PREOPERATIVE EXERCISE FOR PATIENTS WITH PANCREATIC CANCER: FEASIBILITY, INFLUENCES, AND OUTCOMES

A Dissertation

Presented to

The Faculty of the Department

of Health and Human Performance

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Nathan H. Parker

May, 2017

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ABSTRACT

Risk for adverse disease- and treatment-related outcomes increases with older age and prevalent frailty, cachexia, and sarcopenia among patients with pancreatic cancer, the 3rd leading cause of US cancer-related death. Complex surgeries can allow for longer-term survival among patients with resectable tumors, but postoperative recovery is arduous. Preoperative treatment for pancreatic cancer frequently entails chemotherapy and chemoradiation that contribute to reduced fitness. Therefore, maintaining preoperative health and well-being provides an important intervention target. The purpose of this project was to determine the feasibility of multimodal exercise among patients undergoing preoperative treatment for pancreatic cancer and to examine adherence-related influences and outcomes.

Fifty eight patients [48.3% female, mean age 65.8 (SD=7.7)] with localized pancreatic adenocarcinoma enrolled and completed study requirements from 2015-2017. Patients were encouraged to perform ≥120 minutes of moderate-intensity, multimodal exercise per week (≥60 min aerobic and ≥60 min strengthening exercise). Patients received instruction and equipment (resistance tube sets, pedometers), materials (video and printed/photo instructions) and regular phone communication to encourage adherence. Physical activity (PA) and exercise adherence were measured using questionnaires, daily logs, and accelerometers. Socioecological physical activity supports, such as social support from family and friends and perceived neighborhood walkability, were measured using questionnaires. Outcome measures included self-reported health-related quality of life (QOL) and skeletal muscle cross-sectional area in computerized tomography (CT) scans. A subsample participated in structured, qualitative interviews to examine overall satisfaction,

suggestions for improvement, and perceived barriers, facilitators, and outcomes related to participation.

Patients reported significantly higher physical activity at preoperative restaging compared to baseline [mean(SD) weekly metabolic equivalent minutes 2321.4(2282.8) vs. 1370.4(1833.7), $Z(51)=-2.2$, $p=.03$]. Including all preoperative phases (chemotherapy, chemoradiation, and rest), patients reported, on average, 168.3 minutes of multimodal exercise per week (SD=88.2). Patients exceeded the weekly recommendation for aerobic exercise minutes [mean(SD)=124.8(81.2)] but did not meet the weekly strengthening recommendation [mean(SD)=43.3(31.8)]. Average accelerometer-measured moderate-to-vigorous physical activity was 145.8 min/week (SD=135.7). There were no statistically significant differences in physical activity or exercise adherence by phase.

Social support and exercise adherence had weak but statistically significant associations after adjusting for age, sex, and surgical determination. Family participation and weekly strengthening minutes (ß=.36, $p=.03$) and overall strengthening volume (ß=.40, $p=.02$), between family rewards and punishment and strengthening volume (ß=.56, $p<.01$), and between family and friend participation and weekly strengthening minutes (ß=.35, $p=.03$) and strengthening volume (ß=.38, $p=.03$) were all positively associated.

Weekly accelerometer-measured light and total physical activity and QOL at preoperative restaging were positively associated (ß=.35, $p=.04$ and ß=.35, $p=.03$, respectively) after adjusting for age, sex, exercise program duration, and final surgical determination. There were also positive associations between aerobic and multimodal exercise volumes and change in skeletal muscle cross-sectional area (ß=.31, $p=.03$ and ß=.32, $p=.02$, respectively) from baseline to preoperative restaging.

In qualitative interviews, patients expressed general program satisfaction and recommended fitness facility use to increase strengthening exercise adherence. Patients identified disease- and treatment-related fatigue and side effects as exercise barriers. However, patients widely agreed that social support from family and friends and accountability through daily exercise logs and communication with program staff helped them overcome these barriers. Finally, patients perceived reduced fatigue and improved fitness leading to surgery, which they attributed to consistent preoperative exercise.

These findings indicate that exercise is generally feasible for patients undergoing preoperative treatment for pancreatic cancer, but extra support may improve strengthening exercise adherence. Clinicians and researchers should formally incorporate exercise in treatment plans for patients with potentially resectable pancreatic cancer. Future studies should further explore the potential for exercise to improve perioperative health and well-being and identify additional factors influencing exercise motivation in this context.

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I owe a great deal of thanks to many individuals for their invaluable contributions to this project. I thank Dr. Rebecca Lee and Dr. Daniel O'Connor for their fantastic mentorship throughout my doctoral studies and for pushing me to become a better writer and scientist. I thank Dr. Matthew Katz for supervising the clinical aspects of this project and for inviting me to form this collaboration between the University of Houston and the University of Texas MD Anderson Cancer Center. I also thank Dr. Richard Simpson for serving on my dissertation committee and providing helpful advice and feedback during the planning and writing phases of this project.

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CHAPTER 1

1. INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Pancreatic cancer is the 3rd leading cause of cancer-related death in the United States.[1] Approximately 45,000 Americans are diagnosed with pancreatic cancer annually. Combining all disease stages, 1-year and 5-year mortality rates are 80% and 94%, respectively.[2] Surgical tumor resection, or pancreatectomy, is the only potentially curative therapy for pancreatic cancer. Between 18-24% of patients who undergo complete tumor resection survive at least 5-years following surgery.[3] Pancreatectomy is a complex operation that entails arduous recovery involving physical performance, nutritional status, pancreatic function, and health-related quality of life.[4-6]

Pancreatic cancer most commonly afflicts older adults, with the average patient diagnosed at age 71.[7] Approximately two-thirds of patients are diagnosed at age 65 or older.[7] Frailty, or progressive loss of physical function, frequently accompanies pancreatic cancer diagnosis[8] and may be characterized by exhaustion, low physical activity, weak grip strength, slow gait speed, and weight loss.[9] Adverse post-surgical outcomes including major complications, longer hospital stays, and intensive care unit admissions have been associated with preoperative frailty.[10] Obesity, cachexia, sarcopenia, and sarcopenic obesity are also prevalent among patients undergoing therapy for pancreatic cancer.[11-13] These scenarios complicate decisions to perform curative operations and increase risk for adverse post-surgical outcomes.[13-17]

Traditionally, postoperative rehabilitation has been used to improve outcomes for patients who undergo curative surgical resection for pancreatic cancer. A recent, home-based, structured walking program was found to reduce fatigue and improve health-related quality of life among patients who underwent pancreatectomy for pancreatic or periampullary cancer.[18] Although rehabilitation has been successful, anxiety regarding adjuvant therapy or recurrence, concern about healing, and fatigue during the recovery period may be formidable barriers to postoperative exercise adoption for some patients.[19,20]

A growing body of evidence suggests that *pre*operative exercise may provide a more appropriate and effective intervention to improve post-surgical outcomes. Known generally as *cancer prehabilitation*, interventions to optimize health and physical performance prior to surgical intervention have improved disease-related outcomes and quality of life for patients with various cancers.[20] Documented outcomes from cancer prehabilitation include improvements in physical functioning and psychological health and reductions in morbidity, hospital readmission, and cancer-attributable healthcare costs.[20]

The preoperative period may be particularly important for improving care and outcomes for patients with resectable pancreatic cancer. Neoadjuvant chemotherapy and chemoradiation are being used more frequently for pancreatic cancer[8,21] and muscle loss frequently accompanies these treatments.[12] Anxiety and stress that adversely impact psychological well-being and quality of life frequently accompany pancreatic cancer diagnoses and therapies.[22] Prehabilitative exercise may provide important benefits in mitigating muscle loss during neoadjuvant therapy, reducing anxiety and stress, preserving or increasing physical function, and improving health-related quality of life.[19,20] Patients undergoing radiation therapies for other cancer diagnoses have shown increased fatigue and related biomarkers, including C-reactive protein.[23] C-reactive protein has been shown to be an important indicator of prognosis among patients with pancreatic cancer, with lower levels of preoperative C-reactive protein associated with long term survival.[24,25] There exists theoretical basis for preoperative exercise to reduce C-reactive protein and systemic inflammation among patients with cancer, but scientific evidence to date is inconclusive.[26]

The benefits of prehabilitation may continue after surgery, helping to limit the burdens patients face from surgical complications, hospital stays or readmissions, and cancer-attributable healthcare costs.[19,20] Preoperative physical activity may contribute to postoperative recovery of physical function, health-related quality of life, nutritional status, and pancreatic function, all of which have been problematic following curative pancreatectomy.[6] The potential for patients with pancreatic cancer to perform preoperative physical activity through a prehabilitation intervention and to benefit from this program warrant close examination.

Relationships between socioecological factors and physical activity are well-documented among adults and older adults. Such influences include social support from family and friends and access to safe, convenient opportunities and resources for physical activity in home and neighborhood environments.[27-29] Although physical activity is known to be an important component of a healthy lifestyle for cancer survivors across the continuum of diagnosis and treatment, evidence regarding socioecological supports for and barriers to physical activity in this population is limited. Previous studies have exposed difficulties in physical activity adoption and maintenance among survivors of other cancers *after* surgery, but evidence regarding the barriers that explain these difficulties is sparse.[30] To date, no studies have examined factors facilitating or hindering *pre*operative physical activity for patients with any type of cancer.

Patients' networks for social support may vary widely based on age, employment, marital status, and the involvement of friends and family in providing cancer care. Patients from different areas of the United States, like those who seek care from large, referral cancer hospitals like The University of Texas MD Anderson Cancer Center, may experience different environmental influences on physical activity in their home and neighborhood environments. It is important to examine patients' access to and experiences with supportive (or unsupportive) social interactions and environments and how these factors influence physical activity. Without an understanding of the socioecological factors that affect program adherence, prehabilitative exercise programs may not reach their maximum potential to engage or benefit patients with resectable pancreatic cancer.

To date, no studies have measured preoperative physical activity among patients with cancer objectively, such as with accelerometers. Prehabilitation studies have typically relied solely upon self-report using surveys and exercise logs to quantify physical activity levels and assess intervention adherence.[31] Such tools have demonstrated modest validity and reliability, but they are subject to issues with recall and reporting and favorability biases.[32,33] Recent recommendations from behavioral and exercise scientists urge clinicians to utilize objective methods, such as accelerometers, in studies and interventions to increase physical activity.[32]

Multimodal neoadjuvant therapy for pancreas cancer frequently entails chemotherapy, then chemoradiation, then a recovery period before surgery. Chemotherapy and chemoradiation treatments may influence and be influenced by functional status, including physical activity.[8,34-36] Tolerance of toxic systemic treatments, energy, and fatigue that affect exercise program adherence may vary widely for a given patient (across time points and types of treatment) and between patients (based on fitness and physiological reactions to drugs) during neoadjuvant therapy. Exercise programming during these dynamic courses of therapy may benefit from continuous monitoring to objectively capture and quantify patients' physical activity and program adherence. For example, it may be important to increase exercise gradually throughout therapy as patients experience less fatigue and other side effects as they transition from chemotherapy to chemoradiation and, finally, into the preoperative recovery period. Objectively measuring physical activity and examining relationships between physical activity and its potential influences across these contexts will provide important information to aid the design of effective prehabilitation programs.

This project occurred in conjunction with an existing pilot study examining the feasibility of a preoperative exercise program among patients with technically resectable pancreatic cancer at MD Anderson Cancer Center. *Figure 1* provides a general schematic of this pilot study. The exercise prescription in this program included both moderate-intensity aerobic exercise (at least three days per week for at least 20 minutes each day) and moderate-intensity strengthening exercises (at least two days per week for at least 30 minutes each day). The strengthening protocol featured a selection of exercises targeting all major muscle groups. Strengthening exercises were performed using sets of portable, graded elastic resistance tubes. Patients also received detailed written and photo exercise guides, video exercise guides, pedometers, and sets of daily and resistance exercise logs. Research staff conducted follow-up phone calls with each patient every two weeks to encourage adherence, answer questions, and monitor for adverse events.

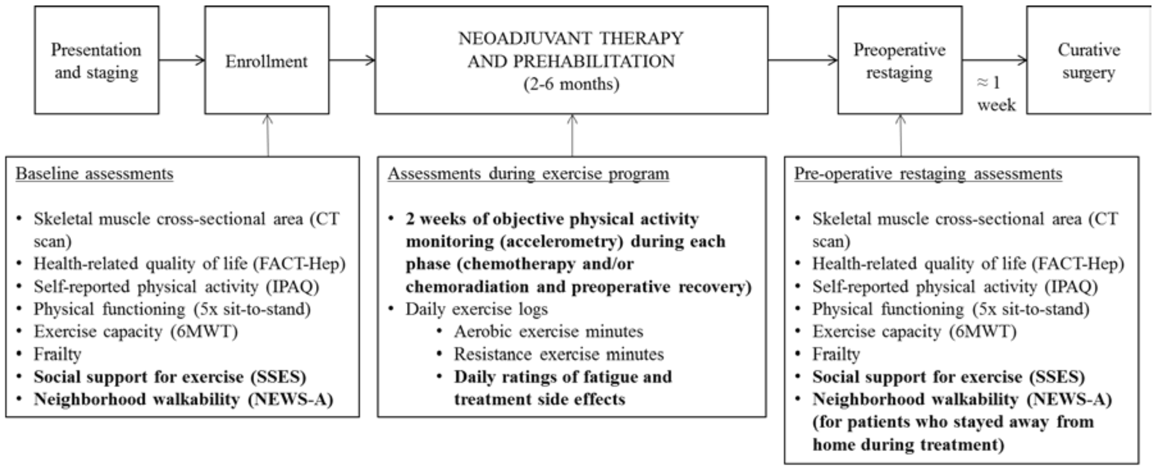


Figure 1. Study schematic.

1.2 PROBLEM STATEMENT

Pancreatic cancer diagnosis and neoadjuvant therapy have substantial physiological and psychological impacts on patients, particularly among older adults who may be frail, obese, cachectic, sarcopenic, or some combination of these conditions.[12,22] Surgery for pancreatic cancer, due to its anatomical complexity and both the arduous recovery and perioperative risks, requires that patients exhibit substantial preoperative robustness.[4] While preoperative exercise shows great promise in improving clinical and quality of life outcomes among patients with other cancer diagnoses, no studies to date have examined formal prehabilitation programs among patients with pancreatic cancer. Prior to this study, there were no scientific findings quantifying the physical activity that patients with pancreatic cancer perform during neoadjuvant therapy or exploring the influences of socioecological supports and barriers on physical activity during a formal, preoperative exercise program. Finally, there were no scientific findings regarding clinical outcomes or psychological health and quality of life outcomes through which patients may benefit from participation in pancreatic cancer prehabilitation.

This study filled important gaps in the scientific understanding of preoperative physical activity for patients undergoing therapy for pancreatic cancer. First, it quantified physical activity objectively as patients transitioned through stages of preoperative treatment while participating in a formal prehabilitation exercise intervention. This study also provided evidence regarding potential benefits from preoperative exercise, including preservation of lean muscle tissue during neoadjuvant therapy, reduction of systemic inflammation, and maintenance or improvement in health-related quality of life. Finally, this study examined potential socioecological influences on physical activity, including social and environmental factors, that preoperative exercise interventions may need to address in order to optimize adherence and benefits.

1.3 SPECIFIC RESEARCH AIMS

Figure 2 shows the study variables and their theoretical relationships that this study examined.

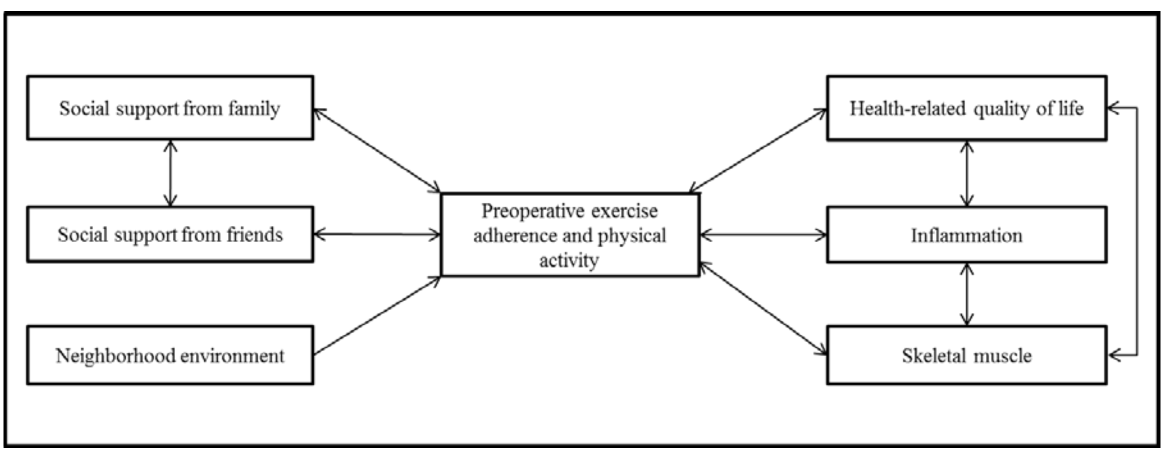


Figure 2. Potential relationships among study variables.

This study involved 3 general research questions, each with 2-3 related questions and hypotheses:

Research question 1: How much aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, and total physical activity do patients with resectable pancreatic cancer perform per week while participating in a preoperative exercise intervention?

Research question 1.1: What percentage of the prescribed guidelines for moderate-intensity aerobic exercise (minimum 60 minutes per week) and moderate-intensity strengthening exercises (minimum 60 minutes per week) do patients with resectable pancreatic cancer report performing during a preoperative exercise intervention?

Research question 1.2: How do weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines vary across stages of neoadjuvant therapy (chemotherapy and chemoradiation) and the preoperative recovery period among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

> ***Hypothesis 1.2*:** Weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would vary across stages of neoadjuvant therapy (chemotherapy and chemoradiation) and the preoperative recovery period among patients with resectable pancreatic cancer participating in a preoperative exercise intervention. Physical activity and exercise adherence would be highest during the recovery period, followed by chemoradiation, then chemotherapy.

Research question 1.3: How are weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines associated with self-reported daily fatigue and treatment side-effects among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Hypothesis 1.3**:** Weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would be negatively associated with self-reported daily fatigue and treatment side-effects among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

The general purpose of **research question 1** was to quantify physical activity among patients undergoing prehabilitation for pancreatic cancer. Prior to this study, no studies had measured preoperative physical activity objectively, such as using accelerometers. Objective monitoring provided important, unbiased information regarding patients' physical activity performance during courses of neoadjuvant therapy that may be physically and emotionally taxing. Objective monitoring quantified performance of light physical activity, moderate-to-vigorous physical activity, and total physical activity. However, accelerometers may not capture moderate-intensity resistance exercise reliably.[37] Therefore, data from daily and resistance exercise logs complemented objective monitoring data by capturing physical activity throughout the entire preoperative period and, more specifically, time spent performing aerobic and resistance exercise. Understanding how physical activity performance changed across different courses of therapy and the levels of fatigue and treatment side-effects that patients reported on a daily basis will help inform future prehabilitation programs. For example, it may be important to prioritize activity during specific time points and better fit patients' needs or to grade exercise prescriptions to adapt to changing functional capabilities during treatments.

Research question 2: How are socioecological supports and barriers associated with aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Research question 2.1: How is social support from family and friends associated with aerobic exercise, resistance exercise, total physical activity, moderate-to-vigorous physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

> ***Hypothesis 2.1*:** Higher social support from family and friends would be positively associated with weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention. This relationship was hypothesized to be bidirectional, as social support may increase as participants engage in an exercise program and become more active.

Research question 2.2: How are home neighborhood walkability and neighborhood sociodemographic characteristics associated with aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Hypothesis 2.2*:* Higher neighborhood walkability would be positively associated with aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

The purpose of **research question 2** was to examine socioecological supports and barriers for physical activity that may influence physical activity adoption or adherence to the preoperative exercise program. Studies have demonstrated that socioecological supports, including social support from family and friends and home and neighborhood resources for physical activity, can influence physical activity among older adults.[38-44] However, no prior studies have examined these influences in the context of a preoperative exercise program for patients undergoing cancer therapy or among patients with pancreatic cancer. Examining supports and barriers for physical activity among patients undergoing prehabilitation for pancreatic cancer helped highlight important, potentially unmet needs in this and other preoperative exercise programs. For example, some patients may benefit from program components that incorporate exercise companionship from friends or significant others. Some patients may live in neighborhoods that lack sidewalks or are otherwise unsafe for walking; for these patients, it may be important to use mapping software to find and plan other safe routes for walking.

Research question 3: How are aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines related to clinical characteristics and quality of life among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Research question 3.1: How are aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines related to preservation of skeletal muscle tissue and systemic inflammation among patients undergoing prehabilitation for pancreatic cancer?

