in the area of physical functioning [98]. Cancer survivors have a two-fold risk of physical function limitations as compared to their general population counterparts [98].

Comorbid conditions, defined as the presence of two or more chronic conditions in an individual, are often found in cancer survivors and can significantly affect physical functioning [99]. Hewitt et al [98] found that survivors who had at least one comorbidity were at a five-to-six fold increased risk of physical function deficits compared to those with no comorbidities. As expected, the number of comorbidities continues to climb in cancer survivors as they age, leading to further potential drops in functional decline[100].

Mental Health in Cancer Survivors

Aside from physical function deficits, cancer survivors also have considerable mental health issues and psychosocial concerns to manage [101]. Cancer survivors are more than two-fold more likely to develop a psychological disability than those in the general public [98]. Survivors may struggle to experience a sense of wholeness and life purpose after a life-altering experience such as a cancer diagnosis [102]. One third of cancer survivors report worries about recurrence, a second cancer, or further symptoms, and these worries are a significant predictor of anxiety and depression[16] .

Depressive symptoms can also intensify the physical disabilities seen in other medical conditions. Coupled with cancer-related problems and potential treatment side effects, this may amplify levels of stress and anxiety while contributing to deteriorating physical function [103]. Anxiety disorders can be just as debilitating as depressive disorders, and over 30 million Americans have a history of anxiety [104]. Anxiety disorders are also often found in cancer survivors [105]. These struggles can negatively affect a cancer survivors' mental health, leading to dramatic declines in HQOL.

Fatigue and Pain in Cancer Survivors

Fatigue and pain may also have a rather large impact on physical and mental health in the cancer survivor population. Fatigue is one of the most prevalent symptoms experienced by cancer patients [106]. As fatigue and pain have been shown to affect physical functioning and the ability to perform ADL, as well as impacting emotional and psychological well-being, this can be a great detriment to the HQOL of survivors [106]. Fatigue can be caused by the cancer itself or by associated treatments [2], and it has been described as a major concern for cancer patients both during treatment, when up to 95% of cancer patients may experience fatigue [106], and for those patients who have completed cancer treatment and are considered disease-free [107]. Fatigue can not only be distressing to cancer survivors, but the limiting of activity throughout the day have made many cancer patients feel as though they could no longer live a “normal” life [108].

Pain has also been observed among survivors of various cancer types [109]. It is estimated that 50% of all cancer survivors experience pain, with that number climbing to 75% in advanced stages [110]. Interestingly, survivors may underreport pain out of fear and concern that the experienced pain may be an indicator of poor prognosis [110]. Post-treatment pain is typically a result of related therapies. The pain experienced by survivors can have a significant impact on both physical and mental health, thereby yielding a less then optimal HQOL [37, 111].

Health Related Quality of Life (HQOL) in NA

As demonstrated above, there are significant HQOL detriments in cancer survivors. It is necessary, however, to evaluate how these deficits may differ between populations. NA suffer disproportionately from many of the constructs that make up HQOL. Studies suggest that rates of physical disabilities in NA far exceed that of other populations [112]. It has been reported that as many as 30% of NA had one or more functional limitations in performing an activity of daily living (ADL) as compared to 17% of whites [112]. Further, older NA have the highest rates of functional limitations among all age strata in adults aged 55 years or older when compared to Whites and African American. Of note, it has also been shown that NA are significantly more likely to report pain than any other racial/ethnic group [37]. As NA experience some of the highest rates of chronic conditions, they may also be at higher risk for comorbidities than that of other populations[113]. While there is very limited information on this topic, one study using a population-based sample found that two-thirds of NA queried had at least one comorbidity[113]. As discussed above, these data suggest that NA cancer survivors may be at great risk for physical challenges.

The mental health outcomes previously described are also important to consider as research suggests that NA suffer a disproportionate burden of mental health problems and disorders from that of other populations [25, 114-116], including depression[116], anxiety, substance abuse[117], suicide rates[118], and PTSD[119]. On average, NA experience psychological distress 1.5 times more than that of the general population[37]. Unfortunately, many of these studies have used diagnostic tools and sampling methods that hinder comparisons both across tribes and with other national estimates of mental health disorders [119, 120]. As such, a 2001 Surgeon General's report [120] concluded that we lack even the most basic information about the relative mental health burdens borne by NA.

These findings suggest that, along with other health disparities, NA in general may also suffer from a lower HQOL than whites and possibly other minority populations [121]. Further, NA cancer survivors may have HQOL challenges specific to their survival, if not disparate from those of other populations. Unfortunately, there is a dearth of information regarding the HQOL of NA [112, 121, 122] and next to none specific to HQOL in NA cancer survivors [123, 124].

To evaluate HQOL in the NA population, a study published in 2004 [121] used BRFFS data of 434 NA form North Carolina (home of the eighth largest NA population in the US). NA had significantly higher percentages of unfavorable outcomes than whites in all five measures of QOL. After controlling for age, gender, education, and household income, more than a quarter of the NA adults studied rated their health as fair or poor, compared to 17.5 percent of white adults. Approximately 14 percent of NA reported having 14 or more poor mental health days and 14 or more poor physical health days within the past month as compared to approximately 9 percent reported by whites. The percentage reporting 14 or more activity-limited days per month was more than twice as high among NA (11.6%) as among whites (5.7%).

In a CDC report delivered in 2005 examining surveillance-based HQOL data from both NHANES and BRFSS spanning the years 1993-2002, it was found that NA reported worse HQOL than any other racial group in the US [122]. Compared with non-Hispanic whites, more NA reported fair or poor health. Reported mean number of physically unhealthy and mentally unhealthy days (per seven day period) was higher among NA men and women than that of any other race (including Non-Hispanic Whites, Blacks, Hispanics, Asians/Pacific Islanders, and “other”). In addition, NA men and women reported more overall unhealthy days, physically unhealthy days, mentally unhealthy days, and activity limitation days per than that of any other race. Limitations of these studies include the cross-sectional nature of the surveys, potential selection bias due to exclusion of households without phones, institutionalized persons and the homeless (all who have potentially worse HQOL than other populations), and the fact that unaccounted/unadjusted for variables may account for potential differences in HQOL observed between races.

A study published in 2007 analyzing Census data from the year 2000 found that NA aged 55 or older have a higher prevalence of physical limitations when compared to both non-Hispanic whites and African Americans [112]. Among the almost 3 million individuals who completed the long form 2000 US Census questionnaire, 36.2% of NA had a functional limitation, 20.6% had a mobility disability, and 11.6% had a self-care disability. NA had 62% increased odds of reporting disabilities as compared to whites, even when adjusting for sociodemographic variables such as gender, race, age, education level, annual income, and metropolitan residence. Unfortunately, there are inherent limitations to using US census data, such as the inability to assess potential confounders such as chronic disease, depression, etc., due to the specific questions asked, the cross-sectional nature of the data, and that each disability construct was a single-item measure. Also of note, US census data uses self-identification of race and may therefore not reflect the narrow definition by certain Native tribes. However, as opposed to most studies that use a geographically defined sample of specific tribes, this study does utilize a nationwide large sample of NA encompassing hundreds of different tribes.

Health Related Quality of Life (HQOL) in NA Cancer Survivors

As previously suggested, NA cancer survivors may have HQOL challenges specific to their survival not experienced, or experienced at a different rate, than that of other populations. It is therefore necessary to evaluate the HQOL of NA cancer survivors independent of other populations. Unfortunately, very little work has been done in this area. In the first study to investigate the HQOL of NA cancer survivors [123], a convenience sample of 266 NA breast cancer survivors completed a HQOL survey. This tool was based on more than fifteen existing tools, with cultural modifications specific to NA made by NA research specialists. The physical health of this sample was generally good, with 49.4% of the sample reporting “good” or “excellent” physical health, which is similar to results found in other cancer survivors [125]. There were, however, significant differences reported between groups when stratified by time since diagnosis, with only 28% of those survivors diagnosed within one year of taking the survey reporting “good” or “excellent” physical health as compared to 58% of those diagnosed greater than 5 years from the time of being surveyed. When looking at specific constructs of HQOL, a large percentage of survivors reported having problems with pain (28.6%), fatigue (29%), weakness (26%), ability to concentrate (87.2%) and depression (16.2%) occurring since diagnosis. Again, these percentages differed by time since diagnosis, with those diagnosed over five years from the time of the survey consistently having fewer of these conditions than those diagnosed less than a year from the time of the survey. These findings are noteworthy in that they may suggest that those newly diagnosed survivors are fearful that their HQOL at time of diagnosis or treatment will not resolve. While this important study was the first of its kind to evaluate the HQOL of a cohort of NA cancer survivors, there were many limitations, perhaps the most notable being the fact that cancer treatments were not controlled for in the analyses. The differences noted in HQOL constructs between time at diagnosis are most likely due to cancer treatments, as these treatments have been previously shown to play a role in cancer morbidities. Further, the self-report nature of the tool used here lends itself to potential recall bias. As this study was cross-sectional, survivors were not evaluated over time making it unclear as to whether survivors HQOL changed over time since diagnosis. Finally, this is a convenience sample of NA, as there is no national sample of NA cancer survivors. This does not allow for comparison of this cohort to other NA cancer survivors and, as such, these findings may not be generalizable to other NA cancer survivors.

In the only study to date to compare the HQOL in NA cancer survivors against that of non-native cancer survivors [124], 596 NA cancer survivors of all cancer types from across the US completed a series of HQOL questionnaires. These questionnaires were based on HQOL items from the QOL-CS, a tool developed by researchers from the City of Hope Cancer center [126], but modified to be culturally relevant to NA communities. The four domains of survivorship covered by both of these measures consist of the physical, psychological, social, and spiritual self. The QOL-CS was originally used to survey 686 non-Native cancer survivors in 1995, allowing for appropriate comparison between populations. When reviewing data from both cohorts in the "physical well-being" domain, NA had significantly lower scores than did non-Natives in the overall physical well-being, nausea, appetite, and fatigue subscales. While NA had significantly worse scores on the usefulness and anxiety subscales, there were no significant differences noted between NA and non-Natives in the overall category or in any other subscale in the "psychological domain". "Social support" was worse in the NA cohort, with significantly worse scores in the overall social, personal relationships, support from others, isolation, home activities, financial burden and family distress subscales when compared to non-

Natives. Natives generally scored better in the “spiritual well-being” domain, with significantly better scores in the hopefulness, life purpose, and positive change subscales, though it should be noted that many NA choose to not answer these questions on the belief of the importance to retain the privacy of spiritual beliefs so that others do not misuse spiritual practices [127]. Interestingly, even though the breakdown by subscale suggests a lower HQOL in NA as compared to non-Natives, both cohorts rated their overall HQOL as the same. These data help to confirm that the differences noted, even if not that dissimilar, are likely due to cultural differences experienced between NA and non-Natives. While this is the largest sample of NA cancer survivors reported in any peer-reviewed journal and the first of its kind to report differences in HQOL between Native and non-Native cancer survivors, there are many limitations to this study. The survey itself is actually different between the two groups due to the cultural modifications made for the NA population, which may make direct comparisons challenging. Besides the use of self-reported measures and the NA cohort being self-selected, the delivery of the survey (NA were offered assistance in completing the survey from patient advocates while non-Natives received the survey in the mail) and the timing of the survey (more than a decade apart) could introduce bias into the analysis.

In summary, most studies report that HQOL is lower in NA than in the general population, or in any other minority group in the US. While NA cancer survivors rated their overall HQOL similar to that of non-Natives, many physical and mental functional deficits considered to be constructs of HQOL were apparent. In order to combat these deficits and further improve HQOL in this population, treatment options must be identified.

Effect of Physical Activity on HQOL

In an attempt to improve the HQOL of cancer survivors, various treatment modalities have been suggested. One such modality that is often discussed is PA. PA and its effects on health have been a focus of research for quite some time. PA can encompass many domains, but has been traditionally defined as “any bodily movement produced by skeletal muscles that results in caloric expenditure” [128]. When discussing the effect PA has on general health, there is a wealth of evidence suggesting a protective role of PA against all-cause mortality and chronic diseases [129]. It has become evident that even moderate increases in PA are associated with health benefits, especially in those that were previously sedentary [130]. Additionally, there is growing evidence suggesting that PA may improve HQOL by enhancing physical, functional, psychological, emotional and social well-being, not only in the general population, but in cancer survivors as well [131-134]. Evidence indicates PA facilitates positive physiologic and psychological benefits in cancer survivors both during and after treatment [13, 41 12, 135-137]. It reduces anxiety, tiredness, pain, and potential worry about the cancer [136]. Exercise may also help to improve the way the survivor views his or her body (a common side-effect of cancer treatment), the way cancer survivors deal with emotions, sexuality, and sleep problems. Interestingly, it appears that HQOL may be a key motivator of PA [136].

While encouraging, there are limitations to these findings and subsequent gaps in our understanding of the relationship between HQOL and PA in cancer survivors. Along with some of the typical limitations found in many studies (i.e. convenience samples, small sample sizes, subjective measures of PA, cross-sectional designs, etc.), there are many other limitations that are specific to examining this relationship. Many studies identified evaluated specific kinds of exercise programs, which varied by type, intensity and total volume of exercise, and as such there are still unresolved issues regarding the relationship between PA and HQOL in cancer survivors (e.g. when to start the program, type of exercise, length of program or exercise session, how hard to exercise, etc.). Also, there are countless ways used in the literature to measure HQOL, making it difficult to compare across studies and synthesize recommendations. More research is needed regarding the effects of PA in general, not just specific to “planned exercise”, but other types and intensities of activity, on these outcomes.

The relationship between HQOL and PA in cancer survivors has previously focused on breast cancer survivors [138-140]. It appears that PA can improve physical function and overall HQOL in these patients, yet the breast cancer survivor population differs greatly than that of other cancer survivor populations. Also of note is the lack of long-term survivors in these studies. Short-term (< 5 years) cancer survivors face a series of physical and mental challenges that may differ from that of long-term (5+ years) survivors [141]. While most studies have shown that meeting the recommended PA guidelines (accumulation of 30 minutes or more of moderate intensity physical activity five days a week) is related to better physical function in adults [142, 143], few have evaluated other types and intensities of PA. This information may be important in that it has also been found that those who simply participate in active lifestyles exhibit a higher functional ability and greater overall HQOL than those who are non-active [134, 143], suggesting that other PA outside that of planned exercise at moderate or vigorous intensity need to be evaluated.

Recently, there has been an increase in research aimed at evaluating PA and HQOL in cancer survivors; however, a great majority of these studies are clinical trials [144]. In order to effectively identify causative relationships and be able to generalize the findings, clinical trials must enroll appropriate populations. Subjects with advanced disease and comorbidities are often excluded from studies, and very few studies enroll minority populations. While these trials are necessary to evaluate causation, they are unable to determine the natural patterns of PA in representative samples of cancer survivors. Observational studies, however, allow for the evaluation of large populations which can provide us with more information regarding a broader range of exposures and have greater generalizability. This type of study design also lends itself to examining natural patterns of PA, which may be of great importance to designing PA interventions specific to a given population.

PA in NA

Unfortunately, few Americans participate in enough PA to reap health benefits[145]. Among the least active segments of the US population are ethnic minorities [146, 147]. While little work has been done to describe the PA behaviors in NA, the US department of Health and Human services indicates that 46% of NA report no leisure-time activity compared to 38% of Whites [146] . Studies have reported that very few NA are meeting

PA guidelines and that PA levels are at least as low as those of other racial/ethnic minorities, if not lower, and are lower than non-Hispanic Whites [148]. Research has shown, however, that, similar to other populations, PA is associated with better health outcomes in NA, including increased levels of high-density lipoprotein cholesterol, lower fasting insulin levels, lower BMI levels, and lower percentage of fat and fat mass [146]. As such, it is important to explore PA in NA cancer survivors. In the process of evaluating PA, it is also important to define the amount and type of PA typically done by this population. As NA in general are not actively participating in the level of PA needed for health benefits, information regarding the specifics of the activities that NA do participate in can potentially lead to interventions to increase these levels. This has the potential to directly affect HQOL in the survivorship phase of the cancer experience.

PA and HQOL in NA

As NA cancer survivors have exhibited a decline in HQOL including both physical and mental function, it is important to explore PA as a way to mitigate the impact of cancer on these outcomes. PA has been shown to be related to HQOL in the survivorship phase of the cancer experience [6, 12, 13, 129, 136, 149, 150]. Unfortunately, there has yet to be a single study to evaluate the relationship between PA and HQOL in NA cancer survivors. However, there are studies evaluating this relationship in non-cancer survivor NA populations, albeit very few. Information gathered from this work may be informative as it can bring further insight into the potential benefits of PA specific to this minority population. In a cross-sectional analysis of PA and HQOL, Poltavski et al [151] surveyed 404 NA from the Northern Plains using the 2003 version of the BRFSS survey. Based on BRFSS questions, five criterion variables of HQOL were used in this study: Overall health rating, unhealthy physical days, unhealthy mental days, good health days, and activity limitation days. PA was categorized as meeting PA recommendations or not meeting PA recommendations. It was found that, after controlling for potential confounders, meeting PA recommendations was significantly associated with better overall health, fewer mentally unhealthy and activity limitation days and a greater number of good health days. While these findings are encouraging and consistent with other studies using BRFSS data with other populations, there were many limitations to this study. The PA variable used in this study has the potential for misclassification error, as the researchers extended the "met PA guidelines" to include those individuals who reported "mostly walking" as part of their job description. The rationale given was that even one hour of walking per day at work during a five day work week would result in ~300 minutes of walking per week, which is well above the PA recommendations. However, this is problematic as these individuals are most likely not walking at a moderate or vigorous intensity level consistent with the PA recommendations. Further, total time walked was not quantified, suggesting that the approximation of 300 minutes a week of PA, even if at a moderate intensity, may be inflated. Another limitation of the study was that, while controlling for potential covariates, many conditions that would likely be considered as confounders were not mentioned in the survey, such as substance abuse, depression, certain types of cancers, sleep disorders, and chronic kidney and liver diseases. These conditions significantly affect morbidity in the NA community, potentially leading to lower HQOL.

In a trial aimed at increasing PA levels in NA elders [152], HQOL was evaluated as a secondary outcome. Participants were randomized into either an activity monitoring arm (n=63), consisting of completing daily self-monitoring PA forms, or an activity monitoring arm augmented with a pedometer (n=62) to track and record their total daily step counts, lasting for a total of six weeks. As part of the intervention, all subjects received two in-clinic education sessions, as well as phone calls every two weeks to review PA logs. HQOL was measured by the SF-36. While researchers did not find a difference in PA across treatment groups, there were significant improvements in levels of PA post intervention. As such, both treatment groups were collapsed into a single sample and changes in HQOL scores form baseline to week six were examined. While each subscale score improved post-intervention, only two were significant: bodily pain and vitality. This finding may be misleading, however, as one of the limitations to the study was that an *a priori* power analysis on these outcome measures was not conducted. Another important limitation to consider is the lack of a true control group, as the personal attention, social interaction, education and feedback from research staff may have confounded the observations of the study.

Another randomized controlled trial [153] evaluated a community-based PA intervention in a group of 22 NA aged 55 and older. Participants recruited from a health clinic were randomly assigned to a six-week exercise class (n=16) or to a non-exercise control group (n=6). Of note, two participants who were originally randomized to the exercise group declined exercise participation and were then placed in the control group. Control subjects agreed to not join an exercise program for the duration of the study. The exercise intervention consisted of a formally structured, instructor-led session of moderate-intensity exercise (as determined by 55%-69% of MHR), with stretching exercises included to address flexibility and mobility as well as decrease pain, and muscular strengthening exercises such as body-weight assisted movements. Each session would last a total of forty minutes, with a ten minute warm-up, a twenty minute low-impact exercise session, and a ten minute cool down, and met twice a week over six weeks. At pre- and post-intervention visits, participants completed a self-assessment health survey consisting of eleven questions designed to measure emotional and physical health. Only ten participants assigned to the intervention arm met the attendance requirement, making it to at least 67% of class visits, resulting in a 37.5% attrition rate. Additionally, two members of the control group dropped out. Within-group analyses showed significant improvements in self-reported physical health state, emotional health state, and an increased ability to perform ADLs. However, while the control group showed no differences between pre- and post- measures, when comparing the control group with the exercise group both pre- and post-intervention, no significant differences were found. Limitations include potential selection bias due to the convenience sample as well as non-random assignment in some cases, losses to follow up, a small sample size, a non-validated measure of self-reported health, and a lack of specific information on the exercises performed.

Section Summary

While evidence is accumulating regarding the PA/HQOL relationship in cancer survivors, there are many gaps that exist in the literature. These include limited information on other types of cancer outside of breast and a lack of long-term survivors studied [133]. Perhaps most notably, however, is the glaring absence of information concerning the relationship between PA and HQOL in NA cancer survivors. As of this writing, there were no studies that have evaluated this relationship. As NA cancer survivors have exhibited a decline in HQOL including both physical and mental function, and PA has been shown to improve these health outcomes in various populations, it is important to explore PA as a way to mitigate the impact of cancer on these outcomes. Further improvement in these areas can directly affect HQOL in the survivorship phase of the cancer experience. Therefore, it is the goal of the proposed research project to help fill these gaps by examining the relationships between PA and HQOL in a sample of NA cancer survivors.

Study 2: Impacts of Exercise on Prognostic Biomarkers in Lung Cancer Patients

Prevalence/Incidence

Lung and bronchial cancers are the second most commonly diagnosed type of cancer (not including non-melanoma skin cancer), accounting for approximately 14% of all new cancers in the US in 2013 [1]. Approximately 6.9% of men and women in the US will be diagnosed with lung and bronchus cancer at some point in their lifetime [71]. The American Cancer Society estimated that there were about 221,190 new cases of lung cancer (118,080 in men and 110,110 in women) in the year 2013 [1]. Lung cancer mainly occurs in older people, with the average age at the time of diagnosis being seventy years old[1]. Every two out of three people diagnosed with lung cancer are 65 or older, with less than 2% of all cases found in people younger than 45 [1].

Lung cancer is also the leading cause of cancer death in the US for both men and women, with an estimated 159,480 deaths from lung cancer (87,260 in men and 72,220 among women) in 2013 [1]. This accounted for 27% of all cancer deaths [1]. More people die from lung cancer each year than from colon, breast, and prostate cancers combined. Lung cancer is the primary cause of cancer deaths in both men and women in the state of Wisconsin [1]. Prognosis of the lung cancer patient is generally quite poor. Over half of those diagnosed with lung cancer die within the first year of being diagnosed [1]. The five-year survival rate for lung cancer (16.3%) is lower than many of the other leading cancer sites, such as breast (90.0%), colon (65.2%), and prostate (99.9%) [71, 84]. Despite these staggering mortality statistics, there are a considerable number of lung cancer survivors. More than 399,000 people alive today have been diagnosed with lung cancer at some point [71]. Mortality rates have been declining by roughly 1.7% over the last ten years and five-year survival rates continue to climb, suggestive of the increasing number of cancer survivors in the US.

Impact/Burden of Survivorship

Cancer diagnosis and treatments can also create physical, emotional, social and financial challenges for the survivor, leading to significant impacts on HQOL [2]. A significant proportion of lung cancer survivors face serious physical and functional declines [154], and may be severely incapacitated by disease-related symptoms such as chest pain, cough, hemoptysis and dyspnea [155]. Detriments in mental health, mainly depression, are also common and persistent in lung cancer patients, especially those with more severe symptoms or functional limitations [156]. Lung cancer survivors can experience heightened levels of fatigue, pain, disturbed sleep, lack of appetite and drowsiness [157-161]. As a consequence of these health challenges, HQOL may be diminished in this population. Previous work evaluating HQOL in lung cancer survivors suggest that lung cancer survivors do not experience the same HQOL as their-aged matched peers or aged-matched survivors of other cancers [162].

Due to the great burden of disease experienced by lung cancer survivors, new therapies are required. These treatments should work to improve prognosis and HQOL while complimenting current management of lung cancer. PA remains an attractive modality due to its documented relationship to prognosis, improvement of physical and mental health outcomes, and HQOL in many different populations. Despite the potential benefits of PA in this population, there are very few well-controlled trials that have examined the effect of PA in this disease. As such, PA needs to be evaluated in the lung cancer population for the role it may play in these outcomes.

PA and Exercise Capacity in Lung Cancer Survivors

One of the many physiologic challenges faced by lung cancer survivors include exercise intolerance [163]. There may be many reasons for this. Lung-based tumors are thought to disrupt gas exchange [164], potentially resulting in increased dyspnea, fatigue, muscle wasting, anemia, and weight loss, all leading to decreased exercise tolerance. Physical inactivity may also be common among lung cancer survivors due to pain, weakness, and therapeutic toxicities [165]. While adoption of a sedentary lifestyle has been associated with increased mortality rates, recent reports suggest that peak oxygen consumption, a common measure of exercise capacity, is a strong independent predictor of overall long term survival for lung cancer patients. An inverse relationship between peak oxygen consumption and perioperative and postoperative lung cancer surgical complications have also been reported [43, 163, 166, 167]. Poor exercise capacity can further dispose patients to other common age-related diseases and detriments in HQOL. As physical inactivity is a strong determinant of poor $VO_{2peak,}$ and may exacerbate the already diminished deconditioning in the cardiovascular system [43], PA appears to be a way to mitigate the poor exercise capacity often observed in this population. While exercise behavior and functional capacity are correlated, they may independently provide distinct information. Very few studies have objectively evaluated the role of exercise in improving exercise capacity in lung cancer survivors.

Currently, only one study has evaluated the effect of an exercise intervention on exercise capacity in lung cancer survivors utilizing a control group [46]. Fifty-three pre-surgical lung cancer patients were randomized to a usual-care control group or a post-operative exercise intervention which consisted of twice daily strength training exercises, walking and recumbent bike exercises at an intensity level between 60% and 80% of their maximal heart rate, and home support once monthly for a total of three visits. Arbane et al [46]. found significant deterioration in exercise capacity at five days post-resection compared with pre-operatively in both groups, as measured by the Six Minute Walking Distance (6MWD) test. There were, however, no significant differences in improvement of exercise capacity reported between the two groups post-intervention, with 6MWD scores returning to pre-operative levels by twelve weeks in both groups.

Using a single group design, Jones et al [168] evaluated a preoperative exercise training program on fitness levels in lung cancer patients. Subjects (n=25) with suspected operable lung cancer participated in a structured exercise training program until time of surgery. Exercise training consisted of five cycle ergometry sessions per week at varying intensities (60% to 100% of VO_{2peak}). Participants underwent cardiopulmonary exercise testing, 6MWD, and pulmonary function testing at baseline, immediately prior to, and 30 days post-surgical resection. Scores were significantly improved on all measures post-baseline prior to surgery. While exercise capacity declined post-surgery, it did not decrease beyond baseline values. These findings highlight the role of an exercise training program in improving exercise capacity in lung cancer patients pre-surgery, though the lack of a control group may hinder findings.

Quist et al [169] conducted a pilot study to evaluate the safety and feasibility of a six-week supervised structured exercise and relaxation training program on estimated peak oxygen consumption, as well as functional capacity, in patients with inoperable lung cancer currently undergoing chemotherapy. Twenty-nine individuals completed baseline measures consisting of a stationary ergometer max test to assess VO_{2peak} and the 6MWD test to measure functional capacity, with twenty-three of the individuals completing the post-assessment testing. The intervention consisted of supervised group training (physical training and relaxation) twice per week and at-home training (walking and relaxation) three days per week for a total of six weeks. Exercises consisted of both cardiovascular training and strength training. At the end of the intervention, there were improvements in estimated VO_{2peak} and six-minute walk distance (6 MWD). While encouraging, the lack of randomization and potential selection bias could impede findings. Also of note, while the adherence rate for the supervised portion of the intervention was 73%, only two of the twenty-three participants participated in the at-home aspect of the intervention, suggesting that at-home training may not be as feasible of an option for this population.

Spruit et al [47], using an eight week multidisciplinary rehabilitation, tested peak exercise capacity in ten post-surgical lung cancer patients with severely impaired pulmonary function. At baseline, patients had low levels of exercise capacity as measured by the 6MWD. These scores improved significantly post-intervention when compared to baseline, suggesting exercise interventions may improve exercise capacity in this population. Of note, this study used a small sample with no control group, which limits the ability to attribute improvement to the intervention. Also, the rehabilitation intervention was multifocal. This could potentially have impacted 6MWD test scores differently than an exercise intervention alone. Future studies are needed to confirm these findings while including a control group and teasing out potential differences in rehabilitation modalities.

A few studies have evaluated the role of pulmonary rehabilitation in improving exercise capacity in this population [170, 171,172]. While most of these were pilot studies or used samples of different types of cancer survivors, Cesario et al [172] used a non-randomized trial to evaluate the efficacy of pulmonary rehabilitation for use in lung cancer patients post-lung resection. Of the 211 patients identified as eligible that went through the lung resection procedure, 25 agreed to participate in the rehabilitation program, consisting of five sessions a week for twenty total sessions of moderate intensity cycling, treadmill, resistance training and educational sessions. The other 186 were used as controls. Functional outcomes including the 6MWD, and dyspnea on exertion were significantly improved in treated patients when baseline versus 1-month figures were compared. The reverse was true of controls, with functional capacity significantly declining. There were no significant differences between groups, though it should be noted that this is most likely due to the much lower functional status found at baseline for those in the rehabilitation group when compared to those in the control group. In a follow-up study two years after this original study, Cesario et al. enrolled an additional 78 patients using the same procedures as the prior study and found once again that exercise/functional capacity significantly improved from baseline in those individuals participating in the rehabilitation program [173]. As such, this is further evidence that PA, in this case a pulmonary rehabilitation program, can improve exercise capacity in lung cancer survivors. Further work using randomized controlled trials are needed.

PA and Biomarkers

Physiological biomarkers have increasingly been examined in PA studies due to their prognostic significance. Of particular interest are biomarkers of inflammation, as inflammation has been linked to several types of cancers, including colorectal, esophagus, and lung [174]. Markers of interest in lung cancer include tumor necrosis factor alpha (TNF-α) and specific interlukins (IL-6, IL-1β) [175]. These markers are inflammation-responsive and proinflammatory cytokines, respectively, and are considered to play a role in pathogenesis and treatment in this population [176]. These cytokines influence C-Reactive protein (CRP) production. CRP is an acute phase protein and widely accepted as a sensitive and reliable biomarker of systemic inflammation [177]. It has been shown to be correlated with many malignancies, an independent predictor of survival in inoperable non-small cell lung cancer patients and, along with IL-6, IL-1β, has been reported to predict postoperative complications and length of hospital stay [49, 177, 178]. Elevated levels of circulating CRP have been found in 75%-80% of patients with inoperable lung cancer. As such, elevated levels of circulating CRP have been used a marker of prognosis in lung cancer patients [177].

Suppression of the inflammatory response through exercise may be one of the important mechanisms through which PA affects cancer prognosis [53]. Self-reported exercise and higher cardiovascular fitness have all been associated with lower levels of systemic inflammation in a number of populations [53, 179-181]. While most of the data regarding the relationship between PA and markers of inflammation in cancer survivors have been derived through observational studies, there have been a limited number of randomized control trials that assess the effect of PA interventions on these prognostic biomarkers. Of the four RCTs identified evaluating this relationship, none have targeted lung cancer survivors [179, 182-184]. Two studies were conducted in breast cancer survivors [179, 182], one in colorectal cancer survivors [183], and one in prostate cancer survivors [184]. In the first study to evaluate breast cancer survivors, Fairey et al. randomly assigned fifty-three subjects to either an exercise intervention (n=25) or control group (n=28)[179]. The intervention consisted of exercising 3 times per week for 15 weeks on cycle ergometers. Exercise intensity was approximately 70–75% of peak oxygen consumption and the duration of the sessions was up to 35 minutes of total exercise. CRP levels were measured at baseline and post-intervention in both study groups. CRP decreased by 1.39 mg/L in the exercise group while increasing 0.10 mg/L in the control group. While this difference didn't reach statistical significance (p=0.07), the mean difference was consistent with previous observational and non-randomized intervention studies. This was the first RCT to evaluate the role of exercise on CRP in breast cancer survivors using standardized blood collection protocols, though it did have a few limitations, including a small sample size, a low recruitment rate, and use of a single blood measurement to classify participants.

The second RCT to evaluate inflammation biomarkers in breast cancer survivors was conducted by Payne et al [182]. Using a sample of older women (aged 55 years or older) receiving hormonal treatment for breast cancer, subjects were randomized to a home-based walking exercise intervention (n=10) or usual care (n=10). The exercise intervention consisted of moderate walking, for twenty minutes in duration, four times a week for fourteen weeks. IL-6 levels, along with a host of other biomarkers having hypothalamic-pituitary-adrenal (HPA) axis neuroendocrine-based regulatory functions, were measured at the initial visit and post-intervention time points. No significant differences were found in IL-6 levels between groups or within groups over time, with mean values for both groups being within the normal range. The main limitations of this study include the small sample size and the use of unsupervised exercise. As researchers were unable to verify actual adherence to the exercise intervention, it is possible that the lack of changes in IL-6 measures were due to non-adherence.

In the only RCT to evaluate exercise and inflammatory markers in prostate cancer survivors, Galvao and colleagues randomized fifty-seven patients with prostate cancer to a twelve week exercise intervention consisting of resistance and aerobic exercise (n = 29) or usual care (n = 28)[184]. CRP was measured at baseline and after the twelve weeks. Post-intervention, CRP levels had decreased in the exercise group from baseline while increasing in the controls, resulting in a significant difference in mean change over the intervention.

Allgayer and colleagues compared the effects of a post-operative moderate-intensity exercise program (55%-65% of maximal aerobic power) to a low-intensity exercise program (30%-40% of maximal aerobic power) on a series of inflammatory markers including IL-1β, IL-6, and TNF-α in patients with curatively-treated colorectal cancer [183]. Once randomized to one of the two exercise groups, subjects (n=23) performed daily exercise for 30–40 min for 2 weeks at the prescribed intensity. A significant decrease of the IL-1 receptor antagonist (IL-1RA)/IL-6 and IL-1RA/IL-1β ratios were found in the moderate-intensity group, whereas in patients completing low-intensity exercise, these markers remained unaffected. Further, thirty minutes after starting moderate-intensity exercise, an increase of IL-1β was found, whereas in patients performing low intensity exercise no such increase was observed. This suggests that moderate-intensity exercise may have beneficial effects in terms of an improved immune response, whereas a low-intensity exercise program may not be effective.