> ***Hypothesis 3.1**:* Higher aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would be associated with preservation of skeletal muscle tissue and reduced inflammation among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

Research question 3.2: How are aerobic exercise, resistance exercise, total physical activity, moderate-to-vigorous physical activity, and general adherence to program guidelines related to health-related quality of life among patients undergoing prehabilitation for pancreatic cancer?

> ***Hypothesis 3.2**:* Higher aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would be associated with improvement in health-related quality of life among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

Research question 3.3: How do changes in skeletal muscle among patients with resectable pancreatic cancer participating in a preoperative exercise intervention compare with those among historical controls?

Hypothesis 3.3: Loss of skeletal muscle would be attenuated among patients with resectable pancreatic cancer participating in a preoperative exercise intervention compared to historical controls.

Inflammation and detrimental changes in body tissue composition are known to occur during neoadjuvant therapies among patients with resectable pancreatic cancer.[6,12] The potential for preoperative physical activity to improve these characteristics among patients with other cancers is unclear,[23,26,45] and these relationships have not been studied in the context of neoadjuvant therapy for pancreatic cancer. Preoperative exercise interventions have potential to impact psychological health and health-related quality of life among patients with cancer.[19,20,46] However, no studies prior to this one had examined health-related quality of life among patients undergoing prehabilitation for pancreatic cancer. **Research question 3** helped inform future prehabilitation programs by highlighting the important benefits of preoperative exercise among patients with pancreatic cancer and by exposing areas of patient health and well-being that may need additional intervention or support. These findings may help guide revision of institutional policies and protocols regarding the optimization of patient health during preoperative therapies for pancreatic cancer and other diagnoses.

1.4 OUTLINE

An overview of the details provided within this dissertation follows.

Chapter 1, the Introduction, introduces the topic for this dissertation. It also serves as a guide for the chapters that will follow.

Chapter 2, the Literature Review, explains the current research available on the topic and points out limitations in the current knowledge. Upon reading this chapter the reader should understand the purpose for the investigation topic.

Chapter 3, the Methodology, will fully describe the planned methodology for executing the research necessary to fulfill Research Aim 1, 2, and 3.

Chapter 4, Manuscript 1, describes research and results regarding Aim 1.

Chapter 5, Manuscript 2, describes research and results regarding Aim 2.

Chapter 6, Manuscript 3, describes research and results regarding Aim 3.

Chapter 7, the Conclusion, summarizes findings from this dissertation and describes future directions, limitations, and implications for research, policy, and practice.

CHAPTER 2

2. LITERATURE REVIEW

2.1 INTRODUCTION

This literature review presents a detailed overview of the current knowledge regarding preoperative exercise for patients with pancreatic cancer. The research project described in this dissertation examined the feasibility of and influences and outcomes related to adherence to a preoperative exercise program among patients undergoing therapy for pancreatic cancer. Prior to this dissertation, no formal research studies have investigated preoperative exercise programs in this population. Therefore, there are no previous scientific findings regarding the outcomes of such programs or factors influencing physical activity or exercise intervention adherence. This literature review thus presents research that is as closely related to the aims of the dissertation project as possible.

Specifically, this document reviews literature in the following domains: 1) benefits of physical activity for patients with cancer, 2) preoperative exercise programs for patients undergoing cancer therapy, 3) potential utility of preoperative exercise for patients undergoing therapy for pancreatic cancer, 4) socioecological models and influences on physical activity, and 5) physical activity influences among patients with cancer. Pancreatic cancer is typically diagnosed later in life, with an average age of 71.[7] Approximately two-thirds of patients with pancreatic cancer are diagnosed at 65 or older.[7] The University of Texas MD Anderson Cancer Center, the site of the proposed research project, provides care for patients with pancreatic cancer who are primarily from the United States. Given these circumstances, this literature review focuses on cancer survivors and older adult populations in the United States.

2.2 BENEFITS OF PHYSICAL ACTIVITY FOR CANCER SURVIVORS

The Centers for Disease Control and Prevention defines a cancer survivor as any individual who has been diagnosed with cancer.[47] A growing body of literature has examined the benefits of physical activity for cancer survivors at various stages in the cancer continuum, from diagnosis through long-term survival. Studies and meta-analyses have demonstrated long-term benefits associated with physical activity among cancer survivors, including improvements in psychological health and well-being, physical fitness, physical functioning, fatigue, quality of life, and weight management.[48-52]

In response to the published benefits of physical activity, the American Cancer Society and American College of Sports Medicine have published guidelines encouraging cancer survivors to be physically active.[53,54] These guidelines mirror those for healthy adults, including recommendations for at least 150 minutes of moderate-to-vigorous aerobic activity or 75 minutes of vigorous activity per week, twice-weekly resistance exercises for all major muscle groups, and avoidance of inactivity as much as possible during diagnosis, treatment, and longer-term survivorship.

Despite recommendations and evidence of its benefits, cancer survivors do very little physical activity. Studies have estimated that fewer than 10% and fewer than 30% of survivors will do any physical activity during treatment and after treatment, respectively.[55,56] The recent paradigm shift in cancer care from focusing on disease-specific treatments to including those that help improve wellness and quality of life comprehensively has made physical activity an important area of research in cancer survivorship. Current consensus is that healthcare providers should develop and improve their understanding and incorporation of physical activity in cancer survivorship.[49] To date, many of the findings regarding physical activity benefits for cancer survivors stem from studies involving prevalent cancers with higher survival rates, such as breast, prostate, and colorectal cancer.[50-52,57-61]

It is important to extend physical activity research to survivors of other cancers, such as pancreatic cancer, and specific contexts within the cancer continuum, such as during preoperative therapy. Pancreatic cancer is the 3rd leading cause of cancer-related death in the United States.[1,2] Approximately 45,000 Americans are diagnosed with pancreatic cancer annually, and, combining all disease stages, 1-year and 5-year mortality rates are 80% and 94%, respectively.[2] Surgical resection is the only potentially curative treatment for pancreatic cancer, and between 18-24% of patients who undergo complete tumor resection survive at least 5-years following surgery.[3]

Pancreatic cancer commonly afflicts older adults.[7] Frailty, cachexia, sarcopenia and sarcopenic obesity associated with both pancreatic cancer and its patients' age profile increase the risk for adverse disease- and treatment-related outcomes.[8,11-13] Surgery for pancreatic cancer is complex, making preoperative fitness important for both decisions to proceed with surgery and to aid postoperative recovery.[4] Surgery is increasingly preceded by systemic therapies that may diminish functional status or be unfeasible or ineffective if functional status is poor.[8,12,34-36,62] Given this context, it is important to understand influences and outcomes related to health optimization, such as through physical activity, among patients undergoing preoperative therapy for pancreatic cancer. Prior to this dissertation, no formal study had examined physical activity influences or outcomes in this setting.

2.2.1 QUALITY OF LIFE

Quality of life is an important, patient-centered outcome that investigators frequently include in investigations involving physical activity and cancer survivorship. Mental, social, emotional, functional, and physical quality of life have all been examined as outcomes for physical activity interventions involving cancer survivors.[49,63]

Several physical activity interventions have demonstrated significant and clinically relevant improvements in psychological health and quality of life. From their 6-month, “Steps to Health” home-based exercise intervention for endometrial cancer survivors, Basen-Engquist et al. reported improvements in psychological aspects including stress and negative emotions.[64] Patients participating in “Steps to Health” received home-based exercise prescriptions and counseling based on Social Cognitive Theory using written materials and telephone calls.[64,65] In their 2012 meta-analysis of quality of life outcomes from physical activity interventions among cancer survivors, Ferrer et al. found that greater volumes of prescribed aerobic exercise conferred greater impacts on psychological health and quality of life.[66] Exercise-associated improvements in health-related quality of life have been studied extensively in the contexts of longer-term survivorship and post-treatment settings for survivors of breast, prostate, and colorectal cancer.[66]

More research is needed to examine the impacts of physical activity on psychological health and quality of life for survivors of other cancers, such as pancreatic cancer. Patients with pancreatic cancer can experience significant fear and anxiety regarding disease progression and treatments and report low psychological health and quality of life following surgery.[22] Therefore, patients with pancreatic cancer may benefit greatly from exercise-related improvements in psychological health and quality of life. The potential for physical activity to improve psychological health and quality of life during other periods of the cancer care continuum, such as during neoadjuvant therapy,[20] warrants further investigation. These potential improvements may also be particularly important for patients with pancreatic cancer, who face complex surgery with arduous recovery when they finish neoadjuvant treatments.[4]

Many studies examining physical activity among cancer survivors have used the Functional Assessment of Cancer Therapy (FACT) questionnaires[67] which were designed specifically for cancer patients.[46,66] The FACT-General (FACT-G) has subscales examining multiple important aspects of quality of life, including physical, social/family, emotional, and functional well-being. Additionally, the FACT provides cancer-specific subscales that examine potential physical and functional problems that patients may experience with a given type of cancer.[68] The FACT-Hepatobiliary (FACT-Hep)[69] has been used to examine self-reported quality of life among patients undergoing neoadjuvant therapy for pancreatic cancer [70] and for patients who underwent curative surgery for pancreatic cancer.[22]

2.2.2 PHYSICAL FITNESS AND PHYSIOLOGICAL OUTCOMES

Exercise interventions among cancer survivors have elicited important outcomes regarding physical fitness and physiological outcomes including cardiorespiratory endurance, muscular strength and endurance, and improvements in cardiometabolic profiles.[49] Cardiorespiratory fitness is known to reduce blood pressure and inflammation and improve insulin sensitivity and blood lipid profiles among the general population.[71] Further, cardiorespiratory fitness is a strong predictor of mortality among survivors of some cancers.[71,72] Evidence from physical activity interventions demonstrates improvements in cardiorespiratory fitness among cancer survivors, potentially in mitigating impairments in fitness due to cancer treatments. Such improvements have been reported among breast cancer survivors participating in a 6-week exercise intervention following surgery[73] and prostate cancer survivors participating in a 12-week program during androgen suppression therapy.[74]

Loss of muscular performance can accompany the decrease in physical activity that typically occurs during therapy for cancer.[49] Studies incorporating resistance training into physical activity programs have shown improvements in muscular endurance and strength,[75] but most of this research has been conducted among breast cancer survivors.[76-78] A review by Ballard-Barbash et al. examining the effects of physical activity on cardiometabolic profile biomarkers, such as leptin, insulin, and inflammatory markers shows that exercise may improve these indices.[79] However, this evidence is still considered preliminary, because few trials have been designed to detect changes in cardiometabolic markers as primary study endpoints [79]. It is important for studies involving exercise and cancer survivorship, including those focusing on the preoperative period, to examine effects on muscular performance and cardiometabolic profile biomarkers.

2.2.3 PHYSICAL FUNCTIONING AND FATIGUE

Quality of life extends to physical functioning and fatigue, which are also important targets for improvement from physical activity interventions among cancer survivors. As Banks et al. reported, psychological distress is most frequently attributable to cancer-related physical disability and loss of physical functioning among cancer survivors.[80] Reduction in one's ability to perform activities of daily living can increase the stress and anxiety involved with cancer therapy.[81] Activities of daily living include walking, climbing stairs, dressing, continence and using a restroom, transferring from bed to foot and vice versa, feeding, cooking, doing housework and laundry, driving or using public transportation, and taking medicine.[82] Loss of independence in accomplishing activities of daily living can increase reliance on caretakers and medical providers and increase the likelihood of hospital or nursing home admittance.[83]

In their recent intervention for prostate cancer survivors undergoing androgen deprivation therapy, Winters-Stone et al. found improvements in self-reported physical functioning and reductions in self-reported disability after 1-year of resistance training.[84] Cancer-related fatigue is common and distressing among cancer survivors.[85] Proinflammatory cytokines and C-reactive protein may increase cancer-related fatigue during cancer therapy.[23] The sensitivity of these biomarkers to exercise[86,87] provides a pathway by which exercise may help reduce fatigue and thus increase quality of life.[88] Intervention studies have shown improvements in cancer-related fatigue with exercise programs for survivors of breast[85] and prostate cancer.[89] More research is needed in order to generalize findings across cancer diagnoses and therapies, such as among patients undergoing neoadjuvant treatments for pancreatic cancer.

Studies frequently assess physical functioning and fatigue, important patient-centered outcomes, using self-report on surveys.[23,85,89,90] The FACT-G includes a subscale measuring self-reported physical functioning, including items that examine ability to perform activities of daily living.[67,91,92] Patients with pancreatic cancer have reported low levels of physical functioning and high levels of fatigue using the FACT,[22,93] and these, too, may be important areas for potential benefit from preoperative exercise programs for patients with resectable tumors.

2.2.4 BODY COMPOSITION

Physical activity is important for healthy weight maintenance, including among older adults.[94] Among cancer survivors, healthy weight maintenance may involve reducing adiposity or maintaining or increasing lean muscle tissue. Obesity has been linked with higher risk for mortality in several cancers, including those of the prostate,[95] breast,[96] and pancreas.[13,97] Physical activity interventions have significantly reduced body mass index (BMI) among survivors of breast, colorectal, prostate, and uterine cancers.[98-100] BMI is easily calculated based on height and weight, which are frequently and inexpensively collected and recorded for patients in clinical settings.[101] However, other measures that specifically quantify adipose tissue or central (abdominal) adiposity, such as body fat percentage, a body shape index (ABSI),[102] and waist circumference, may provide more important information regarding body anthropometric and composition changes due to exercise.

Physical activity interventions have also shown the ability to mitigate sarcopenia, or the loss of muscle mass associated with aging.[103] Certain cancer therapies and progression of metastatic tumors can accelerate sarcopenia,[11,104] and some therapies increase risk for sarcopenic obesity, a particularly dangerous condition in which muscle mass decreases while adiposity increases.[105] Sarcopenia and sarcopenic obesity are associated with adverse outcomes including reduction of mobility, loss of physical functioning, and mortality.[106-108] Few studies have examined the effects of physical activity interventions on sarcopenia or sarcopenic obesity among cancer survivors, although findings among breast cancer survivors show promise in the ability of resistance training to reverse a tendency towards sarcopenia during endocrine therapy.[109] Findings among older patients preparing for gastric cancer surgery indicate that resistance exercise can help reverse sarcopenia.[110] Further research is needed to examine the effects of exercise programs that include resistance exercises on mitigating muscle loss during neoadjuvant treatments, such as for patients with resectable pancreatic cancer. Recently, estimates for specific tissue masses and volumes, including adipose tissue (subcutaneous, visceral, and intramuscular) and skeletal muscle, have been obtained reliably using methods such as dual energy X-ray absorptiometry (DXA) and analyses using computerized axial tomography (CT) scans.[111] The latter, which utilizes computer software (TomoVision, 2012) and CT scans that patients routinely undergo at restaging visits, has been used to analyze changes in body composition during neoadjuvant therapy for pancreatic cancer.[12,35]

2.3 PREOPERATIVE EXERCISE PROGRAMS FOR CANCER SURVIVORS

Preoperative exercise, or “prehabilitation,” has recently emerged as an important element in cancer care for survivors whose course of therapy include plans for surgical resection. Silver, et al. define cancer prehabilitation as a process that “promote(s) physical and psychological health to reduce the incidence and/or severity of future impairments”.[112] The clinical and physiological grounds for cancer prehabilitation are well-documented. Preoperative fitness, as measured by performance on the 6-minute walk test, has been linked to reduced risk of postoperative complications and shorter hospital stay following pulmonary resection for patients with lung cancer.[113] Another study showed that preoperative cardiopulmonary exercise testing could help predict morbidity following surgery for colorectal cancer.[114] Preoperative exercise may be particularly important for older adult patients and or those who have low baseline physical function.[115]

Although most of the literature regarding exercise and cancer survivorship has focused on rehabilitation or physical activity later in cancer survivorship, recent studies have demonstrated the feasibility of and potential benefits from preoperative exercise programs for patients with various cancers. These patients have included those undergoing neoadjuvant therapy or awaiting surgery for cancers of the head and neck,[116] prostate,[117,118] colon,[31,119] and lung.[120,121] Single-patient case studies involving prehabilitative exercise programs have shown benefits for patients with breast cancer[122] and pancreatic cancer[123]. Several studies have demonstrated the efficacy of prehabilitation for older patients undergoing surgery for non-cancer diagnoses.[124-126]

2.3.1 PROGRAM DESIGNS

Few randomized trials have been conducted to test the effects of full-body exercise or general physical activity on perioperative and long-term outcomes among cancer survivors.[31,127-130] Several prehabilitation studies have included exercise prescriptions that target preoperative optimization of body areas or organs that are disease-specific, such as pelvic-floor strengthening exercises for patients with prostate cancer[117] and breathing exercises for patients with lung cancer.[131] Published studies have included both aerobic and resistance training components, and both supervised, in-person sessions and home-based programs. In their 2014 methods article, Santa Mina et al. described a multi-center, randomized controlled trial in which men were prescribed 60 minutes of home-based, moderate-intensity aerobic and strengthening exercise on 3-4 days per week for 4-8 weeks preoperatively. Results from this trial are not yet published, but initial pilot study results suggested that the program was feasible.[117] Gillis et al. conducted a randomized controlled trial testing the effects of a home-based intervention incorporating aerobic and resistance exercises, nutritional counseling, protein supplementation, and relaxation exercises for patients awaiting surgery for colorectal cancer.[31] In their program, patients in the exercise group performed up to 50 minutes of moderate-intensity aerobic and resistance training on at least 3 days per week.[31] Both the Santa Mina et al. trial and the Gillis et al. trial include control groups receiving the current standard of care, and in the Gillis et al. study, both groups receive the same exercise program for 8 weeks postoperatively. Both studies include preoperative and postoperative assessments. Both studies feature the 6-minute walk test as a main outcome and measure of physical fitness.[31,117] Both studies measure physical activity and program adherence by self-report, using exercise logs[31] or questionnaires.[117] Both studies include measures of psychological health, health-related quality of life, and anthropometric characteristics.[31,117] To date, few preoperative exercise studies have employed home-based exercise programming,[129,130] and none involved patients who were concurrently undergoing neoadjuvant treatment.

2.3.2 OUTCOMES AND BENEFITS FROM PREOPERATIVE EXERCISE PROGRAMS FOR PATIENTS WITH CANCER

In their 2014 study, Gillis et al. reported that patients with colorectal cancer in the prehabilitation group maintained or regained functional exercise capacity following surgery more effectively than patients in the traditional, rehabilitation group. Carli et al. reported low adherence in their 2010 study showing results from randomizing colorectal cancer patients to exercise programs featuring either stationary bicycling or walking plus breathing exercises.[127] However, patients who improved physical function during this exercise program (implying adherence) showed significant improvements in mental health, vitality, self-perceived health, and exercise capacity.[132] In their 2013 review, Silver and Baima highlight a wide variety of potential benefits that cancer survivors may gain from prehabilitation, including reduced morbidity, improved physical and psychological health, expanded treatment options, decreased hospital readmissions, and both direct and indirect costs of healthcare attributable to cancer.[20]

2.3.3 ADHERENCE TO PREOPERATIVE EXERCISE PROGRAMS

While physical activity among survivors is low across the cancer continuum,[55,56] evidence regarding supports or barriers to physical activity is limited. Moreover, preoperative exercise interventions prescribing home-based exercise have reported wide ranges of intervention adherence. Among programs including aerobic and/or resistance exercise prescriptions, Mayo, et al. reported low adherence to their prehabilitative exercise program for patients with colorectal cancer, with only 16% of patients completing the program fully.[132] Gillis et al. reported 78% compliance during their intervention.[31]

Generally, physical activity and exercise program adherence have been measured using self-report on questionnaires, such as the Community Healthy Activities Model Program for Seniors (CHAMPS) Physical Activity Questionnaire,[31] and using exercise logs designed specifically for prehabilitation programs.[117] Self-report measures have shown moderate correlations with objective measures of physical activity, but self-report entails issues relating to recall, reporting, and favorability biases.[32] Objective measures of physical activity, such as accelerometer counts or pedometer steps, have been used in interventions involving cancer survivors,[64,133] but not to monitor adherence to exercise programs during the preoperative period. In their 2014 review describing the use of objective monitoring to measure physical activity in clinical settings, Trost and O'Neil highlight the importance of utilizing these measures to obtain unbiased estimates of energy expenditure during exercise programs.[32]

2.3.4 POTENTIAL UTILITY OF PREOPERATIVE EXERCISE AMONG PATIENTS UNDERGOING PREOPERATIVE TREATMENT FOR PANCREATIC CANCER

Preoperative exercise may be both feasible and important for patients undergoing neoadjuvant therapy for pancreatic cancer for a number of reasons. Neoadjuvant therapies serve multiple important purposes. First, systemic therapies help to isolate tumors and slow tumor growth, improving the chance of complete, margin-negative resection.[134] Patients diagnosed with pancreatic cancer are typically older, frequently frail, and often experience comorbid conditions associated with age and frailty including obesity, cachexia, and sarcopenia.[8,12] These conditions make it important to identify patients who are likely to recover adequately from pancreatic resection with minimal risk of perioperative complications. The increasing use of preoperative chemotherapy and/or chemoradiation to improve the chances of margin-negative resection and safe surgeries provides a window of time in which aspects of patients' health can and should be optimized.[8,36,80] Curative surgery for pancreatic cancer entails complex operations[4] and arduous recovery involving physical function, pancreas function, and nutritional status.[5,6,14,24,135] Therefore, it is important to capitalize on the window that neoadjuvant therapies provide to optimize functional status through prehabilitation.