There have been a few non-randomized studies examining the role of exercise on inflammatory markers in cancer survivors. In the only study to evaluate the relationship in lung cancer survivors, Jones and colleagues conducted a pilot study utilizing twelve subjects with operable lung cancer [185]. Using a single-group design, subjects participated in an exercise intervention consisting of five sessions per week of tailored cycle ergometry at an intensity level of 60%-65% of VO_2 max for 30 minutes until the subject had surgical resection. One session a week included interval training.

Inflammatory markers (IL-6, IL-8, CRP and TNF-α) were measured by blood draw at baseline and immediately prior to surgical resection. Although all inflammatory markers were lower following exercise training, these measures did not statistically differ from baseline to post-intervention. The magnitude of the changes, however, were similar to the findings in a sample of breast cancer survivors [179], suggesting that perhaps the non-significant findings were due to the small sample size. As such, these findings may still be of clinical importance. While this study provides preliminary information regarding the relationship between exercise and inflammation in lung cancer survivors, randomized control trials in this population are needed.

Another potential marker of prognosis being evaluated in cancer survivors is that of oxidative stress. Oxidative DNA damage may play a major role in carcinogenesis, with an increase in oxidative damage thought to be involved in tumor formation [187]. A good indicator of oxidative stress in humans is 8-hydroxy-2'-deoxyguanosine (8-OH-dG), as 8-OH-dG is a product of oxidative DNA damage [188]. Tumor formation may be due in part to the genomic instability associated with 8-OH-dG, as the presence of 8-OH-dG in DNA leads to transversion, mutagenesis, or cell death unless correctly repaired prior to DNA replication [187]. Recent studies have shown that non-small cell lung cancer patients with low levels of 8-OH-dG have significantly longer survival times as compared to those with higher levels of 8-OH-dG, with some reports suggesting individuals with high levels of the biomarker having an over three-fold increased hazard of death [189]. Though acute exercise can result in oxidative stress, repeated bouts of exercise in trained individuals has been shown to produce compensatory increases in antioxidant capacity [190]. As this has been hypothesized to be one of the ways in which

PA may affect cancer prognosis [191], studies are beginning to evaluate the effect of exercise on markers of oxidative stress, namely 8-OH-dG. In the first study to assess this relationship in cancer survivors, Allgayer et al [186] examined the effect of a short-term exercise program on 8-OH-dG levels in a sample of post-operative patients with curatively treated colorectal cancer. Subjects (n=19) were randomized to a high-intensity exercise program (55%-65% of maximal aerobic power) or a moderate-intensity exercise program (30%-40% of maximal aerobic power), performed daily for 30–40 minutes over a period of two weeks. Urinary samples of 8-OH-dG were collected in all subjects pre- and post-exercise program. Those in the moderate-intensity group had significantly reduced levels of 8-OH-dG post-intervention, suggesting decreased oxidative DNA damage, whereas those in the high-intensity group had a non-significant increase. Despite the limitations of this study, including a small sample size and five subjects switching to the moderate-intensity group post-randomization, this study highlights the potential importance of exercise on 8-OH-dG levels in cancer survivors. Though comparisons across studies are difficult due to the difference in exercise interventions and 8-OH-dG determination methods (i.e., blood versus urine samples), these findings are consistent with previous works suggesting decreased oxidative damage following moderate exercise[192-194]. However, these studies have used samples of predominately healthy individuals, most of which are athletes. While it is necessary to attempt to replicate these findings in other populations, including cancer survivors of varied types, these studies help further our understanding of this relationship.

In a study designed to investigate the effects of exercise on levels of 8-OH-dG after mild acute exercise in healthy male subjects, Sato et al [195] divided fifteen subjects between two groups: a sedentary group, defined as those individuals who only occasionally exercise, and an active group, defined as those who exercise daily. 8-OH-dG levels were determined by blood draws and taken 5 minutes prior to exercise and at 5 minutes, 60 minutes, 24 hours, and 48 hours after exercise. Subjects were directed not to participate in any strenuous exercise for the three days leading up to the exercise session. Subjects were exercised for 30 minutes at their prescribed target heart rates, which corresponded to approximately 50% VO_{2max} as determined by a submaximal exercise test given seven days prior to the exercise session. The researchers found 8-OH-dG levels of subjects in the active group were significantly lower than those of sedentary subjects at baseline, though after the 30 minute exercise bout, the 8-OH-dG levels of the sedentary subjects significantly decreased while the 8-OH-dG levels of subjects in the active group remained unchanged. Though these results suggest that mild exercise can potentially help to prevent oxidative DNA damage, a small non-randomized sample of healthy, young, non-smoking males was utilized, potentially limiting findings.

Inoue et al [192] measured 8-OH-dG levels in distance runners (n=9) and swimmers (n=9). Venous blood and urine were collected before and after an acute bout of exercise typical of a usual training session. Surprisingly, the amount of 8-OH-dG in the blood post- acute exercise bout declined in both groups, though not statistically in distance runners. This may suggest that existence of exercise-induced repair mechanisms should be considered. Finally, in one of the first studies to investigate the role of PA on 8-hydroxyguanine (8-OH-Gua), another marker of oxidative DNA damage and similar to that of 8-OH-dG, Asami et al [193] collected blood samples in twenty-one healthy male volunteers (ten trained athletes and thirteen untrained men), aged 19–50 years, both before and after an exercise session. Trained athletes showed a lower level of 8-OH-Gua before exercise when compared to that of untrained subjects. Still, mean levels of 8-OH-Gua in untrained subjects also decreased significantly post-exercise. In the trained athletes, 8-OH-Gua levels were not changed post-exercise. These findings suggest that exercise can potentially cause both acute and long-range reduction of oxidative DNA damage, dependent upon individual fitness levels.

PA and HQOL in Lung Cancer Survivors

Improvements in surgical techniques, together with more effective chemotherapy regimens, have led to significant gains in survival in those with operable disease. Still, lung cancer survivors face many serious challenges associated with survival. Significant symptom distress, often plaguing lung cancer patients, has been shown to be negatively correlated to HQOL [64, 67, 69, 155]. HQOL is also closely linked to symptom burden and severity of lung cancer [196-199]. As loss of physical functioning, increased prevalence of mental health disorders such as depression, and increased levels of pain and malaise associated with uncontrollable symptoms and symptom burden is common in this population, lung cancer survivors are at great risk for HQOL deficits [198]. Long term morbidity, along with consequential social and economic burden, is another problem commonly experienced by lung cancer survivors, potentially leading to lessened HQOL [65, 200]. As such, HQOL has been increasingly recognized as an important clinical outcome in the management of lung cancer patients. Patients with lung cancer typically report lower HQOL than do patients of other cancer types [67]. As stated previously, there is growing evidence suggesting that PA may improve HQOL by enhancing both physical and psychological function in not only the general population, but in cancer survivors as well [131]. These studies have mostly focused on breast cancer survivors, though there have been studies that have evaluated this modality specifically in lung cancer survivors. A 2011 systematic review by Granger et al [38] concluded that, based on the sixteen studies reviewed, exercise in patients with non-small cell lung cancer is both safe and associated with various HQOL constructs, both before and after treatment. The majority of work evaluating these relationships, however, has been either observational in nature or case series. As such, these results should be viewed cautiously. Currently, there have only been three RCTs to evaluate the effect of PA on HQOL in lung cancer survivors.

A randomized control trial performed by Arbane et al [46] evaluated the effect of exercise training after lung resection on HQOL in a group of lung cancer survivors. Fifty-three (28 male) subjects were randomized to an exercise intervention group or a control group (usual care). The five-day in-clinic exercise intervention consisted of twice daily strength training from day one post-surgery through day five post-surgery. Additional exercises included walking, as able, marching on the spot and recumbent bike exercises (carried out at bedside) at an intensity level between 60% and 80% of their maximal heart rate for at least five minutes up to a maximum of ten minutes per exercise. Patients in the exercise intervention group also received home support, once monthly for a total of three visits, where they were encouraged to continue with their exercise program. The control group received monthly telephone calls from the research team, providing education only. HQOL, as measured by the European

Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), was recorded at baseline (a pre-operative time point) and a post-intervention time point (twelve weeks post-operative). There were no significant changes in HQOL either within or between groups. However, the extent of surgical resection makes comparisons difficult. There was little deterioration in HQOL after lobectomy in this study. As HQOL was measured prior to resection and then again post-exercise program, this may suggest that exercise may help to mediate the deterioration in HQOL post-surgical intervention. Unfortunately, there was no data regarding adherence to the at-home component of the exercise intervention, making interpretation of these data difficult. Future studies of this nature should be sure to include an additional testing of HQOL following the surgery but prior to the exercise program in an attempt to tease out the potential effects of surgery as just described, as well as adherence data on at-home exercise.

Another RCT evaluated a multidisciplinary rehabilitation program, including exercise, on HQOL in patients who had undergone a thoracotomy for lung cancer [47]. Subjects (n=57) were randomized to rehabilitation or usual care. The intervention consisted of twice-weekly exercise training sessions for 12 weeks, scheduled visits to pain specialists, and medical social work. During exercise sessions, patients exercised between 60% and 80% of their peak cycling load (as determined by a post-operative incremental cycling ergometer test) and performed muscle training. HQOL was measured by the SF-36 and the St. George's respiratory questionnaire (SGRQ) at baseline and after 1, 3, 6, and 12 months. Of note, the study closed prematurely because of the introduction of video-assisted thoracoscopic surgery. Still, of the fifty-seven randomized patients, forty-nine (twenty-three from the intervention group and twenty-six from the control) were analyzed. When compared with the active group, the control group reported less role limitations because of physical problems at the three month time point as reported on the SF-36. However, at 12 months, this difference disappeared. No other HQOL measure was found to be significantly different between groups. Regarding exercise session compliance, less than half participated in the program through week twelve. Of these, only three of the ten patients receiving chemotherapy completed the intervention. Along with these dropouts, premature closure of the study resulted in a lower number of patients than originally calculated, thereby decreasing the power of the study to detect differences. Further limitations of this study include a multidisciplinary approach to rehabilitation, which does not allow a direct evaluation of the exercise intervention on HQOL.

Finally, in a RCT to evaluate similar constructs found in those determining HQOL, Wall et al focused on changes in hope and power among 104 pre-operative lung cancer patients [48]. Hope, defined as “the act by which temptation to despair is actively or victoriously overcome” and power, defined as “the capacity to knowingly participate in change”, “living with intentionality and/or purpose”, and characterized by “awareness, choices, freedom to act intentionally, and involvement in creating change” could all be used in this context as surrogates of HQOL. Participants were randomly assigned to a pre-operative exercise intervention or a non-exercise control. The exercise intervention consisted of a 7- to 10-day home-based program that included walking one mile a day, stair climbing forty steps twice a day, and arm, leg, and breathing exercises to be done in a circuit ten times, twice in a given day. Hope and power were measured by the Herth

Hope Index (HHI) and the Power as Knowing Participation in Change Test, respectively. Hope and power were measured at three points in time. The first was 7 to 10 days before surgery, the second was the day before surgery and for the exercise group coincided with the completion of the exercise program, and the third time point was 4 to 6 days after surgery, but prior to the participants' receiving pathology reports. The exercise group's power increased while the control group's power decreased. No differences in hope emerged. While these findings help to broaden the scope of our understanding regarding the role of PA on HQOL, it is important to note that patients who had received chemotherapy or radiation therapy were excluded, greatly limiting generalizability of the results. Surprisingly, the exercise intervention compliance rate was 83% as determined by PA logs. At home exercise interventions are usually marred by low adherence rates to exercise and, as this intervention seems relatively difficult, this may be hard to replicate in other survivors.

While these findings are encouraging, there are still many gaps that exist in our understanding of the role PA may play in improving HQOL in lung cancer survivors. The majority of studies in the area of PA and HQOL for cancer survivors have been done in breast cancer survivors. It appears that PA can improve physical function and overall HQOL in these patients; however, the breast cancer survivor population differs greatly than that of the lung cancer survivor. Some work has been done specific to lung cancer survivors, but this is mostly observational or case series reports. Of the very few well-controlled trials undertaken, the variability in the exercise interventions, the study populations and sample sizes, along with the timing of the interventions relative to diagnosis and/or treatment, all make drawing conclusions quite difficult. Well-designed

RCTs utilizing exercise interventions that mimic PA recommendations and using validated measures of HQOL specifically designed for lung cancer survivors in order to better understand the burden experienced by these survivors are clearly needed.

Section Summary

Research has shown that lung cancer survivors face many challenges after diagnosis, including that of survival, symptom burden, and other physiological and psychological complications. Prognosis for lung cancer is diminished when compared to that of other cancer survivors, as is HQOL and exercise capacity. Highlighting treatment options to improve these outcomes is of great necessity. PA remains an attractive modality, as it has been shown to improve markers of systemic inflammation and oxidative stress, which have potential prognostic implications, as well as improve HQOL and exercise capacity. Unfortunately, there have been very few well-controlled studies to evaluate the relationship between PA and these outcomes in lung cancer survivors. Most of the work in this area has been observational, or non-randomized studies, done in other types of cancer survivors. Of the very few studies that have begun to evaluate PA in this population, there are methodological concerns that need to be accounted for. As such, more quality RCTs are needed to elucidate the role of PA in mitigating some of the health challenges faced by lung cancer survivors and, in the process, improve health outcomes such as prognosis, HQOL, and exercise capacity. Therefore, the goal of this project is to determine how an exercise intervention alters biomarkers of prognosis, exercise capacity, and quality of life in this population.

Study 3: Impacts of Exercise on HQOL in Informal Caregivers of Lung Cancer Patients

Defining Informal Caregivers

With over 11.7 million cancer survivors living today and over 1.5 million more individuals diagnosed each year, cancer has clearly touched a substantial number of lives [1]. Due to the many potential challenges associated with being a cancer survivor, most cancer survivors will at some point require the support of an informal caregiver [201]. These caregivers are usually defined as unpaid loved ones who provide the survivor with physical and emotional care [202]. Caregivers are typically spouses, partners, significant others, family members, close friends, close relatives, or next of kin, depending upon their relationship to the survivor [202, 203]. Ultimately, the caregiver is defined as such by the survivor, regardless of their family connection [203].

Often considered to be a lifeline to the survivor, these individuals are not trained for the caregiver job, but rather, are there in a supportive role [202]. Demands placed on these individuals to meet the needs of the cancer survivor, including monitoring of treatment, treatment-related symptom management, assistance with personal and instrumental care, as well as other emotional, physical, financial, social and spiritual needs and support have all led to health consequences for the caregiver [58, 204]. These include increased levels of stress, diminished physical health, restrictions of activities [56, 204-206], strain in marital and family relationships [56], economic burden, depressive symptoms, and poor mental health [55, 56, 207-212]. In fact, emotional distress experienced by the caregiver has been shown to be as high as, or even higher than, that of the cancer survivor themselves [72, 209]. All of these health challenges can have a detrimental effect on an individual's HQOL. Although their health may be greatly impacted by a loved one's cancer diagnosis, caregivers have received only minimal attention by most healthcare practitioners, as they are focused primarily upon the physical needs of the patient [154]. As such, it is essential that we not only better define the health burden experienced by these caregivers, but also identify potential modalities to ameliorate some of these health challenges that coincide with providing care to cancer survivors.

HQOL in Informal Caregivers

While health challenges and potential deficits in HQOL experienced by cancer survivors have been well documented for some time, there is now evidence suggesting that caregivers may also experience declines in HQOL based on the care given to the survivor [213]. As discussed in detail previously in this document, HQOL is a multidimensional concept [96]. Within the larger two domains of physical and mental health, there are many different concepts related to HQOL, including, but not limited to, fatigue, general health and bodily pain. As the challenges faced by caregivers continue to grow, along with the number of cancer survivors, health researchers have begun to further address HQOL constructs in this population. A robust literature has developed as of late, with nearly 40 studies published on the topic since 2000 and over 25 studies published since 2010 alone [54, 57, 58, 64, 72, 154, 201, 203, 204, 206, 208, 210, 211, 213-237]. The majority of these studies have utilized samples of caregivers of mixed cancer types, though within these mixed samples, breast cancer is often the predominant cancer type studied. Of the studies evaluating HQOL in caregivers of a specifically defined cancer type, breast cancer remains the most studied [204]. This is important as breast cancer may offer specific challenges to the caregiver. These challenges could be different across cancer survivor populations, potentially affecting HQOL in caregivers differently. As such, it is necessary to evaluate HQOL in caregivers of specific types of cancer survivors directly.

While not as plentiful as other cancer types, there have been studies evaluating caregivers of lung cancer patients [54, 154, 222, 230, 236, 238]. Caregivers of this population certainly face many of the challenges discussed above, but may also face amplified or additional challenges specific to caregiving for lung cancer survivors. These challenges may present themselves at the time of diagnosis and last throughout the trajectory of the disease. As lung cancer patients may face serious physical and functional declines, caregivers are often helping with ambulation, moving or lifting patients, and assistance with nutritional needs and management [154]. Lung cancer survivors usually experience a considerable degree of symptom burden, often experiencing multiple symptoms at once[155]. These symptoms, such as pain, dyspnea, and fatigue, can be difficult to manage from the caregiver's perspective. Overwhelming psychological demands of caregiving, such as anxiety, depression, and other psychological distress, are common in these caregivers, often related to the fact that lung cancer is a disease with frequent recurrence in early stages and death in the later stages of the disease. In fact, caregivers of lung cancer survivors were shown to have higher risk of depression and more psychiatric consultations than caregivers of patients with other cancers [214, 234]. Caregiving spouses of lung cancer patients have been shown to need to take more sick leave than spousal caregiver of other cancer types, which may correlate with higher physical and emotional burdens of care [222]. Further, it is important to note that distress brought on by challenges in one construct related to HQOL may compound challenges in other constructs [222]. Added caregiver stress may result in sleep loss, fatigue, and additional unhealthy behaviors, potentially affecting physical well-being as well as mental well-being.

PA and HQOL in Caregivers of Cancer Survivors

While there is a growing body of literature describing the challenges, and associated HQOL, in caregivers of cancer survivors, little work has been done to evaluate potential interventions to mediate these challenges. Despite the potential benefits, few psychosocial and/or behavioral interventions to enhance caregivers HQOL have been developed [56]. Of the few interventions that have been tested, those that emphasize education on the disease process and associated medical treatments, improvement on problem-solving skills, and psychological counseling appear to be successful in lowering stress levels and improving HQOL of caregivers of cancer survivors, mainly through the improvement of confidence, knowledge, self-efficacy and mood [56, 72, 154, 208, 217, 223]. As PA has been shown to mediate HQOL challenges in a number of populations, it could serve as an appropriate intervention option, yet there is very little evidence to show its effectiveness in this population. At this time, there have not been any studies designed to specifically evaluate PA and HQOL in caregivers of cancer survivors. There have been, however, two studies that have indirectly utilized PA as a secondary intervention to improve HQOL, and a study that highlights PA as a potential preference to reduce stress in caregivers. In the first of the aforementioned studies [216], a randomized control trial was used to test the hypothesis that telephone-delivered psychosocial interventions decrease depression and anxiety in breast cancer survivors and their caregiving partners. Ninety-six cancer survivors paired with their ninety-six caregivers were randomized to either six weeks of telephone counseling, six weeks of self-managed exercise, or a control group. The telephone counseling group received phone calls (cancer patients once a week and their caregivers once every two weeks) from a psychiatric nurse counselor with oncology expertise focusing on cancer education, social support, coping mechanisms, and awareness and management of depression and exercise. The exercise intervention was also delivered via telephone calls (again, cancer patients once a week and their caregivers once every two weeks), encouraging the participants to exercise, focusing on regular, low-impact exercises, and to discuss and track their progress. PA information was also collected during these phone calls, such as number of days exercised in the previous week, total minutes exercised each day, type of activity, and intensity of activity (as determined by a subjective intensity scale from 0-10). The control group received telephone calls, though no counseling or encouragement to exercise occurred. Depression and anxiety were measured through the Center for Epidemiological Studies-Depression (CES-D) scale and an eight-item composite index of previously validated measures, respectively. While there wasn't a significant difference in depression scores for the caregivers between groups, including the controls, there was a significant difference between scores pre- versus post-intervention in all groups, with depression scores decreasing substantially. Unfortunately, as controls also saw a beneficial change in depression scores, it is difficult to suggest that the treatments themselves were effective. As each group received a bi-weekly phone call, the regular attention, social interaction, and concern from research staff may have been enough to mitigate depression in these individuals. Anxiety scores of caregivers were also significantly decreased from baseline to post-intervention in both treatment arms, though not in the controls. Though no significant difference was found between treatment arms, the findings that exercise can influence anxiety are consistent with previous work suggesting that exercise can benefit mental health [129]. It is possible that the phone calls helped to increase adherence rates to an exercise program, yielding these results. A major limitation to this study was depression scores at baseline, with controls scoring below the diagnostic criteria for depression, perhaps indicating a floor effect. Those in the telephone counseling arm had the highest level of pre-intervention depression, and would likely benefit the most from an intervention. Surprisingly, although information on total volume of PA was collected, it wasn't discussed at all in the results or discussion of the paper. Adherence to the PA intervention was also not discussed. It is possible that an improper dose of exercise was used in this study, as certain intensities, types of activity, or total volume of PA, may be needed to affect mental health. As such, this information would be needed to truly evaluate the role of PA on mental health concerns in caregivers of cancer survivors.

A second study touching on this topic evaluated the effect of social support on both HQOL and PA behavior of adult cancer survivors and their caregivers [217]. PA participation was said to be measured through the eight-foot up-and-go functional fitness test and HQOL was measured through the SF-8. While researchers found that those cancer survivors who had higher PA participation scores had higher physical

HQOL scores, this relationship was not seen in caregivers. No other significant relationships were found between PA participation and HQOL in the total sample. This could be due to the many limitations in this study, including the small sample size (n=39), missing data on many of the questionnaires, and the use of a functional fitness test as a measure of PA participation. As such, findings from this study should be tempered at best.

Finally, in a study attempting to evaluate preferences of programs designed at reducing stress and burden in caregivers of those with brain tumors, Swartz et al. interviewed sixty caregivers and asked about partiality toward designed stress-reduction programs aimed at developing internal resources for caregivers [239]. Subjects were to indicate from a list of stress-reduction techniques/programs which they preferred, if they were currently participating in these programs, and if so, to rate their experiences with these programs. The list was populated with techniques and programs by a group of clinicians and researchers who used programs that were both previously shown to reduce stress, as well those that were able to be modified to fit the needs of a general caregiver. Exercise, being listed as one of the eleven possible interventions, was the number one preferred choice of stress relief in the total sample and in both men and women independently. These findings hold when stratified by stress status and tumor grade. These findings are encouraging and suggest that PA interventions tailored to caregivers of cancer survivors may be beneficial. Limitations in this study, such as use of a convenience-sample, small sample size, and the use of a non-validated tool to define intervention preferences, could complicate interpretation.

PA in Caregivers of Other Conditions

While there were no studies directly evaluating PA and HQOL in cancer caregivers found in the literature, there were studies, albeit very limited, that evaluated PA and HQOL in other types of caregivers. In a twelve-month randomized control trial of 100 older women who identified as informal caregivers of a relative with dementia, researchers evaluated an exercise program on HQOL outcomes [240]. Participants were randomized to 12 months of a home-based, telephone-supervised, moderate-intensity exercise training program or to an attention-control program. Exercise consisted of four 30- to 40-minute aerobic exercise sessions per week at an intensity level of 60%-75% of heart rate reserve or 12-16 on the Borg scale. Participants randomized to the exercise arm received an individualized exercise plan based specifically on her exercise preferences and particular caregiving situation. The majority of these participants chose to engage in brisk walking in their immediate neighborhoods though participants who could not leave or find coverage for their caregiving duties, an indoor activity program was developed, included stationary cycling or use of project-provided exercise videotapes. PA information was recorded in activity logs, which were then used by the health educators to counsel them on how to increase their exercise frequency, intensity, and duration via telephone. Participants randomized to the control group received a telephone-based nutrition education program that was matched with the exercise intervention regarding the amount and type of staff contact received (introductory session and 14 telephone contacts). HQOL constructs were measured through the Perceived Stress Scale (PSS) and the Beck Depression Inventory (BDI). Researchers found that caregivers assigned to the exercise intervention did not have significantly different scores on either the PSS or BDI when compared to the control group, but did find notably significant improvements in scores from baseline, with BDI scores dropping below the cut point often used for mild depression. While this was a well-designed study with promising outcomes, evaluation of the relative efficacy of health behavior interventions compared with psychosocial interventions aimed specifically at reducing psychological distress is difficult. Studies are needed that explicitly compare these different interventions directly. The changes in psychological outcomes observed from baseline could be due to actual improvement stemming from participation in a health promotion program, regardless of content, or to other social interactions from researchers.

Section Summary

It has been well documented that caregivers of cancer survivors face potential health challenges, including diminished physical and mental health, all of which may negatively impact HQOL. Further, studies suggest that caregivers of certain types of cancer face specific challenges or, in the case of caregivers of lung cancer, amplified concerns due to high rates of recurrence and death. Regardless of cancer site or of the disease trajectory, modalities need to be evaluated as a way to lessen these challenges and improve HQOL outcomes. While PA is an appealing option due to its impact on various health and QOL outcomes in a host of populations, very little work has been done to test this type of intervention in this setting. This dearth of information points to the great need to evaluate PA as a potential treatment to improve HQOL in caregivers of cancer survivors. Therefore, it is the goal of the proposed research project to help fill these gaps by examining the potential role of PA, in the form of an exercise intervention, to improve HQOL in a sample of caregivers of lung cancer survivors.

Chapter III: Research Design and Methods

Study 1: Physical Activity and Health Related Quality of Life in Native American Cancer Survivors

Overview & Study Design

This study will use a cross-sectional design to analyze the association of PA with HQOL in a cohort of NA cancer survivors. As this is the first study of its kind, the cross-sectional design is an efficient one with which to begin to examine this relationship. Information obtained from this study can be used to generate hypotheses for future prospective studies and, importantly, potential interventions.

Methods

Subjects- This study will utilize a large cohort of NA cancer survivors as assembled by the Native American Cancer Research Corporation (NACR), led by Dr. Linda Burhansstipanov. The NACR, an organization designed specifically for NA cancer survivors to help minimize the effects of cancer diagnoses and treatment and improve HQOL, developed a “NA Cancer Education for Survivors (NACES)” program. This on-line program provides educational materials specific to NA, and is visited by approximately 1,200 visitors from across the country each day. NA may be directed to the site through information given at community-meetings, cancer support groups, conferences, one-on-one or group contacts or general internet searching. Beginning in October 2006, NACES users were invited to participate in a survey to assess HQOL. As of 2009, more than 700 NA have completed the survey and more participants are added each year. Of note, 58% of these survivors are considered long-term survivors (diagnosed more than five years previously). Data for the proposed study will be culled from subjects completing the survey starting in July 2013 with an end date of approximately December 2014. We expect that nearly 100 NA will completely the survey in this time frame.

Survey-The survey utilized in this study was originally developed in the late 1990s and utilizes many standard measures. The NACES QOL Questionnaire is based on several existing instruments, including the Functional Assessment of Cancer Therapy – General (FACT-G), the QOL-CS (City of Hope HQOL measure), and Ferrell's cancer survivorship instruments[17, 126, 241]. All survey items underwent multiple modifications from a panel of experts to make them culturally relevant, acceptable, and understandable to the proposed audience. While NACES staff was unable to obtain a sufficient sample to fully validate this tool, a group of fifty NA cancer survivors provided feedback and suggestions, adding to the tool's face validity. Along with HQOL constructs (physical, psychosocial, spiritual, and social), demographic characteristics, current disease status, lifestyle and health history information are also collected by this tool. Subjects could complete the survey themselves or with the help of friends, family members, or with assistance from a trained NA patient advocate. Previously, nearly 90% of all participants utilize the service of these patient advocates. While the number of NA patient advocates have decreased in the last two years, we still expect a large number of those survivors completing the survey to be assisted by these individuals.

Assessing PA- The choice of method for measuring PA is of great importance. Not only is it important to use valid and reliable tools to avoid bias and error, picking the correct method of measuring PA can help to further define relationships between PA and various health outcomes. While many measures of PA exist, no method is suitable for every disease, every population, or every research situation. In addition to information regarding the amount of PA one participates in, it is important to also examine the type and intensity of the activity being performed, the former of which can currently only be done using self-report methods. Self-report recall instruments are able to capture the type, frequency, duration, relative intensity, and, sometimes, reason for performing PA. These instruments are rather inexpensive, non-invasive and user friendly for subjects, yet recall bias is a possibility that can introduce error into a study.

When choosing an appropriate measure of PA, the experimental population and the method of delivery, in part, dictate the tool of use. As there was no PA measure that has been validated for use in NA cancer survivors, we chose to develop a tool specific to this population. Importantly, questions were asked to attempt to capture culturally relevant PA across a myriad of settings and intensities. Specific activities included were taken from both the Modifiable Activity Questionnaire (MAQ)/Pima Indian Questionnaire [242], a validated questionnaire specifically used in Pima Indians, as well as from suggestions made by researchers and professionals working with this population. The tool itself was modeled after The Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire, which is a comprehensive 41- item questionnaire used to assess frequency, duration, intensity and type of PA in older adults [243]. This reliable and valid instrument [244, 245] is a subjective measurement tool specifically designed for older adults by incorporating physical activities specific to that population. Most activities are of light or moderate intensity and integrate many different domains of PA. As our goal was to also capture similar types of activities that are specific to the NA population, we modeled the types of PA participated in across a number of domains and intensities. Like the CHAMPS, our questionnaire captures activities done in a typical week during the previous four weeks. Questions are formatted as "In the typical week during the past four weeks, did you engage in…?". If the subject answers "yes" to the question, they in turn reply with the total number of hours per week that they spent participating in that activity. The complete questionnaire can be found in Appendix B. Responses will be assigned a MET value based on the PA compendium as described by Ainsworth et al [157]. These data will then be converted into MET-hours/week (MET-hr/wk) equivalents. Values from all questions will then summed to create a total MET-hr/wk energy expenditure variable.

Additional information- Additional information collected includes height, weight, sex, tribal region, insurance coverage, and years of education completed. A brief medical and health history will also be completed that includes information on date of/time since cancer diagnosis, recurrence, type of cancer, family history of cancer, and relevant treatments (both western medicine and traditional medicine).

Analysis- Analyses will be conducted using SAS statistical software (SAS Institute, Inc., Cary, NC). All data will be tested for normality and transformed when necessary so parametric statistics may be used. Regression models will be used to examine the cross-sectional relationships between PA and HQOL. Specifically, analysis of covariance (ANCOVA) will be used to evaluate the relationship between PA with various HQOL constructs/variables. PA will be considered a categorical variable and will be categorized by quantiles of total volume (MET-hrs/wk). PA will also be considered dichotomously in analyses specific to meeting ACSM PA recommendations [246]. Covariates considered for these analyses will include age, sex, smoking status, alcohol consumption, education, comorbidities, treatment type, age at diagnosis, and time since diagnosis. All covariates that appreciably change the association will be included in the model to control for their effect. ANCOVA will also be used to examine the association of PA and HQOL across type (planned exercise and non-exercise PA) and intensities (light, moderate, and vigorous) of physical activity.

Limitations

Due to the cross-sectional design utilized in this study, causality is unable to be established. For example, if PA is found to be associated with higher HQOL scores, this may not necessarily be indicative of those performing more PA having a higher HQOL, but could simply indicate that those who have a higher HQOL are more likely to participate in PA. Also as a consequence of the study design, this work utilizes a convenience sample of non-randomized participants. A convenience sample can lead to selection bias, as only those individuals who have access to the internet and found, or were directed to, the NACES website completed the survey. These individuals may be different from those individuals without internet access. While this is a limitation, a cross-sectional design is an appropriate first step in evaluating associations which can then be used to inform future research designs.

All data collected in this study are from self-reported measures. Self-reported data are often subject to measurement error, which can lead to bias and incorrect conclusions. While objective measures could potentially cut down on measurement error, self-reported data offers a potentially rich source of information. It is the only way of measuring HQOL, which is a very important construct of overall health. When evaluating PA, objective measures are unable to capture information on type of activity. This information is imperative when trying to design future interventions that are culturally relevant to this population. Further, it may not be feasible to fit a population-based sample with objective monitors due to cost, time and resources. As surveys are efficient ways of collecting data at the population level and can provide information on both HQOL and specific constructs of PA not available through objective measures, they will be used in the current study; however, any potential associations observed in these analyses should be tempered due to the lack of precision and potential bias introduced by these instruments.

Another limitation of this study is that our measure of PA has not been validated for use. Utilizing non-validated measures can call estimations into question; however, as there are no instruments that have been validated for use in this population, and our tool was based on previously validated measures, including the Modifiable Activity Questionnaire (MAQ)/Pima Indian Questionnaire [242], we felt its use to be appropriate in this setting. While other valid measures of PA may be more attractive for use in establishing associations between PA and HQOL, we felt that a tool that attempted to evaluate culturally specific PA would provide a much more appropriate assessment of these relationships in NA.

Study 2: Impacts of Exercise on Prognostic Biomarkers in Lung Cancer Patients

Overview & Study Design

This research study will utilize an experimental design to determine how exercise in a sample of lung cancer survivors can alter various health outcomes in this population, including biomarkers of prognosis, exercise capacity, and HQOL. Specifically, this 8-week, randomized, controlled trial will test the effects of a combined at-home (three days per week) and in-clinic (two days per week), exercise intervention, consisting of both aerobic and resistance training, in lung cancer patients. Subjects will be randomized to the training intervention or to usual care.