Sarcopenia frequently accompanies neoadjuvant treatments[12] for pancreatic cancer. Chemotherapy and chemoradiation use toxic drug regimens that can cause functional decline, and their administration also requires substantial physical functioning and performance.[8,36,136] Frailty, cachexia, sarcopenia, obesity, and sarcopenic obesity are all prevalent among patients undergoing therapy for pancreatic cancer.[12,14-16,35,137] These conditions and processes can increase systemic inflammation,[137] complicate decisions to perform curative operations,[17] and lead to adverse post-surgical outcomes.[13,15] Exercise during preoperative therapy may help optimize functional and performance status and mitigate adverse changes in body anthropometrics and inflammatory processes, helping to maintain patients' treatment options and reduce perioperative complications.[19,20,46,110,138,139]

There are clear avenues by which preoperative exercise can improve patients' psychological well-being and health-related quality of life. Anxiety and stress that adversely impact psychological well-being and quality of life frequently accompany pancreatic cancer diagnoses and therapies.[22] Exercise has been shown to reduce anxiety and depressive symptoms and improve health-related quality of life among older adult populations and cancer survivors.[18,66,118] The potential for exercise programs to improve psychological health and quality of life in the preoperative setting for patients with pancreatic cancer warrants examination.

Interventions that help increase or maintain fitness, lean muscle tissue, physical functioning, and psychological quality of life in the preoperative period have the potential to benefit patients with pancreatic cancer enormously. These are all aspects of patients' health and well-being that are important in the context of preoperative therapy for pancreatic cancer. Given the physiological and psychological stresses associated with the disease, neoadjuvant therapy, and pancreatectomy, it is important to determine whether patients with pancreatic cancer benefit from prehabilitative exercise programs.

2.4 SOCIOECOLOGICAL MODELS OF PHYSICAL ACTIVITY

Socioecological models provide an important foundation for research investigating influences on and interventions aiming to increase physical activity. Socioecological models posit that there are many influences on health behaviors, such as physical activity.[140-143] These influences occur at various levels, differing in how proximally they affect a given individual.[28,29,144,145] Socioecological influences include intrapersonal factors, such as attitudes, beliefs, values,[146] and self-efficacy for behavior change;[147] interpersonal factors, including interactions with other individuals; and environmental factors, including aspects of the natural and built environments and policies (or lack thereof) that support (or hinder) health behavior in organizations and various levels of government.[148] Influences in each level interact with influences in other levels to affect human behavior.[27-29] Therefore, interventions should address influences in multiple levels in order to be most effective.

Behavior change, such as the adoption and maintenance of physical activity, is optimized and maximized when individuals have sufficient knowledge about and motivation to change their behavior, when social support and social norms for healthy behavior are strong, and when policies and environments support or encourage healthful choices.[28] Socioecological models of health behavior serve to inform behavior change interventions, providing important areas of influence that should be addressed or considered in the design of interventions.[28,149] Therefore, it is important to consider the social and environmental factors that investigations have found to be important influences on physical activity among adults in any program targeting an increase in this behavior. *Figure 3* shows socioecological influences with hypothesized associations with physical activity among participants in the dissertation project.

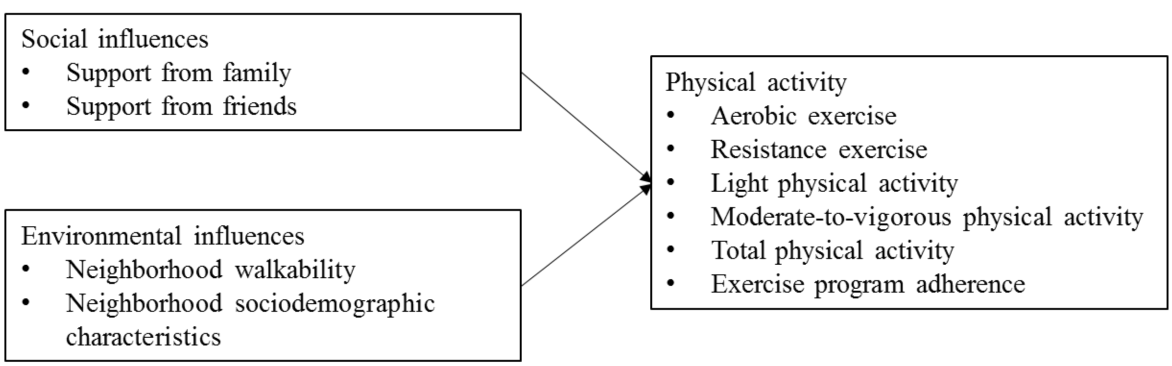


Figure 3. Potential socioecological influences on physical activity in the dissertation project.

2.4.1 SOCIAL INFLUENCES ON PHYSICAL ACTIVITY

Social support for physical activity includes any action on the part of one individual that aids another individual in performing physical activity or reaching desired, physical activity-related goals. Social support for physical activity can come from different people or groups, including spouses, family members, and friends.[150,151] There are three primary forms of social support for physical activity: emotional, informational, and instrumental.[152] Emotional support may increase one's motivation to perform physical activity through encouragement, praise, or companionship that increases enjoyment or accountability. Informational support may help increase physical activity by increasing one's understanding of its benefits or knowledge of where and how to perform physical activity safely and conveniently. Instrumental support from a spouse, family member, or friend may take the form of transportation to a location or event for physical activity or companionship to improve safety.[150,151]

Multiple studies have demonstrated the importance of social influences on physical activity. Emotional, informational, and instrumental social support have been linked directly and indirectly to physical activity among adults and older adults.[153,154] Studies have used surveys, including the Social Support for Exercise Survey (SSES)[155] and qualitative interviews to measure social support.[156]

In their 2013 qualitative examination of physical activity facilitators among highly active, community-dwelling older adults, Franke et al. found that social connections and the social opportunities involved with physical activity were important for maintaining motivation.[41] Older adults participating in qualitative interviews reported social interactions and feelings of connectedness in their communities provided opportunities to maintain physical activity, and vice versa.[41] In their 2014 study involving more than 4,000 older

Americans, Watt et al. found that participants with larger social circles of close friends were more likely to be physically active.[157]

Many studies have shown that maintaining relationships with physically active friends provides social support that helps older adults perform more physical activity.[39,43,153,158,159] These studies and others have found that friends can support physical activity for one another by becoming exercise partners.[43,153,159] Carlson et al. found that having family or friends who provide encouragement or companionship was associated with total physical activity and walking for transportation and leisure among healthy, community-dwelling older adults. Further, the authors found significant interactions between social support and aspects of the built environment in this study.[38] Together, these findings suggest that social support is an important consideration for programs aiming to increase physical activity among older adults.

2.4.2 ENVIRONMENTAL INFLUENCES ON PHYSICAL ACTIVITY

There exists a growing body of literature linking aspects of neighborhood and home environments to physical activity among older adults. The Ecologic Model of Physical Activity (EMPA) posits that multiple environmental levels can influence an individual's physical activity (*Figure 4*).[27,29] The micro-environment level includes the locations in which an individual spends time, including the home, neighborhood, and workplace. Supports and barriers in these environments can facilitate or hinder physical activity, respectively. An individual's own micro-environments are linked dynamically by the meso-environment, such as transportation between them. One person may be linked to another's micro-environments through the exo-environment, such as through conversation. Finally, the broad macroenvironment level includes a community's policies, norms, and social context that may influence physical activity.[27,29].

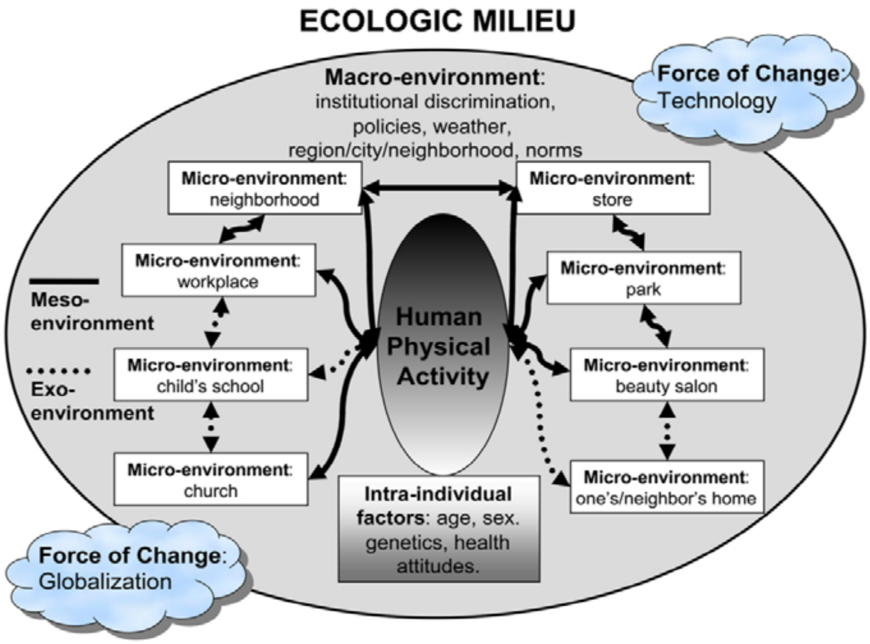


Figure 4. The Ecologic Model of Physical Activity (EMPA)[27,29]

Neighborhood factors may have important influences on the physical activity participants perform during home-based exercise programs, particularly when the program prescribes moderate-intensity walking. A supportive neighborhood may improve the likelihood that a participant adheres to the program's exercise prescription, while a neighborhood that lacks such supports or poses barriers to physical activity may limit participation. A variety of neighborhood characteristics have shown associations with physical activity in these settings. Those of interest in this study can be categorized broadly into walkability (including convenience, aesthetics, and safety), and underlying neighborhood sociodemographic characteristics. Studies have used both objective measures (i.e., audits) and perceived measures (i.e., surveys) to examine these neighborhood factors and their influences on physical activity.

Walkability. Walkability can be measured objectively using indices incorporating neighborhood characteristics such as intersection density, residential density, retail density, and land-use mix [40]. These characteristics are typically compiled using Geographic Information Systems (GIS) shapefiles produced by local governments or councils. In their 2012 study involving older adults from urban communities, Carlson et al. found that walkability, measured objectively with an index that incorporates residential density, retail floor area, intersection density, and land-use diversity,[40] was positively associated with total moderate-to-vigorous physical activity and walking for both transportation and leisure.[38] The same walkability index showed a positive association with walking among older adults living in Metro Atlanta.[40] Older women with access to walking paths and who reported greater degrees of street connectivity and traffic safety measures were more likely to attain the public health goal of 10,000 steps per day in a 2010 study.[42]

Recently, studies have demonstrated mismatches between residents' perceptions of neighborhood walkability and walkability ratings from objective indices.[160,161] Without intervention to correct false perceptions, perceived walkability may be more important in determining physical activity behavior than objective walkability.[162] An individual who perceives his or her neighborhood as low walkable (i.e., walking is inconvenient, unsafe, or boring) may be less likely to walk for recreation or transportation than an individual whose perception is accurate. Instruments such as the Neighborhood Environment Walkability Scale (NEWS) provide measures of perceived neighborhood walkability.[163] The abbreviated version of this survey (NEWS-A) includes subscales examining street layout and intersection density, pedestrian facilities and amenities, aesthetics, and safety from both traffic and crime.[163] High perceived walkability using the NEWS has been linked to more walking for leisure and transportation.[161,162]

Sociodemographic characteristics and neighborhood deprivation. Well-established relationships exist between population and sociodemographic characteristics and the physical activity of residents.[27,164-166] These characteristics include population size and density, and the age, income, employment, ethnicity, and education profiles of neighborhood residents. Neighborhood population density has been positively associated with walking and physical activity.[167,168] Studies have linked indicators of lower neighborhood socioeconomic status to lower physical activity and neighborhood deprivation regarding supports and resources for physical activity among adults and older adults.[169-171] Studies have shown disparate access to quality resources for physical activity, such as pedestrian trails and public parks, in neighborhoods in which residents have lower socioeconomic status[172] or are predominantly of racial or ethnic minority.[173] These neighborhood sociodemographic characteristics may also contribute to participation in home-based exercise programs and should therefore be considered in study design or accounted for in analyses.

2.4.3 PHYSICAL ACTIVITY INFLUENCES AMONG CANCER SURVIVORS

While physical activity participation is low among cancer survivors in all stages of survivorship,[48,55] evidence regarding factors that may increase or hinder physical activity among cancer survivors is limited. Qualitative data from adult cancer survivors suggests that social support, in the forms of companionship, motivation, and health promotion, may influence physical activity participation.[150,174] Characteristics of the home and neighborhood environments, such as the quality and safety of the pedestrian environment and the availability of safe, public parks, have shown important associations with physical activity among older adults[175] and, more specifically, cancer survivors.[176]

To date, no studies have examined socioecological factors facilitating or hindering preoperative physical activity among patients with any cancer diagnoses. Factors facilitating or hindering adherence were not examined in either of the published studies reporting outcomes from preoperative exercise programs for patients with colorectal cancer.[31,127] Previous studies have exposed difficulties in physical activity adoption and maintenance among survivors of other cancers *after* surgery, but only limited and sparse evidence explains these difficulties.[30] Social and environmental influences may be important predictors of physical activity and adherence to formal exercise programs in the preoperative setting. By measuring these variables, studies may provide evidence that improves adherence to, and thus patient outcomes from, future prehabilitation programs.

2.5 SUMMARY

Studies have consistently demonstrated various benefits from activity among cancer survivors. Exercise interventions among cancer survivors have improved health-related quality of life and psychological health, including both anxiety and depressive symptoms. Exercise interventions among cancer survivors have improved functional status, including fitness and physical functioning, and they have reduced fatigue and inflammation. Finally, exercise interventions among cancer survivors have improved anthropometric characteristics and body composition, including reductions in BMI and mitigation of sarcopenia during cancer therapy. Despite consensus regarding physical activity benefits and recommendations to engage in physical activity, participation among cancer survivors is low. Further, most of the evidence regarding the benefits of physical activity and exercise among cancer survivors involve the most prevalent cancers and focus on activity following surgery or in long-term survival. It is important to extend findings regarding the benefits of physical activity to patients with pancreatic cancer. Particularly, physical activity may help improve functional status and quality of life among patients undergoing therapy before curative surgery for pancreatic cancer.

Recent findings support using exercise to optimize health and physical performance prior to cancer surgery. Preoperative exercise interventions have improved physical functioning and health-related quality of life for patients with other cancers, but prior to this dissertation, no formal studies had examined the potential benefits of preoperative exercise among patients with pancreatic cancer. A variety of factors support the potential utility of preoperative exercise for patients undergoing pancreatic cancer therapy. Recovery from pancreatic surgery is difficult and potentially impeded by the typical older age of patients and associated health conditions. Pancreatic cancer diagnosis and therapies involve reductions in both physical and psychological well-being in the preoperative period, and exercise may help mitigate these problems.

To date, the use of only self-report measures to monitor physical activity during preoperative exercise interventions among patients with cancer limits true understanding of program feasibility. Monitoring physical activity objectively as patients participate in an exercise intervention throughout different stages of neoadjuvant therapy can contribute to understanding of how cancer therapies may impact physical activity performance. Additionally, there exists little evidence regarding socioecological factors that may facilitate or hinder preoperative physical activity and program adherence, despite their demonstrated influence on physical activity among adults and older adults.

Taken together, the findings in this literature review demonstrate the importance of studying outcomes and influences related to preoperative exercise among patients undergoing therapy for pancreatic cancer. Preoperative exercise has potential to improve multiple aspects of health and well-being in this population, among whom optimization of health is particularly important. Understanding socioecological influences and monitoring physical activity objectively throughout neoadjuvant treatments can provide important insights regarding program design and feasibility for exercise interventions in the preoperative setting.

CHAPTER 3

3. METHODOLOGY

3.1 DESIGN

This dissertation was a single-group, prospective, longitudinal cohort study. Data were available for comparisons with a historical control group involving skeletal muscle maintenance over the course of preoperative treatment. The study design and procedures generally followed those established and implemented for a prehabilitation pilot study taking place at MD Anderson Cancer Center, but with additional variables and measures.

In the existing pilot study, outcome measures were collected at baseline/enrollment, preoperative restaging (approximately 1 week before surgery) and at postoperative restaging (approximately 1-month after surgery). The proposed research project will add new variables and measures to the current prehabilitation pilot study. Specifically, the new variables added for the proposed study include physical activity (continuous monitoring during the exercise program using accelerometry), social support for physical activity, neighborhood walkability, and potential cancer- and treatment-specific influences on physical activity (fatigue and side-effects). Patients were already recording daily pedometer steps, walking minutes, and resistance exercise minutes in daily exercise logs in the existing prehabilitation study and continued to do so as part of this dissertation project. Health-related quality of life and changes in cross-sectional skeletal muscle area were also operationalized and collected in the previous prehabilitation pilot study, and these variables were outcomes of interest in the proposed project. Operationalization of all variables is explained in detail in the following sections. Frailty, physical functioning, and exercise capacity were measured among all of the same patients participating in the same study, but these measures were not analyzed in this specific dissertation project.

The previous prehabilitation pilot study operated under approval from the MD Anderson Cancer Center Internal Review Board (IRB). All added measures and procedures proposed in this study were approved via revisions to the IRB protocol prior to initiation. Further, the Committee for the Protection of Human Subjects (CPHS) at the University of Houston approved analyses using de-identified data at the University of Houston.

3.2 SETTING

This study was conducted at MD Anderson Cancer Center, a large referral and research hospital in Houston, Texas. MD Anderson provided services to more than 127,000 patients from across Texas, the United States, and the globe in fiscal year 2014, making it one of the world's largest hospitals dedicated to cancer care.[177] The Gastrointestinal Center at MD Anderson treats approximately 1,000 patients with malignancies of the pancreas and periampullary region each year, and approximately 100 of these patients present to MD Anderson with technically resectable adenocarcinomas. These patients typically undergo neoadjuvant chemotherapy and/or chemoradiation prior to surgical resection. This pattern of treatment is being used more frequently among other cancer hospitals and is now the standard of care at MD Anderson.[8,12,21,34]

The typical course of treatment for patients presenting to MD Anderson Cancer Center with technically resectable pancreatic cancer facilitates intervention to optimize functional status. Neoadjuvant therapy thus provides a window to monitor performance status, with tolerance of chemotherapy and chemoradiation suggestive of patients' abilities to tolerate and recover from complex surgery.[134] Additionally, neoadjuvant therapy provides an opportunity for dietary and exercise intervention to improve performance status, such as through prehabilitation.

3.3 PARTICIPANTS AND ELIGIBILITY

Twenty patients enrolled in the previous prehabilitation pilot study, and an additional 50 enrolled in the revised study protocol including all measures for this dissertation project. Enrollment occurred between February 2015 and January 2017. Data from all 70 patients were included Complete data will be available for the 50 patients added under the revised study protocol.

Eligibility criteria included biopsy-proven pancreatic adenocarcinoma diagnosis, intended pancreatectomy with at least 6 weeks until planned resection, treatment plan including neoadjuvant chemotherapy and/or chemoradiation, ability to understand the study and willingness to participate in it, ability to understand the exercise intervention and maintain daily exercise logs, telephone access, and willingness to participate in follow-up calls. Exclusion criteria included lack of English fluency, inability to complete questionnaires or physical assessments at baseline, underlying and unstable cardiac or pulmonary disease or symptomatic cardiac disease (New York Heart Association functional class of III or IV), recent fracture or acute musculoskeletal injury that precludes ability to exercise using all 4 limbs, numeric pain rating of at least 7 out of 10, or myopathic or rheumatologic disease that limited physical function.