Subjects- We will recruit 54 lung cancer survivors for participation in this study. Subjects meeting eligibility criteria, which include being at least eighteen years of age, a confirmed diagnosis of any stage lung cancer (NSCLC or SCLC), and able to understand and read English sufficiently to complete informed consent and to complete the questionnaires, will be identified by their primary oncologists, given an informational flyer, and referred to the study staff. Interested subjects will then call study staff to determine eligibility and to receive more information about the study. Subjects receiving any type of treatment (chemotherapy, radiation therapy, both or neither), curative or non-curative, are eligible. Patients treated with curative intent, and who have not relapsed, must be within one year of their diagnosis of lung cancer as determined by date of diagnostic pathology sample. Subjects will also be screened for exclusion criteria, which includes symptomatic heart disease, congestive heart failure or arrhythmia, documented myocardial infarction in the last three months, CNS metastases that result in impaired ability to participate in an exercise program at the discretion of the study physician, any psychological or physical disease that would impair or prevent participation in an exercise program at the discretion of the study physician, cognitive or reading impairments that would preclude them from completing questionnaires, or current participation in an exercise program. As one previous study found that the at-home component of their combined at-home/clinic exercise intervention had low adherence [169], a support person will undergo the intervention with the patient if assigned to the exercise treatment to increase patient adherence. Should a patient be unable to identify a support person to participate with them, they will still be able to participate. More information regarding these support persons can be found in Study 3.

Protocol- After the initial screening phone call, interested and eligible patients will be enrolled at the University of Wisconsin Hospital, Madison or UW Health Oncology at 1 South Park. All subjects will sign the consent form at the pre-intervention visit with a member of the research team. Subjects will have information extracted from patients' medical records, including past medical history, disease stage, grade, treatment type, and medications. All subjects will provide information on their age, race, ethnicity, education, and smoking status. Height, weight and body fat percentage (via bioelectrical impedance) will be directly measured by research staff in all subjects and typical daily PA levels will be measured by the International Physical Activity Questionnaire-Long Form (IPAQ), a reliable and valid questionnaire frequently used to measure PA [247]. During this pre-intervention visit, subjects will also complete a series of tests to evaluate the biomarkers of interest, exercise capacity, and HQOL. Subjects will be instructed to refrain from exercise for eight hours prior to testing, from alcohol for twelve hours prior, and from using NSAIDs for twenty-four hours prior to testing. Subjects will be rescheduled if they have been diagnosed with an upper respiratory infection due to the effect it may have on inflammatory markers. These outcome measures will be repeated at the post-intervention visit.

Study Procedures/Measures

Randomization- Participants will be stratified by both treatment (active treatment versus non-active treatment) and stage (Stage I, Stage II, and surgical Stage III versus non-surgical Stage III and Stage IV). Block randomization will then be used to assign subjects to the exercise intervention (treatment arm) or usual care (control arm) using a computer random assignment program. The allocation sequence will be generated in the OnCore system and subsequently concealed from the research coordinator and exercise physiologist. Once the allocation sequence assignments are generated, a research assistant will place assignments for each potential subject in an envelope and subjects will be assigned their respective participation groups following the pre-testing to eliminate researcher bias. To improve retention rates, subjects randomized to the control group will be offered an exercise consultation from the exercise physiologist upon completion of the post-test.

Intervention- The exercise intervention is designed to be consistent with the PA guidelines as suggested by the ACSM [13, 246]. The intervention will consist of individual, supervised exercise training two days per week and a prescription for at home exercise three days per week. All in-clinic sessions will be supervised by an exercise physiologist. Each exercise session will be composed of an aerobic component and a resistance training component. This exercise session is to be performed at a moderate level of intensity as determined by the Borg Rating of Perceived Exertion Scale (12-16) [248]. At the initial visit, individual consultations with the exercise specialist will be used to tailor the intervention exercises to the subject. Aerobic training will be done five days/week, including the two days at the clinic. Resistance training will be done two days/week, likely at the clinic visits. If subjects have bone metastases, their exercise plan will be modified in consultation with the study oncologist to assure the safety of the exercises. Specific exercises can be avoided or adapted if the subject is at risk of pathologic fracture. Activity logs will be used by subjects to record their weekly exercise and, along with attendance at in-clinic sessions, will be used to measure program adherence.

Aerobic Training – Subjects will have their choice of walking or stationary cycling as their mode of aerobic exercise during the aerobic component of their intervention. Subjects will progress from a minimum of 10 minutes/session of aerobic activity as needed to 30 minutes/session as tolerated. We will use the Borg Rating of Perceived Exertion Scale [248] (RPE) to judge intensity and ask participants to work at a rating of 12-16 (the ‘somewhat hard’ to ‘hard’ range). RPE will be systematically collected throughout the exercise session to assure participants are exercising at the appropriate intensity.

Resistance Training- We will be using resistance bands with graded resistance for the strength training portion of the intervention. The following exercises are designed to hit all the major muscle groups: chest press, seated row, upright row, triceps extension, bicep curls, squats, shoulder press, and calf raises. These eight exercises will be done in two sets of 10-15 repetitions each. Resistance will be added by advancing through the different bands as 15 repetitions become easy to do. Although the study is designed to have the subjects do their resistance training in the clinic, each subject will receive their own set of resistance bands and instructions on the eight exercises in case the exercises need to be done at home due to missed clinic visits.

Biomarkers: Inflammation and Oxidative Stress- Peripheral blood samples (~10ml) will be drawn at both the pre-intervention visit and post-intervention visit prior to exercise capacity testing. These samples will be collected into a 4mL SST tube, with the serum being divided into three polyvials (0.5 ml per polyvial). Post blood draw, the sample will be inverted 5 times, then allowed to clot at room temperature for 20-30 minutes. Serum will be obtained by centrifuging the test tube at 3000 rpm for 10 minutes. Processed samples will be stored in a below 70 degrees centigrade freezer until time of processing. All samples will be labeled with the date, time of draw, the study number and individual subject identification number.

Some of the hypothesized mechanisms through which PA may be beneficial in lung cancer include a reduction in inflammation and lower levels of oxidative stress [249]. Serum levels of pro-inflammatory cytokines that have been linked to poor survival in lung cancer (interleukin (IL)-1β, IL-6, and TNF-α) will be measured [51]. High sensitivity-CRP, a liver-derived protein that is reflective of systemic inflammation and has been shown to be prognostic for cancer survival of various types, will also be measured in serum [177]. 8-OHdG is a commonly used marker of oxidative stress and has been linked to cancer risk and, potentially, prognosis [187].

Quality of Life- The FACT-L (Functional Assessment of Cancer Therapy-Lung) is a 44-item self-administered instrument which measures multidimensional quality of life specific to lung cancer survivors [250]. The items queried span five domains: physical, social/family, emotional, and functional well-being, along with a lung cancer specific subscale measuring symptoms, cognitive function, and regret of smoking. Each of these subscales are scored on a five-point scale from zero (described as "not at all") to four (described as "very much"). Subscale scores are then added to obtain a total score. The FACT-L has been shown to be both reliable and valid for use in this population [250] and is widely used, allowing us to compare our study population and results to other published studies.

Exercise Capacity- The Long Distance Corridor Walk (LDCW) is a two part test used to measure exercise capacity [251]. It consists of a self-paced two-minute walk, followed by a timed 400-m walk. This test has been shown to be a valid and reliable performance-based measure of functional status in both middle-aged and older adults[252]. Before the test begins, participants will be fitted with a heart rate monitor and have their heart rate and blood pressure measured. The test will not be completed if their resting systolic blood pressure (BP) is 180mmHg or higher; their resting diastolic BP is 110mmHg or higher; their resting heart rate (HR) is less than 40 beats per minute (bpm) or greater than 110 bpm. After placing two small traffic cones set 20 meters apart, participants will first complete a two-minute walk around the cones with the goal to cover as much ground as possible. After a one minute break, participants will complete the 400-m walk. The goal for this test is to complete the walk in the shortest amount of time. At the end of each lap, the participants will be told how many laps are remaining and will be given standardized encouragement. If participants have the need to stop walking during the test, they will be allowed to stand in one place for no longer than 60 seconds. If the rest period is longer than 60 seconds the test will be discontinued. There is no limit to the number of rests allowed; however, the test will be discontinued after 15 minutes. Additionally, subjects will have the option after the two minute walk to decline to participate in the 400m walk, and can withdraw from the test at any time.

Analysis-All measured variables will be checked for normality and transformed as appropriate. Initial descriptive statistics will be calculated and compared between the two arms (treatment vs. usual care) at baseline using unpaired t-tests and Chi-Square analyses where appropriate. For the main analyses (the differences between lung cancer patients outcomes between groups), outcome measures will be treated as continuous variables. A two-way analysis of variance will be used to examine the effects of the treatment over time (pre- to post-intervention) on each of the dependent variables (inflammatory markers, 8-oh-dG, FACT-L, gate speed on LDCW test). Power was calculated using hs-CRP as the primary dependent variable of interest with an overall Type I error rate of 5%, and 80% power. Using the exercise study by Hwang et al [253], we determined that 54 total subjects would be necessary to detect a significant difference in CRP between the two groups of lung cancer patients based on a mean difference of 6 pg/mL and an SD of 7.7.

Limitations- Adherence rates to home based exercise interventions have previously been shown to be quite low in cancer survivors [169]. We have attempted to combat this by adding a support person/informal caregiver to join the patient in the intervention, thereby bolstering participation. Previous work has shown exercise adherence rates to improve when done in the company of others [254]. Still, it is possible that, given the intensity of the exercise, the number of sessions, the need to come to the clinic twice/week, and the fact that this population generally has a low exercise capacity, adherence to the program may be low. Adherence rates will be determined by attendance to the in-clinic sessions and the use of PA logs for home exercise. These rates will be reported with our findings and an intent-to-treat analysis will be used. Should it be the case that adherence rates are low, findings may need to be interpreted with caution.

The intervention offers considerable social interaction for the survivor with research and hospital staff, as well as the informal caregiver. This may cloud findings, as social interaction has been shown to improve health outcomes, including HQOL, in a number of populations, including cancer survivors. Should we observe changes in our measures post-intervention, these changes may be due to the social and potential motivational value of receiving bi-weekly social interaction as part of the exercise intervention as opposed to simply the behavioral act of PA. The design of this study does not allow us to control for this interaction. Still, as research staff will be present during in-clinic visits to assure safety and compliance and the presence of an informal caregiver in the exercise intervention may be needed to increase adherence, we feel that this interaction may still be a necessary part of the intervention. Further, it is doubtful that this social interaction would affect the physiologic biomarkers or exercise capacity measured as part of this study. Observed improvements in these measures post-intervention may help support any documented changes in HQOL outcomes.

Finally, as we are only utilizing one particular exercise treatment arm, observations will be specific to this dose of exercise. It is possible that changes may only occur at certain intensities, types, or volumes of exercise. As such, should we fail to find significant changes in this population, it does not necessarily suggest that an exercise intervention is not a successful treatment modality, but rather that the dose evaluated might be inappropriate. Further, we are using an aerobic and resistive training component in this exercise intervention. As we are only using one treatment arm, we will not be able to tease apart potential differences in outcomes due specifically to aerobic exercise versus resistive training. However, as this intervention mimics the suggested PA recommendations for both the public [246], as well as cancer survivors [13], we feel it is appropriate to use in this setting.

Study 3: Impacts of Exercise on HQOL in Informal Caregivers of Lung Cancer Patients

Overview & Study Design

This research study will utilize an experimental design to analyze how exercise in a sample of informal caregivers of lung cancer survivors can affect HQOL. Specifically, this study will consist of an 8-week, randomized controlled trial utilizing an exercise intervention, consisting of both aerobic and resistance training, in these caregivers. This study is part of the larger study discussed above, which evaluates an exercise intervention in lung cancer survivors. Recall that cancer survivors enlist a caregiver to go through the exercise intervention with them to increase exercise adherence rates.

As such, caregivers will be randomized to the exercise intervention or usual care as a pair with the lung cancer patient to whom they are offering support.

Subjects- We will attempt to recruit 54 caregivers of lung cancer survivors for participation in this study. These subjects will be identified as a result of their participation in a larger study utilizing an exercise intervention to evaluate health outcomes in lung cancer survivors (see study 2). Caregivers will be identified by lung cancer patients to complete the exercise intervention with them in order to increase adherence rates of the survivors. Subjects meeting eligibility criteria, which include aged at least eighteen years and the ability to understand and read in English sufficiently to complete informed consent and to complete the questionnaires, will be able to participate. Potential subjects will also be screened for exclusion criteria, which include symptomatic heart disease, congestive heart failure or arrhythmia, documented myocardial infarction in the last three months, or any cognitive or reading impairment that would preclude them from completing questionnaires.

Protocol- Eligible subjects will be enrolled at the University of Wisconsin Hospital, Madison and UW Health Oncology at 1 South Park. All subjects will sign the consent form at the pre-intervention visit with a member of the research team. All subjects will provide information on their age, race, ethnicity, education, smoking status, and comorbidities. Height and weight will be directly measured by research staff in all subjects and typical daily PA levels will be measured by the International Physical Activity Questionnaire-Long Form (IPAQ), a reliable and valid questionnaire frequently used to measure PA [247]. During this pre-intervention visit, subjects will also complete an exercise capacity test and a HQOL survey. These outcome measures will be repeated at a post-intervention visit. All tests will be administered by trained research staff.

Study Measures:

Exercise Capacity- The Long Distance Corridor Walk (LDCW) is a two part test used to measure exercise capacity, consisting of a self-paced two-minute walk, followed by a timed 400-m walk [251]. For details, please refer to Study 2.

HQOL- When attempting to measure HQOL, there are two methods to consider: generic and specific. Generic measures of HQOL attempt to measure the broader aspects of HQOL by not being specific to a certain medical outcome. A major advantage to generic measures is their ability to address a great range of subjects across an array of medical conditions [92]. By doing so, various populations and treatment modalities and their effects on HQOL can be evaluated. Specific measures, such as the FACT-L, are instruments that directly measure outcomes of a specific disease, population, or clinical problem. These measures are potentially more sensitive, but are difficult to evaluate across varying populations and diseases. Choice of specific versus generic measures is dependent upon the population being studied and the goals and scope of the research at hand.

One of the most recognizable generic measures is the Medical Outcomes Study Short-Form Health Survey (SF-36) [255]. The SF-36 is a 36-item measure encompassing eight individual constructs: physical function, role limitations owing to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations as a result of emotional problems and mental health. Each of these subscales are scored on a scale of 0 -100, with 0 being the worst possible score [256]. These eight distinct domains can be summarized into two summary scores: the physical health component score (PCS) and the mental health component score (MCS) [257]. The SF-36 has been shown to be both reliable and valid for use in general populations as well as in those with specific conditions, including cardiac, pulmonary, orthopedic, and cancer [258-261]. Each subscale of the SF-36 consists of a number of closed-ended questions. The standard SF-36 scoring method will be used [257]. Population based norms have been published for the subscales and associated summary scores and will be used in the analysis [262].

Intervention- As this study is part of the study detailed above (study 2), the details of the intervention are consistent with that previously described. Briefly, the intervention will consist of supervised exercise training two days per week and a prescription for at home exercise three days per week, totaling ~150 minutes of moderate PA each week. Each exercise session will be composed of an aerobic component and a resistance training component. This exercise session is to be performed at a moderate level of intensity as determined by the Borg Rating of Perceived Exertion Scale [248]. As such, caregivers may not be working at the same intensity as the lung cancer patient. At the initial visit, individual consultations with the research assistant will be used to tailor the intervention exercises to subjects. Aerobic training will be done five days/week, including the two days at the clinic. Resistance training will be done two days/week, likely at the clinic visits. Both aerobic and resistive activities are to be done at a moderate-intensity. We will use the Borg Rating of Perceived Exertion Scale [248] to judge intensity, and ask participants to work at a rating of 12-16 (the ‘somewhat hard’ to ‘hard’ range). Of note, depending on the fitness level of the caregiver, while they will be working at the same relative intensity (“moderate”), they may or may not be working at the same specific absolute intensity as that of the lung cancer patient. Specific exercises can be avoided or adapted if the subject has preexisting conditions that require such actions. Activity logs will be used by subjects to record their weekly exercise and, along with attendance at in-clinic sessions, will be used to measure program adherence. For details on exercise modalities, please refer to Study 2.

Analysis-All measured variables will be checked for normality and transformed as appropriate. Initial descriptive statistics will be calculated and compared between the two groups (treatment vs. usual care) at baseline using unpaired t-tests and Chi-Square analyses where appropriate. For this analyses (differences between caregivers of lung cancer patients between treatment groups), a two-way analysis of variance will be used to examine the effects of the treatment over time (pre- to post-intervention) on the dependent variable (SF-36). No power calculation was done specifically for this analysis as this is a sub-analysis as part of Study 2 which focuses on the survivors. Our outcome measures (LDCW time and HQOL) for this study will be treated as continuous variables.

Limitations

As this analysis is part of a larger study, we did not do an *a priori* power analysis. This might hamper our ability to statistically detect differences between groups. We do feel, however, that as this is a preliminary analysis to evaluate the role of PA in these caregivers, this should be a sufficient sample. Further well controlled trials with appropriate power analysis may be warranted.

As discussed in the previous study, we may not be able to tease out exercise from social interaction regarding the role each play on our measured outcomes. HQOL may improve simply by being in the presence of other individuals, which may cloud findings of the exercise intervention. Also, as discussed above, the effect of aerobic versus resistance training will not be able to be discerned based on only having one treatment arm. Finally, caregivers may be influenced by cancer survivors to exercise at an intensity closer to theirs, as opposed to the moderate intensity called for as part of this intervention. While this problem should be avoided with the use of an RPE scale and education from the exercise specialist administering the intervention, a false RPE may be provided. Future studies may need to utilize objective measures of exercise intensity to confirm intervention compliance.

Chapter IV: Manuscripts

Manuscript

Physical activity behaviors and associated health-related quality of life in Native American cancer survivors

Keith M. Thraen-Borowski[1], Ronald Gangnon[2,3], Keith P. Gennuso[2], Linda Burhansstipanov[4], Amy Trentham-Dietz[2,5], Kelli F. Koltyn[1], Alex K. Adams[6], Lisa H. Colbert[1]
University of Wisconsin-Madison, Madison, WI

Affiliations:
[1]Department of Kinesiology, University of Wisconsin-Madison, Madison, WI
[2]Department of Population Health Sciences, University of Wisconsin-Madison, Madison, WI
[3]Department of Biostatistics and Medical Informatics, School of Medicine and Public Health University of Wisconsin-Madison, Madison, WI
[4]Native American Cancer Research Corp, Pine, Colorado
[5]Paul P. Carbone Comprehensive Cancer Center, University of Wisconsin-Madison, Madison, WI
[6]Department of Family Medicine, University of Wisconsin-Madison, Madison, WI

Support for this research was provided by the Virginia Horne Henry Foundation, University of Wisconsin-Madison through grant number 176000.

Corresponding Author:
Keith Thraen-Borowski, MS
Dept. of Kinesiology
University of Wisconsin
2000 Observatory Dr.
Madison, WI 53706
Ph: 608-262-1167
Fax: 608-262-1656
E-mail: thraenborows@wisc.edu

Abstract

***Purpose**:* To describe the physical activity (PA) behaviors in a national sample of Native American cancer survivors (NACS) and examine the relationships of those behaviors with health-related quality of life (HQOL).

***Methods*:** Cancer survivors of all types completed a web-based questionnaire that included information on HQOL (previous seven days), PA (typical week in the past month), cancer-specific outcomes, and demographic information. Descriptive statistics were used to explore PA behaviors and ANCOVA was used to evaluate the cross-sectional relationship between PA and HQOL constructs.

***Results**:* Of our final analytic sample (n=55), 40% were breast cancer survivors, 87% female, 69% between ages 55-74, and 92% were diagnosed within one year of completing the survey. Sixty percent met the current PA recommendations of 150 min/wk of moderate-to vigorous-intensity PA (MVPA). Survivors reported 1,242 MET-min/wk(300-2856) of MVPA and 691 MET-min/wk(324-1434) of light-intensity PA. Regarding PA type, this group reported 735 (312-1,242) MET-min/wk of non-exercise PA and 608 (219 - 1,493) MET-min/wk of planned exercise, and 135 (0 - 662) MET-min/wk of NA-specific PA and 1,104 (609 - 2,168) MET-min/wk of non-native specific PA. Walking was the most common PA (91% participated), followed by light- (87%) and moderate-intensity (53%) housework. After covariate adjustment, meeting PA recommendations was not associated with any HQOL construct (p>0.05) other than physical function (p<0.01). When evaluating intensity- or type-specific PA with HQOL, greater amounts of moderate-intensity PA, planned exercise, and non-native specific PA was associated with higher physical function.

Conclusions: These findings suggest a majority of NACS meet PA guidelines, though this may be the result of over-reporting. Our results also suggest that meeting PA guidelines is associated with better physical function in NACS, but no other HQOL constructs.

Cancer continues to affect an extensive number of lives in this country. With over 1.6 million new cancer cases diagnosed each year [1], it has been estimated that half of all men and one third of all women in the United States (US) will be diagnosed with cancer in their lifetime [2]. Fortunately, advances in screening and improved treatments have led to a recent trend towards longer survival [3]. As a result, the cancer survivor population has grown exponentially in the last few decades, with over 14 million individuals with a history of cancer alive today [1].

While the improvement in cancer survivorship has certainly been welcomed, research has documented that these survivors may face many physical, emotional, social and financial challenges associated with their disease and related treatments [4]. These complications can detrimentally affect one's HQOL [4-6]. Yet, not all populations suffer from these potential challenges equally. One of the groups most affected by these disparities is Native Americans (NA) [7-9]. NA in general suffer disproportionately from many of the constructs that make up HQOL, including higher rates of physical disabilities[10], functional limitations [10], pain [11], chronic conditions, comorbidities [12], depression [13], anxiety [13], substance abuse [14], suicide rates [15], and PTSD [16], suggesting that NA cancer survivors may have HQOL challenges specific to their survival that may be disparate from those of other populations. However, there is a dearth of information specific to HQOL in NA cancer survivors and next to none regarding ways to mediate these conditions [17, 18].

In an attempt to improve the HQOL of cancer survivors, various treatment modalities have been suggested. One such modality that is often discussed in the literature is physical activity (PA). There is growing evidence suggesting that PA may improve HQOL by enhancing physical, functional, psychological, emotional and social well-being, not only in the general population, but in cancer survivors as well [19-22]. While this work is encouraging, many gaps in our understanding still exist. The majority of the literature evaluating these relationships is specific to non-Hispanic Whites [23] and breast cancer survivors [24], leaving a shortage of information on minority populations and other cancer types. Further, most of these studies evaluating PA focus specifically on performing planned moderate-vigorous intensity exercise, such that information on other intensities, types and domains of PA is lacking.

Currently, very little is known about PA in the NA cancer survivor population, nor the relationship between their PA and HQOL. Little work has been done to define the PA behaviors of NA in general [25] and, to date, there has yet to be a single study to describe these behaviors in NA cancer survivors. While research has shown that, similar to other populations, PA is associated with better health outcomes in NA [26], including increased levels of high-density lipoprotein cholesterol, lower fasting insulin levels, lower BMI levels, and lower percentage of fat and fat mass, these relationships cannot necessarily be generalized to that of the NA cancer survivor. As such, it is important to explore the PA behavior of NA cancer survivors and to evaluate its relationship with HQOL in this population. Thus, we conducted a cross-sectional analysis of a national sample of NA cancer survivors to describe the PA behaviors of this population and to evaluate the associations of PA with HQOL. Specifically, we examined the relationship between meeting PA guidelines and HQOL, as well as evaluating if the particular intensity or type of PA mattered regarding this association.

Methods

Subjects- This study utilized a cohort of NA cancer survivors assembled by the Native American Cancer Research Corporation (NACR). The NACR, an organization designed specifically for NA cancer survivors to help minimize the effects of cancer diagnoses and treatment and improve HQOL, developed a "NA Cancer Education for Survivors (NACES)" program [27]. This on-line program provides educational materials specific to NA, and is visited by approximately 1,200 visitors from across the country each day. NA may be directed to the site through information given at community-meetings, cancer support groups, conferences, one-on-one or group contacts, or general internet searching. Beginning in October 2006, NACES users were invited to participate in a survey to assess HQOL. As of 2009, more than 700 NA have completed the survey and more participants are added each year. Data for the current study was culled from subjects completing the survey between July 2013 and September 2014. The total number of individuals to complete the survey in this time frame was 67.

Survey-The survey utilized in this study was originally developed in the late 1990s and utilizes many standard measures. The NACES QOL Questionnaire is based on several existing instruments, including the Functional Assessment of Cancer Therapy – General (FACT-G) [28], the QOL-CS (City of Hope HQOL measure) [29], and Ferrell's cancer survivorship instruments [29]. Physical, psychosocial, emotional, sexual, spiritual, and social constructs of HQOL were addressed. Answer choices were presented on a Likert-scale, ranging from zero to five, with a score of five considered to be the most desirable HQOL. All survey items underwent multiple modifications from a panel of experts to make them culturally relevant, acceptable, and understandable to this audience. While NACES staff was unable to obtain a sufficient sample to fully validate this tool, a group of fifty NA cancer survivors provided feedback and suggestions, adding to the tool's face validity [17]. Along with the HQOL constructs, demographic characteristics, current disease status, lifestyle and health history information were also collected by this tool. For their participation, individuals received a $25 gift card.

Assessing PA- The PA questions used were modeled after The Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire, which is a comprehensive 41- item questionnaire used to assess frequency, duration, intensity and type of PA in older adults [30]. This reliable and valid instrument [31, 32] is a tool specifically designed for older adults by incorporating physical activities most relevant to that population. Various physical activities were queried to capture culturally relevant PA across a myriad of settings and intensities, and were taken from both the Modifiable Activity Questionnaire (MAQ)/Pima Indian Questionnaire [33], a validated questionnaire specifically used in Pima Indians, as well as from suggestions made by researchers and professionals working with this population. Like the CHAMPS, our questionnaire captured activities done in a typical week during the previous four weeks. Questions were formatted as "In a typical week during the past four weeks, did you engage in…?". If the subject answered "yes" to the question, they were instructed to reply with the total number of minutes per week that they spent participating in that activity. Activities were assigned a MET value based on the PA compendium as described by Ainsworth et al [34], and subjects participating in at least 150 minutes of moderate–vigorous-intensity PA (MVPA) (3+ METs) were considered to have met the PA guidelines. MET-minutes per week (MET-min/wk) equivalents were also calculated for each activity and the values from all questions were then summed to create a total MET-min/wk energy expenditure variable.

Additional information- Additional information collected included a brief medical and health history covering information on the date of cancer diagnosis, type of cancer, family history of cancer, and relevant treatments (both Western medicine and traditional NA medicine), as well as sex, tribal region, insurance coverage, and years of education completed.

Analysis- Analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC). Subjects with no discernable history of cancer were excluded from the analysis. Individuals were also excluded from analysis if all PA or HQOL data were missing. Covariates were compared across level of PA using analysis of variance (ANOVA) for continuous variables. Categorical variables were evaluated by using Mantel–Haenszel chi-square or Fisher's exact test when cell sizes were <5. Descriptive statistics were used to assess PA behaviors in this sample and analysis of covariance (ANCOVA) was used to evaluate the cross-sectional relationship between meeting PA guidelines and HQOL constructs, including physical function, emotional QOL, spiritual QOL, fatigue, pain, sleep, cognition, sexual functioning, and social function in this group. All HQOL outcomes were scaled such that the average score per scale was presented on a zero to five scale. Covariates considered for these analyses included age, sex, number of comorbidities, education, treatment type, ever having lived on a reservation, blood quantum (percent of NA ancestry), geographical region, smoking status, alcohol consumption, age at diagnosis, and time since diagnosis. Covariates that changed the statistical significance of the PA terms or reduced the magnitude of the difference appreciably were kept in the models. These included age, sex, and geographical region.

Multiple linear regression analysis was also used to examine the association of PA and HQOL across intensity and type of PA in MET-min/wk. Light-intensity PA included activities <3 METs, moderate-intensity activities included activities consisting of 3.0-6.0 METs, and vigorous-intensity PA included activities >6 METs. Type of PA was categorized as non-exercise PA (including such items as heavy work around the house, light work around the house, heavy or light gardening, working on an automobile, and walking to do errands, etc.) or planned exercise (including activities like lap swimming, jogging, running, lacrosse, basketball, aerobic machines, etc.). We further defined type of PA as NA-specific activities (including activities such as native dancing, drumming, canoeing, hunting, and fishing) and non-native PA (activities not included in the former category). Non-linearity was examined by comparing a model with linear terms only and a model with both linear and non-linear terms. As non-linear models were found to be significant, non-linear polynomial models were used throughout the analysis. Covariates controlled for in the model were the same as those previously identified. Intensity-specific PA was also shown to confound relationships with HQOL and was subsequently included in models assessing intensity of PA (e.g., moderate- and vigorous-intensity PA was included in all PA models exploring light-intensity PA) and type where appropriate. Likewise, type of PA was controlled for in models evaluating type of PA (e.g., non-native specific PA was included in all models exploring native-specific PA). With these models, estimate statements were used to further explore the relationships between specified amounts of PA of varying intensities and types with individual HQOL constructs. Specifically, the change in HQOL score was determined by comparing rounded midpoints (MET-min/wk) of each quartile of intensity-specific and type-specific PA to a reference category. These models held time in all other PA variables constant, thereby depicting the accumulation of intensity- and type-specific PA as that above sedentary time, independent of the other types of activity and confounders.

Results

Study Population. Of the 67 participants to fill out the NACES survey between July 2013 and September 2014, subjects without valid PA data (n=2), unable to confirm a cancer diagnosis (n=8), or missing HQOL data (n=2) were excluded from the analysis. The final analytic sample consisted of 55 subjects, 40% of whom were breast cancer survivors, 87% female, 68.5% between ages 55-74, and 91.8% being diagnosed within one year of completing the survey.

The majority of NA cancer survivors (n=33; 60%) accumulated enough MVPA to meet current PA guidelines. On average, survivors participated in 2,015 (783 - 3,483) MET-min/wk (median (IQR)) of total PA. When PA was categorized by level of intensity, survivors accumulated 204 (0 – 663) MET-min/wk of vigorous-intensity PA, 721 (270 - 1,668) MET-min/wk of moderate-intensity PA, and 692 (324 - 1,434) MET-min/wk of light-intensity PA. The total mod-vig intensity PA was 1,242 (300 - 2,856) MET-min/wk. Regarding the type of PA, NA cancer survivors participated in 735 (312-1,242) MET-min/wk of non-exercise PA and 608 (219 - 1,493) MET-min/wk of planned exercise. When dichotomized by PA considered NA-specific activities, survivors spent 135 (0 -

662) MET-min/wk participating in NA-specific PA and 1,104 (609 - 2,168) MET-min/wk in non-native specific PA. Sample characteristics by level of PA are shown in Table 1. With the exception of tribal region and ever having lived on a reservation, descriptive statistics did not materially differ by level of PA. Of all activities queried, walking was the most common PA (91% participated), followed by light- (87%) and moderate- (53%) intensity housework. Participation in the various physical activities queried is depicted in Figure 1.

When examining the domains of HQOL by level of activity in participants (Table 2), meeting the PA guidelines was not significantly associated with any improved subscale scores after adjusting for age, sex, and region in this sample, with the exception of physical function. Further examination of the role of intensity and type of PA suggested that neither pain, fatigue, sleep health, sexual function in males, nor social HQOL constructs were associated with accumulation of any level of intensity or type of PA (all $p>0.05$; data not shown); however, there were relationships with other HQOL constructs that were statistically significant. Vigorous-intensity PA was negatively associated with cognition ($p=0.04$). Compared to those with no vigorous activity, the cognition of those with 250, 600, and 800 MET-min/wk (corresponding to quartile midpoints) was 0.13 ±0.05 (SE), 0.30 ±0.12, and 0.39 ±0.16 points lower, respectively. Moderate-intensity PA was associated with higher sexual functioning in females ($p=0.03$) and higher physical function overall ($p=0.02$) (the latter results shown in Figure 2). Females with 150, 500, 1,200, and1,700 MET-min/wk of moderate-intensity PA vs. 0 moderate-intensity PA MET-min/wk scored 0.04 ± 0.02, 0.11 ± 0.07, 0.20 ±

0.13, 0.28 ±0.21 higher on the sexual functioning measure, respectively. Participating in greater amounts of light-intensity PA was not associated with any HQOL outcome.

When PA was dichotomized by type (NA-specific activities and non-native specific PA), non-native specific PA was associated with physical function (Figure 2), though NA-specific PA was not associated with any outcome (all p> 0.05; data not shown). Further analysis of type of PA showed that when dichotomized by non-exercise PA and planned exercise, performing planned exercise was negatively associated with spiritual HQOL (p<0.01; 500, 1,000, and 2500 MET-mn/wk vs.100 MET-mn/wk= -0.06 ±0.03, -0.12 ±0.07, -0.33 ±0.19, respectively), negatively associated with emotional HQOL p=0.03; 500, 1,000, and 2500 MET-mn/wk vs.100 MET-mn/wk= -0.06 ±0.06, -0.13 ±0.14, -0.33 ±0.37, respectively), and positively associated with physical function (Figure 2), while performing non-exercise PA was associated with spiritual (500, 1,000, and 2500 MET-mn/wk vs. 200 MET-mn/wk=-0.03 ±0.02, -0.07 ±.06, -0.13 ±0.14, respectively) and emotional HQOL (p=0.03; 500, 1,000, and 2500 MET-mn/wk vs. 200 MET-mn/wk=-0.07 ±0.05, -0.17 ±0.11, -0.35 ±0.28, respectively).