Following approval and recommendation from attending medical oncologists or surgeons at initial consultations, all patients completed the Physical Activity Readiness Questionnaire (PAR-Q)[178] and the first question of the Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function 12a Short Form[179] to determine eligibility to participate in the exercise and nutrition intervention. Both of these questionnaires were adapted for use in the Research Electronic Data Capture (REDCap) (Vanderbilt University, 2015) iPad application, allowing patient responses to be stored immediately in a secure online database to which only appropriate research staff had access. Patients who answered questions 2, 3, 4 on the PAR-Q affirmatively (i.e., those who reported experiencing chest pain, dizziness, loss of balance, or loss of consciousness during physical activity or chest pain at rest) were ineligible for enrollment. Patients who affirmatively answered questions 1 or 6 on the PAR-Q (i.e., those who reported heart conditions and recommendations to only perform physical activity recommended by a doctor, or those who were taking medications for hypertension or other heart conditions) required clearance by a physician in Internal Medicine prior to enrollment. Patients who answered PAR-Q question 5 affirmatively (i.e., those who reported having bone or joint problems that worsened with changes in physical activity) required clearance by a physician in Physical Medicine and

Rehabilitation prior to enrollment. Patients who answered PAR-Q question 7 affirmatively (i.e., those who reported any other reason to be cautious about doing physical activity) required clearance from at least one of the study's co-Principal Investigators. Finally, patients who answered the PF_Screener question from the PROMIS Physical Function 12a Short Form negatively (i.e., those who are unable to walk 25 feet on a level surface) were ineligible for enrollment.

The same guidelines for patient selection that guided the prehabilitation pilot study continued to guide patient selection during the dissertation research project. *Table 1* summarizes initial inclusion and exclusion criteria that were assessed by attending physicians (medical oncologists, pancreas surgeons, or both) and determined by subsequent survey and physical performance measures at baseline/enrollment.

Table 1. Inclusion and exclusion criteria

Screening stage	Inclusion criteria	Exclusion criteria
Assessment by medical oncologist or pancreas surgeon during initial staging appointments	1. Biopsy-proven pancreatic adenocarcinoma 2. Scheduled for intended pancreatectomy with at least 6 weeks until planned resection 3. Scheduled for neoadjuvant chemotherapy and/or chemoradiation 4. Able to understand the description of the study and willing to participate 5. Able to understand the exercise intervention and maintain exercise logs 6. Access to a telephone and willing to engage in biweekly follow-up calls with study staff	1. Non-English speaking 2. Unable to complete the baseline assessment questionnaires or functional assessments 3. Underlying unstable cardiac or pulmonary disease or symptomatic cardiac disease (New York Heart Association functional class III or IV) 4. Recent fracture or acute musculoskeletal injury that precludes the ability to weight bear fully on all 4 limbs in order to participate in an exercise intervention 5. Numeric pain rating scale of ≥7 out of 10 6. Myopathic or rheumatologic disease that impacts physical function
Screening questionnaires	1. Able to complete complete the PAR-Q and PROMIS PF_Screener question	1. Experience chest pain, loss of balance, or loss of consciousness during physical activity or chest pain while at rest (PAR-Q) 2. Heart conditions and recommendations to only perform physical activity recommended by a doctors (PAR-Q) AND no clearance from an Internal Medicine physician 3. Currently taking medications for hypertension or other heart conditions (PAR-Q) AND no clearance from an Internal Medicine physician 4. Bone or joint problems that could be worsened by changes in physical activity (PAR-Q) AND no clearance from a Physical Medicine and Rehabilitation physician

		5. Other reason to be cautious about doing physical activity (PAR-Q) AND no clearance from a study co-Principal Investigator 6. Unable to walk 25 feet on a level surface (PROMIS PF_Screener)
Physical performance tests	1. Able to complete the 10-meter walk test, 5x sit-to-stand test, and Dynamic Gait Index	2. Unable to complete 10-meter walk test, 5x sit-to-stand test, and Dynamic Gait Index

3.4 INTERVENTION

Patients participated in the prehabilitation program from enrollment (initial staging at MD Anderson Cancer Center), through neoadjuvant therapy (chemotherapy and/or chemoradiation), and through the recovery period between neoadjuvant therapy and surgery. The prehabilitation program incorporated both walking and resistance exercises. At enrollment, patients received comprehensive instruction from study staff explaining the prescriptions of both walking and strengthening exercises and step-by-step instructions for setting up and performing each resistance exercise safely.

Patients underwent different courses or durations of therapy prior to surgery. Therefore, the duration of prehabilitation also varied. Regardless of duration, patients received a phone call from research staff at least once every 2 weeks to monitor and encourage adherence to the exercise program, to monitor for adverse events, and to address any study- or program-related questions. In the case of exercise-related injuries or health problems (e.g., dizziness, shortness of breath, chest pain, and persistent musculoskeletal pain), staff members conducting follow-up calls planned to instruct patients to discontinue exercise and to refer them to the appropriate clinicians to follow up with patients and make appropriate medical recommendations. There were no exercise-related injuries or health problems requiring medical intervention or discontinuation of study participation.

Aerobic exercise component. Patients were instructed to perform aerobic exercise for at least 20-30 minutes per day on at least 3 days per week. The goal was for patients to reach moderate exercise intensity while performing aerobic exercise or ratings of 12-13 on the Borg Rating of Perceived Exertion (RPE) scale.[180] Patients who were unable to tolerate brisk walking were instructed to maintain a consistent but tolerable pace for 20-30 minutes for each walking session. Patients were encouraged to perform 5 minutes of stretching exercises before and after walking, following a photo guide included with their program materials (described below). Additionally, patients received a pedometer (Digiwalker SW-200, Yamax Inc.). Patients were instructed to wear pedometers on their right hips during waking hours each day, and to record step counts each day in daily exercise logs (described below). Finally, patients received a copy of the Borg RPE Scale with descriptions of important levels of perceived exertion (e.g. a rating of 12-13 means "somewhat hard – you can speak in short sentences while exercising").

Strengthening component. Patients were instructed to perform resistance exercises for 30-45 minutes per day on at least 2 days per week. The strengthening exercises included in the program were selected to engage most major muscle groups including the proximal upper arms, shoulders, abdominals, back extensors, hips, and legs. Exercises to improve trunk stability were prioritized to improve patients' stability, balance, and ability to walk in the preoperative and postoperative periods. Exercises to maintain and develop the shoulder, back and leg muscles were selected to improve patients' abilities to perform transitional activities such as getting into and out of bed, which is important after an extensive abdominal surgery (such as a pancreatectomy). All of the resistance exercises had options to perform them either sitting or standing, depending on patients' balance and comfort levels with the exercises.

For a given session of resistance exercise, patients were instructed to perform 8 separate exercises, each for 3 sets of 8-12 repetitions. There were a total of 19 exercises from which patients could choose. To ensure that they performed exercises targeting all major muscle groups, patients were encouraged to select 1-2 exercises for their abdominal muscles, 3-4 exercises for muscles in their upper bodies, and 3-4 exercises for muscles in their lower bodies. Exercises are listed in *Table 2*.

Table 2. Prehabilitation program strengthening exercises

Muscle groups	*Exercise name (major muscles and joint actions)*
Abdominal muscles (patients select 1-2 exercises per session)	Knee tucks (abdominal flexion)
	Chair crunches (abdominal flexion)
	Abdominal twists (abdominal oblique rotation)
Upper body (patients select 3-4 exercises per session)	Cross-body shoulder pulls (shoulder abduction and adduction)
	Outward shoulder rotations (shoulder horizontal abduction)
	Front shoulder raises (shoulder flexion)
	Chest press (pectoralis flexion, shoulder horizontal adduction, triceps extension)
	Reverse fly (posterior deltoid rotation)
	Triceps push-down (triceps extension)
	Rows (rhomboids and trapezius retraction)
	Bicep curls (biceps flexion)
Lower body (patients select 3-4 exercises per session)	Knee raises (hip flexion)
	Knee extensions (quadriceps extension)
	Leg press (quadriceps and gluteus extension)
	Calf extension (gastrocnemius flexion)
	Hip butterfly (hip abduction)
	Front hip lifts (hip flexion)
	Backward hip lifts (hip extension)
	Side hip lifts (hip abduction)

Once a patient could perform 3 sets of 12 repetitions for a given exercise, he or she was instructed to progress to the next level of increasing resistance as denoted by the color of the resistance tubes. Patients were instructed to vary the exercises they choose from one strengthening session to the next in order to target all muscle groups and to help maintain interest and motivation in the program. Patients were instructed to perform approximately 5 minutes of stretching and a series of 5 full-body warm-up exercises prior to initiating strengthening exercises, and then follow strengthening exercises with an additional 5 minutes of stretching.

Patients received several materials to help them with the strengthening component of the exercise program. Patients received a detailed guide with photographs of starting and ending positions for each exercise, plus instructions and safety tips for each exercise. Patients also received a video guide (on both DVD and USB flash drive) for warm-up and resistance exercises, providing detailed instruction for setting up and performing each exercise and general instructions explaining sets, repetitions, and exercise selection. Additionally, patients received a set of 3 graded resistance tubes (Black Mountain Products) with clips, handles, a door anchor, and an ankle strap. Each strengthening exercise in the program could be performed using these tubes and accessories. Finally, patients utilized the same Borg RPE scale that guided aerobic exercise intensity to guide intensity during strengthening exercises.

Patients received and completed 2 sets of exercise logs, both created specifically for this prehabilitation program, in order to monitor and encourage adherence. Patients were instructed to complete daily exercise logs each day, from enrollment to preoperative restaging visits. Each day, patients recorded minutes spent performing and average perceived exercise intensity during aerobic exercise, minutes spent performing and average perceived exercise intensity during strengthening exercises, and minutes spent performing and average perceived exercise intensity during other physical activities involved with daily living, such as grocery shopping, household chores, or gardening. Patients were also encouraged to record daily steps (from pedometers) and the duration of pedometer wear during the day (“none,” “part of day,” or “all day”). Finally, patients were encouraged to record any concerns or limitations they faced regarding exercise each day. Patients were instructed to note factors such as therapy-induced nausea or fatigue and schedule limitations due to medical appointments that may have limited their abilities to exercise for a given day. Items monitoring patients' daily levels of fatigue and side effects from treatment (both from the FACT-Hep) were included on exercise logs for patients who enrolled after the study protocol was revised (patients 21-70).

Patients were encouraged to complete resistance exercise logs each time they performed strengthening exercises. Each resistance exercise log allowed patients to view the selection of exercises for abdominal muscles, upper body muscles, and lower body muscles and to record the number of sets, repetitions, and the tube color used to perform each of the 8 exercises they selected. Resistance exercise logs also contained reminders and checkboxes for patients to complete stretching (before and after resistance exercises) and warm-up exercises (before resistance exercises) during each session.

The prehabilitation intervention also included an individualized nutrition component. At baseline, patients met with a registered dietitian to discuss nutritional status. Patients received individualized recommendations for calorie, protein, and fluid intake and established goals for weight maintenance, weight gain, or weight loss depending on status at presentation. During the preoperative exercise intervention, patients were instructed to consume high protein snacks or meals (supplying approximately 20g of protein) within one hour of completing strengthening exercises. The dietitian provided patients with lists of protein bars and powders with favorable nutrient profiles for supplementation. Adherence to the nutritional intervention component was monitored and encouraged during the same biweekly calls through which program staff monitored and encouraged adherence to the exercise program.

3.5 MEASURES

All in-person assessments occurred during patients' standard visits to MD Anderson Cancer Center for appointments with the medical oncologists and surgeons who coordinated patients' preoperative treatment and care. Assessments for this study required patients to make no additional hospital visits. A research nurse responsible for consenting and enrolling patients monitored patients' clinic schedules and coordinated with doctors to establish times for prehabilitation assessments. In-person assessments were conducted at baseline and preoperative restaging (typically 2-6 months after initial staging, depending on course of neoadjuvant therapy) by trained research nurses and a PhD candidate in kinesiology. Patients completed survey measures using the REDCap application on iPads or via printed, paper forms. In-person assessments included some measures collected for standard care and other measures included for this study (described below). Remote assessments (objective measurement of physical activity, described below) occurred while patients are undergoing neoadjuvant therapies and exercising as per the prehabilitation protocol.

Figure 1 displays all variables that were examined for this dissertation project and additional variables that were included for other aspects of the prehabilitation pilot study. The next several sections describe operationalization of all variables that were included in the dissertation project. Variables that were not included in this project (e.g., exercise capacity and physical functioning) are not described in the following sections.

3.5.1 PHYSICAL ACTIVITY

Physical activity was monitored objectively using accelerometers (ActiGraph GT3X+, ActiGraph Corp 2011) in coordination with the MD Anderson Center for Energy Balance in Cancer Prevention and Survivorship (EB). At baseline/enrollment, patients received in-person instruction regarding accelerometer wear protocols, including placement on the right hip and recording wear time and device removal in daily accelerometer logs. Patients received accelerometers initialized to match their study identification numbers, elastic waistbands, instructions for wear, and accelerometer logs during clinic appointments or via mail at targeted periods for accelerometer monitoring. The targeted periods for accelerometry occurred at the approximate mid-points of each course of neoadjuvant treatment and spanned 2 consecutive weeks. Patients returned accelerometers to research staff when they present to MD Anderson for treatment planning appointments in between treatment courses or via prepaid return envelopes.

Table 3 shows two different courses of neoadjuvant therapy and time points for physical activity monitoring that occurred using accelerometers. Patients wore accelerometers to monitor physical activity once during each phase of neoadjuvant therapy and the preoperative recovery period. Therefore, a patient who underwent chemotherapy, then chemoradiation, then preoperative recovery prior to surgery had 3 periods of accelerometry. Patients who underwent only chemotherapy or only chemoradiation followed by preoperative recovery had 2 periods of accelerometry.

Table 3. Courses of neoadjuvant therapy and accelerometry time points.

Example 1: Neoadjuvant chemotherapy and chemoradiation	Example 2: Neoadjuvant chemoradiation
Patient received accelerometer #1	
Weeks 1-6: Chemotherapy *Accelerometry during weeks 3-4*	Weeks 1-5: Chemoradiation *Accelerometry during weeks 3-4*
Patient returned accelerometer #1 and received accelerometer #2	
Weeks 7-11: Chemoradiation *Accelerometry during weeks 9-10*	Weeks 6-10: Preoperative recovery *Accelerometry during weeks 8-9*
Patient returned accelerometer #2 and received accelerometer #3	
Weeks 12-16: Preoperative recovery *Accelerometry during weeks 14-15*	
Patient returned accelerometer #3	*Patient returned accelerometer #2*

Each instance of accelerometer monitoring involved a wear protocol lasting 2 consecutive weeks. Research staff called patients 1-2 days before a targeted period of accelerometry monitoring began to provide a reminder to wear the device. Patients were instructed to begin wearing accelerometers on the first targeted morning and to record this date and time in their accelerometry logs. Study staff contacted participants by phone at least once during each period of accelerometer wear in order to encourage proper accelerometer use and completion of logs. In daily accelerometer logs, patients recorded the times at which they took accelerometer belts on and off during the day.[181]

Accelerometer counts were processed according to definitions of acceptable days, with at least 10 hours of wear time constituting an acceptable day.[181] Counts were analyzed in 1-minute epochs.[181] For a period of objective physical activity measurement to be included in analyses, patients must have recorded at least 8 valid days over the course of the 14 possible days.[181] Accelerometer counts were processed according to established cutpoints for adults[182] in order to determine minutes of light physical activity, moderate-to-vigorous physical activity, and total physical activity per week.

Physical activity was also measured by self-report at baseline and preoperative restaging using the International Physical Activity Questionnaire – Short Form (IPAQ). Patients reported physical activity in the week preceding exercise program enrollment and in the final week of the exercise program at these two time points. The IPAQ form was adapted for use in the REDCap iPad application. The IPAQ-SF has shown acceptable validity and Total energy expenditure from physical activity in the aforementioned weeks was estimated by multiplying average duration, weekly frequency, and metabolic equivalent task (MET) intensity for each activity domain (vigorous physical activity, moderate physical activity, and walking) and creating a sum across domains, per standard scoring protocol.[183] This produced estimates of total MET-minutes of physical activity per week at baseline and preoperative restaging.

3.5.2 SOCIAL INFLUENCES ON PHYSICAL ACTIVITY

Social support for exercise for family and friends were measured using the Social Support for Exercise Survey (SSES).[155] The SSES lists 13 items that family members or friends may do or say to someone who is trying to exercise regularly, from emotional support (e.g. "Gave me encouragement to stick to my exercise program") to instrumental support (e.g. "Helped plan activities around my exercise"). The SSES also captures social influences that may hinder exercise (e.g. "Complained about the time I spend exercising). Patients will score items for friends and family separately, each item on a scale from 1=none to 5=very often based on how frequently they engaged in the listed behavior in the previous 3 weeks. Scores for “family participation,” “family rewards and punishment,” and “friend participation” will be computed as per published protocols.[155] Patients who enrolled in the study protocol after this dissertation project was proposed completed the SSES at baseline and at preoperative restaging. Social support for exercise from family and friends were assessed at both baseline and preoperative restaging, due to potential for support to change over the course of the exercise program. The SSES was adapted for use with the REDCap iPad application and was scored according to established guidelines.[155] The SSES has been shown to have acceptable reliability and validity.[155]

3.5.3 ENVIRONMENTAL INFLUENCES ON PHYSICAL ACTIVITY

Potential environmental influences on physical activity were assessed at the neighborhood level. Neighborhood assessments captured both objective and perceived characteristics that may have influenced patients’ physical activity during the home-based exercise program. Therefore, characteristics of neighborhood socioeconomic status (median household income, proportion of residents below the Federal Poverty Line, and proportion of residents with at least a high school diploma) and population characteristics (population density, proportion of population identifying as non-Hispanic white, proportion of population 65 years or older) were collected at the Census tract level using publically-available data from the United States Census.[184] Census tracts were identified using the Address Search tool on the US Census American FactFinder website and patients’ home addresses as recorded in the MD Anderson Electronic Medical Record. Zip codes were used to identify Census tracts for patients whose addresses were post office boxes.[185]

Several subscales from the Neighborhood Environment Walkability Scan-Abbreviated (NEWS-A)[163,167] were used to examine patients' perceptions of neighborhood factors that may support or inhibit walking for exercise, since walking was a recommended activity for patients to engage in moderate-intensity aerobic exercise. The NEWS-A contains subscales relating primarily to walking for transportation (e.g., access to mixed land uses and residential density) and subscales relating primarily to walking for recreation/exercise. To fit the purpose of this study, in which walking was recommended as an aerobic exercise modality, and to reduce the length of surveys patients were required to complete, patients completed only the subscales relating to walking for recreation/exercise. These subscales included places for walking and cycling (6 items), neighborhood surroundings/aesthetics (4 items), traffic hazards (3 items), and crime (3 items). Patients who enrolled in the study protocol under the revisions proposed for this dissertation project completed NEWS-A at their preoperative restaging visits, after having completed the exercise program during their neoadjuvant treatments. The NEWS-A subscales listed above were adapted for use with the REDCap iPad application and scored according to established procedures.[163,167] The NEWS-A has shown acceptable reliability and validity.[163]

3.5.4 CANCER- AND TREATMENT-RELATED INFLUENCES ON PHYSICAL ACTIVITY

Cancer- and treatment-related influences on physical activity were measured throughout neoadjuvant treatments and the preoperative exercise program using two modified items from the FACT-Hep listed on patients' daily exercise logs (revised version). Patients rated their fatigue and treatment-related side effects each day on Likert scales ranging from 0 (not at all) to 4 (very much). Daily scores for these items were averaged over each stage of neoadjuvant treatment (chemotherapy and/or chemoradiation and the preoperative recovery period) to provide average scores for fatigue and treatment-related side effects. The inclusion of these items on daily exercise applied only to patients who enrolled under the revised study protocol incorporating measures for this dissertation project.

Cancer- and treatment-related influences on physical activity were also examined qualitatively, using semi-structured telephone interviews involving a subsample of patients (*n*=10). Primary questions and probing questions for qualitative interviews focused on the following constructs:

1. Energy level and side-effects during chemotherapy and how they affected ability and/or motivation to exercise
2. Energy level and side-effects during chemoradiation and how they affected ability and/or motivation to exercise
3. Energy level and side-effects during preoperative recovery period and how they affected ability and/or motivation to exercise
4. Possible time and logistical issues with the exercise program
5. Sources of motivation (or lack thereof) for exercise

Interviews were conducted via telephone, recorded, and transcribed. Two trained members of the project coded interviews using NVivo software version 10 (QSR International, 2015). Interviews were conducted postoperatively, following patients' postoperative restaging visits, in order to minimize study burden on patients during neoadjuvant therapy and postoperative recovery.

3.5.5 HEALTH-RELATED QUALITY OF LIFE

The FACT-Hep was administered at baseline and preoperative restaging throughout the prehabilitation pilot study to measure health-related quality of life. The instrument is designed specifically for patients with cancers of the liver, bile duct, or pancreas through its inclusion of a subscale of 18 symptoms that patients may experience due to hepatobiliary tumors or systemic therapies. The FACT-Hep also includes the 4 general subscales assessing physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well-being (7 items). Each item lists a symptom or emotion and asks patients to rate how frequently they have experienced it in the previous 7 days, via Likert scales with scores ranging from 0=not at all to 4=very much.[68,69] The FACT-Hep will be scored according to established procedures.[68,69] The FACT-Hep has shown acceptable validity and reliability.[68]

3.5.6 INFLAMMATION

Inflammation was measured using blood serum levels of C-reactive protein (CRP) and albumin (ratio of CRP to albumin, or CRP/alb) for a subsample of patients who had complete data at baseline and preoperative restaging. CRP/alb has been shown to be an important, prognostic indicator of inflammation among patients with pancreatic cancer.[24,25] Values for serum CRP and albumin were read and recorded in the Electronic Medical Record by trained laboratory technicians and were extracted from the ELECTRONIC MEDICAL RECORD by study staff with appropriate access. Blood extraction did not necessarily take place on the same day as other study assessments at baseline and preoperative restaging. In these cases, the closest date of blood draw to the recorded visits for other prehabilitation assessments (typically 1-2 days before these assessments) was used to indicate CRP and albumin levels for that specific time point.

3.5.7 ANTHROPOMETRICS AND SKELETAL MUSCLE

Anthropometrics and skeletal muscle were measured at baseline and preoperative restaging using BMI and cross-sectional areas of skeletal muscle in abdominal computed tomography (CT) scans. Height and weight were measured at staging visits by trained clinicians per standard care, and these values were extracted from the ELECTRONIC MEDICAL RECORD for computation of BMI (kg/m^2). Estimation abdominal skeletal muscle tissue was performed using SliceOMatic image analysis software, version 5.0 (TomoVision, 2012) and CT scans obtained during each staging and restaging visit. SliceOMatic uses differences between pixel density in standard CT scans to differentiate between and calculate cross-sectional areas of subcutaneous fat, visceral fat, intramuscular fat, and skeletal muscle tissue. SliceOMatic and CT images at the L3 vetebra have recently been used to determine tissue cross-sectional areas throughout the perioperative period among patients with pancreatic cancer.[12] Cross-sectional area skeletal muscle from CT images at the L3 vertebra have shown strong correlations with full-body tissue volumes.[186] *Figure 5* provides an example of a CT image “slice” at the L3 vertebra that has been analyzed for cross-sectional areas of skeletal muscle and adipose tissue.

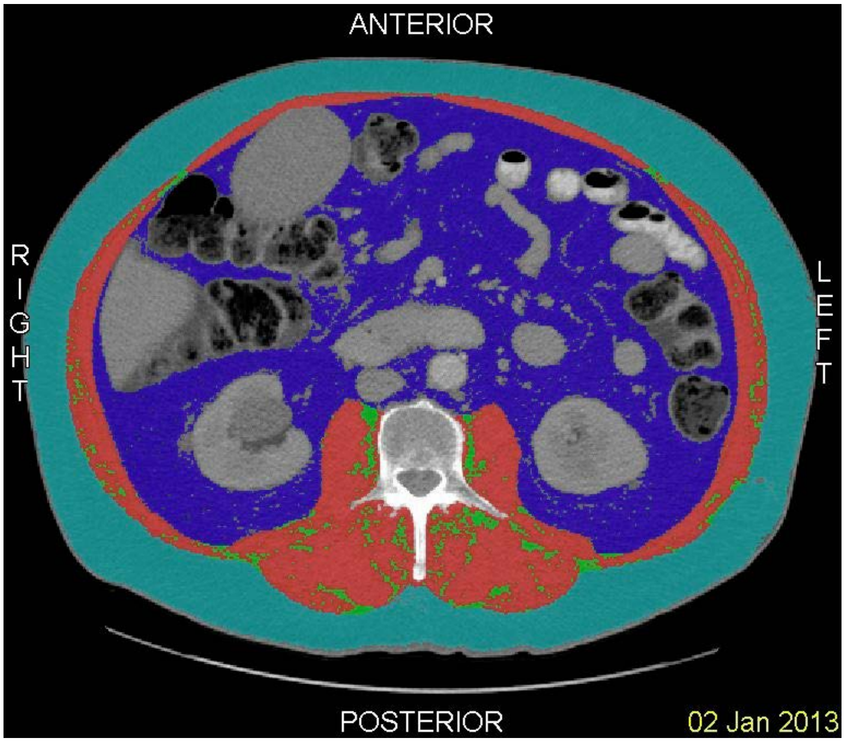


Figure 5. L3 vertebra CT image slice showing skeletal muscle cross sectional area (in red)

CT image "slices," standardized at the L3 vertebra, were provided by a physician in the Department of Diagnostic Radiology for staging and restaging scans from baseline and preoperative restaging, respectively. If CT image dates did not match the dates of other assessments for the same time point, the CT taken closest to the date on which survey measures were completed was selected for analyses. Tissues in these scans were coded in SliceOMatic by trained research staff to obtain values for the cross-sectional area of skeletal muscle (cm^2). Cross-sectional areas were standardized to the square of patients' heights, producing a standardized measure of skeletal muscle (cm^2/m^2). Rate of change in skeletal muscle tissue was computed using cross-sectional areas at baseline and preoperative restaging and the elapsed time between these scans. Differences between cross-sectional tissue areas at consecutive time points were also calculated.

Patients who have received care for pancreatic cancer at MD Anderson have CT images stored in the electronic medical record. For patients with resectable tumors, typical time points for CT imaging include both baseline and preoperative restaging visits, aligning with those assessed for patients enrolled in the exercise program. Therefore, a subsample of patients who had CT images at both time points and were not enrolled in the prehabilitation intervention served as historical controls for comparisons regarding skeletal muscle changes over the course of preoperative treatment. Historical controls (*n*=127) underwent neoadjuvant treatment and surgical resection for pancreatic cancer at MD Anderson Cancer Center between 2009 and 2012.

3.5.8 DATA MANAGEMENT

As enrollment in this study occured on a rolling basis, data from baseline/enrollment and preoperative restaging were screened and cleaned as they were compiled. Data were screened for any data entry errors or values that are extreme or unrealistic.

Paper logs and forms were stored in a secure, locked cabinet in an office in the MD Anderson Department of Surgical Oncology. Data collected via the REDCap application on secure, Department-owned iPads was stored immediately on a secure MD Anderson server. All data from paper forms, the electronic medical record, and REDCap surveys were transferred to electronic databases stored on a secure, encrypted server behind Institutional firewall at MD Anderson Cancer Center. Only the Principal Investigator and approved study staff had access to data. Data used for analyses at the University of Houston was completely de-identified.

3.6 ANALYSES

3.6.1 ANALYSIS PLAN

Descriptive analyses were conducted to examine distributional characteristics of data for all physical activity and exercise variables, potential socioecological influences on physical activity, clinical and quality of life outcomes. Data for measures that were collected consistently for all patients under both protocols (exercise and program adherence based on exercise logs, health-related quality of life from the FACT-Hep, anthropometric changes, and systemic inflammation) were pooled for analyses. *Table 4* lists all ways in which study variables were operationalized for analyses.

Table 4. Operationalization of study variables for analyses.

Variable	Measure	Source	Time points or changes of interest	Operationalization
Physical activity and exercise	Aerobic exercise minutes	Daily exercise logs	• Each stage of therapy • Entire preoperative period	• Total minutes/hours (volume) • Average weekly minutes
	Strengthening exercise minutes			
	Program adherence (yes/no)		• Each week during preoperative period	• Number of adherent weeks • Percentage of enrolled weeks that were adherent
	Light physical activity	Accelerometry	• Each stage of therapy • Entire preoperative period	• Total minutes/hours (volume) • Average weekly minutes
	Moderate-to-vigorous physical activity			
	Total physical activity			
	Self-reported physical activity	IPAQ-SF	• Baseline (regarding the week preceding exercise program) • Preoperative restaging (regarding the final week of the exercise program)	• Metabolic equivalent minutes (MET-minutes) of physical activity
Social support for exercise	Social support for exercise from family	SSES	• Baseline • Preoperative restaging	• Family participation

	Social support for exercise from friends			• Family rewards/punishment • Friends participation • Family and friends participation
Neighborhood supports and resources for physical activity	Neighborhood places for walking and cycling	NEWS-A	• Baseline • Preoperative restaging (for NEWS-A, among patients who stay away from home and close to MD Anderson for treatment during the preoperative period)	• Subscale scores (for NEWS-A) • Figures or percentages (for neighborhood sociodemographic characteristics)
	Neighborhood surroundings/aesthetics			
	Neighborhood traffic hazards			
	Neighborhood crime			
	Neighborhood sociodemographic characteristics	US Census (Census tract level estimates)	• Baseline	
Disease- and treatment-related influences on physical activity and exercise	Daily fatigue	FACT-Hep items on daily exercise logs	• Each stage of therapy • Entire preoperative period	• Average daily score
	Daily treatment-related side effects			
Health-related quality of life	FACT-G	FACT-Hep (historical controls available)	• Baseline • Preoperative restaging	• Total score for each subscale
	FACT-Hep			
Anthropometrics	BMI	CT images	• Baseline	• Total cross-sectional area

	Skeletal muscle	(historical controls available)	• Preoperative restaging	• Change in cross-sectional area • Rate of change in cross-sectional area
Inflammation	C-reactive protein and albumin	Blood draws during staging and restaging visits (subsample)	• Baseline • Preoperative restaging	• CRP/alb

3.6.2 STATISTICAL ANALYSES

Analytical procedures are organized by study research questions in the following sections.

Research question 1: How many minutes of aerobic exercise, resistance exercise, total physical activity, and moderate-to-vigorous physical activity do patients with resectable pancreatic cancer perform per week while participating in a preoperative exercise intervention?

Research question 1.1: What percentage of the prescribed guidelines for moderate-intensity aerobic exercise (minimum 60 minutes per week) and moderate-intensity strengthening exercises (minimum 60 minutes per week) do patients with resectable pancreatic cancer report performing during a preoperative exercise intervention?

Research question 1.2: How do weekly minutes of aerobic exercise, strengthening exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines vary across stages of neoadjuvant therapy (chemotherapy and chemoradiation) and the preoperative recovery period among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Research question 1.3: How are weekly minutes of aerobic exercise, strengthening exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines associated with self-reported daily fatigue and treatment side-effects among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Descriptive statistics (frequencies and percentages or means and standard deviations) were used to quantify patients' sociodemographic, disease, and treatment characteristics and to quantify self-reported exercise, accelerometer physical activity, and fatigue and side effects across and within treatment phases. Chi-square tests and independent t-tests were used to evaluate differences in sociodemographic and clinical characteristics between patients who were lost to follow up vs. patients who completed the study and between patients who proceeded to curative surgery vs. patients who did not.

Due to the positively-skewed distributions of self-reported energy expenditure from physical activity, Wilcoxon signed rank tests were used to compare changes in MET-minutes from baseline to preoperative restaging (paired observations).[187] Chi-square tests were used to evaluate whether patients were more likely to meet aerobic or strengthening recommendations and whether there were differences in meeting exercise recommendations between sexes.[188] Due to the positively-skewed distributions of exercise and physical activity minutes, Mann-Whitney U-tests were used to compare differences in self-reported aerobic, strengthening, and multi-modal exercise and accelerometer MVPA, LPA, and TPA between sexes. Tests for differences in physical activity and exercise minutes and in meeting exercise program recommendations were performed in the full sample and also stratified by sex due to previous evidence of sex-related differences in exercise intervention adherence among cancer survivors.[189] All of the aforementioned analyses were performed using SPSS Statistics Version 24 (IBM Corp., 2016).

Two-level, linear mixed models were used to compare self-reported exercise minutes, accelerometer physical activity, fatigue, and treatment-related side effects among the three neoadjuvant treatment phases. The first set of models were run with only treatment phase as a fixed effect and study ID as a random effect, and the second set of models included sex, age, surgery (yes/no), overall exercise program duration, and interactions between treatment phase and fatigue and treatment phase and side-effects as possible covariates. Restricted maximum likelihood estimation with the Kenward Roger approximation was used to adjust for small-sample bias and account for differences in the number of patients with exercise and physical activity data within each treatment phase. Marginal means estimations created means adjusted for sample size imbalance between phases and for sex, age, surgery (yes/no), overall exercise program duration, and interactions between treatment phase and fatigue and treatment phase and side-effects. Linear mixed models were performed using Stata Statistical Software Version 14 (StataCorp LP., 2015).

Expected findings:

Hypothesis 1.2**:** It was hypothesized that weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would vary across stages of neoadjuvant therapy (chemotherapy and chemoradiation) and the preoperative recovery period among patients with resectable pancreatic cancer participating in a preoperative exercise intervention. It was hypothesized that physical activity and exercise adherence would be highest during the recovery period, followed by chemoradiation, then chemotherapy.

***Hypothesis 1.3*:** It was hypothesized that weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would be negatively associated with self-reported daily fatigue and treatment side-effects among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

Explanation of null or contrary findings:

It was expected that null findings may result from small sample size or the absence of true variability in physical activity across stages of neoadjuvant therapy. Further, there may have been no true relationships between daily fatigue and/or treatment-related side effects and physical activity. Reductions in physical activity from chemotherapy to chemoradiation and preoperative recovery would have been contrary to hypothesis 1.2. This finding may have resulted if patients lost motivation to perform physical activity over the preoperative period. A positive association between daily fatigue and treatment-related side effects and physical activity would have been contrary to hypothesis 1.3. This finding may have resulted if patients were highly motivated to exercise during chemotherapy and overcome fatigue and treatment-related side effects to exercise consistently, but then lost motivation to exercise as fatigue and treatment-related side effects improved.

Research question 2: How are socioecological supports and barriers associated with aerobic exercise, strengthening exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Research question 2.1: How is social support from family and friends associated with aerobic exercise, resistance exercise, total physical activity, moderate-to-vigorous physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Research question 2.2: How are home neighborhood walkability and neighborhood sociodemographic characteristics associated with aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Descriptive statistics were used to quantify sociodemographic, disease, and treatment characteristics; self-reported exercise, accelerometer physical activity; and social support and neighborhood characteristics at baseline and preoperative restaging. Due to the non-normal distributions of social support and neighborhood walkability variables, Wilcoxon signed rank tests were used to compare changes in social support subscale scores from baseline to preoperative restaging and, for a subsample of patients who stayed near MDACC for extended periods for chemoradiation treatments, to compare neighborhood walkability between home and these alternative locations.[187] Linear regression models were used to estimate associations of socioecological influences and exercise and physical activity. Separate models were used to estimate the associations between each potential socioecological influence and each potential exercise or physical activity outcome. All linear regression models included age, sex, and final surgical determination (yes/no) as covariates based on theory and evidence suggesting differences in exercise or physical activity based on these covariates. All analyses were performed using SPSS Statistics Version 24 (IBM Corp., 2016).

Expected findings:

***Hypothesis 2.1*:** It was hypothesized that higher social support from family and friends would be positively associated with weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention. This relationship was hypothesized to be bidirectional, as social support may increase as participants engage in an exercise program and become more active.

***Hypothesis 2.2**:* It was hypothesized that higher neighborhood walkability would be positively associated with weekly minutes of aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

Explanation of null or contrary findings:

It was expected that null findings may have resulted from small sample size or the absence of true associations between social and environmental supports and physical activity in this population and/or context. For example, cancer- and treatment-related concerns may be responsible for most of the variability in preoperative physical activity among patients undergoing neoadjuvant treatment, leaving little variability to be explained by socioecological influences. Negative associations between social and environmental supports and physical activity would have been contrary to hypotheses 2.1 and 2.2. These findings may have resulted if unmeasured behavioral characteristics, such as motivation or self-efficacy, were drastically more influential for physical activity in this population than socioecological factors.

Research question 3: How are aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines related to clinical characteristics and quality of life among patients with resectable pancreatic cancer participating in a preoperative exercise intervention?

Research question 3.1: How are aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines related to preservation of skeletal muscle tissue and systemic inflammation among patients undergoing prehabilitation for pancreatic cancer?

Research question 3.2: How are aerobic exercise, resistance exercise, total physical activity, moderate-to-vigorous physical activity, and general adherence to program guidelines related to health-related quality of life among patients undergoing prehabilitation for pancreatic cancer?

Research question 3.3: How do changes in skeletal muscle among patients with resectable pancreatic cancer participating in a preoperative exercise intervention compare with those among historical controls?

Descriptive statistics were used to quantify sociodemographic, disease, and treatment characteristics; self-reported exercise, accelerometer physical activity; and QOL, skeletal muscle, and inflammation at baseline and preoperative restaging. Due to their non-normal distributions, Wilcoxon signed rank tests were used to compare QOL and CRP/alb from baseline to preoperative restaging. Paired t-tests were used to compare skeletal muscle and BMI from baseline to preoperative restaging. Independent t-tests were used to compare skeletal muscle, BMI, and changes in both outcomes between exercise program patients and historical controls.

Linear regression models were used to measure associations among exercise and physical activity and outcome measures. Separate models were used to measure the associations between exercise or physical activity and each outcome measure, which included preoperative restaging and change scores (preoperative restaging – baseline) for each outcome. Linear regression models were also fit with baseline values for outcome measures (QOL, skeletal muscle, and inflammation) predicting exercise adherence and physical activity to assess potential effects of baseline health status on program adherence All linear regression models were adjusted for age, sex, and final surgical determination (yes/no) based on theoretical basis and evidence suggesting differences in exercise or physical activity based on these covariates. Models involving skeletal muscle at preoperative restaging and change in skeletal muscle from baseline to preoperative restaging were also adjusted for exercise program duration. Linear regression models were also used to compare change in skeletal muscle between exercise program patients and historical controls. This model was adjusted for age, sex, baseline BMI, and preoperative duration. Because of the arbitrary scale of the outcomes measures (except the model comparing skeletal muscle change), standardized coefficients were interpreted to describe the associations among predictor and outcome variables. All analyses were performed using SPSS Statistics Version 24 (IBM Corp., 2016).

Expected findings:

Hypothesis 3.1*:* It was hypothesized that higher aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would be associated with preservation of skeletal muscle tissue and reduced inflammation among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

Hypothesis 3.2*:* It was hypothesized that higher aerobic exercise, resistance exercise, light physical activity, moderate-to-vigorous physical activity, total physical activity, and general adherence to program guidelines would be associated with improvement in health-related quality of life among patients with resectable pancreatic cancer participating in a preoperative exercise intervention.

Hypothesis 3.3: It was hypothesized that loss of skeletal muscle would be attenuated among patients with resectable pancreatic cancer participating in a preoperative exercise intervention compared to historical controls.

Explanation of null or contrary findings:

It was expected that null or contrary findings may have resulted from low sample size or the absence of true associations between physical activity and clinical and quality of life outcomes among patients undergoing preoperative therapy for pancreatic cancer. Such findings may have been attributable to overwhelming harmful effects from either disease or treatments on these outcomes during the preoperative period.

CHAPTER 4

MANUSCRIPT 1: FEASIBILITY OF HOME-BASED EXERCISE FOR PATIENTS UNDERGOING PREOPERATIVE TREATMENT FOR PANCREATIC CANCER.

4.1 INTRODUCTION

Pancreatic cancer is the third leading cause of cancer-related death in the United States.[190] Patients diagnosed with pancreatic cancer are generally older adults and frequently present with age- and disease-associated comorbidities including obesity, frailty, sarcopenia, and cachexia.[7,8,11-13] For patients with early-stage pancreatic cancer (i.e., potentially or borderline resectable), surgery provides hope for cure.[3] Surgeries involving pancreatic resection are complex, require an optimal physiologic status, and entail an often arduous recovery.[4-6] Therefore, it is important to develop interventions aimed at optimizing preoperative health among patients with resectable pancreatic cancer.

Physical activity and exercise are increasingly prioritized in cancer care and survivorship. Previous studies have demonstrated broad and plentiful benefits from physical activity and exercise for cancer survivors, including improvements in treatment outcomes, quality of life, and survival. [49,66,79] Published guidelines from the American Cancer Society (ACS) and the American College of Sports Medicine (ACSM) encourage cancer survivors to be physically active, with recommendations mirroring those for the healthy.[53,54] Recently, for cancer survivors whose treatment plans include surgery, the paradigm in exercise and cancer treatment has been shifting from one that prioritized exercise in the post-operative period (*rehabilitation*) to one that prioritizes exercise in the preoperative period (*prehabilitation*).[19,20,115] Preoperative exercise programs have shown utility in improving fitness and physical functioning to accelerate post-operative recovery, reducing fatigue, and improving health-related quality of life.[20,115] To date, however, most studies involving preoperative exercise have involved supervised, in-person exercise programming among patients with more prevalent cancer types who are not actively undergoing neoadjuvant treatment.[19,31,191] No studies to date have evaluated the feasibility of preoperative exercise for patients with resectable pancreatic cancer.