Discussion

This is the first study to evaluate PA behaviors in a group of NA cancer survivors. In this nationally represented sample of NA cancer survivors of all types, our observations suggest that the majority (60%) of these individuals are meeting the recommended amount of PA. Compared with previous population studies using subjective measures to quantify PA, these findings suggest a greater number of NA cancer survivors meet the PA guidelines than that of the general population [35 36, 37]. While most data from population-based surveys conclude that around 39% of US adults meet PA guidelines [35 36, 37], studies using BRFSS and NHANES data have reported this percentage to be as high as 49% and 51%, respectively [37 38]. Our findings also suggest that a greater percentage of NA cancer survivors in this sample meet PA guidelines than other cancer survivors [39 40 41 42 43]. A population-based study by Bellizzi et al [43] examining PA in over 7,000 cancer survivors of all types found that 30% of survivors queried were meeting recommendations, and a study by Stevinson et al [41] evaluating self-reported PA in 359 women diagnosed with ovarian cancer found that 31% of participants met PA guidelines. While there have been few studies looking specifically at NA PA behaviors [44 45 46 47 48 37], findings are mixed. Schoenborn et al [44] suggest that 27% of NA do not meet PA guidelines while a study conducted by Storti et al [46] using pedometers to objectively measure step counts suggest that a “large proportion” of their sample is not meeting PA recommendations. Further, Eyler et al [47] found that 78% of NA participated in “Lifestyle activity” (defined as accumulating 300 min of combined exercises, sports, physically active hobbies, vigorous household chores, or occupational physical activity per week). One study, however, reported similar percentages of the NA population meeting the PA recommendations as that of our study [48]. Data from the EARTH study [48], which also used self-reported PA measures that queried both typical PA and NA-specific PA, suggest 48% of NA met PA guidelines, though that number climbs to 56% when looking specifically at males. The inconsistencies in NA PA data across studies likely stem from the difference in PA measures used, as the measurement tools varied greatly between studies. Further, regional and tribal differences, while accounted for in some studies, could also potentially add to the discrepancies noted. Finally, our sample had a very high rate of individuals with a greater than high school education (85%) as compared to typical NA samples (14%) [49]. As PA is often found to be higher in more educated individuals with higher SES [50, 51], it is likely that we received responses from survivors who do more PA than that of the typical NA cancer survivor.

While the high percentage of this sample meeting PA guidelines is possible, our results may also stem from over reporting. Self-reported PA has been shown to be overestimated, especially in sedentary individuals [52]. Previous work estimating the percentage of adults meeting PA guidelines using both objective and subjective measures have found large discrepancies between the two [38]. Using NHANES data from 2003-2004, Troiano et al found that the percentage of US adults meeting guidelines according to data collected from objective measures of PA to be less than 5%, whereas the percentage when using subjective measures (including transportation PA and household activities) was 51% [38]. It is important to note, however, that if the potential over-reporting in our study is consistent across levels of PA, it should not affect our ability to compare across intensities and types of PA.

When further describing PA behavior performed by this sample by intensity, we found that these survivors accumulated more PA in the moderate- to vigorous- intensity category (1,242 (300 – 2856) MET-min/wk) than the light intensity category (691.4 (324 – 1434) MET-min/wk). This is likely due to the number of MVPA activities surveyed (n=27) vs. light-intensity activities (n=9). When categorizing PA by type, we found that the most common PA participated in was walking, followed by light- and moderate-intensity housework. Further investigation of type of activity revealed that this sample tended to participate in more non-NA specific PA than in NA-specific PA, though again, this is likely due to walking being the most reported PA in this group. While walking is consistently noted as the most common activity performed in the general population, housework is not traditionally seen at the top of the list [53]; yet, other work evaluating PA in the NA community have found similar results [48, 54]. Duncan et al [48], who also found that the majority of time NA were physically active was in the "household" category, noted that this may be due to levels of poverty and unemployment, education, and other characteristics common to many NA communities, as these demographic variables have previously been linked to decreased leisure –time PA [55]. Other living-conditions associated with NA could perhaps necessitate a need for the increased housework noted in this study. These findings are important, as they bring insight on how to potentially best tailor future PA interventions to this community.

Meeting PA guidelines was typically not associated with better HQOL in this sample. As noted above, we did, however, find a positive relationship between PA and physical function, as meeting PA recommendations was associated with an increase in physical function scores by 0.80 points (Figure 2). This is similar to other work, as PA has consistently been associated with physical function in many populations [56, 57], including cancer survivors [22 58 59]. This finding is important in that, while cancer survivors may suffer losses in all health domains, their losses are typically the most profound in the area of physical functioning [60]. Cancer survivors have a two-fold risk of physical function limitations as compared to their general population counterparts [60], suggesting that PA may be an appropriate modality in mediating functional declines in this group.

As the relationship between meeting PA guidelines and physical function was the only significant HQOL outcome of all constructs queried, the current findings are at odds with previous investigations into this relationship in other cancer survivor populations. While this is the first study to evaluate the relationship between PA and HQOL in a sample of NA cancer survivors, PA has traditionally been shown to be positively related to HQOL in the survivorship phase of the cancer experience [61 62 63-66]. However, when evaluating PA and HQOL specifically in NA, the findings, while limited, are less consistent. Poltavski et al [67] surveyed 404 NA using the 2003 version of the BRFSS and found that meeting PA recommendations was significantly associated with better overall health, fewer mentally unhealthy and activity limitation days and a greater number of good health days. In another study evaluating PA levels and HQOL in NA elders[68], researchers found that only two of the eight subscale scores of the SF-36 (bodily pain and vitality) were significantly related to higher PA. As these inconsistencies regarding HQOL in NA can add perspective to our findings, there are other possible interpretations for the lack of associations found in this sample. The potential over reporting by this group could have resulted in misclassification of individuals, thereby inflating the number of individuals meeting PA guidelines, thus weakening potential associations. Further, the relatively small sample size used in this study (n=55) could also have been responsible for the inconsistencies of our findings.

When evaluating intensity- or type-specific PA with HQOL, very few relationships were determined to be significant (Appendix A). In the instances where a significant relationship was found, the magnitude of the association did not appear to be meaningful, or in some cases the association was negative, as in the case of sexual functioning and cognition. In these latter instances though, the magnitude of the differences was small, and not clinically relevant. However, we again found meaningful, positive relationships between PA and physical function. In all analyses where the relationship between PA and physical function was significant (moderate-intensity PA, planned exercise, and non-native specific PA), moving from the referent group to the highest participation group was associated with an increase in physical function scores by ~1 point (Figure 2). The consistency among these analyses adds credence to the suggestion that PA participation may play a role in lessening the functional declines often observed in this population.

This study has many inherent strengths, including the novelty of being the first study to both explore PA behaviors in NA cancer survivors, and to evaluate the relationship between PA and HQOL in this population. Our analysis benefited from using a measure that queried both PA and HQOL constructs that were specific to NA, allowing for a much better idea of the paradigms in this culture. Further, this tool surveyed not only leisure-time PA, but household, occupational, and transportation-based PA. This information can be used to design future PA interventions specific to this population. Finally, this sample was a nationally represented sample of NA.

As in other studies, this work also has many limitations to consider. The cross-sectional analysis used here, while an appropriate first step in evaluating these associations in this population, is unable to establish causation. It is possible that those who had a higher HQOL (in this case, physical function) were more likely to participate in PA, rather than PA resulting in higher HQOL. As a further consequence of this study design, this work utilizes a convenience sample of participants. Our sampling procedure could lead to selection bias, as only those who have access to the internet and found, or were directed to, the NACES website completed the survey. It is possible that these individuals may be different from individuals without internet access, including having a higher socioeconomic status (SES) and being more educated, and as pointed out previously our sample had higher levels of education than population-based studies would suggest. As such, conclusions regarding PA in the larger NA cancer survivor population must be tempered. This study was also limited by the fact that all PA data collected was from self-reported measures. Self-reported data are often subject to measurement error, which can lead to bias and spurious findings. Further, our measure of PA has not yet been validated for use. Utilizing non-validated measures can call estimations into question; however, as there are no instruments that have been validated for use in this population, and our tool was based on previously validated measures, including the Modifiable Activity Questionnaire (MAQ)/Pima Indian Questionnaire [33], we felt its use to be appropriate in this setting. Additionally we thought it was most important to evaluate culturally- relevant PA in this population. Validity could also be a concern for our measure of HQOL. This tool, while made up of many previously validated measures, has also not been validated for use. The fact that it is a unique tool makes comparisons across studies difficult. However, use of this measure brings additional insight into an already under-studied population, as it provides culturally relevant information specific to the HQOL of NA. Finally, our relatively small sample size (n=55) likely hindered our ability to further elucidate the relationship between PA and HQOL. Continued studies into this population with larger sample sizes will help to mitigate this limitation.

In conclusion, this study has shown that a large percentage of NA cancer survivors are sufficiently active enough to meet PA guidelines, though over-reporting is possible. Of the typical PA participated in by these survivors, walking and housework are the most common activities. This group also tended to participate more in non-NA specific PA than in traditional NA-specific PA. This information should be considered when designing future interventions for this population. This study did not find a relationship between meeting PA guidelines and HQOL. Further, while physical function scores were associated with greater amounts of PA of varying intensities and types, our sample size was too small to rule out an association between PA and fatigue, sexual function in males, and social QOL. Despite the limited findings presented, this work is a necessary first step in our understanding of the NA cancer survivor in relation to their PA patterns and its association with HQOL. Further research in this area is warranted, as additional work is needed to close the gap in the health disparities seen between NA and other communities.

Table 1: Characteristics of Native American Cancer Survivors by Level of Physical Activity

	Met Physical Activity Recommendations		
	No (n=22)	Yes (n=33)	p-value
Characteristic			
Age Range¥			0.58
26-35	0	2	
36-45	1	2	
46-55	3	4	
56-65	6	15	
66-75	8	8	
76-85	3	2	
Cancer Type ¤			0.65
Breast	8	14	
Colon	4	1	
Lung	2	1	
Ovary	1	0	
Cervix	4	7	
Prostate	1	1	
gallbladder	0	1	
other	11	5	
Time since dx (years) ¥			0.77
< 1 year	18	27	
1-4 years	0	2	
>5 years	1	1	
Age at time of dx (years) ¥			0.45
21-30	1	5	
31-40	2	4	
41-50	7	6	
51-60	5	12	
61-70	6	5	
71+	0	1	
Sex (number of females)	18	30	0.42
Blood Quantum ¥ (% with):			0.09
Less than 25%	0	1	
25%-49%	1	8	
50%-74%	2	4	
75%-99%	3	5	
100%	14	9	
Tribe/Region: ¥			0.03
NE	1	0	
Northern Plains	13	10	
Southern Plains	3	15	
SE	2	7	
SW	3	0	

Categorical variables compared between categories by chi-square, continuous variables compared using ANOVA, or Fisher's exact test was used due to cell size. Tx=treatment; Blood Quantum=percent of NA ancestry for an individual.
¤ Some individuals reported more than one cancer ¥ Subjects missing from analysis: Age range (n=1); Time since dx (n=6); Age at dx (n=1); Blood Quantum (n=8); Tribe/Region (n=1).

Table 1continued: Characteristics of Native American Cancer Survivors by Level of Physical Activity

	Met Physical Activity Recommendations		
	No (n=22)	Yes (n=33)	p-value
Characteristic			
Reservation ¥			
Ever	12	9	0.04
Never	9	24	
Current	2	5	0.48
Current smoker	4	5	0.15
Treatment			0.28
Currently receiving tx	3	1	
Previously received tx	17	30	
Never/yet to receive tx	2	2	
Used Traditional tx	9	8	0.23
Education			0.13
<High School	0	2	
High School	0	3	
>High School	22	28	
Television viewing time ¥			0.15
<1 hours	4	3	
1-4.5 hours	7	20	
5-8.5 hours	4	7	
>9 hours	5	2	

Categorical variables compared between categories by chi-square, continuous variables compared using ANOVA, or Fisher's exact test was used due to cell size. Tx=treatment; Blood Quantum=percent of NA ancestry for an individual.
¥ Subjects missing from analysis: Reservation-ever (n=1); Television viewing time (n=2).

Table 2: Physical Activity and Health-related Quality of Life (mean ± SE).

HQOL Construct	Did not meet PA recommendations (n=22)	Met PA recommendations (n=33)	p-value
Physical Function	3.00 (±0.23)	3.79 (±0.26)	p=<0.01
Pain	2.80 (±0.33)	2.42 (±0.39)	P=0.30
Fatigue	3.28 (±0.27)	2.94 (±0.30)	p=0.23
Sleep Health	1.76 (±0.18)	1.78 (±0.20)	p=0.94
Sexual Function (male)	1.12 (±0.16)	1.37 (±0.18)	p=0.15
Sexual Function (female)	1.31 (±0.21)	1.68 (±0.24)	p=0.11
Cognition	2.28 (±0.22)	2.13 (±0.24)	p=0.54
Social QOL	2.98 (±0.26)	3.30 (±0.29)	p=0.24
Spiritual QOL	0.69 (±0.09)	0.64 (±0.11)	p=0.66
Emotional QOL	1.57 (±0.19)	1.47 (±0.21)	p=0.59

ANCOVA with adjustment for age, sex, and region.

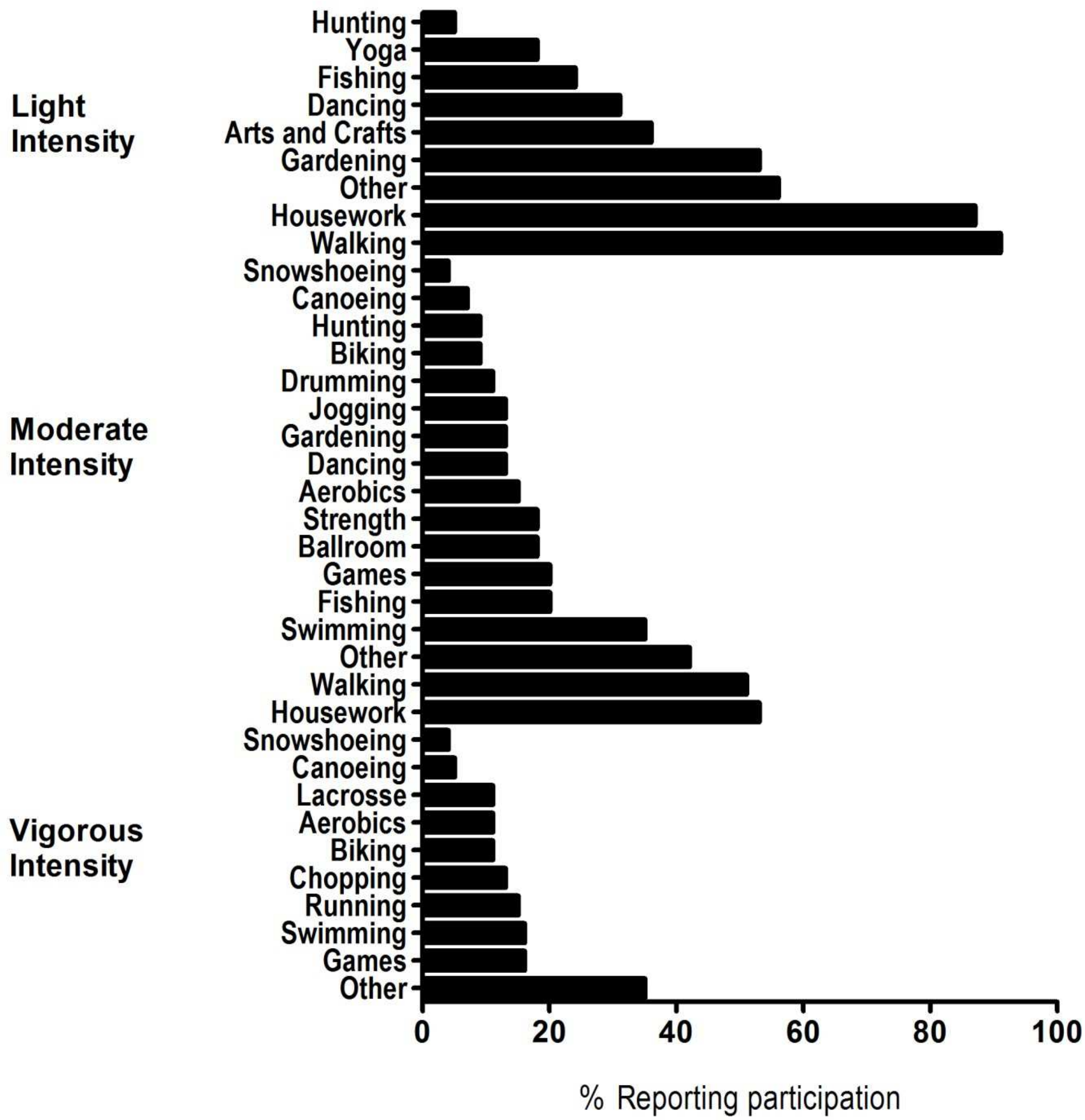


Figure 1: Percentage of sample reporting participation in various physical activities (separated by level of intensity).

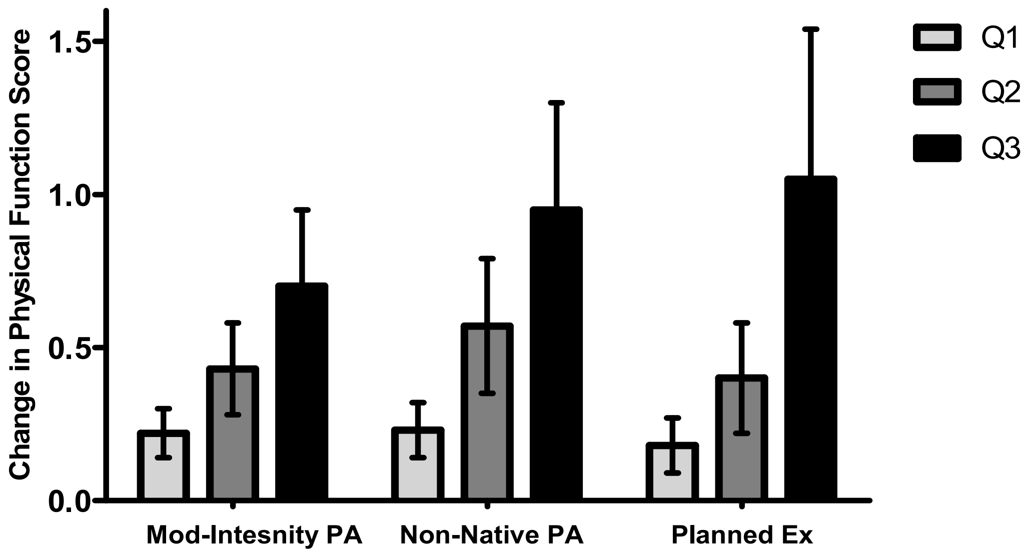


Figure 2: Difference in physical function scores when moving from the referent group to greater participation group. Multiple Linear Regression with adjustment for age, sex, and region. Moderate- intensity PA was also adjusted for light- and vigorous-intensity PA; non-NA PA was also adjusted for NA-specific PA; planned exercise was also adjusted for light intensity PA. Mod MET-mn/wk Q1:0 vs 500; Q2: 0 vs 1000; Q3: 0 vs 1700. Non-traditional MET-mn/wk Q1:300 v 750; Q2 300 vs 1500; Q3 300 vs 2500. Planned Exercise MET-mn/wk Q1:100 v 500; Q2 100 vs 1000; Q3 100 vs 2500.

References

1. American Cancer Society. Cancer Facts and Figures, 2015. Atlanta, GA: ACS; 2015.

2. Hewitt ME, Greenfield S, Stovall E. From cancer patient to cancer survivor: lost in transition: Natl Academy Pr; 2006.

3. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Questionnaire (Examination Protocol, or Laboratory Protocol). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2011.

4. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors--a systematic review. International journal of psychiatry in medicine 2010;40(2):163-181.

5. Deimling GT, Sterns S, Bowman KF, Kahana B. The health of older-adult, long-term cancer survivors. Cancer nursing 2005;28(6):415.

6. Deimling GT, Kahana B, Bowman KF, Schaefer ML. Cancer survivorship and psychological distress in later life. Psycho-Oncology 2002;11(6):479-494.

7. Gone JP, Trimble JE. American Indian and Alaska Native mental health: diverse perspectives on enduring disparities. Annu Rev Clin Psychol 2012;8:131-60.

8. Office of the General Counsel USCoCR. Native American Health Care Disparities Briefing: Executive Summary. www.law.umaryland.edu/marshall/usccr/documents/nativeamericanhealthcaredis.pdf; 2004.

9. Frieden TR, (CDC) CfDCaP. Forward: CDC Health Disparities and Inequalities Report - United States, 2011. MMWR Surveill Summ 2011;60 Suppl:1-2.

10. Goins RT, Moss M, Buchwald D, Guralnik JM. Disability among older American Indians and Alaska Natives: an analysis of the 2000 Census Public Use Microdata Sample. Gerontologist 2007;47(5):690-6.

11. Chowdhury PP, Balluz L, Strine TW. Health-related quality of life among minority populations in the United States, BRFSS 2001-2002. Ethn Dis 2008;18(4):483-7.

12. Goins RT, Pilkerton CS. Comorbidity among older American Indians: the native elder care study. J Cross Cult Gerontol 2010;25(4):343-54.

13. Indian Health Institute SIBoH. Depression Among American Indians and Alaska Natives:A Literature Review. In. Seattle, WA: Urban Indian Health Institute; 2012.

14. United States Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Office of Applied S. National Survey on Drug Use and Health, 2006. 2013.

15. Dinges NG, Duong-Tran Q. Stressful life events and co-occurring depression, substance abuse and suicidality among American Indian and Alaska Native adolescents. Cult Med Psychiatry 1992;16(4):487-502.

16. Beals J, Novins DK, Whitesell NR, Spicer P, Mitchell CM, Manson SM. Prevalence of mental disorders and utilization of mental health services in two American Indian reservation populations: mental health disparities in a national context. Am J Psychiatry 2005;162(9):1723-32.

17. Burhansstipanov L, Krebs LU, Seals BF, Bradley AA, Kaur JS, Iron P, et al. Native American breast cancer survivors' physical conditions and quality of life. Cancer 2010;116(6):1560-1571.

18. Burhansstipanov L, Dignan M, Jones KL, Krebs LU, Marchionda P, Kaur JS. Comparison of quality of life between Native and non-Native cancer survivors: Native and non-Native cancer survivors' QOL. Journal of cancer education : the official journal of the American Association for Cancer Education 2012;27 Suppl 1:S106-13.

19. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Current Opinion in Psychiatry 2005;18(2):189.

20. Courneya KS, Friedenreich CM. Physical exercise and quality of life following cancer diagnosis: a literature review. Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine 1999;21(2):171-179.

21. Courneya KSCKS, Karvinen KHKKH. Exercise, aging, and cancer. Applied Physiology, Nutrition, and Metabolism 2007;32(6):1001-1007.

22. Thraen-Borowski KM, Trentham-Dietz A, Edwards DF, Koltyn KF, Colbert LH. Dose-response relationships between physical activity, social participation, and health-related quality of life in colorectal cancer survivors. J Cancer Surviv 2013;7(3):369-78.

23. Aziz NM, Rowland JH. Cancer survivorship research among ethnic minority and medically underserved groups. Oncol Nurs Forum 2002;29(5):789-801.

24. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. Social science & medicine 2000;51(6):843-857.

25. Coble JD, Rhodes RE. Physical activity and Native Americans: a review. Am J Prev Med 2006;31(1):36-46.

26. Rhodes RE. Physical Activity and Native American Indians: A Review. American Journal of Preventive Medicine 2006;31(1):36-46.

27. Burhansstipanov L, Gilbert A, LaMarca K, Krebs LU. An innovative path to improving cancer care in Indian country. Public health reports (Washington, DC: 1974) 2001;116(5):424-433.

28. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of clinical oncology 1993;11(3):570-579.

29. Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 1995;4(6):523-531.

30. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. Medicine & Science in Sports & Exercise 2001;33(7):1126.

31. Colbert LH, Matthews CE, Havighurst TC, Kim K, Schoeller DA. Comparative validity of physical activity measures in older adults. Medicine and science in sports and exercise 2011;43(5):867-876.

32. Harada ND, Chiu V, King AC, Stewart AL. An evaluation of three self-report physical activity instruments for older adults. Medicine & Science in Sports & Exercise 2001;33(6):962.

33. Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, et al. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. Diabetes care 1990;13(4):401-411.

34. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Medicine and science in sports and exercise 2000;32(9 Suppl):S498.

35. Physical Activity Guidelines Advisory C. Physical activity guidelines advisory committee report, 2008. Washington, DC: US Department of Health and Human Services 2008;2008.

36. Wallace LS, Buckworth J. Characteristics related to meeting CDC/ACSM physical activity guidelines in adults. Medicine & Science in Sports & Exercise 2002;34(5):S227.

37. Haskell WL, Lee I, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Medicine and science in sports and exercise 2007;39(8):1423.

38. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Medicine & Science in Sports & Exercise 2008;40(1):181.

39. Blanchard CM, Courneya KS, Stein K. Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. In: J Clin Oncol. United States; 2008. p. 2198-204.

40. Bellizzi KM, Rowland JH, Arora NK, Hamilton AS, Miller MF, Aziz NM. Physical activity and quality of life in adult survivors of non-Hodgkin's lymphoma. In: J Clin Oncol. United States; 2009. p. 960-6.

41. Stevinson C, Tonkin K, Capstick V, Schepansky A, Ladha AB, Valance JK, et al. A population-based study of the determinants of physical activity in ovarian cancer survivors. J Phys Act Health 2009;6(3):339-46.

42. Courneya KS, Katzmarzyk PT, Bacon E. Physical activity and obesity in Canadian cancer survivors: population-based estimates from the 2005 Canadian Community Health Survey. Cancer 2008;112(11):2475-82.

43. Bellizzi KM, Rowland JH, Jeffery DD, McNeel T. Health behaviors of cancer survivors: examining opportunities for cancer control intervention. In: J Clin Oncol. United States; 2005. p. 8884-93.

44. Schoenborn CA, Adams PF, Barnes PM, Vickerie JL, Schiller JS. Health behaviors of adults: United States, 1999-2001. Vital Health Stat 10 2004(219):1-79.

45. Denny CH, Holtzman D, Cobb N. Surveillance for health behaviors of American Indians and Alaska Natives. Findings from the Behavioral Risk Factor Surveillance System, 1997-2000. Morbidity and mortality weekly reportSurveillance summaries (Washington, DC: 2002) 2003;52(7):1-13.

46. Storti KL, Arena VC, Barmada MM, Bunker CH, Hanson RL, Laston SL, et al. Physical activity levels in American-Indian adults: the Strong Heart Family Study. Am J Prev Med 2009;37(6):481-7.

47. Eyler AA, Brownson RC, Donatelle RJ, King AC, Brown D, Sallis JF. Physical activity social support and middle- and older-aged minority women: results from a US survey. In: Soc Sci Med. England; 1999. p. 781-9.

48. Duncan GE, Goldberg J, Buchwald D, Wen Y, Henderson JA. Epidemiology of physical activity in American Indians in the Education and Research Towards Health cohort. Am J Prev Med 2009;37(6):488-94.

49. Aud S, Fox MA, KewalRamani A. Status and Trends in the Education of Racial and Ethnic Groups. NCES 2010-015. National Center for Education Statistics 2010.

50. Cauley JA, Donfield SM, Laporte RE, Warhaftig NE. Physical activity by socioeconomic status in two population based cohorts. Med Sci Sports Exerc 1991;23(3):343-51.

51. Droomers M, Schrijvers CT, van de Mheen H, Mackenbach JP. Educational differences in leisure-time physical inactivity: a descriptive and explanatory study. In: Soc Sci Med. England; 1998. p. 1665-76.

52. Duncan GE, Sydeman SJ, Perri MG, Limacher MC, Martin AD. Can sedentary adults accurately recall the intensity of their physical activity? Preventive Medicine 2001;33(1):18-26.

53. Eyler AA, Brownson RC, Bacak SJ, Housemann RA. The epidemiology of walking for physical activity in the United States. Med Sci Sports Exerc 2003;35(9):1529-36.

54. Fischer ID, Brown DR, Blanton CJ, Casper ML, Croft JB, Brownson RC. Physical activity patterns of Chippewa and Menominee Indians: the Inter-Tribal Heart Project. In: Am J Prev Med. Netherlands; 1999. p. 189-97.

55. Crespo CJ, Ainsworth BE, Keteyian SJ, Heath GW, Smit E. Prevalence of physical inactivity and its relation to social class in U.S. adults: results from the Third National Health and Nutrition Examination Survey, 1988-1994. Med Sci Sports Exerc 1999;31(12):1821-7.

56. Cress ME, Buchner DM, Questad KA, Esselman PC, deLateur BJ, Schwartz RS. Exercise: effects on physical functional performance in independent older adults. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 1999;54(5):M242.

57. Brach JS, Simonsick EM, Kritchevsky S, Yaffe K, Newman AB. The association between physical function and lifestyle activity and exercise in the health, aging and body composition study. Journal of the American Geriatrics Society 2004;52(4):502-509.

58. Johnson BL, Trentham-Dietz A, Koltyn KF, Colbert LH. Physical activity and function in older, long-term colorectal cancer survivors. Cancer Causes and Control 2009;20(5):775-784.

59. Lynch BM, Cerin E, Owen N, Aitken JF. Associations of leisure-time physical activity with quality of life in a large, population-based sample of colorectal cancer survivors. Cancer Causes and Control 2007;18(7):735-742.

60. Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2003;58(1):M82.

61. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2005;14(7):1588-95.

62. Brown JC, Winters-Stone K, Lee A, Schmitz KH. Cancer, physical activity, and exercise. Compr Physiol 2012;2(4):2775-809.

63. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42(7):1409-26.

64. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2006;174(6):801-809.

65. Courneya KS. Physical activity in cancer survivors: a field in motion. Psychooncology 2009;18(4):337-42.

66. Barbaric M, Brooks E, Moore L, Cheifetz O. Effects of physical activity on cancer survival: a systematic review. Physiotherapy Canada = Physiotherapie Canada 2010;62(1):25-34.

67. Poltavski D, Holm J, Vogeltanz-Holm N, McDonald L. Assessing health-related quality of life in Northern Plains American Indians: prominence of physical activity as a health behavior. Am Indian Alsk Native Ment Health Res 2010;17(1):25-48.

68. Sawchuk CN, Charles S, Wen Y, Goldberg J, Forquera R, Roy-Byrne P, et al. A randomized trial to increase physical activity among native elders. Prev Med 2008;47(1):89-94.

Manuscript

Impact of Exercise on Prognostic Biomarkers, Health-related Quality of Life, and Exercise Capacity in Lung Cancer Patients: A Pilot Study

Keith M. Thraen-Borowski[1], Ronald Gangnon[2,3], Keith P. Gennuso[2], Amy Trentham-Dietz[2,4], Kelli F. Koltyn[1], Alex K. Adams[5], Lisa H. Colbert [1]
University of Wisconsin-Madison, Madison, WI

Affiliations:
[1]Department of Kinesiology, University of Wisconsin-Madison, Madison, WI
[2]Department of Population Health Sciences, University of Wisconsin-Madison, Madison, WI
[3]Department of Biostatistics and Medical Informatics, School of Medicine and Public Health University of Wisconsin-Madison, Madison, WI
[4]Paul P. Carbone Comprehensive Cancer Center, University of Wisconsin-Madison, Madison, WI
[5]Department of Family Medicine, University of Wisconsin-Madison, Madison, WI

Support for this research was provided by the Carbone Cancer Center, University of Wisconsin-Madison. This work is also supported in part by NIH/NCI P30 CA014520- UW Comprehensive Cancer Center Support

Corresponding Author:
Keith Thraen-Borowski, MS
Dept. of Kinesiology
University of Wisconsin
2000 Observatory Dr.
Madison, WI 53706
Ph: 608-262-1167
Fax: 608-262-1656
E-mail: thraenborows@wisc.edu

Abstract

Purpose*:* To determine the feasibility and effects of an exercise intervention on biomarkers of prognosis, HQOL, and exercise capacity in lung cancer survivors.

Methods**:** Participants were recruited over 13 months for this eight-week intervention. Subjects were randomized to usual care or an intervention consisting of supervised exercise training two days per week in-clinic and a prescription for at-home exercise three days per week, totaling 150 min/wk of moderate-intensity PA. Exercise capacity (LDCW), health-related quality of life (FACT-L), and serum levels of inflammatory biomarkers (IL-6, IL-8, IL-10, TNF-α, and hs-CRP) and oxidative stress (8-OHdG) were measured pre- and post-intervention. Descriptive statistics and effect sizes (Cohen's *d*) were calculated .

Results*:* Of all eligible subjects (n=191), less than 7% agreed to participate, leaving a final analytic sample of 11 survivors (n=5 treatment; n=6 control) with a mean age of 63 (±7.3) years, 64% of which were female, 91% white, and 100% diagnosed with non-small cell lung cancer. Those randomized to the exercise arm more frequently had Stage IV cancer (80% vs. 17% in controls) and were currently receiving cancer treatment (60% vs. 0%). Both the retention and adherence rate in our exercise group was 83%. Negative effects of our treatment were observed in some outcomes (IL-8, IL-10, 8-OHdG, FACT-L), though hs-CRP was lowered (*d*= -0.66) and exercise capacity was maintained.

Conclusions: For individuals interested in and well enough to participate, exercise training appears to be safe and feasible. The majority of our sample was compliant with the intervention, though our small sample size did not allow for a thorough evaluation of the effectiveness of this intervention as it relates to biomarkers of prognosis, HQOL, and exercise capacity.

Lung cancer remains a major health concern in the United States (US). Lung and bronchial cancers are the second most commonly diagnosed type of cancer (not including non-melanoma skin cancer), with about 221,200 expected new cases of lung cancer in the year 2015 [1]. Approximately 7% of all men and women in the US will be diagnosed with lung and bronchus cancer at some point in their lifetime [1]. Unfortunately, prognosis of the lung cancer patient is generally quite poor. Lung cancer continues to be the leading cause of cancer deaths in the US for both men and women, expected to account for 27% of all cancer deaths in 2015 [1]. More people die from lung cancer each year than from colon, breast, and prostate cancers combined. Over half of those diagnosed with lung cancer die within the first year of being diagnosed [1]. The five-year survival rate for lung cancer (17%) is lower than many of the other leading cancer sites, such as breast (90%), colon & rectum (65%), and prostate (99%) [1, 2].