Neoadjuvant chemotherapy, chemoradiation, or a sequence of both therapies are increasingly used to treat patients with potentially and borderline resectable pancreatic cancer.[8,12,21,34] A "rest period" of several weeks prior to surgery frequently follows use of these therapies. While the timing of these treatment strategies provides convenient, preoperative "windows" to optimize patients' health through exercise, the therapies involve cytotoxic regimens that can be difficult for older adults with age- and disease-related comorbidities to tolerate.[192] Previous research has shown that physical fitness decreases over the course of neoadjuvant chemotherapy.[193] and among patients with pancreatic cancer, specifically, increased loss of skeletal muscle tissue during neoadjuvant treatment is related to shorter correlates with disease-free survival.[12] While plausible that preoperative exercise could help mitigate the adverse effects of neoadjuvant treatment on perioperative fitness, it is important to determine whether such programs are feasible in this context and whether feasibility varies among preoperative phases (i.e., chemotherapy, chemoradiation, rest).

Studies involving preoperative exercise for patients undergoing neoadjuvant treatment have involved highly-supervised, in-person programming.[194-196] Few preoperative exercise studies have employed home-based exercise programming,[129,130] and none involved patients who were concurrently undergoing neoadjuvant treatment. Further, studies involving home-based, preoperative exercise interventions among patients with cancer have not incorporated objective measurement of physical activity, such as using accelerometers. In-person, preoperative exercise strategies may be less feasible in the pancreatic cancer context, in which patients with potentially resectable tumors frequently travel to large, comprehensive cancer centers for treatment planning and surgery but return home to actually receive neoadjuvant treatment. To increase generalizability and accommodate all patients undergoing neoadjuvant treatment for pancreatic cancer, it is important to study the feasibility of home-based exercise programming in this context and to utilize objective strategies (i.e., accelerometers) to measure program adherence. However, given the complicated and potentially variable factors that could affect exercise adherence during different phases of neoadjuvant treatment for pancreatic cancer, it is important for early research efforts to also utilize patient-reported methods (e.g., exercise logs, surveys) to fully understand feasibility in this context.

The purpose of this study was to assess the feasibility of a home-based, multi-modal, preoperative exercise program among patients undergoing preoperative therapy for pancreatic cancer. We hypothesized that, on average, patients would be able to meet exercise program recommendations of 60 minutes of aerobic exercise and 60 minutes of muscle strengthening exercise per week across treatment phases. We also aimed to measure and compare program adherence among patients undergoing chemotherapy, chemoradiation, and a sequence of both strategies to fully understand potential differences in feasibility over the preoperative time course. Due to well-known side-effects of chemotherapy regimens used frequently to treat resectable pancreatic cancer,[197,198] we hypothesized that self-reported exercise, accelerometer physical activity, and program adherence would be lowest during chemotherapy, followed by improvements during chemoradiation and highest levels during preoperative rest.

4.2 METHOD

4.2.1 STUDY SETTING

Recruitment for this study took place at The University of Texas MD Anderson Cancer Center (MDACC), a comprehensive cancer center in Houston, TX. All study activities were approved by the MDACC Internal Review Board, with offsite analyses of de-identified data also approved through a data sharing agreement by the Committee for the Protection of Human Subjects at the University of Houston.

Physicians in the Gastrointestinal (GI) Center at MDACC treat approximately 1,000 patients with pancreatic and periampullary neoplasms per year, with approximately 100 of these patients presenting with technically resectable pancreatic ductal adenocarcinoma (PDAC). Some of these patients present to the GI Surgical Oncology

Clinic at MDACC having already received neoadjuvant therapy at outside institutions and thus proceed to surgery, but only a minority at this institution (approximately 5%) proceed to surgery without receiving neoadjuvant therapy. This treatment pattern, which provides a preoperative "window" to optimize patients' fitness and physical functioning, represents the standard of care at MDACC for patients with potentially and borderline resectable PDAC and is increasingly used at other cancer hospitals.[8,12,21,34]

4.2.2 ELIGIBILITY AND ENROLLMENT

Target participants in this study were patients presenting to the MDACC Gastrointestinal Surgery Clinic to undergo treatment planning for potentially and borderline resectable PDAC between February, 2015 and January, 2017. Eligibility requirements included: biopsy-proven diagnosis of PDAC; intended pancreatectomy with at least six weeks until planned resection; treatment plan including neoadjuvant chemotherapy, chemoradiation, or both; fluency in English; telephone access; and willingness to maintain exercise logs and participate in follow-up calls. Exclusion criteria included underlying and unstable cardiac or pulmonary disease or symptomatic cardiac disease (New York Heart Association functional class of III or IV), recent fracture or acute musculoskeletal injury that precluded ability to exercise using all four limbs, numeric pain rating of at least 7 out of 10, or myopathic or rheumatologic disease that limited physical function.

Following approval and recommendation from attending medical oncologists or surgeons at initial consultations, all patients completed the Physical Activity Readiness Questionnaire (PAR-Q)[178] and the first question of the Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function 12a Short Form[179] ("Can you walk 25 feet on a level surface, with or without support?”). Patients who reported chest pain, dizziness, loss of balance, or loss of consciousness during physical activity or chest pain at rest on the PAR-Q were ineligible for enrollment. Patients who reported heart conditions and recommendations to only perform physical activity recommended by a doctor and those who reported currently taking medications for hypertension or other heart conditions on the PAR-Q required clearance by a physician in Internal Medicine prior to enrollment. Patients who reported bone or joint problems that could worsen with an increase in physical activity on the PAR-Q required clearance by a physician in Physical Medicine and Rehabilitation prior to enrollment. Patients who reported any other reason to be cautious about physical activity on the PAR-Q required clearance from at least one of the physicians serving as a co-Principal Investigator on the study. Finally, patients who reported inability to walk 25 feet on a level surface via the PROMIS screening question were ineligible for enrollment.

4.2.3 EXERCISE PROGRAM

Patients engaged in a multi-modal, home-based exercise program incorporating both aerobic and strengthening exercise components from enrollment (i.e., initial staging appointments at MDACC), through neoadjuvant therapy (chemotherapy and/or chemoradiation), and through the rest period between neoadjuvant therapy and surgery (Figure 1). The exercise program was based on recommendations for cancer surivors from the ACS and ACSM,[53,54] but reduced from ≥150 minutes of moderate-intensity exercise per week to ≥120 minutes of moderate-intensity exercise per week in an effort to accommodate patients’ older age and toxic therapy regimens. Patients received comprehensive instruction from study staff explaining exercise prescriptions and demonstrating set-up and proper form for all strengthening exercises. Patients received a phone call at least once every 2 weeks from research staff to monitor and encourage adherence to the exercise program, to monitor for adverse events, and to address any study- or program-related questions.

Aerobic exercise component. Patients were encouraged to walk briskly or perform a preferred aerobic exercise (e.g., stationary cycling or elliptical training) for at least 20 minutes per day on at least 3 days per week (minimum weekly aerobic exercise prescription 60 minutes). Patients were encouraged to maintain moderate intensity during aerobic exercise, corresponding to ratings of 12-13 on the Borg Rating of Perceived Exertion (RPE) scale (i.e., maintaining ability to speak in short sentences while exercising).[180] Patients were also encouraged to perform 5 minutes of stretching exercises before and after walking.

Strengthening component. Patients were encouraged to perform strengthening exercises for at least 30 minutes per day on at least 2 days per week (minimum weekly strengthening prescription 60 minutes). Prescribed strengthening exercises engaged most major muscle groups including the proximal upper arms, shoulders, abdominals, back extensors, hips, and legs. Exercises to improve trunk stability were prioritized to improve patients' stability, balance, and ability to walk pre- and post-operatively. When possible, strengthening exercises had sitting or standing options to accommodate various levels of comfort and balance. For a given strengthening session, patients were encouraged to select 8 exercises and perform 3 sets of 8- 12 repetitions per exercise. To ensure that they targeted all major muscle groups, patients were encouraged to select 1-2 exercises for their abdominal muscles, 3-4 exercises for upper body muscle groups, and 3-4 exercises for lower body muscle groups in each session. There were 19 exercises from which patients could choose, and they were encouraged to vary the exercises they selected from session to session. The strengthening component was designed for patients to perform using provided resistance tube sets (described below), but patients who preferred to perform strengthening exercises using other equipment (i.e., dumbbells or weight machines) were encouraged to do so and provided with examples of similar exercises. Patients were encouraged to maintain moderate exercise intensity (i.e., Borg RPE 12-13) while performing strengthening exercises and to perform 5 minutes of both stretching and warm up exercises before and 5 minutes of stretches after each session.

Exercise program materials and equipment. Patients received a binder introducing the study and providing tips for exercising safely. To facilitate the aerobic exercise component, patients received a pedometer (Digiwalker SW-200, Yamax Inc.) and were encouraged to wear the pedometer over the right hip each day and record daily step counts in exercise logs (described below). To facilitate the strengthening exercise component, patients received 3 graded exercise tubes (Stackable Resistance Band Set, Black Mountain Products, Inc.) with attachable handles and door anchor and ankle straps. Program binders contained written and photo instructions showing proper set-up and starting and finishing positions for each prescribed stretch, warm-up, and strengthening exercise. Patients also received a DVD with videos demonstrating proper set-up and form for each of the stretches, warm-up, and strengthening exercises. Finally, patients received a copy of the Borg RPE Scale with descriptions of perceived exertion to guide proper exercise intensity (e.g., a rating of 12-13 means “somewhat hard – you can speak in short sentences while exercising”).

Nutrition component. Patients met with a registered dietitian within 7 days of study enrollment to review nutritional status, individualized daily targets for calories and protein, and suggestions for incorporating additional protein into their diets. Patients were encouraged to consume snacks or meals containing ≥20 grams of protein following sessions of strengthening exercise. Nutritional status was monitored by exercise program staff during follow-up calls, with patients referred to a registered dietitian if they reported difficulty with weight management or calorie or protein intake. As is standard of care at MDACC, patients met with a registered dietitian to review nutritional status and information at preoperative restaging appointments and were encouraged to purchase and consume an immune enhancing supplement (*Nestlé Impact Advanced Recovery*; 3 servings per day each of the 5 days preceding surgery).

4.2.4 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The following sociodemographic and clinical characteristics were collected using the MDACC electronic medical record: age at enrollment (years), sex, location of primary residence (≤100 miles from study location vs. >100 miles from study location, confirmed using zip codes in Google Maps), body mass index (BMI, kg/m^2), radiographic stage at presentation (potentially resectable, borderline resectable, or locally advanced), course of neoadjuvant treatment during the exercise program (chemotherapy alone, chemoradiation alone, or chemotherapy followed by chemoradiation), duration of exercise program (overall and separately during each phase of neoadjuvant treatment), and outcome following neoadjuvant treatment (stable or improved disease; curative surgery or disease progression; no curative surgery).

For patients who underwent final surgical evaluation, exercise program duration was calculated as the number of weeks (rounded to the nearest whole number) between the enrollment date and the preoperative restaging date. For patients who had disease progression prior to final surgical evaluation, exercise program duration was calculated as the number of weeks between the enrollment date and the date of progressive disease diagnosis. Durations of exercise during each treatment phase were calculated as the number of weeks between the day on which the specific treatment plan was finalized and the day on which the final treatment was received, or the day on which the treatment plan changed. For example, if physicians determined on March 1st that a patient would receive chemotherapy and then on April 24th that the patient would undergo chemoradiation, the patient was considered to have spent 8 weeks in the chemotherapy phase (54 days=7.7 weeks, rounded to 8 weeks).

4.2.5 PHYSICAL ACTIVITY MEASUREMENT

Questionnaire. Patients completed the International Physical Activity Questionnaire Short Form (IPAQ-SF) at baseline (T0) and preoperative restaging (T1) to quantify total physical activity in the week prior to starting the exercise program and the final week of the exercise program. The IPAQ-SF has shown acceptable validity and reliability compared to other self-reported physical activity measures.[183] Per standard protocol, total energy expenditure from physical activity in the aforementioned weeks was estimated by multiplying average duration, weekly frequency, and metabolic equivalent task (MET) intensity for each activity domain (vigorous physical activity, moderate physical activity, and walking) and creating a sum across domains.[183] This data processing protocol produced estimates of total MET-minutes of physical activity per week at baseline and preoperative restaging.

Exercise adherence. Patients were instructed to record total minutes of moderate-intensity aerobic exercise and strengthening exercise in daily exercise logs each day during the exercise program. Patients selected whether they would keep paper exercise logs or complete them via automated email survey invitations sent through the Research Electronic Data Capture (REDCap) system (Vanderbilt University, 2015). For both paper and REDCap protocols, patients were instructed to complete logs each night, just before bed. Weekly totals were computed for aerobic exercise, strengthening exercise, and multi-modal exercise (aerobic + strengthening) for each 7-day period from enrollment day to the day of preoperative restaging. Exercise minutes were set to 0 for fields left blank and on days for which patients did not complete exercise logs. Average weekly aerobic, strengthening, and multi-modal exercise minutes were then computed across all exercise program weeks and across weeks spent in each phase of neoadjuvant therapy. Average weekly minutes of aerobic, strengthening, and multi-modal exercise were compared to program recommendations (i.e., 60 minutes/week aerobic exercise and 60 minutes/week strengthening exercise) to assess overall exercise adherence.

Objective physical activity. Physical activity was monitored objectively using accelerometers (ActiGraph GT3X+, ActiGraph Corp 2011). Patients were instructed to wear accelerometers over their right hips during all waking hours for 2 consecutive weeks at the approximate midpoint of each phase of neoadjuvant treatment. For example, a patient who underwent chemotherapy followed by chemoradiation and then preoperative rest underwent (3) 14-day accelerometer wear protocols (one in each phase).

Two-week accelerometer wear protocols were selected to capture the potentially cyclical nature of fatigue and side effects from chemotherapy regimens, which are frequently administered in cycles of approximately 10-14 days.[197] Patients received in-person instruction regarding accelerometer wear protocols at enrollment, including placement on the right hip and recording wear time and device removal in daily accelerometer logs. When possible, accelerometers were delivered in-person to provide repeat instruction, but when necessary, accelerometers were mailed with instructional packets. When accelerometers and packets were mailed, study staff called patients 1-2 days before intended wear periods to ensure that they had received the devices and to remind them of the wear protocol. Patients returned accelerometers to research staff when they returned to MDACC for restaging appointments or using prepaid and addressed return envelopes. It is important to note that accelerometer physical activity measurement was implemented after the first 20 patients had already enrolled in the study; therefore, these patients are not included in analyses involving objective physical activity.

Accelerometers were initialized to collect data at 60 Hz and processed to provide counts in 1-minute epochs.[181] A minimum of 8 wear days, each with a minimum of 10 hours of accelerometer wear time, was required to compute physical activity for each wear period. Non-wear time was defined by at least consecutive minutes of zero counts. Raw accelerometer counts were processed according to standard cutpoints for adults (Freedson 1998) to provide weekly estimates of moderate-to-vigorous physical activity (MVPA), light physical activity (LPA), and total physical activity (TPA, MVPA+LPA) for each wear period.[199] Accelerometer physical activity was compiled separately by treatment phase and also averaged across each treatment phases for each patient.

4.2.6 FATIGUE AND TREATMENT-RELATED SIDE-EFFECTS

Fatigue and treatment-related side effects were measured throughout the exercise program and concurrent neoadjuvant treatments with two modified items from the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)[68] included on daily exercise logs. Patients rated their fatigue and side effects from treatment (i.e., “I felt fatigued” and “I was bothered by side effects of treatment”) each day, with Likert scales ranging from 0 (not at all) to 4 (very much). Items were modified to reflect the past day instead of the past 7 days, as stated by FACT-Hep instructions. Daily scores on these items were summed and averaged to provide average daily ratings of fatigue and side effects during the entire exercise program and separately during each phase of neoadjuvant treatment. It is important to note that measurement of daily fatigue and treatment-related side effects was implemented after the first 20 patients had already enrolled in the study; therefore, these patients are not included in analyses involving these variables.

4.2.7 ANALYSES

Descriptive statistics (frequencies and percentages or means and standard deviations) were used to quantify patients’ sociodemographic, disease, and treatment characteristics and to quantify self-reported exercise, accelerometer physical activity, and fatigue and side effects across and within treatment phases. Chi-square tests and independent t-tests were used to evaluate differences in sociodemographic and clinical characteristics between patients who were lost to follow up vs. patients who completed the study and between patients who proceeded to curative surgery vs. patients who did not.

Due to the positively-skewed distributions of self-reported energy expenditure from physical activity, Wilcoxon signed rank tests were used to compare changes in MET-minutes from baseline to preoperative restaging (paired observations).[187] Chi-square tests were used to evaluate whether patients were more likely to meet aerobic or strengthening recommendations and whether there were differences in meeting exercise recommendations between sexes.[188] Due to the positively-skewed distributions of exercise and physical activity minutes, Mann-Whitney U-tests were used to compare differences in self-reported aerobic, strengthening, and multi-modal exercise and accelerometer MVPA, LPA, and TPA between sexes. Tests for differences in physical activity and exercise minutes and in meeting exercise program recommendations were performed in the full sample and also stratified by sex due to previous evidence of sex-related differences in exercise intervention adherence among cancer survivors.[189] All of the aforementioned analyses were performed using SPSS Statistics Version 24 (IBM Corp., 2016).

Two-level, linear mixed models were used to compare self-reported exercise minutes, accelerometer physical activity, fatigue, and treatment-related side effects among the three neoadjuvant treatment phases. The first set of models were run with only treatment phase as a fixed effect and study ID as a random effect, and the second set of models included sex, age, surgery (yes/no), overall exercise program duration, and interactions between treatment phase and fatigue and treatment phase and side-effects as possible covariates. Restricted maximum likelihood estimation with the Kenward Roger approximation was used to adjust for small-sample bias and account for differences in the number of patients with exercise and physical activity data within each treatment phase.

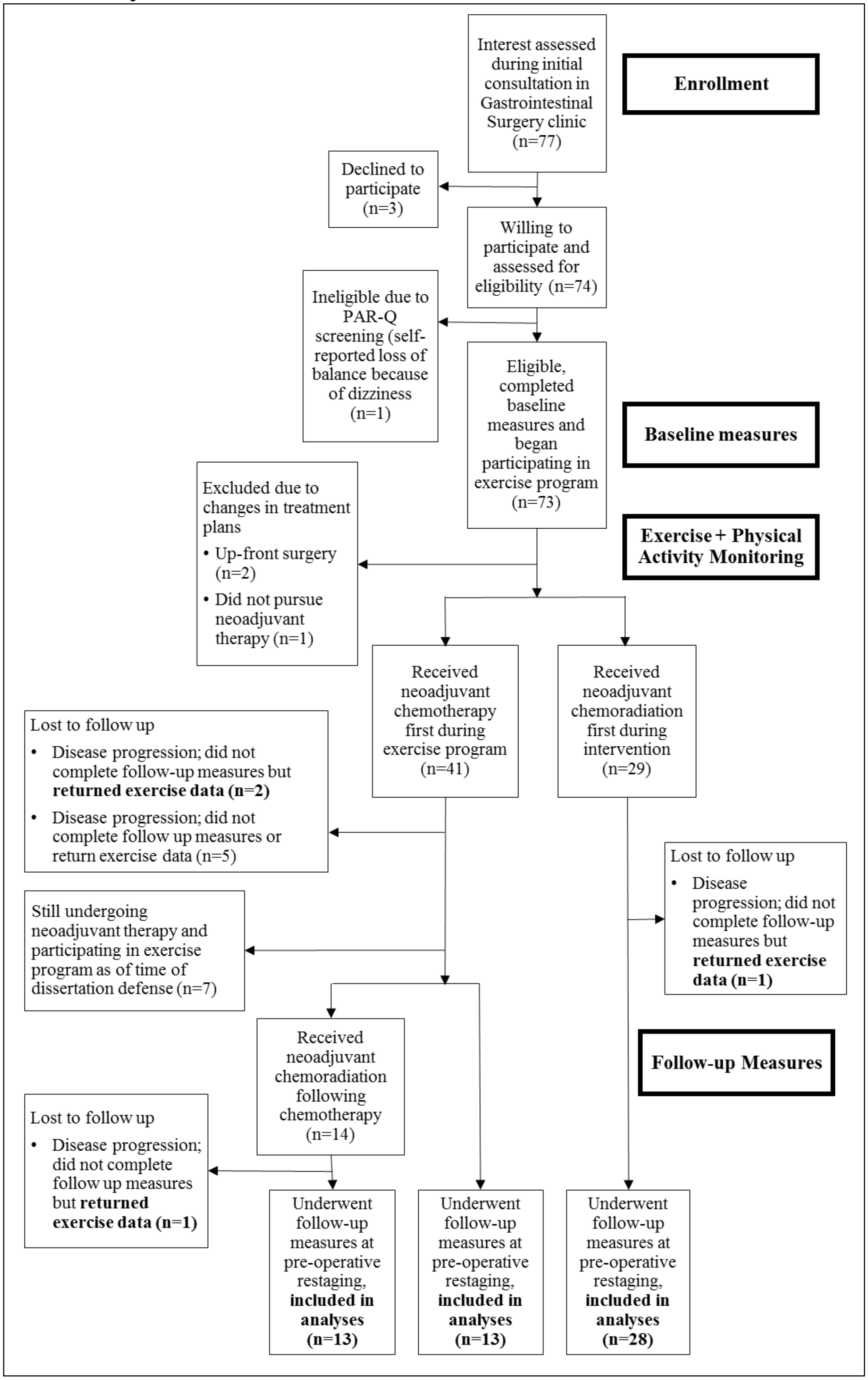
Marginal means estimations created means adjusted for sample size imbalance between phases and for sex, age, surgery (yes/no), overall exercise program duration, and interactions between treatment phase and fatigue and treatment phase and side-effects. Linear mixed models were performed using Stata Statistical Software Version 14 (StataCorp LP., 2015).