Despite these staggering mortality statistics, there are a considerable number of lung cancer survivors. Nearly 400,000 people alive today have been diagnosed with lung cancer at some point and mortality rates have declined over the last ten years by roughly 1.7% [1]. Yet, while these improvements in survival are welcomed, a lung cancer diagnosis and its associated treatments can create substantial challenges for the survivor, leading to significant impacts on health-related quality of life (HQOL) [3]. A significant proportion of lung cancer survivors face serious physical and functional declines [4], and may be severely incapacitated by disease-related symptoms such as chest pain, persistent cough, voice change, recurring pneumonia or bronchitis, hemoptysis and dyspnea [5]. Detriments in mental health are also common and persistent in lung cancer patients, especially those with more severe symptoms or functional limitations [6]. Lung cancer survivors can experience heightened levels of fatigue, pain, disturbed sleep, lack of appetite and drowsiness [7-11]. As a consequence of these health challenges, HQOL may be diminished in this population.

Due to the great burden of disease experienced by lung cancer survivors, new therapies are required. These treatments should work to improve prognosis and HQOL while complimenting current management of lung cancer. Physical activity (PA) remains an attractive modality due to its improvement of physical and mental health outcomes in many different populations, including cancer survivors [12] [13] [14], as well as its potential to improve prognosis in these survivors [15]. Some of the hypothesized mechanisms through which PA may be beneficial in lung cancer include a reduction in inflammation, which is considered to play a role in pathogenesis [16-18], and lower levels of oxidative DNA damage [19], which may play a major role in carcinogenesis [20]. Further, as lung-based tumors are thought to disrupt gas exchange [25], potentially resulting in increased dyspnea, fatigue, muscle wasting, anemia, and weight loss, which can all lead to decreased exercise tolerance, recent reports suggest that exercise capacity is a strong independent predictor of overall long-term survival for lung cancer patients [21-24]. Despite the potential benefits of PA in this particular population, there has been little work to evaluate these relationships specifically in lung cancer survivors [26-31], and to date, there have been very few well-controlled trials that have examined the effect of PA in this disease [32-34]. As such, we conducted a randomized control trial to determine how an exercise intervention alters biomarkers of prognosis, HQOL, and exercise capacity, as well as the feasibility of such a program, in this population.

Methods

Overview & Study Design- This pilot study utilized an experimental design to determine the effects of an 8-week exercise intervention, consisting of both aerobic and resistance training, in lung cancer patients. Subjects were randomized to the exercise training intervention or to usual care.

Subjects- Lung cancer survivors were recruited for participation from the University of Wisconsin-Madison Hospital System from January 2014 – February 2015. Subjects meeting eligibility criteria, which included being at least eighteen years of age, a confirmed diagnosis of any stage lung cancer (non-small cell or small cell lung cancers), and the ability to understand and read English sufficiently to complete informed consent and the study questionnaires, were identified by their primary oncologists, given an informational flyer, and referred to the study staff via a permission to contact form. Subjects receiving any type of treatment (chemotherapy, radiation therapy, both or neither), curative or non-curative, were also eligible. Patients treated with curative intent, and who had not relapsed, must have been within one year of their diagnosis of lung cancer as determined by date of diagnostic pathology sample. Subjects were also screened for exclusion criteria, which included symptomatic heart disease, congestive heart failure or arrhythmia, documented myocardial infarction in the last three months, central nervous system metastases that result in impaired ability to participate in an exercise program at the discretion of the study physician, any psychological or physical disease that would impair or prevent participation in an exercise program at the discretion of the study physician, cognitive or reading impairments that would preclude them from completing questionnaires, or current participation in an exercise program. Those potential participants determined to be eligible by study staff received a phone call from research personnel and were given more information about the study.

As one previous study found that the at-home component of their combined at-home/clinic exercise intervention had low adherence [27], subjects were asked to identify a support person to participate in the study with them, such that if the survivor was randomized to the exercise treatment, it could potentially increase patient adherence. This support person could be of any relation to the patient. Should a patient be unable to identify a support person to participate with them, they were still able to participate.

Protocol- After the initial screening phone call, interested and eligible subjects were enrolled at the University of Wisconsin Hospital-Madison during a pre-intervention visit. Once consented, health information was extracted from patients' medical records, including past medical history, disease stage, treatment information, and medications. All subjects provided additional information on their age, race, ethnicity, and education. Height, weight and body fat percentage (via bioelectrical impedance) was directly measured by research staff in all subjects and typical daily PA levels were measured by the International Physical Activity Questionnaire-Long Form (IPAQ), a reliable and valid questionnaire frequently used to measure PA [35]. During this pre-intervention visit, subjects also completed tests to evaluate their exercise capacity and HQOL, and blood was drawn for the measurement of specific biomarkers of interest. Subjects were instructed to refrain from exercise for eight hours prior to testing, consume no alcohol twelve hours prior, and not to use NSAIDs for twenty-four hours prior to testing. Subjects were rescheduled if they had been diagnosed with an upper respiratory infection due to the effect it may have on inflammatory markers. All outcome measures were repeated at the post-intervention visit.

Study Procedures/Measures

Randomization- Participants were stratified by both treatment (active treatment versus non-active treatment) and stage (Stage I, Stage II, and surgical Stage III versus non-surgical Stage III and Stage IV). Block randomization was then used to assign subjects to the exercise intervention (treatment arm) or usual care (control arm) using a computer-generated random assignment. Once generated, the allocation sequence assignments were placed into envelopes by a research assistant, such that the research coordinator was blind to the assignments. Subjects were assigned their respective participation groups following the pre-testing session. To improve retention of subjects in the control group, these individuals were offered an exercise consultation from a trained exercise physiologist after post-testing was completed.

Intervention- The exercise intervention was designed to be consistent with the PA recommendations for cancer survivors as suggested by the American College of Sports Medicine [36, 37]. The intervention consisted of supervised exercise training two days per week at the clinic and a prescription for at-home exercise three days per week. Each exercise session was composed of an aerobic training component and a resistance training component. At the initial visit, individual consultations with the exercise specialist were used to tailor the intervention exercises to the subject. In total, aerobic training was done five days per week, including the two days at the clinic. Resistance training was done two days per week at the clinic visits unless subjects were absent from clinic visits, in which case subjects were instructed to complete at home. Activity logs were used by subjects to record their weekly exercise and, along with attendance at in-clinic sessions, were used to measure program adherence.

Aerobic Training – Subjects had their choice of walking, stationary cycling, or a series of aerobic exercise videos designed for older adults as their mode of aerobic exercise during the aerobic component of their intervention; however, all subjects chose walking as their preferred method of activity. When necessary, subjects progressed from a minimum of 10 minutes/session of aerobic activity to the prescribed 30 minutes/session. The Borg Rating of Perceived Exertion Scale [38] (RPE) was used to judge intensity. Participants were instructed to work at a rating of 12-16 (the ‘somewhat hard’ to ‘hard’ range). RPE was systematically collected throughout the exercise session to assure participants were exercising at the appropriate intensity. A five minute warm-up period and five minute-cool down period were used each session.

Resistance Training- Resistance bands were used for the strength training portion of the intervention. The following exercises were used, as this particular set of exercises was designed to hit all major muscle groups: chest press, seated row, upright row, triceps extension, bicep curls, squats, shoulder press, and calf raises. All exercises were done in two sets of 10 repetitions each. If 10 repetitions became easy to perform, resistance was added by advancing through the different bands.

Biomarkers: Inflammation and Oxidative Stress- Serum levels of pro-inflammatory cytokines (interleukin (IL)-6, IL-8 and tumor necrosis factor-alpha (TNF-α) [18], as well as IL-10, an anti-inflammatory cytokine, were measured. Serum levels of high sensitivity-CRP (hs-CRP), a liver-derived protein that is reflective of systemic inflammation [39] and of 8-OHdG, a marker of oxidative stress that has been linked to cancer risk and, potentially, prognosis [40], were also measured. Peripheral blood samples (~10ml) were drawn at both the pre-intervention visit and post-intervention visit prior to exercise capacity testing. Following clotting, samples were centrifuged and serum was aliquoted into separate polyvials. Processed samples were stored at $-70^{o}C$ until assayed. All biomarkers were measured in serum. We used an electrochemiluminescence platform, multi-cytokine array (V-PLEX, Rockville, Maryland) for IL-6, IL-8, IL-10,and TNF-α, and an enzyme-linked immunosorbent assay kit (ELISA) (Cayman Chemical, Ann Arbor, MI) for 8-OHdG. To measure hs-CRP, an immunonephelometric method was used (BN II, Siemens Healthcare, USA).

HQOL- The FACT-L (Functional Assessment of Cancer Therapy-Lung) is a 44-item self-administered instrument which measures multidimensional HQOL specific to lung cancer survivors [41]. The items queried span five domains: physical, social/family, emotional, and functional well-being, along with a lung cancer-specific subscale measuring symptoms, cognitive function, and regret of smoking. Each of these subscales are scored on a five-point scale from zero (described as “not at all”) to four (described as “very much”). Subscale scores are then added to obtain a total score. The FACT-L has been shown to be both reliable and valid for use in this population [41].

Exercise Capacity- The Long Distance Corridor Walk (LDCW) is a two part test used to measure exercise capacity [42]. It consists of a self-paced two-minute walk, followed by a timed 400-m walk. Participants first completed the two-minute walk with the goal to cover as much ground as possible. After a one minute break, participants completed the 400-m walk. The goal for this test is to complete the walk in the shortest amount of time. This test, typically reported as meters walked per second, has been shown to be a valid and reliable performance-based measure of exercise capacity in both middle-aged and older adults [43].

Analysis- Analyses were conducted using SPSS statistical software version 20 (IBM Corp.). Descriptive statistics were calculated and compared between the two groups (treatment vs. usual care) at baseline. Power was calculated for a two-way analysis of variance using hs-CRP as the primary dependent variable of interest with an overall Type I error rate of 5%, and 80% power. Using the exercise study by Hwang et al [44], we determined that 54 total subjects would be necessary to detect a significant difference in hs-CRP between the two groups of lung cancer patients based on a mean difference of 6 pg/mL and a standard deviation of 7.7. As our enrollment for this study was quite low, we were under-powered to run this analysis. Therefore, means and standard deviations (SD) for the pre- and post-tests for each treatment group were reported for each dependent variable (inflammatory markers, 8-OHdG, FACT-L, gate speed on LDCW test). To assess the effect of the treatment, effect sizes (ES) for these analyses were calculated using Cohen's *d* with correction for positive bias [45]. Cohen's *d* is a standardized measure of ES and provides information on the amount of change from pre-test to post-test between treatment groups relative to the variation within the measure.

Results

Study Population- Initially, 282 participants were identified by University of Wisconsin-Madison oncologists for potential participation in this study. Of those who were eligible (n=191), 36 signed permission to contact forms (18.8%). After being contacted by research staff for further information, 19 declined participation and 4 additional participants were determined to be ineligible for participation, leaving a total of 13 lung cancer survivors consented. A flow chart of recruitment is shown in Figure 1. Of the 13 participants randomized, two subjects were unable to complete post-testing. One subject was too ill to continue and one subject didn't respond to contact from study staff regarding post-testing, leaving a final analytic sample of 11 survivors (n=5 treatment; n=6 control). The mean age (±SD) of participants at baseline was 63.0 (±7.3) years, 63.6% of which were female, and 90.9% identifying as white. All survivors in our analytic sample were diagnosed with non-small cell lung cancer (NSCLC). Nearly half of those (n=5) had stage IV cancer, with the majority of subjects (72.7%) not receiving cancer treatment at time of enrollment. Baseline PA levels, as indicated by IPAQ scores, were 3810 (426-6465) MET-min/wk (median (IQR)). Of the 11 survivors participating in the study, eight were able to identify a support person to complete the study with them. Sample characteristics by treatment group are shown in Table 1. Individuals in the treatment group tended to be female, currently receiving treatment, diagnosed with stage IV cancer, more educated, and had fewer comorbidities.

Program Adherence- The overall retention rate in our exercise intervention arm was 83%, as one participant opted to withdraw due to feeling too ill to continue. With regards to adherence to the exercise treatment arm, participants completed 66 of 80 potential in-clinic exercise sessions (83%). As subjects were instructed to complete missed in-clinic visits at home, we found that, per PA logs completed by subjects, 80% (n=4) of subjects met the intervention goals of completing 150 minutes of moderate-intensity PA each week. No injuries, falls, or adverse reactions of any kind were reported throughout the intervention. With regards to the control group, one subject was lost to follow up and did not complete post-testing.

Biomarkers- Biomarker results for each treatment group are presented in Table 2. With regards to the change in scores between the two groups, the ES of the pro-inflammatory cytokines were mixed. We found no effect of the treatment for TNF-α (*d*= -0.04), a small, negative effect for IL-6 (*d*= -0.16), yet found a small, positive effect for IL-8 (*d*= 0.28). We also observed a medium, negative effect of our treatment (*d*= -0.66) for hs-CRP. Of note, as we would expect exercise to lower levels of these pro-inflammatory cytokines and hs-CRP, a negative effect in this case is favorable. This holds true for our measure of oxidative stress, 8-OHdG, for which we observed a large, positive ES (*d*= 1.62), suggesting an adverse effect of our treatment. With regards to our anti-inflammatory marker, IL-10, we observed a large, negative effect (*d*= -2.0). Here, as we would expect an exercise program to increase anti-inflammatory effects, it is suggestive of an adverse response to treatment.

HQOL- When evaluating HQOL using the FACT-L, subjects randomized to the control group had a mean score of 105.3 (± 8.6) on the pre-test and 108.2 (± 8.0) on the post-test. The treatment group scored, on average, 106.2 (± 13.3) on the pre-test and 100.8 (± 13.4) on the post-test. The ES regarding the change in score between the two groups (*d*= -0.88) suggests a large, negative effect of our treatment.

Mean scores (± SD) on each of the five subscales of the FACT-L are presented in Table 3. All subscale scores, with the exception of physical well-being, improved from pre-test to post-test in the control group, whereas the only improvements in the treatment group were on the physical well-being and the functional well-being subscales.

Exercise Capacity- With regards to exercise capacity, we found that subjects in both groups improved their LDCW scores over time. The control group walked, on average, at a pace of 1.23 (± 0.15) m/sec on the pre-test and 1.48 (± 0.15) m/sec on the post-test, while the treatment group walked at a pace of 1.28 (± 0.23) m/sec and 1.32 (± 0.14) m/sec, respectively (data not shown). The ES between groups (d= -1.17) showed a large, negative effect, as the control group improved on the post-test to a much larger degree than that of the treatment group.

Discussion

This study, the first controlled trial to evaluate exercise and its relationship with biomarkers of prognosis in a group of lung cancer survivors, as well as one of the few controlled trials to evaluate HQOL and exercise capacity in this group, adds to the overall body of literature regarding the use of exercise as a therapeutic modality in cancer survivorship. However, challenges in recruiting lung cancer survivors to participate in an exercise program greatly hindered our ability to evaluate true differences between our treatment and control groups. Our low sample size (n=11) led to an unsuccessful randomization between groups, as participants in the treatment group were more likely to have late stage cancer (80% compared to just 17% in controls) and were more likely to be currently undergoing treatment (60% of subjects as compared to zero in controls). While this low sample size also left us underpowered to statistically test our outcome measures, the information gleaned from this pilot study, taken in context with previous work exploring PA in lung cancer survivors, provides valuable information about the feasibility and potential successes of this type of intervention.

Similar to other studies [26-29], our enrollment rate is indicative of the distinct challenges associated with recruiting lung cancer survivors for participation in an exercise intervention. Less than 7% (n=13) of all eligible subjects assessed for participation (n=187) were willing to participate in this study. Of those that were eligible and chose not to participate (n=155), almost half of these subjects (46%) considered themselves too ill to participate, 39% were not willing to travel to the clinic twice a week due to their geographic location, and 15% refused due to a lack of interest. Previous work in recruiting lung cancer survivors for participation in an exercise intervention have found a much smaller percentage of their population eligible for study (10% [26], 27% [28], 26% [27]) when compared to our eligibility rate of 66%, though this is likely due to these studies including geographical location/inability to travel as part of their exclusion criteria. As 50%-61% of those determined to be ineligible in those studies were due to geographic location, this is fairly similar to that of our population. Our findings suggest that future studies may want to consider recruiting only those with earlier stage disease, while also attempting to limit the travel burden associated with participation.

Interestingly, while we had substantial difficulty in recruiting participants for this study, the retention, adherence, compliance and safety rates suggest that the feasibility of this intervention, once enrolled, appears promising. As noted in the results, we retained 83% of our study sample. Further, adherence rates for the intervention were notable, as participants attended 83% of all in-clinic exercise sessions, with 80%

meeting the 150 min/wk PA goal. These observations are quite consistent with the few comparable studies testing exercise interventions in lung cancer survivors [26-29]. In a study by Jones et al [28], using a single group design (n=19) to test the feasibility and safety of a 14-week supervised exercise intervention in a sample of lung cancer survivors, they observed a retention rate of 95% and a very similar adherence rate of 85%. Another study utilizing a supervised exercise intervention in a sample of 23 late-stage lung cancer survivors retained 79% of participants and found an overall adherence rate of 73% [27]. Peddle-McIntyre et al [26] evaluated the feasibility of a ten-week resistance training program in lung cancer survivors (n=17). Again, retention and adherence rates paralleled our study (88% and 82%, respectively). Finally, in the most recent and largest study to date, Quist et al [29] utilized a six-week group exercise intervention to evaluate a series of HQOL outcomes. While lower than ours, their observed rates of retention and adherence (62% and 68%, respectively) were found in a much larger sample (n=114) than all previous studies. Also of note, our study had no reported injuries or adverse events. This was also true for three of the four previously reported studies [27-29], with one study [26] reporting three minor events that were all successfully resolved. As such, our findings continue to suggest that an exercise intervention appears to be a safe and feasible option for lung cancer survivors.

Unique to our study was our finding regarding at-home exercise program adherence. In the only study discussed previously to utilize an at-home training component in their intervention, Quist et al suggest that home training may not be a valid option for this population, as only 2 of their 29 subjects performed any at-home training [27]. When participants in that study were queried as to the reason for the low adherence, lack of self-discipline and doubts about exercise yielding any benefits were commonly given. Conversely, four of the five participants in our study completed the at-home training portion of the intervention per instruction, while the individual that did not still completed ~80% of home-based exercise. As most participants (n=4) were able to identify a support person to go through the exercise intervention with them, it is possible that the support person offered encouragement to combat the potential barriers observed in the Quist et al study. These findings suggest that having participants identify support persons to perform at-home exercise with may be necessary to improve at-home exercise adherence rates in lung cancer survivors.

As we were unable to test the statistical significance of any intervention effects on our outcomes due to our sample size, we utilized ES to evaluate the potential effects in an appropriately powered study. Although there were variable results, the ES calculated suggests that there are potential adverse effects of our treatment on specific biomarkers. We saw a negligible or negative effect of our treatment in most inflammatory markers (IL-8, IL-10, and TNF-α), and in our marker of oxidative stress, 8-OHdG. While these findings are somewhat alarming, suggesting that our treatment generally worsened the majority of these objective outcomes in this population, this may be a function of our rather unsuccessful randomization. The subjects in our treatment group had later stage disease and more of them were currently undergoing treatment than those in the control group. Further, as 60% of our treatment group expired either during or shortly after the completion of this study, it is expected that their health was worse near the end of the study (post-test scores) as compared to that of the beginning of the study (pre-test scores). Scores on the FACT-L lung cancer subscale (LCS), which have been used as a stand-alone indicator of clinical status [41], add weight to this theory, as subjects in the control group increased LCS scores, on average, from pre-test to post-test (1.1 points) whereas those in the treatment group had an average decrease in LCS scores (0.8 points). Consequently, although we think our findings are the result of a sicker treatment group, it must also be considered that exercise was detrimental to health in this sample.

In regards to our HQOL scores, we failed to see an improvement in FACT-L total scores from pre-test to post-test in our treatment group, which is similar to previous findings in studies evaluating exercise interventions in lung cancer survivors [26, 27, 29, 46]. The emotional- and social well-being score was principally responsible for the drop in scores, as there was a 1.2 and 3.8 point decrease, respectively, between pre- and post-testing, also similar to previous work [27-29, 46]. Of note, we observed higher scores on the FACT-L at baseline than that of other lung cancer survivors in previous studies. In a study conducted by Iyer et al (2013), a nationwide cohort of 450 lung cancer survivors reported a mean FACT-L total score of 71.7, which is more than 30 points lower than the baseline scores for our sample (105.7 (± 10.4)). Interestingly, as in our study, other studies evaluating exercise interventions and its effect on HQOL reported higher baseline FACT-L scores than that of the larger lung cancer survivor population, including pre-test scores of 91.7 (±16.7) [27], 94.9 (±12.6) [26], 97.0 (±23) [28], and 103.4 (±14.9) [46]. One of the possible reasons for the lack of improvement in HQOL over time could be due to these high baseline scores, which are suggestive of ceiling effects. While subjects reported a high overall HQOL, it should be noted that the mean scores on the (LCS) at both pre- and post-test time points (21.6 (±2.3), 21.8 (±4.2), respectively) were below the cut point of 24, which is indicative of the presence of clinical symptoms [47]. This suggests that, even while experiencing clinical symptoms and having a potentially poor prognosis, lung cancer survivors enrolling in an exercise program still report a relatively high HQOL.

In regards to exercise capacity, we saw a large improvement in our controls (+0.25 m/sec) as compared to a small improvement in our treatment group (+0.04 m/sec). The improvement in our treatment group is fairly consistent with other exercise interventions used in this population. Temel et al [46] found a non-statistically significant 0.07 m/sec increase in gate speed from baseline to post-test, whereas Quist et al [27] found a 0.10 m/sec increase. When explaining the larger improvement in the control group versus our treatment group, we can once more likely point to the difference in these groups at baseline. In a 2009 study, Kasymjanova et al [48] found that lung cancer patients with advanced disease or receiving chemotherapy had significantly lowered exercise capacity. Specifically, after just two cycles of chemotherapy, subjects walked, on average, 0.11 m/sec less than they did at baseline. Jones et al [28] also reported a non-significant increase in exercise capacity ($VO_{2\ peak}$) in lung cancer survivors post exercise intervention, but found that those improvements were largely limited to those not currently receiving chemotherapy. As such, our findings suggest that our intervention may have helped to maintain levels of functional capacity in these individuals dealing with the health challenges associated with ongoing treatment and late stage disease.

There are a number of strengths and limitations to this pilot study that warrant discussion. As lung cancer survivors are an understudied population with regards to exercise, this work lends insight into the potential barriers of recruitment to, as well as the feasibility and safety of, an exercise intervention in this population. While underpowered to detect significant differences, this study used a series of validated and reliable outcome measures which allow for comparisons with other work. Our main limitation in this study was our small sample size. As such, while randomized, our treatment groups were non-comparable at baseline and the study was underpowered to show statistical differences between groups, making interpretation of this data challenging. More work with larger sample sizes is needed to elucidate true relationships between exercise and health outcomes, including markers of prognosis and HQOL. Further, while our results point to the potential feasibility of an exercise intervention for use in this clinical population, it is important to note that the difficulty in recruitment, as well as the particular treatment being studied, suggests that selection bias is likely. When considering the very low number of survivors that were successfully enrolled in this study, it presents a unique subgroup of lung cancer survivors that were both healthy enough and motivated to join and participate in an exercise program, such that this work may not be generalizable to the greater population of lung cancer survivors. As survivors were instructed to identify a support person to participate in the exercise program with them, it is possible that the success rate, as measured by adherence, was influenced by this support person. Also, at-home adherence rates were measured by self-reported PA logs, potentially leading to potential measurement error. Finally, all exercise sessions were led by the researchers that conducted pre- and post-testing, leading to the potential for investigator bias.

In conclusion, this pilot study found that recruitment of lung cancer survivors for an exercise intervention was challenging, suggesting that this type of intervention may not be palatable to those lung cancer survivors who consider themselves to be too sick or the travel burden to be too great. However, in those individuals interested in exercise programming and considered well enough to participate in it, exercise training appears to be safe and feasible in this population. The great majority of our sample was compliant with the intervention and was able to meet PA recommendations of 150 minutes of moderate-intensity PA per week. Both supervised in-clinic sessions, as well as at-home exercise, appear to be good options for survivors. In particular, our at-home compliance, better than seen in previous work, suggests that having survivors identify a support person to exercise with may improve program adherence. Due to our small sample size, and the imbalance of disease severity and current treatment in our study arms, we were unable to thoroughly evaluate the effectiveness of this intervention as it relates to biomarkers of prognosis, HQOL, and exercise capacity. Therefore, larger randomized trials focusing on testing the effectiveness of an exercise intervention on these same outcomes in lung cancer survivors is warranted.

Table 1: Characteristics of Lung Cancer Survivors (by group).

Characteristic		Total Sample (n=11)	Control Group (n=6)	Treatment Group (n=5)
Age		63.0 (±7.3)	62.7 (±9.5)	63.3 (±5.7)
Sex (percent female)		7 (63.6%)	3 (50%)	4 (80%)
Cancer Stage				
	I	2 (18.2%)	2 (33.3%)	0
	II	1 (9.1%)	1 (16.7%)	0
	III	3 (27.3%)	2 (33.3%)	1 (20%)
	IV	5 (45.5%)	1 (16.7%)	4 (80%)
Current Cancer Treatment (percent yes)		3 (27.3%)	0	3 (60%)
Number of Current Medications				
	0	1 (9.1%)	0	1 (20%)
	1-3	3 (27.3%)	2 (33.3%)	1 (20%)
	4-9	2 (18.2%)	2 (33.3%)	0
	10+	4 (36.4%)	2 (33.3%)	2 (40%)
Employment (percent currently employed)		4 (36.4%)	2 (33.3%)	2 (40%)
Education (highest level completed)				
	High School	1 (9.1%)	1 (16.7%)	0
	College	2 (18.2%)	1 (16.7%)	1 (20%)
	Graduate School	8 (72.7%)	4 (66.7%)	4 (80%)
Race				
	White	10 (90.9%)	6 (100%)	4 (80%)
	Pacific Islander	1 (9.1%)	0	1 (20%)
BMI		25.5 (±4.3)	25.3 (±4.5)	25.7 (±4.4)
Marital Status (percent married)		10 (90.9%)	6 (100%)	4 (80%)
Number of Comorbidities				
	1	1 (9.1%)	0	1 (20%)
	2	3 (27.3%)	1 (16.7%)	2 (40%)
	3	4 (36.4%)	3 (50%)	1 (20%)
	4+	3 (27.3%)	2 (33.3%)	1 (20%)

Mean (SD) presented for all data unless otherwise noted.

Table 2: Prognostic Biomarkers of Inflammation and Oxidative Stress in Lung Cancer Survivors (by group).

Biomarker	Control Group (n=6)		Treatment Group (n=5)	
	Pre-test	Post-test	Pre-test	Post-test
IL-6, $pg.mL^{-1}$	1.24 (±0.4)	1.33 (±0.5)	1.76 (±1.9)	1.65 (±1.3)
IL-8, $pg.mL^{-1}$	21.41 (±8.2)	22.39 (±5.1)	46.89 (±42.4)	54.28 (±61.3)
IL-10, $pg.mL^{-1}$	0.21 (±0.1)	0.25 (±0.1)	0.29 (±0.2)	0.21 (±0.1)
TNF-α, $pg.mL^{-1}$	1.92 (±0.2)	2.28 (±0.4)	2.07 (±0.4)	2.42 (±0.9)
hs-CRP, $mg.L^{-1}$	4.20 (±4.2)	4.53 (±5.3)	13.96 (±25.4)	7.14 (±8.1)
8-OHdG, $pg.mL^{-1}$	9.68 (±3.6)	8.32 (±2.5)	6.57 (±1.7)	7.62 (±1.1)

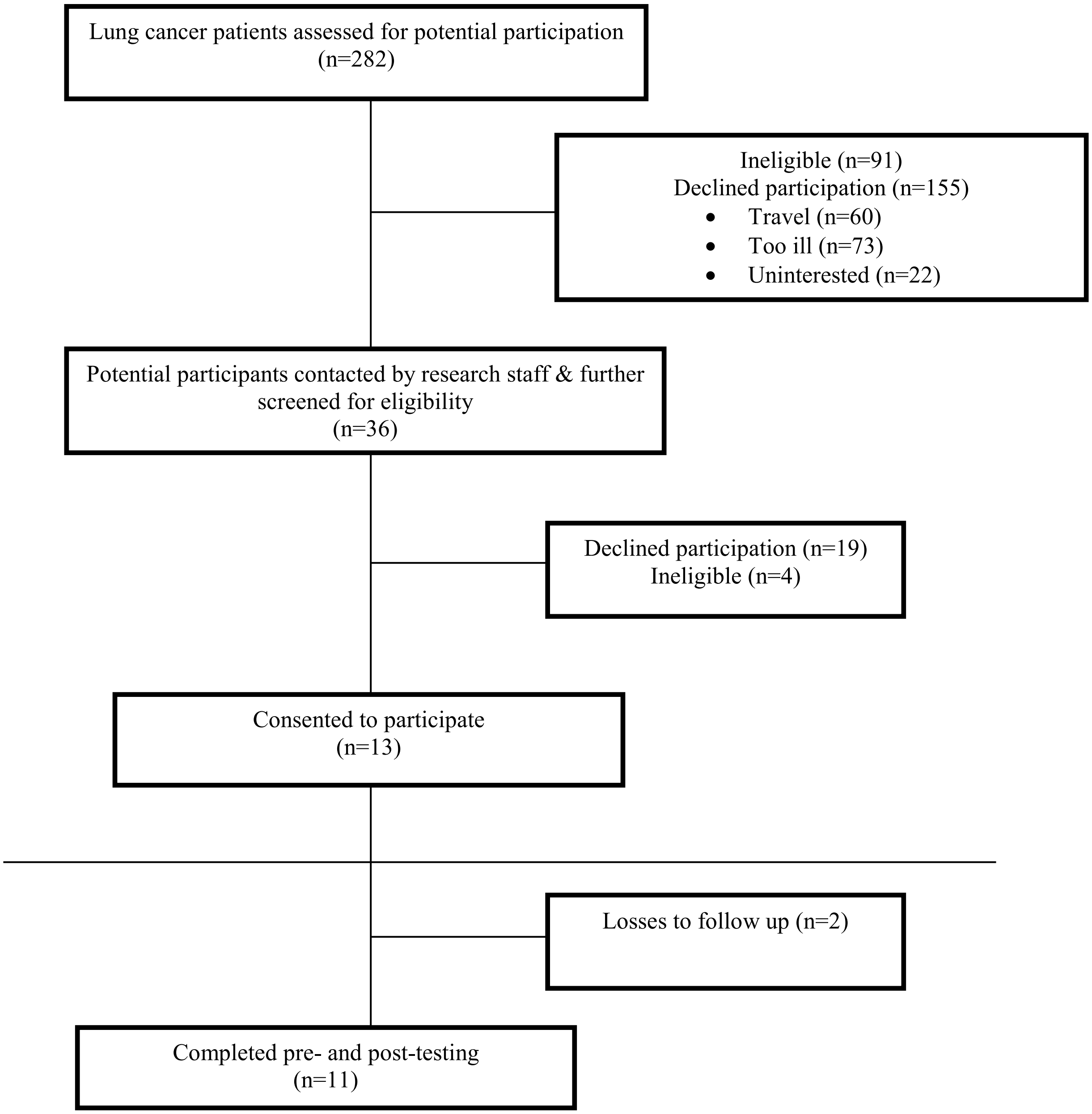
Mean scores (±SD) presented for total and all subscales.

Table 3: Health-related Quality of Life in Lung Cancer Survivors (by group).

FACT-L Subscale	Control Group (n=6)		Treatment Group (n=5)	
	Pre-test	Post-test	Pre-test	Post-test
Physical well-being	21.7 (±3.3)	21.2 (±4.1)	23.4 (±2.4)	23.6 (±2.9)
Social well-being	22.5 (±4.3)	23.7 (±2.3)	25.2 (±2.7)	21.4 (±2.1)
Emotional well-being	19.0 (±4.9)	19.3 (±2.7)	17.4 (±3.9)	16.2 (±4.3)
Functional well-being	19.7 (±2.3)	20.3 (±2.9)	19.8 (±4.3)	20.0 (±4.9)
Lung Cancer Subscale	22.5 (±1.2)	23.7 (±3.1)	20.4 (±2.9)	19.6 (±4.3)
FACT-L Total	105.3 (±8.6)	108.2 (±8.0)	106.2 (±13.3)	100.8 (±13.4)

Mean FACT-L scores (±SD) presented for total and all subscales.

Figure 1: Subject enrollment flow chart.



References

1. Altekruse Sf. SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/,based on November 2013 SEER data submission, posted to SEER website 2014.

2. American Cancer Society, Atlanta, GA. Cancer Facts and Figures; ACS, 2015.

3. Hewitt ME, Greenfield S, Stovall E. From cancer patient to cancer survivor: lost in transition: Natl Academy Pr; 2006.

4. Grant M, Sun V, Fujinami R, Sidhu R, Otis-Green S, Juarez G, et al. Family caregiver burden, skills preparedness, and quality of life in non-small cell lung cancer. Oncol Nurs Forum 2013;40(4):337-46.

5. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. J Pain Symptom Manage 2000;19(2):137-53.

6. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 2000;18(4):893-903.

7. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Medicine and science in sports and exercise 2000;32(9 Suppl):S498.

8. Cleeland CS. Measurement and prevalence of pain in cancer. Semin Oncol Nurs 1985;1(2):87-92.

9. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994;330(9):592-6.

10. Cleeland CS. Cancer-related symptoms. Semin Radiat Oncol 2000;10(3):175-90.

11. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. J Natl Cancer Inst Monogr 2007(37):16-21.

12. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Current Opinion in Psychiatry 2005;18(2):189.

13. Courneya KS. Physical activity in cancer survivors: a field in motion. Psychooncology 2009;18(4):337-42.

14. Thraen-Borowski KM, Trentham-Dietz A, Edwards DF, Koltyn KF, Colbert LH. Dose-response relationships between physical activity, social participation, and health-related quality of life in colorectal cancer survivors. J Cancer Surviv 2013;7(3):369-78.

15. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst 2012;104(11):815-40.

16. Il'yasova D, Colbert LH, Harris TB, Newman AB, Bauer DC, Satterfield S, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev 2005;14(10):2413-8.

17. O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. Br J Cancer 2001;85(4):473-83.

18. Shacter E, Weitzman S. Chronic Inflammation and Cancer. Oncology 2002;16(229):217-226.

19. Friedenreich CM, Neilson HK, Woolcott CG, Wang Q, Stanczyk FZ, McTiernan A, et al. Inflammatory marker changes in a yearlong randomized exercise intervention trial among postmenopausal women. Cancer Prev Res (Phila) 2012;5(1):98-108.

20. Poulsen HE, Prieme H, Loft S. Role of oxidative DNA damage in cancer initiation and promotion. Eur J Cancer Prev 1998;7(1):9-16.

21. Jones LW, Eves ND, Haykowsky M, Freedland SJ, Mackey JR. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. Lancet Oncol 2009;10(6):598-605.

22. Jones LW. Physical activity and lung cancer survivorship. Recent Results Cancer Res 2011;186:255-74.

23. Benzo R, Kelley GA, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: A meta-analysis. Respiratory medicine 2007;101(8):1790-1797.

24. Villani F, De Maria P, Busia A. Exercise testing as a predictor of surgical risk after pneumonectomy for bronchogenic carcinoma. Respiratory medicine 2003;97(12):1296-1298.

25. Travers J, Dudgeon DJ, Amjadi K, McBride I, Dillon K, Laveneziana P, et al. Mechanisms of exertional dyspnea in patients with cancer. J Appl Physiol (1985) 2008;104(1):57-66.

26. Peddle-McIntyre CJ, Bell G, Fenton D, McCargar L, Courneya KS. Feasibility and preliminary efficacy of progressive resistance exercise training in lung cancer survivors. Lung Cancer 2012;75(1):126-32.

27. Quist M, Rørth M, Langer S, Jones LW, Laursen JH, Pappot H, et al. Safety and feasibility of a combined exercise intervention for inoperable lung cancer patients undergoing chemotherapy: A pilot study. Lung Cancer 2012;75(2):203-208.

28. Jones LW, Eves ND, Peterson BL, Garst J, Crawford J, West MJ, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. Cancer 2008;113(12):3430-9.

29. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. Integrative cancer therapies 2015:1534735415572887.

30. Leach HJ, Devonish JA, Bebb DG, Krenz KA, Culos-Reed SN. Exercise preferences, levels and quality of life in lung cancer survivors. Supportive Care in Cancer 2015:1-9.

31. Paramanandam VS, Dunn V. Exercise for the management of cancer-related fatigue in lung cancer: a systematic review. European journal of cancer care 2015;24(1):4-14.

32. Arbane G, Tropman D, Jackson D, Garrod R. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. Lung Cancer 2011;71(2):229-34.

33. Wall LM. Changes in hope and power in lung cancer patients who exercise. Nurs Sci Q 2000;13(3):234-42.

34. Brocki BC, Andreasen J, Nielsen LR, Nekrasas V, Gorst-Rasmussen A, Westerdahl E. Short and long-term effects of supervised versus unsupervised exercise training on health-related quality of life and functional outcomes following lung cancer surgery - A randomized controlled trial. Lung Cancer 2014;83(1):102-8.

35. Hallal PC, Victora CG. Reliability and validity of the International Physical Activity Questionnaire (IPAQ). Med Sci Sports Exerc 2004;36(3):556.

36. Haskell WL, Lee I, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Medicine and science in sports and exercise 2007;39(8):1423.

37. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42(7):1409-26.

38. Borg G. An introduction to Borg's RPE-scale: Mouvement Publications; 1985.

39. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci 2011;48(4):155-70.

40. Shen J, Deininger P, Hunt JD, Zhao H. 8-Hydroxy-2'-deoxyguanosine (8-OH-dG) as a potential survival biomarker in patients with nonsmall-cell lung cancer. Cancer 2007;109(3):574-80.

41. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12(3):199-220.

42. Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T. Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. Journal of the American Geriatrics Society 2001;49(11):1544-1548.

43. Pettee GKK, Rankin RL, Lee C, Charlton ME, Swan PD, Ainsworth BE. Test-retest reliability and validity of the 400-meter walk test in healthy, middle-aged women. Journal of physical activity & health 2010;7(5):649.

44. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. Supportive Care in Cancer 2012;20(12):3169-3177.

45. Cohen J. Statistical power analysis for the behavioral sciences: Academic press; 2013.

46. Temel JS, Greer JA, Goldberg S, Vogel PD, Sullivan M, Pirl WF, et al. A structured exercise program for patients with advanced non-small cell lung cancer. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 2009;4(5):595.

47. Cella DF, Bonomi AE. Measuring quality of life: 1995 update. Oncology-Huntington 1995;9(11):47-60.

48. Kasymjanova G, Correa JA, Kreisman H, Dajczman E, Pepe C, Dobson S, Lajeunesse L, Sharma R, Small D. Prognostic value of the six-minute walk in advanced non-small cell lung cancer. J Thorac Oncol. 2009;4:602–607.

Manuscript

Impacts of Exercise on Health-related Quality of Life in Informal Caregivers of Lung Cancer Survivors: A Pilot Study

Keith M. Thraen-Borowski[1], Ronald Gangnon[2,3], Keith P. Gennuso[2], Amy Trentham-Dietz[2,4], Kelli F. Koltyn[1], Alex K. Adams[5], Lisa H. Colbert [1]
University of Wisconsin-Madison, Madison, WI

Affiliations:
[1]Department of Kinesiology, University of Wisconsin-Madison, Madison, WI
[2]Department of Population Health Sciences, University of Wisconsin-Madison, Madison, WI
[3]Department of Biostatistics and Medical Informatics, School of Medicine and Public Health University of Wisconsin-Madison, Madison, WI
[4]Paul P. Carbone Comprehensive Cancer Center, University of Wisconsin-Madison, Madison, WI
[5]Department of Family Medicine, University of Wisconsin-Madison, Madison, WI

Support for this research was provided by the Carbone Cancer Center, University of Wisconsin-Madison. This work is also supported in part by NIH/NCI P30 CA014520- UW Comprehensive Cancer Center Support

Corresponding Author:
Keith Thraen-Borowski, MS
Dept. of Kinesiology
University of Wisconsin
2000 Observatory Dr.
Madison, WI 53706
Ph: 608-262-1167
Fax: 608-262-1656
E-mail: thraenborows@wisc.edu

Abstract

Purpose*:* To determine the role of exercise in improving HQOL and exercise capacity in a sample of lung cancer survivor caregivers.

Methods**:** Lung cancer survivors were recruited for an 8-week exercise intervention in which they were to enlist a caregiver. For the current study, caregivers were randomized to an exercise or usual care arm as a dyad with the survivor. The intervention consisted of supervised, in-clinic exercise training 2 days/wk and a prescription for at-home exercise 3 days/wk, performed at moderate-intensity for 150 min/wk total. Subjects completed measures of exercise capacity (LDCW) and HQOL (SF-36) pre- and post-intervention. Descriptive statistics are reported along with effect sizes (Cohen's *d)*.

Results*:* Our sample of seven caregivers (n=4 treatment; n=3 control) had a mean age at baseline of 59.2 (± 7.6), 57.1% of which were female. Baseline mental HQOL scores (SF-36 MCS) were a clinically-relevant 5.1 points lower than the general population. The retention rate in our exercise group was 80%, as was our adherence rate (48/60 in-clinic sessions). ES of our treatment suggest that our intervention was unsuccessful (LDCW: *d*= 0.08; SF-36 MCS: *d*= -0.37; SF-36 PCS: *d*= 0.36).

Conclusions: Due to the challenges associated with lung cancer patients participating in exercise programs, our sample size was quite low, hindering our ability to examine training effects on HQOL and exercise capacity. Despite that, those randomized to the exercise group were compliant with the intervention, and were able to meet PA guidelines through the combination of an in-clinic and at-home intervention, suggesting exercise to be a safe and feasible option for caregivers of cancer survivors.

With over 14 million cancer survivors living today and over 1.6 million more individuals diagnosed each year, cancer clearly affects a considerable number of lives [1]. Due to the many potential challenges associated with being a cancer survivor, most cancer survivors will at some point require the support of an informal caregiver [2]. These caregivers, defined as unpaid loved ones who provide the survivor with physical and emotional care [3], are typically spouses/partners, significant others, family members, close friends or relatives, or next of kin [3, 4]. Demands placed on these individuals to meet the needs of the cancer survivor, including monitoring of treatment, treatment-related symptom management, assistance with personal and instrumental care, as well as other emotional, physical, financial, social and spiritual needs and support, can all lead to health consequences for the caregiver [5, 6]. Caregivers can experience increased levels of stress, diminished physical health, restrictions of activities, strain in marital and family relationships, economic burden, depressive symptoms, and poor mental health [7-14]. In fact, emotional distress experienced by the caregiver has been shown to be as high as, or even higher than, that of the cancer survivor themselves [11, 15]. All of these health challenges can have a detrimental effect on an individual's health- related quality of life (HQOL).

While a robust literature focusing on HQOL concerns in caregivers of cancer survivors has developed as of late, [5, 6, 8, 9, 15-20] few focus on the caregivers of lung cancer survivors [16, 21-25]. These caregivers certainly face many of the challenges discussed above, but may also face amplified or additional challenges specific to the diagnosis. Lung cancer patients usually experience a considerable degree of symptom burden, frequently experiencing multiple symptoms at once, including pain, dyspnea, and fatigue, which can be difficult to manage from the caregiver's perspective[26].As these patients may face serious physical and functional declines, caregivers are often helping with ambulation, moving or lifting patients, and assisting with nutritional needs and management [22]. Overwhelming psychological demands of caregiving, such as anxiety, depression, and other psychological distress, are common in these caregivers, often related to the fact that lung cancer is a disease with frequent recurrence in early stages and death in the later stages of the disease. In fact, caregivers of lung cancer survivors were shown to have a higher risk of depression and more psychiatric consultations than caregivers of patients with other cancers [27, 28]. Caregiving spouses of lung cancer patients have been shown to need to take more sick leave than spousal caregiver of other cancer types, which may correlate with higher physical and emotional burdens of care [21]. Further, it is important to note that distress brought on by challenges in one construct related to HQOL may compound challenges in other constructs [21]. Though the health of these caregivers may be greatly impacted by a loved one's cancer diagnosis, caregivers have received only minimal attention by most healthcare practitioners, as they are focused primarily upon the physical needs of the patient [22]. As such, it is essential that we not only better define the health burden experienced by these caregivers, but also identify potential modalities to ameliorate some of these health challenges that coincide with providing this care.

While there is a body of literature describing the challenges and associated decrements in HQOL in cancer survivor caregivers, little work has been done to evaluate potential interventions to mediate these challenges. Despite the potential benefits, few psychosocial and/or behavioral interventions to enhance caregivers HQOL have been developed [9]. As physical activity (PA) has been shown to potentially mediate HQOL challenges in a number of populations through enhancements in physical, functional, psychological, emotional and social well-being, it could serve as an appropriate intervention option for this group [29-32]; yet, there is very little evidence to show its effectiveness in this population. At this time, there have been very few studies evaluating PA and HQOL in caregivers of any type [33 34], and to date, there have been next to none designed to specifically evaluate this relationship in caregivers of cancer survivors [35]. As such, we addressed these knowledge gaps by conducting a pilot study to examine the potential role of PA, in the form of an exercise intervention, in improving HQOL and exercise capacity in a sample of caregivers of lung cancer survivors.

Methods

Overview & Study Design-This study consisted of an 8-week, randomized controlled trial of exercise, consisting of both aerobic and resistance training, in lung cancer caregivers. This study was part of a larger study we conducted examining the effect of PA in lung cancer survivors. That study, also using a randomized design, determined how an exercise intervention alters biomarkers of prognosis, exercise capacity, and HQOL in lung cancer survivors. The cancer survivors were to enlist a caregiver to go through the exercise intervention with them to increase exercise adherence rates. As such, for the current study, caregivers were randomized to the exercise intervention or usual care arm as a dyad with the lung cancer patient to whom they were offering support. Caregivers randomized to the usual care group did not receive any information or advice regarding their physical activity.

Subjects- Potential subjects were identified as a result of their participation in the larger study described above. Caregivers meeting eligibility criteria, which included being at least eighteen years old and having the ability to understand and read in English sufficiently to complete informed consent and to complete the questionnaires, were able to participate. Potential subjects were also screened for exclusion criteria, which included symptomatic heart disease, congestive heart failure or arrhythmia, documented myocardial infarction in the last three months, or any cognitive or reading impairment that would preclude them from completing questionnaires.

Protocol- Eligible subjects were enrolled at the University of Wisconsin-Madison Hospital from January 2014 – February 2015. All subjects signed the consent form at the pre-intervention visit with a member of the research team. Subjects provided information on their age, race, ethnicity, education, and comorbidities. Height and weight were directly measured by research staff and typical weekly PA levels were measured by the International Physical Activity Questionnaire-Long Form (IPAQ), a reliable and valid questionnaire frequently used to measure PA [36]. During this pre-intervention visit, subjects also completed a HQOL survey, as well as an exercise capacity test, described below, in order to measure the potential success of the intervention itself. These outcome measures were repeated at a post-intervention visit. All testing was administered by trained research staff.

Study Measures:

*HQOL- T*he Medical Outcomes Study Short-Form Health Survey (SF-36) [37] was used to evaluate HQOL. The SF-36 is a 36-item measure encompassing eight individual constructs: physical function, role limitations owing to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations as a result of emotional problems and mental health. Each of these subscales are scored on a scale of 0 -100, with 0 being the worst possible score [38]. These eight distinct domains were then summarized using the standard scoring method into two summary scores: the physical health component score (PCS) and the mental health component score (MCS) [39]. The SF-36 has been shown to be both reliable and valid for use in general populations as well as in those with specific conditions, including cardiac, pulmonary, orthopedic, and cancer [40-43].

Exercise Capacity- The Long Distance Corridor Walk (LDCW) is a two part test used to measure exercise capacity [44]. It consists of a self-paced two-minute walk, followed by a timed 400-m walk. Participants first completed the two-minute walk with the goal to cover as much ground as possible. After a one minute break, participants completed the 400-m walk. The goal for this test is to complete the walk in the shortest amount of time. This test, with results typically reported as meters walked per second on the 400-m walk, has been shown to be a valid and reliable performance-based measure of functional status in both middle-aged and older adults[45].

Intervention- The intervention was designed to mimic the current ACSM PA recommendations [46]. As such, it consisted of supervised exercise training two days per week and a prescription for at home exercise three days per week, totaling 150 minutes of moderate-intensity PA each week. Each exercise session was comprised of an aerobic training component and a resistance training component. All exercise sessions were performed at a moderate level of intensity as determined by the Borg Rating of Perceived Exertion Scale [47]. At the initial visit, individual consultations with the research assistant were used to tailor the intervention exercises to subjects. Aerobic training was done five days per week, 30 minutes per session, while resistance training was done two days per week, usually at the clinic visits. Specific exercises were avoided or adapted if the subject had preexisting conditions that required such actions. Activity logs were used by subjects to record their weekly exercise and, along with attendance at in-clinic sessions, were used to measure program adherence.

Aerobic Training - Subjects had their choice of walking, stationary cycling, or exercise videos vetted by research staff as their mode of aerobic exercise during the aerobic component of the intervention. The Borg Rating of Perceived Exertion Scale [47] was reported by subjects during the exercise session in order to judge intensity. Participants were asked to work at a rating of 12-16 (the 'somewhat hard' to 'hard' range). As all participants were physically able to complete 30 minutes of moderate-intensity activity from the first session, a progression period was not necessary. A five minute warm-up period and five minute-cool down period were used each session.

Resistance Training- Resistance bands with graded resistance were used for the strength training portion of the intervention. The following exercises were completed each session, as the program was designed to hit all the major muscle groups: chest press, seated row, upright row, triceps extension, bicep curls, squats, shoulder press, and calf raises. These eight exercises were done in two sets of 10 repetitions each. Resistance was added by advancing through the different bands as 10 repetitions became too easy to perform. Although the study was designed to have the subjects do their resistance training in the clinic, each subject received their own set of resistance bands and instructions on the eight exercises such that the exercises could be done at home in the case of missed clinic visits.

Analysis- Analyses were conducted using SPSS statistical software version 20 (IBM Corp.). Descriptive statistics were calculated and compared between the two groups (treatment vs. usual care) at baseline. As our sample size for this pilot study was quite small, we conducted a post-hoc power analysis and found that we were under powered to run a statistical analysis. Therefore, means and standard deviations (SD) for the pre- and post-tests for each treatment group were reported for the main analyses. To gauge the magnitude of potential mean differences, effect sizes (ES) for these analyses were calculated using Cohen's *d* with correction for positive bias [48]. Cohen's *d* is a standardized measure of ES and provides information on the amount of change from pre-test to post-test between treatment groups relative to the variation within the measure.

Results

Study Population- A total of eight caregivers were identified for participation by cancer survivors enrolled in the companion study. Of the eight participants randomized, one subject was unable to complete post-testing due to the cancer subject she was providing care for withdrawing from the study, leaving a final analytic sample of seven caregivers (n=4 treatment; n=3 control). The mean age of participants at baseline was 59.2 (±7.6) years, 57.1% of which were female, and 100% identified as white. Regarding the relationship of the caregiver to the cancer survivor, 86% of participants identified themselves as spouses. Baseline PA levels, as indicated by IPAQ scores, were 3849 (3198-4740) MET-min/wk (median (IQR)). Sample characteristics by treatment group are shown in Table 1.

HQOL- When evaluating mental HQOL using the MCS scores of the SF-36, subjects randomized to the treatment group had a mean score (±SD) of 44.3 (±15.8) on the pre-test and 46.5 (±12.6) on the post-test, whereas subjects in the control group had mean scores of 45.7 (±20.5) and 51.0 (±12.3), respectively. The ES regarding the change in score on the MCS between groups (*d*= -0.37) suggests a small, negative effect, as the mean change in controls (+2.3) was greater than that of the treatment group (+5.3). Individual subject pre- and post-test scores on the MCS can be found in Figure 1. When assessing physical HQOL scores as measured by the PCS, we found that subjects in the treatment group, on average, scored 59.5 (±5.8) on the pre-test and 59.6 (±4.5) on the post-test while participants in the control group scored, on average, 46.7 (±12.8) and 45.0 (±13.7), respectively. There was a small treatment effect (*d*=0.36) for the change score on the PCS, as the treatment group improved their scores while scores in the control group, on average, decreased form pre-test to post-test. Individual subject PCS scores are presented in Figure 2.

Means scores (±SD) of all eight of the SF-36 subscales (physical function, role limitations owing to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations as a result of emotional problems and mental health) are reported in Table 2. Vitality, bodily pain, physical function, and role-emotional subscale scores on the post-test improved in the treatment group when compared to the pre-test. Further, with the exception of the role-physical and social function subscales, the control group also scored higher on the post-test in every category compared to the pre-test.

Exercise Capacity-When evaluating the success of the intervention to improve exercise capacity, we found that subjects in both groups improved their scores on the LDCW from pre-test to post-test. The treatment group, on average, walked 1.71 (±0.06) m/sec on the pre-test, and 1.77 (±0.02) on the post-test, whereas the control group walked 1.19 (±0.59) m/sec and 1.24 (±0.36), respectively (data not shown). The difference in effect between the two groups was negligible (d= 0.08).

Program Compliance- Regarding our retention rate of the exercise intervention, 80% (n=4) of subjects completed the program and associated post-testing. Our overall adherence rate was 80%, as 48 of 60 potential in-clinic visits were completed by participants. According to PA logs recorded by subjects, three of the four subjects to complete the program met the PA recommendations of 150 minutes of moderate-intensity PA per week for the full eight week intervention. No injuries, falls, or accidents were reported during the intervention. All subjects in the control group (n=3) were retained and completed post-testing.

Discussion

This is the first study to evaluate the role of PA, specifically exercise, in improving HQOL in a group of lung cancer survivor caregivers. As this study was part of a larger study involving the recruitment of lung cancer survivors, our enrollment of caregivers to this study was predicated upon our success in enlisting lung cancer patients to participate in an exercise intervention. Due to the small size of our lung cancer study, the number of caregivers we enrolled (n=7) is quite low. Though the sample size accrued for this preliminary study has hindered our ability to show potential statistical differences in HQOL and exercise capacity between groups, these data have helped to better describe this population while also examining the feasibility of PA interventions in caregivers of cancer survivors.

While enrollment is not a great indicator of feasibility in this particular study, due to it being driven by the recruitment of lung cancer survivors, we can consider the study retention, adherence, compliance, and safety, all of which we found was quite good in this small sample. While there are no published adherence rates in the few previous PA studies in caregiver populations in which to compare these rates to, Swartz et al [49] conducted a study to determine the preferences of cancer survivor caregivers to stress-reduction programs. They found that of the eleven program choices offered, PA was overwhelmingly the first choice amongst caregivers (73%). When the sample was separated by gender, stress status, and tumor grade, these relationships held, with PA still remaining the first choice in stress reduction. Further, a qualitative study conducted by Anton et al [50] to explore cancer caregivers' perceptions of participation in a structured exercise program alongside the survivor that they care for found that exercise was viewed positively amongst caregivers. While over-reporting is likely with regards to our IPAQ data, it still suggests that this might be an active group that is able and willing to participate in PA. This information is vital in trying to find potential therapeutic modalities to lessen stress and improve HQOL in this population. As our study shows that an exercise intervention may be feasible in this group, it is imperative that more work with larger samples be conducted to detail the potential benefits in HQOL.

Demographically, our study population was similar to that of previous studies of cancer survivor caregivers, in that the majority of our sample was female (57%), had earned a college degree (57%), and identified themselves as spouses of the cancer survivors (86%) [2, 4, 11, 19]. Baseline IPAQ scores (3849 (3198-4740) MET-min/wk) suggest a highly active group, though, again, over-reporting on the IPAQ is likely. When comparing our baseline data with population-based norms [38] , our sample scored lower on the MCS (44.86 ±16.3) than that of the general US population (50.0 ±10.0), and specifically those aged 55-64 (51.71 ±10.3), which encompasses our participants' mean age [51]. Of note, the difference in HQOL score between our sample and that of the general population is considered to be "clinically relevant", previously defined by Ware et al to be a 5-10 point difference in SF-36 scores [51].

When looking across each individual subscale of the SF-36 in the whole sample, we found that mean baseline scores on six of the eight individual subscales were similar to the published age-based population norms [38]; however, the role-emotional and mental health subscales were considerably lower than the general US population. The mean role-emotional score among all participants was 39.2 (±22.2), as compared to the role-emotional scores for US adults between the ages of 55-64 of 49.8 (±10.7) [38]. Similarly, the mental health mean scores in our sample were 48.5 (±11.4) as compared to the population norm for 55-64 year olds (51.3 ±10.2) [38]. As lung cancer survivors typically have a very poor prognosis, with a five-year relative survival rate (all stages) of 17% [1], the health of the survivor that they were providing care for may have greatly influenced these scores. During palliative care periods, caregivers of cancer survivors have reported heightened levels of caregiving burden [52], greatly impacting psychological distress [52 53]. Further, caregivers have reported significant fluctuations in sleep patterns during this time [54], as well as an increase in risky health behaviors, such as smoking and alcohol use [55], all potentially leading to deficits in HQOL. This points to the potential deficits in HQOL experienced by this group and the need to identify ways to mediate these challenges.

As we were unable to test the statistical significance of any intervention effects on HQOL due to our sample size, we used ES to make some inferences regarding what might happen in an appropriately powered study. Our ES for each composite score suggest that our exercise intervention did not appear beneficial for mental HQOL (d= -0.37), but did, though modestly, for physical HQOL (d=0.36). In regards to only seeing a small effect in PCS scores observed in the treatment group, this can potentially be explained by the high PCS scores at baseline. These baseline scores in the treatment group were, on average, 9.5 points higher than the general population. In the cases of the physical function, role-physical, and bodily pain, ceiling effects were found (typically defined as 15% or more of respondents scoring 100 on a given subscale [56]), suggesting that there was little room for improvement in physical HQOL. Our MCS scores, however, suggest a deleterious effect of our treatment, though this is likely due to the wide range of scores observed in our small sample of controls. When evaluating exercise capacity using the LDCW, we found little effect (d=0.08), suggesting that the treatment didn't effect performance to a greater degree than that of the control group. Interestingly, the average gait speed at baseline on the LDCW was 1.48 (± 0.44) m/sec. This is lower than maximum gait speed values (1.93 (±0.36) m/sec for men in our age range and 1.77 (±0.25) m/sec for women in our age range) reported by Bohannon et al in a group of 230 healthy subjects [57]. It is possible that in a group already reporting high levels of PA, the 150 min/week of exercise and/or its moderate intensity was not enough to improve exercise capacity in this group. Alternatively, as the desire to participate in an exercise program appeared to be the deciding factor for most cancer survivors to enroll in our study, individuals randomized to the control group may have still participated in weekly exercise, thereby contaminating the control group.

There are several limitations to the current pilot study that must be considered. Our main limitation was the small sample size. As a result, this study was underpowered to detect changes in HQOL or exercise capacity and yielded a large range of scores on these metrics, thereby making interpretation of these data challenging. Future work needs to be conducted with a larger sample to better elucidate relationships between PA and HQOL outcomes. Another limitation of this study was the generalizability of our findings as participants were recruited by, and asked to participate with, the cancer survivor in whom they care for, such that it it is likely that these individuals may be considerably more motivated than caregivers not specifically asked to exercise by the survivor that they offer support to. Adherence of at-home sessions of the exercise intervention were measured by self-report, thereby potentially leading to measurement error. Finally, it should be noted that researchers leading the exercise sessions also collected all pre-test and post-test data, thereby leading to potential investigator bias.

There are several important strengths of this preliminary study, including being the first study to test an exercise intervention specifically for this population. While we were unable to test statistical differences, a randomized design allowed for preliminary work into evaluating the effectiveness of an exercise intervention on HQOL and exercise capacity in this group. Further, our valid measures of HQOL (SF-36) and exercise capacity (LDCW) allowed for comparison with other work and, in the case of the SF-36, population-based norms. Finally, our assessing the feasibility of an exercise program in this sample can lead to future work regarding the use of an exercise intervention in this population.

In conclusion, we found that exercise does appear to be a feasible intervention in caregivers of lung cancer survivors. In general, the recruitment of this specific population was difficult due to the related barriers of recruiting lung cancer patients to an exercise intervention. Despite that, those randomized to the exercise group were compliant with the exercise intervention, and were able to meet the current PA guidelines through the combination of an in-clinic and at-home intervention. The wide range of baseline HQOL scores is indicative of specific caregiving needs associated with lung cancer survivors. As we were unable to show that our intervention was effective at improving HQOL scores compared to those randomized to a control group due to our small sample size, future work should be dedicated to further elucidation of this relationship.

Table 1: Characteristics of Support Persons of Lung Cancer Survivors (by group).

Characteristic	Total Sample (n=7)	Control Group (n=3)	Treatment Group (n=4)
Age	59.2 (±7.6)	64.5 (±5.5)	55.3 (±6.8)
Sex (percent female)	4 (57.1%)	2 (66.7%)	2 (50%)
Relation to cancer survivor			

Spouse	6 (85.7%)	3 (100%)	3 (66.6%)
Son/Daughter	1 (14.3%)	0	1 (33.3%)
Employment (percent currently employed)	3 (42.9%)	1 (33%)	2 (50%)
Education (highest level completed)			
High School	3 (42.9%)	2 (66.7%)	1 (25%)
College	4 (57.1%)	1 (33.3%)	3 (75%)
Race (percent white)	7 (100%)	3 (100%)	4 (100%)
BMI	26.4 (±4.9)	24.0 (±5.6)	28.3 (±4.2)
Marital Status (percent married)	6 (85.7%)	3 (100%)	3 (75%)
Number of Comorbidities			
0	2 (28.6%)	0	2 (50%)
1	1 (14.3%)	1 (33.3%)	0
2	2 (28.6%)	1 (33.3%)	1 (25%)
3+	2 (28.6%)	1 (33.3%)	1 (25%)

Median (IQR) reported for Typical PA level. Mean (SD) presented for all other data unless otherwise noted.

Table 2: Health-related Quality of Life in Support Persons of Lung Cancer Survivors (by group).

SF-36 Subscale	Control Group (n=3)		Treatment Group (n=4)	
	Pre-test	Post-test	Pre-test	Post-test
MCS	45.7 (±20.5)	51.0 (±12.3)	44.3 (±15.8)	46.5 (±12.6)
PCS	46.7 (±12.8)	45.0 (±13.7)	59.5 (±5.8)	59.6 (±4.5)
Vitality	49.2 (±3.8)	52.5 (±13.8)	51.5 (±9.7)	55.2 (±10.9)
Bodily Pain	43.8 (±7.9)	48.7 (±9.0)	55.5 (±8.5)	56.6 (±8.5)
Physical Function	45.1 (±13.4)	47.21 (±15.2)	55.4 (±2.0)	56.5 (±1.1)
Role-physical	40.5 (±15.0)	37.3 (±17.0)	56.9 (±0.1)	56.9 (±0.1)
Role-emotional	32.6 (±23.3)	45.5 (±9.0)	44.3 (±23.3)	48.1 (±15.5)
Social Function	51.4 (±9.4)	47.8 (±8.3)	52.8 (±8.2)	52.8 (±5.2)
Mental Health	50.6 (±15.6)	52.1 (±13.0)	47.3 (±9.7)	47.2 (±5.4)
General Health	52.8 (±9.0)	53.6 (±7.3)	55.0 (±7.9)	54.4 (±10.1)

Mean SF-36 scores (±SD) presented for all subscales and both composite scores.

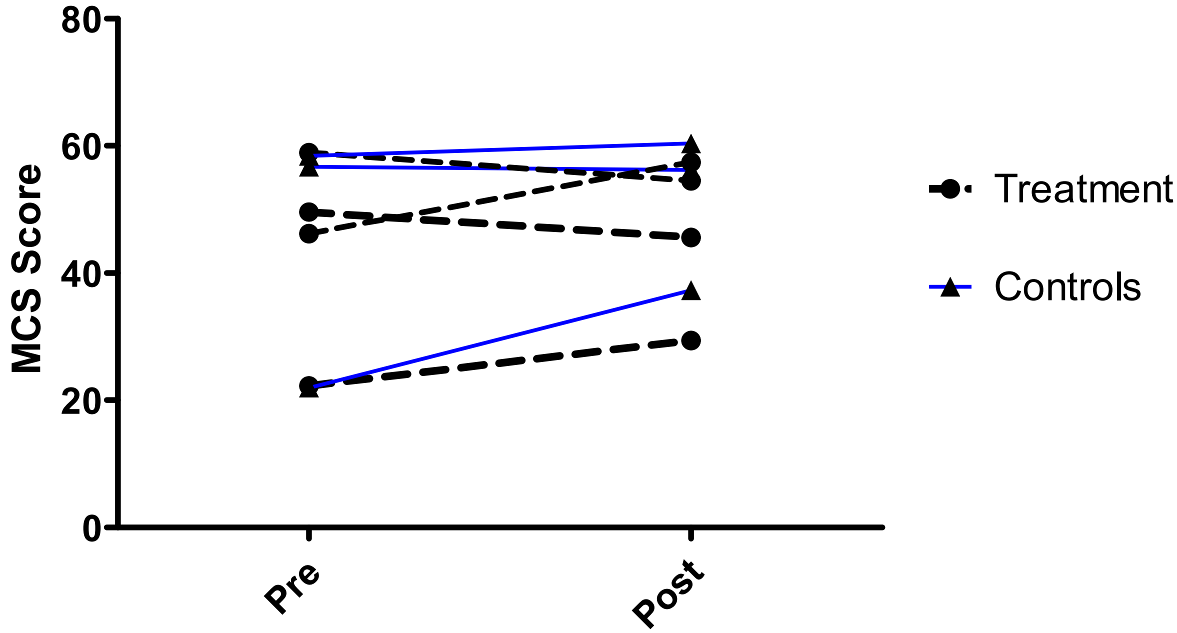


Figure 1: Individual subject pre-test and post-test scores on the MCS.

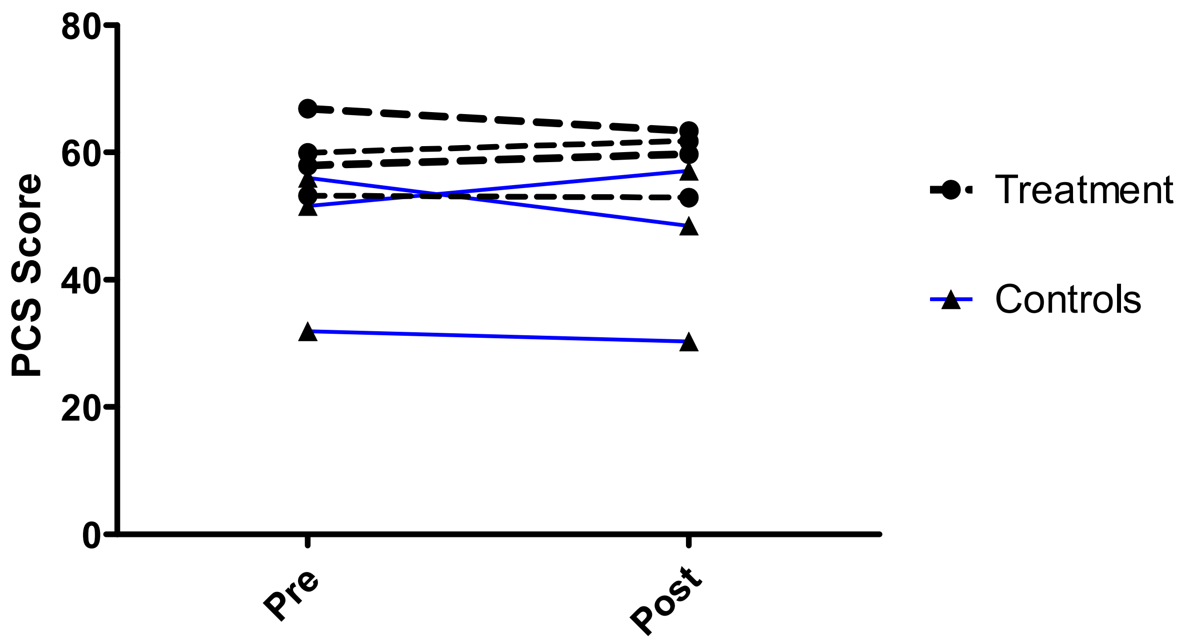


Figure 2: Individual subject pre-test and post-test scores on the PCS.