4.3 RESULTS

4.3.1 SAMPLE

Figure 1 shows the flow of patients through the study. Among the 77 patients whose interest was assessed during consultations with physicians in Gastrointestinal Surgery clinic, only 3 (3.9%) declined to participate. Only 1 of the 74 patients (1.4%) who were willing to participate was ineligible due to lack of readiness to engage in physical activity. Three of the 73 patients (4.1%) who enrolled became ineligible soon thereafter due to changes in treatment plans, providing a final sample of 70 patients. Of these 70 patients, 29 (41.4%) began preoperative chemoradiation after enrolling in the exercise study, and the remaining 41 (58.6%) began preoperative chemotherapy. Of the 41 patients who began chemotherapy initially, 14 (34.1%) underwent chemoradiation following chemotherapy.

Figure 1. Study flow chart



Five patients (7.1%) had progressive disease (i.e., primary tumors grew to be locally advanced or distant metastases were discovered) and were considered lost to follow up. At the time of this dissertation, 7 patients (10%) were still undergoing neoadjuvant treatment and participating in the exercise program. Patients who completed exercise logs, underwent accelerometer physical activity monitoring, or returned for follow-up measures at preoperative restaging were included in respective analyses involving each outcome.

Table 1 shows sociodemographic and clinical characteristics for the 58 patients for whom adherence or follow-up data had been collected at the time of this dissertation. Patients were generally older adults, with mean age 65.8 years on the date of enrollment (SD=7.7). Patients were nearly 50% female (48.3%), and nearly 80% had primary residences at least 100 miles from the zip code of the study location (79.3%). Nearly 40% of patients were classified as overweight (39.7%), and nearly 25% were obese (24.1%) at baseline, based on BMI ($25.0 \leq BMI < 30.0$ and $BMI \geq 30$, respectively). The vast majority of patients had potentially resectable (60.3%) or borderline resectable (37.9%) tumors at baseline, based on standard criteria for radiographic staging.[200]

Fifty percent of the final sample underwent chemoradiation alone during the exercise program, while the other 50% underwent chemotherapy, either alone (25.9%) or followed by chemoradiation (24.1%). On average, patients underwent 14.9 weeks (SD=7.1) of neoadjuvant treatment and preoperative rest while enrolled in the exercise program. The 29 patients who underwent chemotherapy during the exercise program had, on average, 12.8 weeks (SD=5.9) of chemotherapy. The 43 patients who underwent chemoradiation (either alone or following chemotherapy) during the exercise program had, on average, 4.3 weeks (SD=2.1) of chemoradiation. Forty nine patients underwent a rest period (after treatment but before surgery) during the exercise program, with mean duration 6.0 weeks (SD=1.8). Thirty one patients (50.8%) had stable or improved disease following neoadjuvant treatment and underwent surgical resection, while 27 patients (46.6%) had had diagnoses of progressive disease (locally advanced primary tumors or distant metastases) that precluded attempted curative resection.

Chi-square tests revealed no significant differences in the proportion of patients who underwent curative resection by neoadjuvant treatment course or by initial treatment during the exercise program. Patients who were lost to follow up were more likely to have undergone initial chemotherapy following enrollment (p=.05), but there were no other significant differences in clinical or demographic characteristics (all p>.05).

Table 1. Characteristics of study sample (*N*=58), exercise program duration, and status following preoperative treatment.

Variable		*n*(%)	Mean(SD)
Age at enrollment (years)			65.8(7.7)
Sex			
	Female	28(48.3)	
	Male	30(51.7)	
Location of primary residence			
	≤100 miles from study location	12(20.7)	
	>100 miles from study location	46(79.3)	
Body mass index (kg/m^2)			27.4(5.3)
Radiographic stage at presentation			
	Potentially resectable	35(60.3)	
	Borderline resectable	22(37.9)	
	Locally advanced	1(1.7)	
Neoadjuvant treatment course during exercise program			
	Chemotherapy alone	15(25.9)	
	Chemoradiation alone	29(50.0)	
	Chemotherapy followed by chemoradiation	14(24.1)	
Exercise program duration (weeks)			14.9(7.1)
	During chemotherapy (weeks)		12.8(5.9)
	During chemoradiation (weeks)		4.3(2.1)
	During preoperative rest (weeks)		6.0(1.8)
Outcome following neoadjuvant treatment			
	Stable or improved disease; curative surgery	31(53.4)	
	Disease progression; no curative surgery	27(46.6)	

4.3.2 SELF-REPORTED PHYSICAL ACTIVITY AND EXERCISE ADHERENCE

Table 2 shows self-reported physical activity (converted to MET-minutes of physical activity in the previous 7 days) at baseline and preoperative restaging. In the full sample, patients reported significantly higher physical activity at preoperative restaging (i.e., in the final week of the exercise program) than at baseline (i.e., in the week preceding the exercise program) [$Z(51)=-2.2$, $p=.03$]. The 51 patients who completed the IPAQ-SF at both time points reported an average increase of 902.9 MET-minutes of physical activity from baseline to preoperative restaging (SD=2763.0). This self-reported increase in physical activity translates to approximately 273.6 additional minutes of walking (3.3 METs) per week or 225.7 additional minutes of moderate-intensity physical activity (4.0 METs) per week at preoperative restaging compared to baseline. The increases in self-reported physical activity at baseline and preoperative restaging were not statistically significant in strata by sex (both $p>.05$), but the increase approached statistical significance in men ($Z(27)=-1.9$, $p=.06$). There were no significant differences in self-reported physical activity between sexes at either time point.

Table 2. Self-reported physical activity at baseline and preoperative restaging

	Baseline		Preoperative restaging		Tests for differences[a]		
	n	MET-min [mean(SD)]	*n*	MET-min [mean(SD)]	*n*	*Z*	*p*
All patients	57	1370.4(1833.7)	51	2321.4(2282.8)	51	-2.2	.03
Female	28	1513.9(1923.4)	24	2391.7(2471.5)	24	-1.3	.18
Male	29	1231.8(1765.5)	27	2259.0(2147.1)	27	-1.9	.06

[a]Wilcoxon signed ranks tests for differences in MET-minutes between baseline and preoperative restaging.

Table 3 shows average weekly aerobic, strengthening, and multi-modal exercise (self-reported, from daily exercise logs) and average weekly MVPA, LPA, and TPA (from accelerometers), compiled across all treatment phases. Table 3 also shows the proportion of patients who met program guidelines (≥60 min/week of aerobic exercise, ≥60 min/week of strengthening exercise, ≥60 min/week of each exercise modality, and ≥120 min/week of multi-modal exercise) based on self-reported weekly exercise minutes.

On average, patients completed exercise logs for 71.9% of possible exercise days (SD=35.8). On average, patients reported 124.8 minutes of aerobic exercise per week

(SD=81.2), which was more than twice the weekly recommendation. More than 80% of patients (n=43) met or exceeded the weekly recommendation for aerobic exercise, on average. Female patients reported more minutes of aerobic exercise per week compared to men [mean(SD)=131.3(85.4) vs. 119.2(78.5)], and a slightly higher proportion of females met or exceeded the weekly recommendation (87.5% vs. 78.6%), but neither difference was statistically significant (all p>.05).

On average, patients reported 43.3 minutes of strengthening exercise per week (SD=31.8), which was less than the weekly recommendation. Roughly 25% of patients (*n*=14) met or exceeded the weekly recommendation for strengthening exercise, on average. Male patients reported more minutes of strengthening exercise per week compared to men [mean(SD)=45.4(36.0) vs. 40.9(26.7)], and a higher proportion of females met or exceeded the weekly recommendation (35.7% vs. 16.7%), but neither difference was statistically significant (all *p*>.05).

Combining aerobic and strengthening exercise, patients reported, on average, 168.3 minutes of multi-modal exercise per week (SD=88.2). Nearly 75% of patients (*n*=38) reported at least 120 weekly minutes of multi-modal exercise, on average; however, only 12% (*n*=12) met both aerobic and strengthening recommendations based on average weekly minutes. Female patients reported more minutes of multi-modal exercise per week compared to men [mean(SD)=172.4(93.9) vs. 164.9)(84.5)], but higher proportions of males met or exceeded 120 minutes, on average (75.0% vs. 70.8%) and met or exceeded the recommendation for both exercise modalities (28.6% vs. 16.7%). However, neither of these differences were statistically significant (all *p*>.05). Mann-

Whitney U-tests showed no significant differences between average self-reported minutes of aerobic and strengthening minutes in the complete sample or by sex (all $p>.05$).

Table 3. Overall exercise program adherence across treatment phases

	All [mean(SD)]	Female [mean(SD)]	Male [mean(SD)]
Aerobic exercise	*n*=52	*n*=24	*n*=28
Average min/week	124.8(81.2)	131.3(85.4)	119.2(78.5)
Achieved weekly recommendation [n(%)][a]	43(82.7)	21(87.5)	22(78.6)
Strengthening exercise	*n*=52	*n*=24	*n*=28
Average min/week	43.3(31.8)	40.9(26.7)	45.4(36.0)
Achieved weekly recommendation [n(%)][a]	14(26.9)	4(16.7)	10(35.7)
Multi-modal exercise	*n*=52	*n*=24	*n*=28
Average min/week	168.3(88.2)	172.4(93.9)	164.9(84.5)
≥120 min/week [n(%)][a]	38(73.1)	17(70.8)	21(75.0)
Achieved weekly aerobic AND strengthening recommendations [n(%)][a]	12(23.1)	4(16.7)	8(28.6)
Accelerometer physical activity (min/week)	*n*=40	*n*=21	*n*=19
MVPA	145.8(135.7)	125.5(122.1)	168.3(149.4)
LPA	847.9(274.5)	851.8(274.6)	977.3(343.1)
TPA	993.7(342.2)	977.3(343.1)	1011.8(348.5)

[a]Weekly recommendations were ≥60 min/week of aerobic exercise and ≥60 min/week of strengthening exercise, or ≥120 min/week of multi-modal exercise.

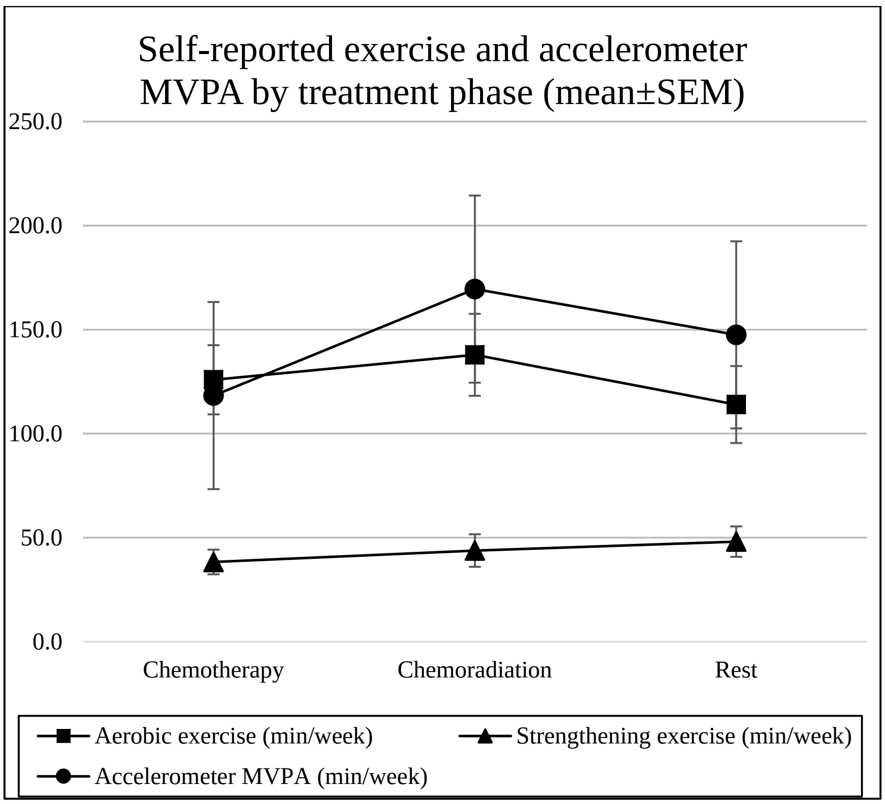
4.3.3 DIFFERENCES IN SELF-REPORTED PHYSICAL ACTIVITY, EXERCISE, FATIGUE, AND SIDE-EFFECTS BETWEEN PREOPERATIVE PHASES

Figure 2a shows self-reported aerobic and strengthening exercise and accelerometer MVPA by treatment phase, as predicted by unadjusted linear mixed models. Weekly minutes of aerobic exercise were highest during chemoradiation [mean(SD)=137.9(150.0)], followed by chemotherapy [mean(SD)=125.9(126.4)] and preoperative rest [mean(SD)=114.0(140.9)]. Weekly minutes of strengthening exercise were highest during preoperative rest [mean(SD)=48.1(55.6)], followed by chemoradiation [mean(SD)=43.8(59.4)] and chemotherapy [mean(SD)=38.3(44.9)]. Weekly minutes of accelerometer MVPA were highest during chemoradiation [mean(SD)=169.5(375.5)], followed by preoperative rest [mean(SD)=147.5(357.9)] and chemotherapy [mean(SD)=118.3(304.6)]. Weekly minutes of multi-modal exercise were highest in chemoradiation [mean(SD)=183.4(175.9)], followed by chemotherapy [mean(SD)=162.3(142.4)] and preoperative rest [mean(SD)=162.0(166.8)] (not pictured). Weekly minutes of accelerometer LPA were highest during preoperative rest [mean(SD)=908.2(741.0)], followed by chemoradiation [mean(SD)=873.2(774.5)] and chemotherapy [mean(SD)=764.6(621.4)] (not pictured). Finally, weekly minutes of accelerometer TPA were highest during preoperative rest [mean(SD)=1055.8(907.0)], followed by chemoradiation [mean(SD)=1042.5(948.2)] and chemotherapy [mean(SD)=882.3(763.8)]. There were no significant associations between treatment phase and weekly minutes of any self-reported exercise or accelerometer-measured physical activity in unadjusted models (all $p>.05$). There were no significant associations between treatment phase and self-reported exercise or accelerometer physical activity in models adjusted for age, sex, surgery (yes/no), overall exercise program duration, and the interactions between treatment phase and self-reported fatigue and side-effects (all $p>.05$).

Figure 2b shows changes daily averages of self-reported fatigue and side effects by preoperative phase in models adjusted for age, sex, and surgery (yes/no). Both fatigue and treatment-related side effects were highest during chemotherapy [mean(SD)=3.0(1.5) and 2.5(1.5), respectively], followed by chemoradiation [mean(SD)=2.0(1.5) and 1.5(1.5), respectively] and preoperative rest [mean(SD)=1.0(1.5) and .5(1.5), respectively]. Fatigue was significantly lower during preoperative rest compared to chemotherapy (*p*=.02), but there were no other significant associations between treatment phase and fatigue or treatment-related side-effects.

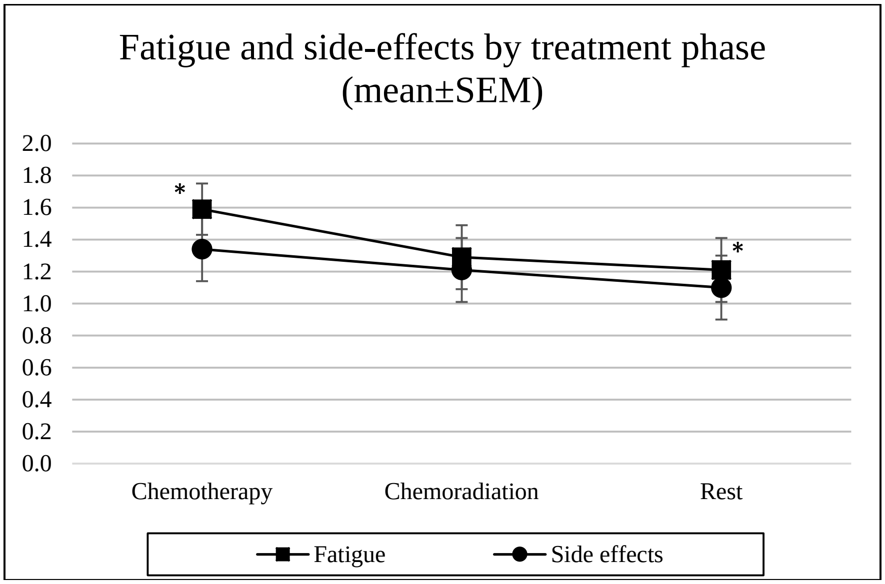
Figure 2. Self-reported exercise minutes, accelerometer physical activity, fatigue, and side-effects by treatment phase

2a. Exercise minutes and accelerometer MVPA by treatment phase[a]



[a]Means are adjusted for imbalance between phases and age, sex, surgery (yes/no), program duration, and interactions between treatment phase and fatigue and treatment phase and side-effects.

2b. Fatigue and treatment-related side effects by treatment phase[a]



*p<.05.

[a]Means are adjusted for imbalance between phases and age, sex, surgery (yes/no), and program duration.

4.4 DISCUSSION

The purpose of this study was to determine whether a home-based, multi-modal exercise program is feasible for patients undergoing neoadjuvant treatment for pancreatic cancer. The secondary purpose was to determine whether exercise feasibility varied by preoperative phase (e.g., chemotherapy, chemoradiation, preoperative rest). Our findings generally supported our hypotheses regarding overall exercise feasibility. On average, patients reported significantly higher physical activity at preoperative restaging compared to baseline, exceeded the weekly recommendation for aerobic exercise and performed nearly 75% of the weekly recommendation for strengthening exercise. Nearly 83% of patients reported meeting the weekly aerobic exercise recommendation, on average. Objective physical activity monitoring corroborated self-reported exercise adherence, with patients performing 145.8 minutes of MVPA per week on average, over all preoperative phases.

Given the unique program context (home-based exercise with patients undergoing preoperative treatment concurrently), it is difficult to draw comparisons with adherence data from previous studies involving preoperative exercise among patients with cancer. However, the proportion of patients meeting the recommendation for multi-modal exercise per week (≥120 minutes/week) in this intervention (mean 14.9 weeks) was similar to adherence to a shorter (4 weeks) preoperative exercise program for patients with colorectal cancer that recommended ≥150 minutes of multi-modal exercise per week (73% vs. 78% adherence, respectively).[31] Patients in the current study underwent concurrent preoperative chemotherapy and/or chemoradiation, while patients in the colorectal cancer study did not.

Contrary to hypotheses, we found no evidence of differences in self-reported exercise or physical activity by treatment phase. Only self-reported strengthening minutes followed the hypothesized trend (preoperative rest > chemoradiation > chemotherapy), with both self-reported aerobic activity and accelerometer MVPA peaking during chemoradiation. Self-reported fatigue and side-effects from treatment tended to decrease from chemotherapy to chemoradiation and preoperative rest. The only statistically significant difference by phase between these variables was in fatigue, between chemotherapy and preoperative rest.