References

1. American Cancer Society. Cancer Facts and Figures, 2015. Atlanta, GA: ACS.; 2015.

2. Schumacher KL, Stewart BJ, Archbold PG, Caparro M, Mutale F, Agrawal S. Effects of caregiving demand, mutuality, and preparedness on family caregiver outcomes during cancer treatment. Oncol Nurs Forum 2008;35(1):49-56.

3. American Cancer Society: Being a Caregiver. http://www.cancer.org/treatment/caregivers/caregiving/index;2013.

4. Valeberg BT, Grov EK. Symptoms in the cancer patient: of importance for their caregivers' quality of life and mental health? Eur J Oncol Nurs 2013;17(1):46-51.

5. Given BA, Given CW, Kozachik S. Family support in advanced cancer. CA Cancer J Clin 2001;51(4):213-31.

6. Li QP, Mak YW, Loke AY. Spouses' experience of caregiving for cancer patients: a literature review. Int Nurs Rev 2013;60(2):178-87.

7. Kim Y, Duberstein PR, Sörensen S, Larson MR. Levels of depressive symptoms in spouses of people with lung cancer: effects of personality, social support, and caregiving burden. Psychosomatics 2005;46(2):123-30.

8. Kim Y, Given BA. Quality of life of family caregivers of cancer survivors. Cancer 2008;112(S11):2556-2568.

9. Kim Y, Given BA. Quality of life of family caregivers of cancer survivors: across the trajectory of the illness. Cancer 2008;112(11 Suppl):2556-68.

10. Fitzell A, Pakenham KI. Application of a stress and coping model to positive and negative adjustment outcomes in colorectal cancer caregiving. Psychooncology 2010;19(11):1171-8.

11. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. Psychol Bull 2008;134(1):1-30.

12. Matthews BA, Baker F, Spillers RL. Oncology professionals and patient requests for cancer support services. Support Care Cancer 2004;12(10):731-8.

13. Matthews JT, Dunbar-Jacob J, Sereika S, Schulz R, McDowell BJ. Preventive health practices: comparison of family caregivers 50 and older. J Gerontol Nurs 2004;30(2):46-54.

14. Perz J, Ussher JM, Butow P, Wain G. Gender differences in cancer carer psychological distress: an analysis of moderators and mediators. Eur J Cancer Care (Engl) 2011;20(5):610-9.

15. Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. CA Cancer J Clin 2010;60(5):317-39.

16. Braun M, Mikulincer M, Rydall A, Walsh A, Rodin G. Hidden morbidity in cancer: spouse caregivers. J Clin Oncol 2007;25(30):4829-34.

17. Li Q, Loke AY. A spectrum of hidden morbidities among spousal caregivers for patients with cancer, and differences between the genders: a review of the literature. Eur J Oncol Nurs 2013;17(5):578-87.

18. Mellon S, Northouse LL, Weiss LK. A population-based study of the quality of life of cancer survivors and their family caregivers. Cancer nursing 2006;29(2):120-131.

19. Humpel N, Magee C, Jones SC. The impact of a cancer diagnosis on the health behaviors of cancer survivors and their family and friends. Supportive care in cancer 2007;15(6):621-630.

20. Chen ML, Chu L, Chen HC. Impact of cancer patients' quality of life on that of spouse caregivers. Support Care Cancer 2004;12(7):469-75.

21. Fujinami R, Otis-Green S, Klein L, Sidhu R, Ferrell B. Quality of life of family caregivers and challenges faced in caring for patients with lung cancer. Clin J Oncol Nurs 2012;16(6):E210-20.

22. Grant M, Sun V, Fujinami R, Sidhu R, Otis-Green S, Juarez G, et al. Family caregiver burden, skills preparedness, and quality of life in non-small cell lung cancer. Oncol Nurs Forum 2013;40(4):337-46.

23. Milbury K, Badr H, Fossella F, Pisters KM, Carmack CL. Longitudinal associations between caregiver burden and patient and spouse distress in couples coping with lung cancer. Support Care Cancer 2013;21(9):2371-9.

24. Ostlund U, Wennman-Larsen A, Persson C, Gustavsson P, Wengström Y. Mental health in significant others of patients dying from lung cancer. Psychooncology 2010;19(1):29-37.

25. Siminoff LA, Wilson-Genderson M, Baker S, Jr. Depressive symptoms in lung cancer patients and their family caregivers and the influence of family environment. Psychooncology 2010;19(12):1285-93.

26. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. J Pain Symptom Manage 2000;19(2):137-53.

27. Akechi T, Akizuki N, Okamura M, Shimizu K, Oba A, Ito T, et al. Psychological distress experienced by families of cancer patients: preliminary findings from psychiatric consultation of a Cancer Center Hospital. Jpn J Clin Oncol 2006;36(5):329-32.

28. Rhee YS, Yun YH, Park S, Shin DO, Lee KM, Yoo HJ, et al. Depression in family caregivers of cancer patients: the feeling of burden as a predictor of depression. J Clin Oncol 2008;26(36):5890-5.

29. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Current Opinion in Psychiatry 2005;18(2):189.

30. Courneya KS, Friedenreich CM. Physical exercise and quality of life following cancer diagnosis: a literature review. Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine 1999;21(2):171-179.

31. Courneya KSCKS, Karvinen KHKKH. Exercise, aging, and cancer. Applied Physiology, Nutrition, and Metabolism 2007;32(6):1001-1007.

32. Thraen-Borowski KM, Trentham-Dietz A, Edwards DF, Koltyn KF, Colbert LH. Dose-response relationships between physical activity, social participation, and health-related quality of life in colorectal cancer survivors. J Cancer Surviv 2013;7(3):369-78.

33. King AC, Baumann K, O'Sullivan P, Wilcox S, Castro C. Effects of Moderate-Intensity Exercise on Physiological, Behavioral, and Emotional Responses to Family Caregiving A Randomized Controlled Trial. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2002;57(1):M26-M36.

34. Fleming A, Cook KF, Nelson ND, Lai EC. Proxy reports in Parkinson's disease: caregiver and patient self-reports of quality of life and physical activity. Mov Disord 2005;20(11):1462-8.

35. Stoutenberg M, Sogor A, Arheart K, Cutrono SE, Kornfeld J. A Wellness Program for Cancer Survivors and Caregivers: Developing an Integrative Pilot Program with Exercise, Nutrition, and Complementary Medicine. Journal of Cancer Education 2015:1-8.

36. Hallal PC, Victora CG. Reliability and validity of the International Physical Activity Questionnaire (IPAQ). Med Sci Sports Exerc 2004;36(3):556.

37. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide: The Health Institute, New England Medical Center; 1993.

38. Ware JE, Kosinski M, Keller S. SF-36 physical and mental health summary scales: a user's manual: Health Assessment Lab.; 1994.

39. Ware JE. User's manual for the SF-36v2 health survey: Quality Metric; 2007.

40. Reulen RC, Zeegers MP, Jenkinson C, Lancashire ER, Winter DL, Jenney ME, et al. The use of the SF-36 questionnaire in adult survivors of childhood cancer: evaluation of data quality, score reliability, and scaling assumptions. Health and quality of life outcomes 2006;4(1):77.

41. Mosconi P, Cifani S, Crispino S, Fossati R, Apolone G. The performance of SF-36 health survey in patients with laryngeal cancer. Head and Neck Cancer Italian Working Group. Head & neck 2000;22(2):175-182.

42. Perkins AJ, Stump TE, Monahan PO, McHorney CA. Assessment of differential item functioning for demographic comparisons in the MOS SF-36 health survey. Quality of life research 2006;15(3):331-348.

43. Pinar R. Reliability and construct validity of the SF-36 in Turkish cancer patients. Quality of life research 2005;14(1):259-264.

44. Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T. Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. Journal of the American Geriatrics Society 2001;49(11):1544-1548.

45. Pettee GKK, Rankin RL, Lee C, Charlton ME, Swan PD, Ainsworth BE. Test-retest reliability and validity of the 400-meter walk test in healthy, middle-aged women. Journal of physical activity & health 2010;7(5):649.

46. Haskell WL, Lee I, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Medicine and science in sports and exercise 2007;39(8):1423.

47. Borg G. An introduction to Borg's RPE-scale: Mouvement Publications; 1985.

48. Cohen J. Statistical power analysis for the behavioral sciences: Academic press; 2013.

49. Swartz JJ, Keir ST. Program preferences to reduce stress in caregivers of patients with brain tumors. Clinical Journal of Oncology Nursing 2007;11(5):723-727.

50. Anton PM, Partridge JA, Morrissy MJ. Cancer caregivers' perceptions of an exercise and nutrition program. Supportive Care in Cancer 2013;21(3):803-810.

51. Ware JE. SF-36 health survey update. The use of psychological testing for treatment planning and outcomes assessment 2004;3:693-718.

52. Grunfeld E, Coyle D, Whelan T, Clinch J, Reyno L, Earle CC, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. CMAJ 2004;170(12):1795-801.

53. Raveis VH, Karus DG, Siegel K. Correlates of depressive symptomatology among adult daughter caregivers of a parent with cancer. In: Cancer. United States; 1998. p. 1652-63.

54. Carter PA. Caregivers' descriptions of sleep changes and depressive symptoms. Oncol Nurs Forum 2002;29(9):1277-83.

55. Beach SR, Schulz R, Yee JL, Jackson S. Negative and positive health effects of caring for a disabled spouse: longitudinal findings from the caregiver health effects study. Psychol Aging 2000;15(2):259-71.

56. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Medical care 1995;33(4 Suppl):AS264-79.

57. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. Age Ageing 1997;26(1):15-9.

Chapter V: Summary and Conclusions

This dissertation, when viewed as a whole, was designed to further our understanding of the role of PA in cancer survivorship. Three individual studies were intended to answer questions regarding the relationship between PA and a series of health outcomes in understudied populations related to cancer survivorship. Specifically, these studies evaluated the PA behaviors and their relationship to HQOL in a cohort of NA cancer survivors, the effect of exercise on measures of prognosis and HQOL in a group of lung cancer survivors, and the effect of exercise in improving HQOL in the caregivers of these lung cancer survivors. This chapter will summarize the findings of this project, offer some greater themes of this collective work, and discuss potential future directions.

The first study, entitled "Physical Activity Behaviors and Associated Health-related Quality of Life in Native American Cancer Survivors", was the first study conducted to evaluate PA in NA cancer survivors. As great health disparities exist between NA and both whites and other non-white minorities, including cancer-related outcomes, we felt that this could greatly add to the cancer survivorship literature. Thus, we conducted a cross-sectional analysis of a national sample of NA cancer survivors, describing the PA behaviors of this population and evaluating the associations of PA with HQOL. Specifically, we examined the relationship between meeting PA guidelines and HQOL, and evaluated if the particular intensity or type of PA was of importance regarding this association.

While our main finding suggested that there was not a significant relationship between meeting PA guidelines and HQOL, nor, with the exception of physical function, was accumulating amounts of PA of varying intensities and types associated with higher HQOL constructs, we were encouraged by the findings regarding the PA behaviors in this group. Our study suggests that a large percentage of these NA cancer survivors were sufficiently active enough to meet PA guidelines, though over-reporting of PA must be considered. Further, of the typical PA participated in by these survivors, walking and housework were the most common activities. This group also tended to participate more in non-NA specific PA than in traditional NA-specific PA, though they did participate in roughly the same amount of non-exercise PA as planned exercise. As this is the first study to evaluate these behaviors, this information may be helpful in designing future PA interventions for this population.

The second study in this project, “Impacts of Exercise on Prognostic Biomarkers, Health-related Quality of Life, and Exercise Capacity in Lung Cancer Patients: A Pilot Study” again dealt with an understudied population with regard to PA. As it is one of the very few randomized control trials to evaluate an exercise intervention and its relationship with health outcomes in lung cancer survivors, we aimed to assess the feasibility of exercise programming in this population, while also identifying potential effects of an exercise intervention on inflammatory and oxidative stress markers, exercise capacity, and HQOL.

Here, our main finding was actually the great difficulty involved in recruiting and enrolling lung cancer survivors to participate in an exercise program. As fewer than 7% of eligible subjects actually participated in this study, it suggests that this type of intervention may not be palatable to all lung cancer survivors. Specifically, a great deal of potential participants considered themselves to be too sick or the travel burden to be too great to participate. However, there were individuals that were quite interested in starting an exercise program and, regardless of actual prognosis and current treatment regimen, did consider themselves well enough to participate. In those individuals, exercise training appears to be safe and feasible. Further, the vast majority of our sample was compliant with the intervention and was able to meet PA recommendations of 150 minutes of moderate-intensity PA per week. We also concluded that supervised in-clinic sessions, as well as at-home exercise, appear to be good options for survivors. As previous work suggested at-home exercise programs were not feasible due to extremely low adherence rates, our inclusion of a support person may have influenced the high at-home adherence rates observed in our study and should be considered when implementing future at-home programs. As many lung cancer survivors are not willing to participate in structured exercise interventions due to travel to the clinic, this finding that at-home exercise programs are feasible in this population suggests that an at-home exercise intervention with a support person and minimal clinic visits may be a promising intervention design. Unfortunately, we were unable to truly evaluate the effectiveness of this intervention on our main outcomes of interest, as our small sample size left us underpowered to test treatment effects and additionally resulted in ineffectual randomization with greater disease severity and more prevalent current cancer treatment in the exercise group. While biomarkers of prognosis, HQOL, and exercise capacity were initially the primary aims of this study, the findings regarding barriers to recruitment and the feasibility of exercise programming are a beneficial addition to the cancer survivorship literature promoting PA in this population.

The third study in this series of work, entitled “Impacts of Exercise on HQOL in Informal Caregivers of Lung Cancer Survivors: A Pilot Study” again deals with a population that, while often studied in regards to other behaviors and treatments, has been infrequently so in the context of PA. This study was developed out of our lung cancer study. Specifically, as we were hoping to increase the adherence rates of the at-home portion of our exercise intervention in lung cancer survivors, we asked these survivors to enlist a caregiver to participate in the study with them. After an extensive literature review of informal caregivers, it became clear that informal caregivers of cancer survivors, especially those of lung cancer survivors, were suffering from their own set of unique HQOL challenges, including potentially worse emotional HQOL than the cancer survivors themselves. Yet, there was very little work dedicated to trying to mediate these conditions through the use of PA. As such, we conducted a randomized trial of exercise on HQOL and exercise capacity in a sample of caregivers of lung cancer survivors.

In this study, we again found that exercise appears to be a feasible intervention in caregivers of lung cancer survivors. Those in the exercise group were compliant with the exercise intervention, and were able to meet the current PA guidelines through the combination of an in-clinic and at-home intervention. Regrettably, the recruitment of lung cancer survivors, as discussed above, was quite difficult, leaving us with a very small sample size of caregivers. As such, we were unable to show that our intervention was successful at improving HQOL scores compared to those randomized to a control group. This work, however, is still encouraging in that it appears as though exercise may still be an attractive and feasible option to mediate HQOL concerns in this population.

When considering these three distinctive studies collectively as one project, a few global conclusions present themselves. Overall, this project adds to the already robust literature suggesting that PA, specifically moderate-intensity exercise, is both feasible and safe in cancer survivors. The ACSM guidelines for cancer survivors, which parallel those for healthy adults, recommend 150 minutes of moderate-intensity PA per week. In our first study, 60% of the NA queried met these recommendations. While over reporting is likely, their self-report suggests that these individuals were performing a good deal of moderate-intensity PA, and that they spent almost as much time in planned exercise as in non-exercise PA. In our study of lung cancer survivors, 80% of survivors met the PA goal of 150 min/wk, again with planned exercise, and the one individual that didn’t still exercised multiple days a week, meeting this goal for more weeks than not over the course of the eight-week intervention. In that time, no injuries or adverse events were reported. As these understudied populations often have poorer health outcomes than that of other cancer survivors, this information is critically important, as it adds to the already robust literature suggesting that exercise is safe and feasible in cancer survivors. NA cancer survivors, as described elsewhere in this document, suffer disproportionally from many health consequences. Lung cancer survivors have much lower 5-year survival rates than those with other cancer types, as well as other unique health challenges specific to their diagnosis and treatment.   It should also be noted that exercise appears to be a safe and feasible option for caregivers of cancer survivors, as our third study observed adherence and adverse event rates similar to that of our lung cancer survivors. As such, these findings add merit to the literature that suggests that exercise may be a potentially safe modality for these individuals.

The other major theme found in this collective work is that while exercise is potentially safe and feasible in these groups, it may not be palatable to all cancer survivors and/or their caregivers. Along with walking, we found that the vast majority of PA participated in by NA cancer survivors occurred in the household or domestic domain. Further, more than half of all PA participated in by this group came in the form of non-exercise PA. In addition, while exercise appeared to be feasible for the five lung cancer survivors who participated in our second study, it may not have been for the 155 survivors who were eligible for the study but declined participation due to considering themselves too ill to perform exercise, unwilling to travel to in-clinic exercise visits, or simply not being interested in partaking in an exercise program. Also of note, while we suggest exercise is an appropriate, safe, and feasible option for caregivers of cancer survivors, we again realize that this was specific to this quite small sample (n=4). As the majority of the support person's relationship to the cancer survivor was as a spouse/partner, which is similar to other studies concerning informal caregivers of cancer survivors, we must consider what the general population of cancer caregivers might look like. Cancer is often considered a disease of the aged. As such, the majority of spousal caregivers may also be of older age, such that the functional declines that are related to HQOL may potentially make exercise unattractive to this group. Our group of caregivers were a relatively young (59 years), educated, healthy group. While exercise was accessible to this population, that may not be the case for all caregivers of cancer survivors. As such, other PA options, especially within the context of potential future interventions and/or elucidating relationships with health outcomes, must be explored.

One promising direction is that of light-intensity, non-exercise PA. As more and more work comes forward warning of the dangers and accompanying poor health associated with sedentary behavior [263], and as light-intensity PA is perhaps the easiest way to displace time spent in sedentary behavior, this may be an especially attractive option for this population. In regards to our NA cancer survivors, many reported participating in non-exercise PA. However, we utilized a self-reported measure of PA, which has been shown to do a relatively poor job of measuring light-intensity, non-exercise PA [264]. We also queried fewer light- than moderate-intensity activities, perhaps not painting the complete picture of where the majority of time spent physically active is allocated. Along with misclassification of volume of PA due to over-reporting, this lack of accurately-measured light-intensity PA may help to explain our null findings with regards to HQOL in this group. More work is needed to better describe the light-intensity behaviors of NA cancer survivors and their potential relationship with HQOL. In our lung cancer survivor study, we noted that perhaps an additional reason that we didn't observe an increase in HQOL following the exercise intervention, aside from having a small sample of non-comparable groups, could be the high baseline HQOL scores observed in this group. We went on to report that, along with other studies evaluating an exercise intervention in lung cancer survivors, our baseline HQOL scores were considerably higher than that of the larger lung cancer population not participating in an exercise program. This could suggest that the HQOL in individuals that are not well enough nor motivated enough to partake in an exercise program may have a lower HQOL than those individuals that do participate. As such, light-intensity may not only be more accessible to those who do not wish to travel or are too ill to participate in a standard exercise intervention, but may also help to improve HQOL in this subset of lung cancer survivors. Finally, since the time commitment is a commonly cited barrier to exercise in cancer survivor caregivers, and since a great majority of their free time is spent offering care, non-exercise, light-intensity PA may be a great benefit to this population.

Future studies in these populations should address some of the major themes found in this work. With regards to NA cancer survivors, studies need to be dedicated to further describing PA behavior using objective measures. This is especially important with regards to light-intensity, non-exercise PA. As subjective self-report measures of PA do a poor job of capturing these activities, future studies need to consider using objective measures to better determine the relative amount of light-intensity PA participated in by this population. Further, this work should explore the relationship between light-intensity PA and HQOL. As the emerging field of sedentary behavior has suggested that increased sitting time is related to all-cause mortality and select morbidities [265], it is entirely possible that the replacement of sitting time with light-intensity PA may be a beneficial modality for NA cancer survivors. Lastly, well controlled trials are needed to evaluate the role of PA in mediating HQOL concerns. As our work showed that NA appeared to participate in a substantial amount of moderate-intensity PA, specifically exercise, well controlled trials are needed to test exercise interventions in regards to safety, feasibility, and their effect on HQOL. Additionally, interventions limiting sedentary time should also be explored in the context of randomized controlled trials to examine their impact on HQOL.

In regards to lung cancer survivors, more work needs to be done to show the effectiveness of exercise as a therapeutic modality in this population. While we were encouraged that exercise is feasible and safe in this group, our studies did little to show the effectiveness of an exercise intervention. As such, randomized trials with larger sample sizes are needed to better explore the relationship between exercise and cancer-specific health outcomes. This work also needs to consider the true generalizability of findings in this population. Low sample sizes among studies, coupled with the likelihood of sampling bias, suggest a unique population of cancer survivors that partake in PA studies. As such, large, well-controlled studies trials are needed, as are studies looking at the potential barriers to exercise and non-exercise PA. To specifically address the large percentage of lung cancer survivors who are not willing or able to participate in exercise program, studies addressing the feasibility and potential impact of limiting sedentary time are warranted. These should, again, come in the form of well controlled trials. Of note, health outcomes explored should be limited to HQOL to start, as it is unlikely that decreasing sedentary time would have an influence on our tested measures of prognosis (including exercise capacity and markers of inflammation and oxidative stress).

Finally, future studies are needed to continue to evaluate PA as a potential treatment modality in caregivers of cancer survivors. While this was the first study to show that exercise appears to be both safe and feasible in this group, we were unable to evaluate its effectiveness at improving HQOL. Well controlled trials with large sample sizes should be utilized to better explore this relationship. Further, in the case of exercise not being a suitable intervention due to the time spent providing care, as well as potential health concerns experienced by the caregiver, work should be done to objectively evaluate time spent in sedentary behavior and its association with HQOL. Should this observational work provide promising results, well controlled trials featuring interventions to limit sedentary time would be justified.

References

1. American Cancer Society. Cancer Facts and Figures 2013. Atlanta, GA: ACS Vol; 2013.

2. Hewitt ME, Greenfield S, Stovall E. From cancer patient to cancer survivor: lost in transition: Natl Academy Pr; 2006.

3. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Questionnaire (or Examination Protocol, or Laboratory Protocol). Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Vol 2011; 2011.

4. U.S. Cancer Statistics Working Group. United States Cancer Statistics: – Incidence and Mortality Web-based Report. Atlanta : Department of Health and Human Services CfDC, Available at hwcgu. United States Cancer Statistics: 1999–2007 Incidence and Mortality Web-based Report. Vol 2011; 2010.

5. Lee I-M, Oguma Y. Cancer Epidemiology and Prevention. New York, NY: Oxford University Press; 2006.

6. Brown JC, Winters-Stone K, Lee A, Schmitz KH. Cancer, physical activity, and exercise. *Compr Physiol.* 2012;2:2775-2809.

7. Irwin ML, Smith AW, McTiernan A, et al. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity, and lifestyle study. *J Clin Oncol.* 2008;26:3958-3964.

8. Meyerhardt JA, Giovannucci EL, Holmes MD, et al. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol.* 2006;24:3527-3534.

9. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol.* 2006;24:3535-3541.

10. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA.* 2005;293:2479-2486.

11. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst.* 2012;104:815-840.

12. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2005;14:1588-1595.

13. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc.* 2010;42:1409-1426.

14. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's not over when it's over: long-term symptoms in cancer survivors--a systematic review. *International journal of psychiatry in medicine.* 2010;40:163-181.

15. Deimling GT, Sterns S, Bowman KF, Kahana B. The health of older-adult, long-term cancer survivors. *Cancer nursing.* 2005;28:415.

16. Deimling GT, Kahana B, Bowman KF, Schaefer ML. Cancer survivorship and psychological distress in later life. *Psycho-Oncology.* 2002;11:479-494.

17. Cella DF, Bonomi AE. Measuring quality of life: 1995 update. *Oncology-Huntington.* 1995;9:47-60.

18. Research IoSaE. Alaska Native Health and Health Care: Report of the U.S. Health Task Force. UAA-ISER. Accessed 11/2013, 2013.

19. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. *CA: a cancer journal for clinicians.* 2004;54:78-93.

20. Office of the General Counsel USCoCR. Native American Health Care Disparities Briefing: Executive Summary. Accessed 11/2013, 2013.

21. Truman BI, Smith KC, Roy K, et al. Rationale for regular reporting on health disparities and inequalities - United States. *MMWR Surveill Summ.* 2011;60 Suppl:3-10.

22. Frieden TR, (Centers for Disease Control and Prevention). Forward: CDC Health Disparities and Inequalities Report - United States, 2011. *MMWR Surveill Summ.* 2011;60 Suppl:1-2.

23. Lau M, Lin H, Flores G. Racial/ethnic disparities in health and health care among U.S. adolescents. *Health Serv Res.* 2012;47:2031-2059.

24. Warne D. Research and educational approaches to reducing health disparities among American Indians and Alaska Natives. *Journal of transcultural nursing : official journal of the Transcultural Nursing Society / Transcultural Nursing Society.* 2006;17:266-271.

25. Gone JP, Trimble JE. American Indian and Alaska Native mental health: diverse perspectives on enduring disparities. *Annu Rev Clin Psychol.* 2012;8:131-160.

26. Burhansstipanov L. Cancer mortality among Native Americans. *Cancer.* 1998;83:2247-2250.

27. Warne D, Kaur J, Perdue D. American Indian/Alaska Native cancer policy: systemic approaches to reducing cancer disparities. *Journal of cancer education : the official journal of the American Association for Cancer Education.* 2012;27 Suppl 1:S18-23.

28. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. *Cancer.* 2011;117:1994-2003.

29. Holm JE, Vogeltanz-Holm N, Poltavski D, McDonald L. Assessing health status, behavioral risks, and health disparities in American Indians living on the northern plains of the U.S. *Public health reports (Washington, DC: 1974).* 2010;125:68-78.

30. Denny CH, Holtzman D, Cobb N. Surveillance for health behaviors of American Indians and Alaska Natives. Findings from the Behavioral Risk Factor Surveillance System, 1997-2000. *Morbidity and mortality weekly reportSurveillance summaries (Washington, DC: 2002).* 2003;52:1-13.

31. Steele CB, Cardinez CJ, Richardson LC, Tom-Orme L, Shaw KM. Surveillance for health behaviors of American Indians and Alaska Natives-findings from the behavioral risk factor surveillance system, 2000-2006. *Cancer.* 2008;113:1131-1141.

32. Kaur JS, Coe K, Rowland J, et al. Enhancing life after cancer in diverse communities. *Cancer.* 2012.

33. Jemal A, Clegg LX, Ward E, et al. Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. *Cancer.* 2004;101:3-27.

34. Doshi SR, Jiles R. Health behaviors among American Indian/Alaska Native women, 1998-2000 BRFSS. *J Womens Health (Larchmt).* 2006;15:919-927.

35. Joe JR. The health of American Indian and Alaska Native women. *J Am Med Womens Assoc.* 1996;51:141-145.

36. Mahoney MC, Michalek AM. The health status of American Indians and Alaska Natives: 2. Lessons for cancer educators. *Journal of cancer education : the official journal of the American Association for Cancer Education.* 1999;14:23-27.

37. Chowdhury PP, Balluz L, Strine TW. Health-related quality of life among minority populations in the United States, BRFSS 2001-2002. *Ethn Dis.* 2008;18:483-487.

38. Granger CL, McDonald CF, Berney S, Chao C, Denehy L. Exercise intervention to improve exercise capacity and health related quality of life for patients with Non-small cell lung cancer: a systematic review. *Lung Cancer.* 2011;72:139-153.

39. Lin YY, Wu YC, Rau KM, Lin CC. Effects of physical activity on the quality of life in taiwanese lung cancer patients receiving active treatment or off treatment. *Cancer Nurs.* 2013;36:E35-41.

40. Jones LW, Eves ND, Waner E, Joy AA. Exercise therapy across the lung cancer continuum. *Curr Oncol Rep.* 2009;11:255-262.

41. Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K. Exercise training for people following lung resection for non-small cell lung cancer - A Cochrane systematic review. *Cancer Treat Rev.* 2013.

42. Coups EJ, Park BJ, Feinstein MB, et al. Physical activity among lung cancer survivors: changes across the cancer trajectory and associations with quality of life. *Cancer Epidemiol Biomarkers Prev.* 2009;18:664-672.

43. Jones LW. Physical activity and lung cancer survivorship. *Recent Results Cancer Res.* 2011;186:255-274.

44. Solberg Nes L, Liu H, Patten CA, et al. Physical activity level and quality of life in long term lung cancer survivors. *Lung Cancer.* 2012;77:611-616.

45. Brocki BC, Andreasen J, Nielsen LR, Nekrasas V, Gorst-Rasmussen A, Westerdahl E. Short and long-term effects of supervised versus unsupervised exercise training on health-related quality of life and functional outcomes following lung cancer surgery - A randomized controlled trial. *Lung Cancer.* 2014;83:102-108.

46. Arbane G, Tropman D, Jackson D, Garrod R. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. *Lung Cancer.* 2011;71:229-234.

47. Spruit MA, Janssen PP, Willemsen SC, Hochstenbag MM, Wouters EF. Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. *Lung Cancer.* 2006;52:257-260.

48. Wall LM. Changes in hope and power in lung cancer patients who exercise. *Nurs Sci Q.* 2000;13:234-242.

49. Il'yasova D, Colbert LH, Harris TB, et al. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. *Cancer Epidemiol Biomarkers Prev.* 2005;14:2413-2418.

50. O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. *Br J Cancer.* 2001;85:473-483.

51. Shacter E, Weitzman S. Chronic Inflammation and Cancer. *Oncology.* 2002;16:217-226.

52. Poulsen HE, Prieme H, Loft S. Role of oxidative DNA damage in cancer initiation and promotion. *Eur J Cancer Prev.* 1998;7:9-16.

53. Jones LW, Eves ND, Peddle CJ, et al. Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. *Appl Physiol Nutr Metab.* 2009;34:197-202.

54. Braun M, Mikulincer M, Rydall A, Walsh A, Rodin G. Hidden morbidity in cancer: spouse caregivers. *J Clin Oncol.* 2007;25:4829-4834.

55. Kim Y, Given BA. Quality of life of family caregivers of cancer survivors. *Cancer.* 2008;112:2556-2568.

56. Kim Y, Given BA. Quality of life of family caregivers of cancer survivors: across the trajectory of the illness. *Cancer.* 2008;112:2556-2568.

57. Li Q, Loke AY. A spectrum of hidden morbidities among spousal caregivers for patients with cancer, and differences between the genders: a review of the literature. *Eur J Oncol Nurs.* 2013;17:578-587.

58. Li QP, Mak YW, Loke AY. Spouses' experience of caregiving for cancer patients: a literature review. *Int Nurs Rev.* 2013;60:178-187.

59. Mellon S, Northouse LL, Weiss LK. A population-based study of the quality of life of cancer survivors and their family caregivers. *Cancer nursing.* 2006;29:120-131.

60. Baider L, Kaufman B, Perez T, al. e. Mutuality of Fate: Adaptation and psychological distress in cancer patients and their partners. Chichester, England: John Wiley and Sons, Inc.; 1996.

61. Mikulincer M, Rydall A, Walsh A, Rodin G. Hidden morbidity in cancer: spouse caregivers. *J Clin Oncol.* 2007;25:4829-4834

62. Kim Y, Spillers RL, Hall DL. Quality of life of family caregivers 5 years after a relative's cancer diagnosis: follow-up of the national quality of life survey for caregivers. *Psychooncology.* 2012;21:273-281.

63. Talley RC, Crews JE. Framing the public health of caregiving. *Am J Public Health.* 2007;97:224-228.

64. Maliski SL, Sarna L, Evangelista L, Padilla G. The aftermath of lung cancer: balancing the good and bad. *Cancer Nurs.* 2003;26:237-244.

65. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR. Quality of life in lung cancer patients: as an important prognostic factor. *Lung Cancer.* 2001;31:233-240.

66. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: a systematic review. *Lung Cancer.* 2013;81:11-26.

67. Sugimura H, Yang P. Long-term survivorship in lung cancer: a review. *Chest.* 2006;129:1088-1097.

68. Yang P. Epidemiology of lung cancer prognosis: quantity and quality of life. *Methods Mol Biol.* 2009;471:469-486.

69. Yang P, Cheville AL, Wampfler JA, et al. Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol.* 2012;7:64-70.

70. Centers for Disease Control and Prevention (CDC). Cancer survivors--United States, 2007. *MMWR Morb Mortal Wkly Rep.* 2011;60:269-272.

71. Altekruse SF. SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to SEER website 2010. Vol 2011.

72. Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. *CA Cancer J Clin.* 2010;60:317-339.

73. Bureau USC. The American Indian/Alaska Native Population Report:2010 Census Briefs. Accessed 1/2014, 2014.

74. US Department of Indian Affairs (US.DotI-I). Tribal Directory. Accessed 01/2014, 2014.

75. Gone JP. "We never was happy living like a Whiteman" : mental health disparities and the postcolonial predicament in American Indian communities. *Am J Community Psychol.* 2007;40:290-300.

76. Pevar SL. The Rights of Indians and Tribes: The Authoritative ACLU guide to Indian and Tribal Rights. 3rd ed. ed. New York, NY: New York University; 2004.

77. US Department of Health and Human Services. Indian Health Care Improvement Act. Accessed 01/2014, 2014.

78. Dixon M, Roubideaux Y. Promises to keep : public health policy for American Indians and Alaska natives in the 21st century. Washington, DC: American Public Health Association.; 2001.

79. Lillie-Blanton M, Roubideaux Y. Understanding and addressing the health care needs of American Indians and Alaska Natives. *Am J Public Health.* 2005;95:759-761.

80. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA: a cancer journal for clinicians.* 2008;58:71.

81. Centers for Disease Control and Prevention (CDC). Leading Causes of Death in Females, 2007. Available at: http://www.cdc.gov/women/lcod/2007/07_all_females.pdf. Accessibility verified January 21, 2013.

82. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer.* 2009;116:544-573.

83. Cueto CV, Szeja S, Wertheim BC, Ong ES, Tsikitis VL. Disparities in treatment and survival of white and Native American patients with colorectal cancer: a SEER analysis. *J Am Coll Surg.* 2011;213:469-474.

84. American Cancer Society. ACS. Cancer Facts and Figures Atlanta, GA; Vol 2005.

85. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer.* 2013.

86. Horm JW, Devesa SS, Burhansstipanov L. Cancer incidence, mortality, and survival among racial and ethnic minority groups in the United States. *Cancer Epidemiology and Prevention (Schottenfel D, Fraumeni JF Jr, eds)2nd edNew York: Oxford University Press.* 1996:192-235.

87. Fraumeni Jr. JF. Introduction to New Malignancies Among Cancer Survivors-NIH Publication No. 05-4722; 2006.

88. Burhansstipanov L. Native American Community-Based Cancer Projects: Theory Versus Reality. *Cancer control : journal of the Moffitt Cancer Center.* 1999;6:620-626.

89. Constitution of the World Health Organization. Geneva: World Health Organization. Vol 2011.

90. Trask PC, Hsu MA, McQuellon R. Other paradigms: health-related quality of life as a measure in cancer treatment: its importance and relevance. *The Cancer Journal.* 2009;15:435.

91. Conroy T, Blazeby JM. Health-related quality of life in colorectal cancer patients. *Expert Review of Anticancer Therapy.* 2003;3:493-504.

92. Fontaine KR, Barofsky I. Obesity and health-related quality of life. *Obesity Reviews.* 2001;2:173-182.

93. Bloom JR, Petersen DM, Kang SH. Multi-dimensional quality of life among long-term (5 years) adult cancer survivors. *Psycho-Oncology.* 2007;16:691-706.

94. American Society of Clinical O. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. *J Clin Oncol.* 1996;14:671-679.

95. Johnson JR, Temple R. Food and Drug Administration requirements for approval of new anticancer drugs. *Cancer treatment reports.* 1985;69:1155.

96. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical care.* 1992;30:473-483.

97. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer.* 2008;112:2577-2592.

98. Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58:M82.

99. Ramsey SD, Berry K, Moinpour C, Giedzinska A, Andersen MR. Quality of life in long term survivors of colorectal cancer. *The American Journal of Gastroenterology.* 2002;97:1228-1234.

100. Yates JW. Comorbidity considerations in geriatric oncology research. *CA: a cancer journal for clinicians.* 2001;51:329-336.

101. Ganz PA. Quality of life across the continuum of breast cancer care. *The breast journal.* 2000;6:324-330.

102. Ferrell, BR. Quality of Life Issues: Cancer Patients' Perspectives. Presentation at the meeting of the IOM Committee on Cancer Survivorship Meeting, Irvine, CA.

103. Ganz PA, Guadagnoli E, Landrum MB, Lash TL, Rakowski W, Silliman RA. Breast cancer in older women: quality of life and psychosocial adjustment in the 15 months after diagnosis. *Journal of Clinical Oncology.* 2003;21:4027.

104. Regier DA, Boyd JH, Burke Jr JD, et al. One-month prevalence of mental disorders in the United States: based on five Epidemiologic Catchment Area sites. *Archives of General Psychiatry.* 1988;45:977.

105. Mackenzie CS, Reynolds K, Chou KL, Pagura J, Sareen J. Prevalence and correlates of generalized anxiety disorder in a national sample of older adults. *American Journal of Geriatric Psych.* 2011;19:305.

106. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *The oncologist.* 2007;12:4.

107. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment:: prevalence, correlates and interventions. *European journal of cancer.* 2002;38:27-43.

108. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *The oncologist.* 2000;5:353.

109. Van den Beuken-van Everdingen MHJ, De Rijke JM, Kessels AG, Schouten HC, Van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Annals of oncology.* 2007;18:1437.

110. Burton AW, Fanciullo GJ, Beasley RD, Fisch MJ. Chronic pain in the cancer survivor: a new frontier. *Pain Medicine.* 2007;8:189-198.

111. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain. *Cancer.* 2010.

112. Goins RT, Moss M, Buchwald D, Guralnik JM. Disability among older American Indians and Alaska Natives: an analysis of the 2000 Census Public Use Microdata Sample. *Gerontologist.* 2007;47:690-696.

113. Goins RT, Pilkerton CS. Comorbidity among older American Indians: the native elder care study. *J Cross Cult Gerontol.* 2010;25:343-354.

114. Neligh G. Major mental disorders and behavior among American Indians and Alaska Natives. *Am Indian Alsk Native Ment Health Res Monogr Ser.* 1988;1:116-150 discussion 151-119.

115. Duran B, Sanders M, Skipper B, et al. Prevalence and correlates of mental disorders among Native American women in primary care. *Am J Public Health.* 2004;94:71-77.

116. Indian Health Institute SIBoH. Depression Among American Indians and Alaska Natives:A Literature Review. Seattle, WA: Urban Indian Health Institute; 2012.

117. United States Department of Health and Human Services. Substance Abuse and Mental Health Services Administration. Office of Applied S. National Survey on Drug Use and Health, 2006. 2013.

118. Dinges NG, Duong-Tran Q. Stressful life events and co-occurring depression, substance abuse and suicidality among American Indian and Alaska Native adolescents. *Cult Med Psychiatry.* 1992;16:487-502.

119. Beals J, Novins DK, Whitesell NR, Spicer P, Mitchell CM, Manson SM. Prevalence of mental disorders and utilization of mental health services in two American Indian reservation populations: mental health disparities in a national context. *Am J Psychiatry.* 2005;162:1723-1732.

120. US Department of Health and Human Services. Mental Health: Culture, Race, and Ethnicity: A Supplement to Mental Health: A Report of the Surgeon General. in: Administration, ed. Rockville, MD: http://www.ncbi.nlm.nih.gov/books/NBK44243/; 2001.

121. Gizlice Z, Huston S. Health Risks and Conditions among American Indians in North Carolina. A Special Report Series by the State Center for Health Statistics. Raleigh, N.C.: North Carolina Department of Public Health; 2004.

122. Zahran HS, Kobau R, Moriarty DG, et al. Health-related quality of life surveillance--United States, 1993-2002. *MMWR Surveill Summ.* 2005;54:1-35.

123. Burhansstipanov L, Krebs LU, Seals BF, et al. Native American breast cancer survivors' physical conditions and quality of life. *Cancer.* 2010;116:1560-1571.

124. Burhansstipanov L, Dignan M, Jones KL, Krebs LU, Marchionda P, Kaur JS. Comparison of quality of life between Native and non-Native cancer survivors: Native and non-Native cancer survivors' QOL. *Journal of cancer education : the official journal of the American Association for Cancer Education.* 2012;27 Suppl 1:S106-113.

125. Richardson LC, Wingo PA, Zack MM, Zahran HS, King JB. Health-related quality of life in cancer survivors between ages 20 and 64 years: population-based estimates from the Behavioral Risk Factor Surveillance System. *Cancer.* 2008;112:1380-1389.

126. Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 1995;4:523-531.

127. Burhansstipanov L, Lovato MP, Krebs LV. Native American cancer survivors. *Health care for women international.* 1999;20:505-515.

128. Caspersen CJ. Physical activity epidemiology: concepts, methods, and applications to exercise science. *Exercise and sport sciences reviews.* 1989;17:423.

129. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2006;174:801-809.

130. Blair SN, Kohl HW, Gordon NF, Paffenbarger RS, Jr. How much physical activity is good for health? *Annual Review of Public Health.* 1992;13:99-126.

131. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Current Opinion in Psychiatry.* 2005;18:189.

132. Courneya KS, Friedenreich CM. Physical exercise and quality of life following cancer diagnosis: a literature review. *Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine.* 1999;21:171-179.

133. Courneya KS, Karvinen KH. Exercise, aging, and cancer. *Applied Physiology, Nutrition, and Metabolism.* 2007;32:1001-1007.

134. Thraen-Borowski KM, Trentham-Dietz A, Edwards DF, Koltyn KF, Colbert LH. Dose-response relationships between physical activity, social participation, and health-related quality of life in colorectal cancer survivors. *J Cancer Surviv.* 2013;7:369-378.

135. Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol.* 2005;23:899-909.

136. Rajarajeswaran P, Vishnupriya R. Exercise in cancer. *Indian J Med Paediatr Oncol.* 2009;30:61-70.

137. Knols R, Aaronson NK, Uebelhart D, Fransen J, Aufdemkampe G. Physical exercise in cancer patients during and after medical treatment: a systematic review of randomized and controlled clinical trials. *J Clin Oncol.* 2005;23:3830-3842.

138. Young-McCaughan S, Sexton DL. A retrospective investigation of the relationship between aerobic exercise and quality of life in women with breast cancer. *Oncology nursing forum.* 1991;18:751-757.

139. Pinto BM, Trunzo JJ, Reiss P, Shiu SY. Exercise participation after diagnosis of breast cancer: trends and effects on mood and quality of life. *Psycho-Oncology.* 2002;11:389-400.

140. Courneya KS, Friedenreich CM. Relationship between exercise during treatment and current quality of life among survivors of breast cancer. *Journal of Psychosocial Oncology.* 1997.

141. Keating NL, Nørredam M, Landrum MB, Huskamp HA, Meara E. Physical and Mental Health Status of Older Long-Term Cancer Survivors. *Journal of the American Geriatrics Society.* 2005;53:2145-2152.

142. Cress ME, Buchner DM, Questad KA, Esselman PC, deLateur BJ, Schwartz RS. Exercise: effects on physical functional performance in independent older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 1999;54:M242.

143. Brach JS, Simonsick EM, Kritchevsky S, Yaffe K, Newman AB. The association between physical function and lifestyle activity and exercise in the health, aging and body composition study. *Journal of the American Geriatrics Society.* 2004;52:502-509.

144. Lynch BM, Cerin E, Owen N, Aitken JF. Associations of leisure-time physical activity with quality of life in a large, population-based sample of colorectal cancer survivors. *Cancer Causes and Control.* 2007;18:735-742.

145. Physical Activity Guidelines Advisory C. Physical activity guidelines advisory committee report, 2008. *Washington, DC: US Department of Health and Human Services.* 2008;2008.

146. Coble JD, Rhodes RE. Physical Activity and Native Americans: A Review. *American Journal of Preventive Medicine.* 2006;31:36-46.

147. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Medicine & Science in Sports & Exercise.* 2008;40:181.

148. Storti KL, Arena VC, Barmada MM, et al. Physical activity levels in American-Indian adults: the Strong Heart Family Study. *Am J Prev Med.* 2009;37:481-487.

149. Barbaric M, Brooks E, Moore L, Cheifetz O. Effects of physical activity on cancer survival: a systematic review. *Physiotherapy CanadaPhysiotherapie Canada.* 2010;62:25-34.

150. Courneya KS. Physical activity in cancer survivors: a field in motion. *Psychooncology.* 2009;18:337-342.

151. Poltavski D, Holm J, Vogeltanz-Holm N, McDonald L. Assessing health-related quality of life in Northern Plains American Indians: prominence of physical activity as a health behavior. *Am Indian Alsk Native Ment Health Res.* 2010;17:25-48.

152. Sawchuk CN, Charles S, Wen Y, et al. A randomized trial to increase physical activity among native elders. *Prev Med.* 2008;47:89-94.

153. Kochevar AJ, Smith KL, Bernard MA. Effects of a community-based intervention to increase activity in American Indian elders. *J Okla State Med Assoc.* 2001;94:455-460.

154. Grant M, Sun V, Fujinami R, et al. Family caregiver burden, skills preparedness, and quality of life in non-small cell lung cancer. *Oncol Nurs Forum.* 2013;40:337-346.

155. Cooley ME. Symptoms in adults with lung cancer. A systematic research review. *J Pain Symptom Manage.* 2000;19:137-153.

156. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. *J Clin Oncol.* 2000;18:893-903.

157. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and science in sports and exercise.* 2000;32:S498.

158. Cleeland CS. Measurement and prevalence of pain in cancer. *Semin Oncol Nurs.* 1985;1:87-92.

159. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med.* 1994;330:592-596.

160. Cleeland CS. Cancer-related symptoms. *Semin Radiat Oncol.* 2000;10:175-190.

161. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. *J Natl Cancer Inst Monogr.* 2007:16-21.

162. Ostroff JS, Krebs P, Coups EJ, et al. Health-related quality of life among early-stage, non-small cell, lung cancer survivors. *Lung Cancer.* 2011;71:103-108.

163. Jones LW, Eves ND, Haykowsky M, Freedland SJ, Mackey JR. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. *Lancet Oncol.* 2009;10:598-605.

164. Travers J, Dudgeon DJ, Amjadi K, et al. Mechanisms of exertional dyspnea in patients with cancer. *J Appl Physiol (1985).* 2008;104:57-66.

165. Thompson E, Sola I, Subirana M. Non-invasive interventions for improving well-being and quality of life in patients with lung cancer--a systematic review of the evidence. *Lung Cancer.* 2005;50:163-176.

166. Benzo R, Kelley GA, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: A meta-analysis. *Respiratory medicine.* 2007;101:1790-1797.

167. Villani F, De Maria P, Busia A. Exercise testing as a predictor of surgical risk after pneumonectomy for bronchogenic carcinoma. *Respiratory medicine.* 2003;97:1296-1298.

168. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer.* 2007;110:590-598.

169. Quist M, Rørth M, Langer S, et al. Safety and feasibility of a combined exercise intervention for inoperable lung cancer patients undergoing chemotherapy: A pilot study. *Lung Cancer.* 2012;75:203-208.

170. Sekine Y, Chiyo M, Iwata T, et al. Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *The Japanese Journal of Thoracic and Cardiovascular Surgery.* 2005;53:237-243.

171. Glattki GP, Manika K, Sichletidis L, Alexe G, Brenke R, Spyratos D. Pulmonary rehabilitation in non-small cell lung cancer patients after completion of treatment. *Am J Clin Oncol.* 2012;35:120-125.

172. Cesario A, Ferri L, Galetta D, et al. Post-operative respiratory rehabilitation after lung resection for non-small cell lung cancer. *Lung Cancer.* 2007;57:175-180.

173. Cesario A, Dall'Armi V, Cusumano G, et al. Post-operative pulmonary rehabilitation after lung resection for NSCLC: A follow up study. *Lung Cancer.* 2009;66:268-269.

174. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet.* 2001;357:539-545.

175. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G. Inflammation and cancer: how hot is the link? *Biochem Pharmacol.* 2006;72:1605-1621.

176. Kayser K, Bülzebruck H, Ebert W, Merkle NM, Vogt-Moykopf I. Local tumor inflammation, lymph node metastasis, and survival of operated bronchus carcinoma patients. *J Natl Cancer Inst.* 1986;77:77-81.

177. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci.* 2011;48:155-170.

178. Srimuninnimit V, Ariyapanya S, Nimmannit A, Wonglaksanapimon S, Akewanlop C, Soparattanapaisarn N. C-reactive protein as a monitor of chemotherapy response in advanced non-small cell lung cancer (CML study). *J Med Assoc Thai.* 2012;95 Suppl 2:S199-207.

179. Fairey AS, Courneya KS, Field CJ, et al. Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. *Brain Behav Immun.* 2005;19:381-388.

180. Zoppini G, Targher G, Zamboni C, et al. Effects of moderate-intensity exercise training on plasma biomarkers of inflammation and endothelial dysfunction in older patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis.* 2006;16:543-549.

181. Oberbach A, Tonjes A, Kloting N, et al. Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. *Eur J Endocrinol.* 2006;154:577-585.

182. Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. *Oncol Nurs Forum.* 2008;35:635-642.

183. Allgayer H, Nicolaus S, Schreiber S. Decreased interleukin-1 receptor antagonist response following moderate exercise in patients with colorectal carcinoma after primary treatment. *Cancer Detect Prev.* 2004;28:208-213.

184. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol.* 2010;28:340-347.

185. Jones LW, Eves ND, Peterson BL, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. *Cancer.* 2008;113:3430-3439.

186. Allgayer H, Owen RW, Nair J, et al. Short-term moderate exercise programs reduce oxidative DNA damage as determined by high-performance liquid chromatography-electrospray ionization-mass spectrometry in patients with colorectal carcinoma following primary treatment. *Scand J Gastroenterol.* 2008;43:971-978.

187. Shen J, Deininger P, Hunt JD, Zhao H. 8-Hydroxy-2'-deoxyguanosine (8-OH-dG) as a potential survival biomarker in patients with nonsmall-cell lung cancer. *Cancer.* 2007;109:574-580.

188. M. D. Mechanism of free radical damage to DNA. London, England: OICA International; 1998.

189. Dherin C, Radicella JP, Dizdaroglu M, Boiteux S. Excision of oxidatively damaged DNA bases by the human alpha-hOgg1 protein and the polymorphic alpha-hOgg1(Ser326Cys) protein which is frequently found in human populations. *Nucleic Acids Res.* 1999;27:4001-4007.

190. Duncan K, Harris S, Ardies CM. Running exercise may reduce risk for lung and liver cancer by inducing activity of antioxidant and phase II enzymes. *Cancer Lett.* 1997;116:151-158.

191. Rogers CJ, Colbert LH, Greiner JW, Perkins SN, Hursting SD. Physical activity and cancer prevention : pathways and targets for intervention. *Sports Med.* 2008;38:271-296.

192. Inoue T, Mu Z, Sumikawa K, Adachi K, Okochi T. Effect of Physical Exercise on the Content of 8-Hydroxydeoxyguanosine in Nuclear DNA Prepared from Human Lymphocytes. *Cancer Science.* 1993;84:720-725.

193. Asami S, Hirano T, Yamaguchi R, Itoh H, Kasai H. Reduction of 8-hydroxyguanine in human leukocyte DNA by physical exercise. *Free Radic Res.* 1998;29:581-584.

194. Sumida S, Doi T, Sakurai M, Yoshioka Y, Okamura K. Effect of a single bout of exercise and beta-carotene supplementation on the urinary excretion of 8-hydroxy-deoxyguanosine in humans. *Free Radic Res.* 1997;27:607-618.

195. Sato Y, Nanri H, Ohta M, Kasai H, Ikeda M. Increase of human MTH1 and decrease of 8-hydroxydeoxyguanosine in leukocyte DNA by acute and chronic exercise in healthy male subjects. *Biochem Biophys Res Commun.* 2003;305:333-338.

196. Buccheri G, Ferrigno D. Prognostic factors in lung cancer: tables and comments. *Eur Respir J.* 1994;7:1350-1364.

197. Anant M, Guleria R, Pathak AK, et al. Quality of life measures in lung cancer. *Indian J Cancer.* 2005;42:125-132.

198. Gridelli C, Perrone F, Nelli F, Ramponi S, De Marinis F. Quality of life in lung cancer patients. *Ann Oncol.* 2001;12 Suppl 3:S21-25.

199. Gridelli C, De Vivo R, Monfardini S. Management of small-cell lung cancer in the elderly. *Crit Rev Oncol Hematol.* 2002;41:79-88.

200. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR. How quality of life data contribute to our understanding of cancer patients' experiences? A study of patients with lung cancer. *Qual Life Res.* 2003;12:157-166.

201. Schumacher KL, Stewart BJ, Archbold PG, Caparro M, Mutale F, Agrawal S. Effects of caregiving demand, mutuality, and preparedness on family caregiver outcomes during cancer treatment. *Oncol Nurs Forum.* 2008;35:49-56.

202. The American Cancer Society. Being a Caregiver. Accessed 11/2013, 2013.

203. Valeberg BT, Grov EK. Symptoms in the cancer patient: of importance for their caregivers' quality of life and mental health? *Eur J Oncol Nurs.* 2013;17:46-51.

204. Given BA, Given CW, Kozachik S. Family support in advanced cancer. *CA Cancer J Clin.* 2001;51:213-231.

205. Nijboer C, Tempelaar R, Sanderman R, Triemstra M, Spruijt RJ, Van Den Bos GAM. Cancer and caregiving: the impact on the caregiver's health. *Psycho-Oncology.* 1998;7:3-13.

206. Weitzner MA, McMillan SC, Jacobsen PB. Family Caregiver Quality of Life: Differences Between Curative and Palliative Cancer Treatment Settings. *Journal of pain and symptom management.* 1999;17:418-428.

207. Kim Y, Duberstein PR, Sörensen S, Larson MR. Levels of depressive symptoms in spouses of people with lung cancer: effects of personality, social support, and caregiving burden. *Psychosomatics.* 2005;46:123-130.

208. Fitzell A, Pakenham KI. Application of a stress and coping model to positive and negative adjustment outcomes in colorectal cancer caregiving. *Psychooncology.* 2010;19:1171-1178.

209. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC. Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. *Psychol Bull.* 2008;134:1-30.

210. Matthews BA, Baker F, Spillers RL. Oncology professionals and patient requests for cancer support services. *Support Care Cancer.* 2004;12:731-738.

211. Matthews JT, Dunbar-Jacob J, Sereika S, Schulz R, McDowell BJ. Preventive health practices: comparison of family caregivers 50 and older. *J Gerontol Nurs.* 2004;30:46-54.

212. Perz J, Ussher JM, Butow P, Wain G. Gender differences in cancer carer psychological distress: an analysis of moderators and mediators. *Eur J Cancer Care (Engl).* 2011;20:610-619.

213. Humpel N, Magee C, Jones SC. The impact of a cancer diagnosis on the health behaviors of cancer survivors and their family and friends. *Supportive care in cancer.* 2007;15:621-630.

214. Akechi T, Akizuki N, Okamura M, et al. Psychological distress experienced by families of cancer patients: preliminary findings from psychiatric consultation of a Cancer Center Hospital. *Jpn J Clin Oncol.* 2006;36:329-332.

215. Alfano CM, Rowland JH. Recovery issues in cancer survivorship: a new challenge for supportive care. *The Cancer Journal.* 2006;12:432-443.

216. Badger T, Segrin C, Dorros SM, Meek P, Lopez AM. Depression and anxiety in women with breast cancer and their partners. *Nurs Res.* 2007;56:44-53.

217. Barber FD. Effects of social support on physical activity, self-efficacy, and quality of life in adult cancer survivors and their caregivers. *Oncol Nurs Forum.* 2013;40:481-489.

218. Beesley VL, Price MA, Webb PM. Loss of lifestyle: health behaviour and weight changes after becoming a caregiver of a family member diagnosed with ovarian cancer. *Support Care Cancer.* 2011;19:1949-1956.

219. Chen ML, Chu L, Chen HC. Impact of cancer patients' quality of life on that of spouse caregivers. *Support Care Cancer.* 2004;12:469-475.

220. Cora A, Partinico M, Munafo M, Palomba D. Health risk factors in caregivers of terminal cancer patients: a pilot study. *Cancer Nurs.* 2012;35:38-47.

221. Fontaine KR, Barofsky I, Bartlett SJ, Franckowiak SC, Andersen RE. Weight loss and health-related quality of life: results at 1-year follow-up. *Eating Behaviors.* 2004;5:85-88.

222. Fujinami R, Otis-Green S, Klein L, Sidhu R, Ferrell B. Quality of life of family caregivers and challenges faced in caring for patients with lung cancer. *Clin J Oncol Nurs.* 2012;16:E210-220.

223. Honea NJ, Brintnall R, Given B, et al. Putting Evidence into Practice: nursing assessment and interventions to reduce family caregiver strain and burden. *Clin J Oncol Nurs.* 2008;12:507-516.

224. Khanna D, Tsevat J. Health-related quality of life-an introduction. *American Journal of Managed Care.* 2007;13:218.

225. Kim Y, Baker F, Spillers RL. Cancer caregivers' quality of life: effects of gender, relationship, and appraisal. *J Pain Symptom Manage.* 2007;34:294-304.

226. Kim Y, Spillers RL. Quality of life of family caregivers at 2 years after a relative's cancer diagnosis. *Psychooncology.* 2010;19:431-440.

227. Kuhne F, Krattenmacher T, Bergelt C, et al. [Parenthood and cancer: dyadic analysis of psychological distress and -health-related quality of life of cancer parents with minor children]. *Psychother Psychosom Med Psychol.* 2013;63:473-481.

228. Leow MQ, Chan MF, Chan SW. Predictors of Change in Quality of Life of Family Caregivers of Patients Near the End of Life With Advanced Cancer. *Cancer Nurs.* 2013.

229. Mancini J, Baumstarck-Barrau K, Simeoni MC, et al. Quality of life in a heterogeneous sample of caregivers of cancer patients: an in-depth interview study. *Eur J Cancer Care (Engl).* 2011;20:483-492.

230. Milbury K, Badr H, Fossella F, Pisters KM, Carmack CL. Longitudinal associations between caregiver burden and patient and spouse distress in couples coping with lung cancer. *Support Care Cancer.* 2013;21:2371-2379.

231. Murray SA, Kendall M, Boyd K, Grant L, Highet G, Sheikh A. Archetypal trajectories of social, psychological, and spiritual wellbeing and distress in family care givers of patients with lung cancer: secondary analysis of serial qualitative interviews. *Bmj.* 2010;340:c2581.

232. Park B, Kim SY, Shin JY, et al. Prevalence and predictors of anxiety and depression among family caregivers of cancer patients: a nationwide survey of patient-family caregiver dyads in Korea. *Support Care Cancer.* 2013;21:2799-2807.

233. Persson C, Ostlund U, Wennman-Larsen A, Wengstrom Y, Gustavsson P. Health-related quality of life in significant others of patients dying from lung cancer. *Palliat Med.* 2008;22:239-247.

234. Rhee YS, Yun YH, Park S, et al. Depression in family caregivers of cancer patients: the feeling of burden as a predictor of depression. *J Clin Oncol.* 2008;26:5890-5895.

235. Salonen P, Rantanen A, Kellokumpu-Lehtinen PL, Huhtala H, Kaunonen M. The quality of life and social support in significant others of patients with breast cancer - a longitudinal study. *Eur J Cancer Care (Engl).* 2013.

236. Siminoff LA, Wilson-Genderson M, Baker S, Jr. Depressive symptoms in lung cancer patients and their family caregivers and the influence of family environment. *Psychooncology.* 2010;19:1285-1293.

237. Spencer SM, Goins RT, Henderson JA, Wen Y, Goldberg J. Influence of caregiving on health-related quality of life among American Indians. *J Am Geriatr Soc.* 2013;61:1615-1620.

238. Ostlund U, Wennman-Larsen A, Persson C, Gustavsson P, Wengström Y. Mental health in significant others of patients dying from lung cancer. *Psychooncology.* 2010;19:29-37.

239. Swartz JJ, Keir ST. Program preferences to reduce stress in caregivers of patients with brain tumors. *Clinical Journal of Oncology Nursing.* 2007;11:723-727.

240. King AC, Baumann K, O'Sullivan P, Wilcox S, Castro C. Effects of Moderate-Intensity Exercise on Physiological, Behavioral, and Emotional Responses to Family Caregiving A Randomized Controlled Trial. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2002;57:M26-M36.

241. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of clinical oncology.* 1993;11:570-579.

242. Kriska AM, Knowler WC, LaPorte RE, et al. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. *Diabetes care.* 1990;13:401-411.

243. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Medicine & Science in Sports & Exercise.* 2001;33:1126.

244. Colbert LH, Matthews CE, Havighurst TC, Kim K, Schoeller DA. Comparative validity of physical activity measures in older adults. *Medicine and science in sports and exercise.* 2011;43:867-876.

245. Harada ND, Chiu V, King AC, Stewart AL. An evaluation of three self-report physical activity instruments for older adults. *Medicine & Science in Sports & Exercise.* 2001;33:962.

246. Haskell WL, Lee I, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Medicine and science in sports and exercise.* 2007;39:1423.

247. Hallal PC, Victora CG. Reliability and validity of the International Physical Activity Questionnaire (IPAQ). *Med Sci Sports Exerc.* 2004;36:556.

248. Borg G. An introduction to Borg's RPE-scale: Mouvement Publications; 1985.

249. Friedenreich CM, Neilson HK, Woolcott CG, et al. Inflammatory marker changes in a yearlong randomized exercise intervention trial among postmenopausal women. *Cancer Prev Res (Phila).* 2012;5:98-108.

250. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer.* 1995;12:199-220.

251. Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T. Measuring fitness in healthy older adults: the Health ABC Long Distance Corridor Walk. *Journal of the American Geriatrics Society.* 2001;49:1544-1548.

252. Pettee GKK, Rankin RL, Lee C, Charlton ME, Swan PD, Ainsworth BE. Test-retest reliability and validity of the 400-meter walk test in healthy, middle-aged women. *Journal of physical activity & health.* 2010;7:649.

253. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. *Supportive Care in Cancer.* 2012;20:3169-3177.

254. Dishman RK, Sallis JF, Orenstein DR. The determinants of physical activity and exercise. *Public health reports.* 1985;100:158.

255. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide: The Health Institute, New England Medical Center; 1993.

256. Ware JE, Kosinski M, Keller S. SF-36 physical and mental health summary scales: a user's manual: Health Assessment Lab.; 1994.

257. Ware JE. User's manual for the SF-36v2 health survey: Quality Metric; 2007.

258. Reulen RC, Zeegers MP, Jenkinson C, et al. The use of the SF-36 questionnaire in adult survivors of childhood cancer: evaluation of data quality, score reliability, and scaling assumptions. *Health and quality of life outcomes.* 2006;4:77.

259. Mosconi P, Cifani S, Crispino S, Fossati R, Apolone G. The performance of SF-36 health survey in patients with laryngeal cancer. Head and Neck Cancer Italian Working Group. *Head & neck.* 2000;22:175-182.

260. Perkins AJ, Stump TE, Monahan PO, McHorney CA. Assessment of differential item functioning for demographic comparisons in the MOS SF-36 health survey. *Quality of life research.* 2006;15:331-348.

261. Pinar R. Reliability and construct validity of the SF-36 in Turkish cancer patients. *Quality of life research.* 2005;14:259-264.

262. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Medical care.* 1995;33:AS264-279.

263. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. *Appl Physiol Nutr Metab.* 2010;35:725–40.

264. Haskell WL. Physical activity by self-report: A brief history and future issues. *J Phys Act Health* 9 [Suppl 1]: S5–S10, 2012.

265. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. *Exercise Sport Science Rev* 2010; 38:105-113.

Appendix A

The following tables present p-values for the analysis evaluating intensity- or type-specific PA with HQOL. Specifically, we tested whether a given intensity or type of PA mattered in relation to individual HQOL constructs. When p-values were significant, pairwise comparisons between a referent group and participation in greater amounts of PA are presented.

	PF	Pain	Fatigue	Sleep	M_SEX	F_SEX	Cognition	Spirit	Social	Emotional
VIG	.70	.33	.31	.63	.72	.39	.04	.36	.37	.47
MOD	.02	.92	.73	.27	.06	.03	.55	.22	.53	.81
LIGHT	.72	.78	.82	.05	.15	.07	.81	.83	.70	.54

Dependent Variable: Physical Function

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
Mod_METS 150 v 0	0.07	0.03	0.02	0.12
Mod_METS 500 v 0	0.22	0.08	0.05	0.38
Mod_METS 1000 v 0	0.43	0.15	0.11	0.74
Mod_METS 1700 v 0	0.70	0.25	0.20	1.20

Dependent Variable: Sleep

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
Lt_METS 150 v 0	-0.14	0.06	-0.27	-0.02
Lt_METS 500 v 0	-0.41	0.17	-0.75	-0.06
Lt_METS 1000 v 0	-0.69	0.28	-1.25	-0.12
Lt_METS 1500 v 0	-0.84	0.33	-1.51	-0.18

Dependent Variable: Sexual Function (Female)

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
Mod_METS 150 v 0	0.04	0.02	-0.01	0.08
Mod_METS 500 v 0	0.11	0.07	-0.02	0.25
Mod_METS 1000 v 0	0.20	0.13	-0.06	0.47
Mod_METS 1700 v 0	0.28	0.21	-0.14	0.71

Dependent Variable: Cognition

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
vig_mets 250 v 0	-0.13	0.05	-0.23	-0.02
vig_mets 600 v 0	-0.30	0.12	-0.54	-0.05
vig_mets 800 v 0	-0.39	0.16	-0.71	-0.07

	PF	Pain	Fatigue	Sleep	M_SEX	F_SEX	Cognition	Spirit	Social	Emotional
Trad	.65	.33	.29	.96	.91	.92	.15	.12	.21	.59
Non-Trad	.007	.18	.15	.49	.41	.28	.14	.07	.20	.08

Dependent Variable: Physical Function

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
NON_TRAD 750 v 300	0.23	0.09	0.05	0.41
NON_TRAD 1500 v 300	0.57	0.22	0.13	1.01
NON_TRAD 2500 v 300	0.95	0.35	0.25	1.66

	PF	Pain	Fatigue	Sleep	M_SEX	F_SEX	Cognition	Spirit	Social	Emotional
Exercise	.01	.28	.31	.42	.17	.11	.66	.009	.06	.03
Non-Ex PA	.20	.46	.86	.29	.22	.14	.33	.01	.07	.03

Dependent Variable: Physical Function

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
Ex 500 v 100	0.19	0.09	0.01	0.36
Ex 1000 v 100	0.40	0.18	0.02	0.77
Ex 2500 v 100	1.05	0.49	0.06	2.04

Dependent Variable: Spiritual

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
Ex 500 v 100	-0.06	0.03	-0.13	0.01
Ex 1000 v 100	-0.12	0.07	-0.27	0.02
Ex 2500 v 100	-0.33	0.19	-0.72	0.05

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
NON_Ex 500 v 200	-0.03	0.02	-0.07	0.02
NON_Ex 1000 v 200	-0.07	0.06	-0.19	0.05
NON_Ex 2500 v 200	-0.13	0.14	-0.42	0.16

Dependent Variable: Emotional

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
NON_Ex 500 v 200	-0.07	0.05	-0.16	0.02
NON_Ex 1000 v 200	-0.17	0.11	-0.40	0.06
NON_Ex 2500 v 200	-0.35	0.28	-0.90	0.21

Pair-wise comparisons	Estimate	Standard Error	95% Confidence Limits	
Ex 500 v 100	-0.06	0.07	-0.19	0.08
Ex 1000 v 100	-0.12	0.14	-0.40	0.16
Ex 2500 v 100	-0.33	0.37	-1.08	0.41