Although there were no significant interaction effects of fatigue or side-effects by treatment phase on exercise or physical activity variables, it is possible that reductions in fatigue and side-effects contributed to increases in aerobic exercise and MVPA from chemotherapy to chemoradiation and in strengthening exercise from each phase to the next. The vast majority of patients underwent chemoradiation while staying in close proximity to MD Anderson Cancer Center for several weeks at a time. The stable performance of strengthening exercise and increases (albeit not statistically significant) in aerobic exercise and MVPA during the chemoradiation phase suggest that patients may be more likely to adhere to the program while in frequent contact with physicians and the hospital environment. Null findings regarding preoperative phase and exercise and physical activity may have resulted from small sample sizes, or there may be an absence of true variability across phases. Therefore, future exercise programs for patients undergoing preoperative treatment for pancreatic cancer should continue to target the entire course of therapy, but they should also continue to measure potential differences in adherence, motivation, and barriers by phase. Given the lower adherence to strengthening exercise compared to aerobic exercise components, it will be important for future exercise programs in this context to explore barriers and motivation involving this modality specifically. The wide variability in all exercise and physical activity variables suggests that it is important to explore facilitators, barriers, and motivation that contribute to large differences in adherence among patients.

This is also the first study to measure adherence to preoperative exercise recommendations using both self-reported and objective measures. Tools measuring self-reported exercise have demonstrated modest validity and reliability, but they are subject to issues with recall and reporting and favorability biases.[32,33] Including objective physical activity measurement with accelerometers is a distinct strength of this study, because these data help corroborate and validate self-reported adherence. Self-reported aerobic exercise and accelerometer MVPA were similar in scale and changed via similar trends over the course of preoperative phases. Given the extensive duration of the exercise program for many patients and that patients were undergoing toxic therapies, retention of participants was strong.

The wide variability in treatment courses and durations (reflecting the true nature of clinical care in this context) created statistical limitations that future studies should attempt to control using stratification or matching with suitable historical controls. Completion of daily exercise logs was variable, possibly introducing bias in the summation of self-reported aerobic and strengthening exercise. We addressed this favorability reporting bias conservatively by setting exercise minutes to be zero on days for which reports were missing, but future studies should prioritize or incentivize exercise log completion to more accurately understand exercise adherence. Finally, although frequent contact between study personnel and patients likely contributed to exercise motivation and adherence and was a study strength, this may limit generalizability if other clinical teams are unable to offer the same degree of support.

This is the first study of exercise feasibility among patients undergoing neoadjuvant treatment for pancreatic cancer. It offers an important contribution to the study of preoperative exercise in the cancer context, because patients with pancreatic cancer are generally older adults and increasingly undergo neoadjuvant treatment. These conditions suggest that feasibility in this context may generalize to a variety of other preoperative cancer contexts. Future studies should include larger groups of patients, ideally stratified by expected treatment course in order to assess the efficacy of preoperative exercise for improving perioperative well-being and outcomes among patients with pancreatic cancer. If preoperative exercise is shown to provide important benefits for patients with pancreatic cancer, as it has among patients with other cancers, then the simple, home-based exercise program described in this study offers a feasible strategy to increase exercise and potentially bestow improved cancer survival outcomes.

4.5 CONCLUSION

Home-based exercise is feasible among patients undergoing preoperative treatment for pancreatic cancer. There were no significant differences in feasibility among chemotherapy, chemoradiation, or preoperative rest, suggesting that it is important to target the entire preoperative course with exercise interventions like this one. Future studies should focus on the potential benefits of exercise in this context in order to further cement formal exercise promotion as an important strategy in clinical care for pancreatic cancer.

CHAPTER 5

MANUSCRIPT 2: SOCIOECOLOGICAL INFLUENCES ON EXERCISE AND PHYSICAL ACTIVITY AMONG PATIENTS UNDERGOING PREOPERATIVE TREATMENT FOR PANCREATIC CANCER

5.1 INTRODUCTION

Exercise has the potential to improve health and treatment outcomes of patients treated with preoperative chemotherapy and/or chemoradiation for pancreatic cancer, which is a leading cause of cancer-related death.[190] Complex operations provide hope for long-term survival of patients with early stage cancer,[3] but preoperative performance status and anticipated postoperative recovery factor heavily into decisions to perform these procedures.[4-6] Preoperative exercise may help maintain or improve fitness of patients whose treatment plans include surgery-- these are generally older adults, who are frequently frail, and who are treated with cytotoxic regimens that can impact health and well being in a negative manner.[7,8,11-13,21,34] Given patients' older age and the impacts of both disease and the therapies used to treat it, the potential for exercise-related benefits is unfortunately coupled with potentially significant barriers to exercise adherence. Therefore, it is important to examine socioecological factors that may influence exercise adherence and physical activity in this context.

A growing body of literature has documented the benefits of physical activity for cancer survivors at various stages in the cancer continuum. Current consensus is that healthcare providers should develop and improve their understanding and incorporation of physical activity in cancer survivorship.[49] The American Cancer Society (ACS) and the American College of Sports Medicine (ACSM) recommend that cancer survivors maintain the same volume and intensity of physical activity as healthy adults.[53,54] Despite these recommendations, cancer survivors perform very little physical activity. Studies have estimated that fewer than 10% and fewer than 30% of survivors will engage in any intentional exercise during treatment and after treatment, respectively.[55,56] To the extent that exercise is beneficial, it is important to investigate socioecological influences of cancer survivors in order to increase their physical activity and maximize their adherence to interventions.

Socioecological models provide a foundation for investigating physical activity influences, positing that a variety of behavioral influences operate at various levels, from proximal to distal from individuals.[28,29,144,145] These influences and levels include *intrapersonal factors*, such as attitudes, beliefs, values[146] and self-efficacy for behavior change;[147] *interpersonal factors*, including interactions with other individuals; and *environmental factors*, including aspects of natural and built environments.[148] Influences in each level interact with influences in other levels to affect behavior, so it is important for interventions to address influences in multiple levels in order to be most effective.[27-29] Socioecological models inform behavioral interventions, providing important areas of influence that should be addressed in program design.[28,149] Social support and neighborhood environment are two such areas of influence and form the focus of this study.

Social support for physical activity can come from different people or groups, including spouses, family members, and friends.[150,151] Social support for physical activity can be emotional (i.e., encouragement or praise), informational (i.e., improving one's understanding of safe and effective physical activity), or instrumental (i.e., providing transportation or companionship). Studies using both surveys and qualitative interviews have demonstrated the importance of social support for physical activity adoption and maintenance among older adults.[38,41] For example, social connections were important for maintaining exercise motivation,[41] and having family or friends provide encouragement or companionship was positively associated with physical activity among older adults.[38] Evidence regarding social support among cancer survivors is limited but suggests that social support may influence physical activity.[150,174] To date, no studies involving preoperative exercise interventions or exercise interventions during cancer treatment have examined social support for physical activity.

Neighborhood factors also influence physical activity adoption and maintenance. Perceived neighborhood walkability, such as how convenient, safe, and enjoyable it is to exercise in a neighborhood, has been shown to be positively associated with physical activity.[161,162] Objectively-measured characteristics describing neighborhood social environments have also been linked to residents' physical activity and access to physical activity resources. For example, studies have shown positive associations between population density and physical activity[168] and disparate access to resources such as parks and trails in neighborhoods in which residents have lower socioeconomic status or are predominantly racial or ethnic minorities.[172,173] Evidence regarding neighborhood factors among cancer survivors is also limited but suggests that favorable neighborhood environments help increase physical activity.[176]

To date, preoperative exercise programs for patients undergoing cancer treatment have involved highly structured, in-person exercise programming.[194-196] This format may not be feasible for patients who undergo treatment planning and surgery at large, comprehensive cancer centers but undergo therapy locally, near home. These circumstances necessitate home-based exercise programming and dictate that clinicians and researchers cannot directly determine or control the microenvironments in which patients exercise. In these cases, social and neighborhood influences and resources may be important influences on program adherence and thus warrant thorough examination.

The purpose of this study was to investigate relationships among socioecological factors and exercise adherence and physical activity among patients enrolled in a home-based exercise program while undergoing preoperative treatment for pancreatic cancer. We aimed to use a combination of self-reported, objective, and qualitative methods to characterize potential influences and outcomes. We hypothesized that social support from family and friends would be positively associated with self-reported aerobic and strengthening exercise and accelerometer-measured physical activity. Further, we hypothesized that neighborhood walkability and socioeconomic status would be positively associated with self-reported exercise and objective physical activity.

5.2 METHOD

5.2.1 STUDY SETTING

Recruitment occurred at a comprehensive cancer center in Houston, TX (the University of Texas MD Anderson Cancer Center, MDACC). All study activities were approved by the MDACC Internal Review Board. Off-site analyses of de-identified data via data sharing agreement were approved by the Committee for the Protection of Human Subjects at the University of Houston.

Gastrointestinal Center physicians at MDACC treat approximately 150 patients with potentially curable, surgically resectable pancreatic ductal adenocarcinoma (PDAC) per year. The vast majority of these patients undergo preoperative chemotherapy, chemoradiation, or a sequence of both therapies, a treatment pattern that represents the standard of care at MDACC and is increasingly used for patients with localized pancreatic cancer at other institutions.[8,21,34,62] This preoperative treatment strategy provides approximately 2-6 months during which it is important to improve and optimize patients' health and well-being prior to surgery.

5.2.2 ELIGIBILITY AND ENROLLMENT

Patients presenting to the MDACC Pancreatic Cancer Clinic to undergo treatment planning for technically resectable PDAC between February, 2015 and January, 2017 were targeted for inclusion in this study. Eligibility requirements included intended pancreatectomy for biopsy-proven PDAC; treatment plan including at least 2-6 weeks neoadjuvant chemotherapy and/or chemoradiation followed by rest before final surgical evaluation; English fluency and telephone access; and willingness to engage in follow-up calls every 2 weeks and maintain daily exercise logs. Patients who had underlying and unstable cardiac or pulmonary disease or symptomatic cardiac disease (New York Heart Association functional class of III or IV), acute musculoskeletal injury or fracture that affected exercise ability, intense pain (numeric rating ≥7 out of 10), or other disease that limited physical function were excluded.

Patients completed the Physical Activity Readiness Questionnaire (PAR-Q)[178] and the Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function 12a Short Form[179] screener question ("Can you walk 25 feet on a level surface, with or without support?") following approval and recommendation from attending medical oncologists or surgeons at initial consultations. Patients who reported losing balance, chest pain, dizziness, or loss of consciousness during physical activity and for those who reported inability to walk 25 feet on a level surface (PROMIS screening question) were not enrolled. Clearance from a physician in Physical Medicine and Rehabilitation was required for patients who reported potential for bone or joint problems to worsen with physical activity. Clearance from a physician in Internal Medicine was required for patients who reported heart conditions and recommendations to only perform physical activity recommended by a doctor and those who reported currently taking medications for hypertension or other heart problems. Clearance from at least one physician serving as co-Principal Investigator on the study was required for patients who reported needing to be cautious about physical activity for any other reasons.

5.2.3 EXERCISE PROGRAM

Patients were encouraged to engage in home-based, multimodal exercise from enrollment until final surgical evaluation. Exercise recommendations were based on ACS and ACSM recommendations for cancer survivors but attenuated to accommodate older age and simultaneous neoadjuvant treatment among target patients.[53,54] The target exercise period spanned the entirety of preoperative therapy (chemotherapy and/or chemoradiation) and preoperative "rest" (Figure 1). At enrollment, study staff explained exercise prescriptions and provided instruction on proper form for all strengthening exercises. Study staff conducted follow up phone calls with patients at least once every 2 weeks to encourage adherence, and monitor for adverse events.

Aerobic exercise component. Patients were encouraged to perform preferred aerobic exercise (e.g., brisk walking, elliptical trainers, or stationary bicycles) for ≥20 min/day on ≥3 days/week. Patients were also encouraged to perform 5 minutes of stretching exercises before and after aerobic exercise sessions. Patients received Borg Rating of Perceived Exertion (RPE) scales[180] and were instructed to exercise at moderate intensity by maintaining the ability to carry on conversations speaking in short sentences while exercising. Patients received pedometers (Digiwalker SW-200, Yamax Inc.) and were encouraged to wear them daily and record step counts in daily logs.

Strengthening component. Patients were encouraged to perform strengthening exercises for ≥30 min/day, ≥2 days/week. Instruction and written/photo and video guides demonstrated strengthening exercises engaging major muscle groups. Sitting and standing options were included when possible to improve comfort and accommodate various levels of balance. Instruction and guides covered 19 different strengthening exercises, and patients were encouraged to select 8 different exercises (1-2 for abdominal muscles, 3-4 for upper body, and 3-4 for lower body) and to perform 3 sets of 8-12 repetitions each for a strengthening session. Patients received portable resistance tube sets (Stackable Resistance Band Set, Black Mountain Products, Inc.) to perform all recommended strengthening exercises, but if patients preferred to use weights or strengthening machines to perform comparable exercises, they were encouraged to do so. Patients were encouraged to perform 5 minutes of both stretching and warm up exercises before and 5 minutes of stretching after strengthening sessions and to maintain moderate exercise intensity.

5.2.4 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The following sociodemographic and clinical variables were collected using the MDACC electronic medical record: age at enrollment, sex, location of residence (≤100 miles from study location vs. >100 miles from study location, confirmed by zip code using Google Maps), body mass index (BMI, kg/m^2), radiographic stage at presentation (potentially resectable, borderline resectable, or locally advanced), neoadjuvant treatment course during the exercise program (chemotherapy alone, chemoradiation alone, or chemotherapy followed by chemoradiation), exercise program duration (overall and separately by phase), and outcome following neoadjuvant treatment (stable or improved disease; curative surgery or disease progression; no curative surgery).

5.2.5 PHYSICAL ACTIVITY AND EXERCISE ADHERENCE

Exercise adherence. Patients were instructed to complete an exercise log for each day they were enrolled in the exercise program. Patients were instructed to complete logs at night, just before going to bed. Exercise logs had spaces for patients to record aerobic and strengthening exercise minutes separately. Exercise logs were provided in program binders, or patients could select to complete them via automated daily surveys using the Research Electronic Data Capture (REDCap) system (Vanderbilt University, 2015). Weekly totals of aerobic, strengthening, and multimodal (aerobic plus strengthening) exercise (aerobic + strengthening) were compiled for each 7-day period from enrollment date to preoperative restaging date. Weekly averages for aerobic, strengthening, and multimodal exercise minutes were then computed across weeks spent in each preoperative phase across all exercise program week. Total volumes of aerobic, strengthening, and multimodal exercise were computed by adding all self-reported exercise from enrollment to preoperative restaging. Total volumes were converted from minutes to hours to improve interpretability.

Objective physical activity. Physical activity was monitored objectively using accelerometers (ActiGraph GT3X+, ActiGraph Corp 2011). Patients received accelerometers and were instructed to wear them over their right hips for 2 consecutive weeks (all waking hours) at approximately the midpoint of each preoperative phase. Two-weeks of accelerometer wear protocols were targeted capture the potentially cyclical nature of fatigue and side effects from chemotherapy regimens in which patients receive one treatment every several days.[201] For example, a patient who underwent chemoradiation followed by preoperative rest underwent two 14-day accelerometer wear protocols (one in each phase). At enrollment, patients received instruction regarding accelerometer wear, including placement and recording periods of wear in daily accelerometer logs. Accelerometers were delivered and collected in-person (at MDACC appointments) whenever possible to provide repeat instruction, but they were mailed with instructional packets and prepaid and addressed return envelopes when necessary. Study staff called patients 1-2 days before intended wear periods to ensure that they had received the devices and to provide additional instruction regarding wear protocols. Accelerometer physical activity measurement was implemented after the first 20 patients had already enrolled in the study; therefore, these patients are not included in objective physical activity analyses.

Accelerometers collected data at 60 Hz, and counts were processed in 1-minute epochs.[181] A minimum of 10 hours of wear time on each of at least 8 days were required to include a wear period in analyses. Freedson adult (1998) cutpoints were used to provide weekly estimates of light physical activity (LPA), moderate-to-vigorous physical activity (MVPA), and total physical activity (TPA, MVPA+LPA) for each wear period.[199] Accelerometer physical activity for each intensity was averaged across each treatment phase for each patient. Total exercise volumes were computed by multiplying average weekly minutes during a given preoperative phase by the number of weeks the patient spent in that phase and then adding the products from all phases.

5.2.6 SOCIOECOLOGIAL INFLUENCES

Social support for exercise. Social support for exercise from family and friends were measured using the Social Support for Exercise Survey (SSES).[155] The SSES lists 13 items that family members or friends may do or say to someone who is trying to exercise regularly, from providing emotional support (e.g.,“Gave me encouragement to stick to my exercise program”) to providing instrumental support (e.g., “Helped plan activities around my exercise”). The SSES also captures social influences that may hinder exercise (e.g., “Complained about the time I spend exercising). Patients responded to each item separately for friends and family, scoring each item on a Likert scale from

1=none to 5=very often. Scores for family participation, family rewards and punishment, and friend participation were computed following published protocols. For all subscales, a higher score denotes higher social support for exercise.[155] An overall score for family and friend participation was computed by adding the scores for each of these subscales. The SSES has shown acceptable validity and reliability.[155] The SSES was implemented after the first 20 patients had already enrolled in the study; therefore, those patients were not included in analyses involving social support.

Perceived neighborhood walkability. Subscales from the Neighborhood Environment Walkability Scan-Abbreviated (NEWS-A)[163,167] were used to examine patients' perceptions of neighborhood factors that may support or inhibit walking for exercise. To fit the purpose of this study and reduce the length of surveys patients were required to complete, patients only completed subscales related to walking for exercise and did not complete subscales relating primarily to walking for transportation (e.g., access to mixed land uses and residential density). Completed subscales includes places for walking and cycling (6 items), neighborhood surroundings/aesthetics (4 items), traffic hazards (3 items), and crime (3 items). A higher score on the crime subscale suggests lower walkability, but a higher score on the other three subscales suggests higher walkability.[163,167] The NEWS-A subscales were implemented after the first 20 patients had already enrolled in the study; therefore, these patients are not included in analyses involving social support. The NEWS-A has shown acceptable validity and reliability.[163]

Neighborhood sociodemographic characteristics. Census tract-level sociodemographic characteristics describing patients' home neighborhoods were collected using 2015 5-year estimates from the American Community Survey.[184] These variables included population density (residents per square mile), percentage of population with age ≥65, percentage of population that identifies as non-Hispanic white, median household income, percentage of population living below the federal poverty level, and percentage of population with a high school diploma or higher education level. Zip code-level estimates were used in place of Census tracts for patients whose mailing addresses in the electronic medical record were post office boxes.[185]

5.2.7 QUALITATIVE INTERVIEWS

Program satisfaction and influences on exercise adherence and physical activity were examined qualitatively through structured interviews with a subsample of patients (*n*=10). Primary questions and probing questions for qualitative interviews focused on the following constructs: energy and side-effects during neoadjuvant treatment phases and how they affected exercise abilities or motivation; time and logistical issues involving exercise during neoadjuvant treatment; the roles of family, friends, and neighborhood or community resources on physical activity and exercise adherence; satisfaction with the exercise program; and suggestions for improvement. The interview guide included 17 open-ended, non-leading questions covering these topics. To minimize study burden on patients during neoadjuvant treatment and post-operative recovery, interviews were conducted approximately 1-2 months following surgery. Interviews lasted approximately 30 minutes and were conducted via telephone, recorded, and transcribed by the first author, who has training in qualitative interviewing. Transcriptions were compared with audio recordings for accuracy.

5.2.8 STATISTICAL ANALYSES

Quantitative analyses. Descriptive statistics were used to quantify sociodemographic, disease, and treatment characteristics; self-reported exercise, accelerometer physical activity; and social support and neighborhood characteristics at baseline and preoperative restaging. Due to the non-normal distributions of social support and neighborhood walkability variables, Wilcoxon signed rank tests were used to compare changes in social support subscale scores from baseline to preoperative restaging and, for a subsample of patients who stayed near MDACC for extended periods for chemoradiation treatments, to compare neighborhood walkability between home and these alternative locations.[187] Linear regression models were used to estimate associations of socioecological influences and exercise and physical activity. Separate models were used to estimate the associations between each potential socioecological influence and each potential exercise or physical activity outcome. All linear regression models included age, sex, and final surgical determination (yes/no) as covariates based on theory and evidence suggesting differences in exercise or physical activity based on these covariates. All analyses were performed using SPSS Statistics Version 24 (IBM Corp., 2016).

Qualitative analyses. Two members of the research staff were trained in qualitative analyses and coded qualitative interviews using NVivo software version 10 (QSR International, 2015) and a constant comparison approach.[202] Principles involving physical activity adoption and maintenance from Social Cognitive[65,133,147] and ecologic theories[27,29] informed the coding approach. The coders first created a list of *a priori* codes and themes and then coded five interviews independently, each adding emergent codes and themes to the list and rearranging *a priori* codes that fit emerging themes. The coders then reviewed the first five interviews together, discussing similarities and discrepancies in coding to reach consensus on the list of codes and themes. This process was repeated for interviews 6-10 and followed by a final meeting between coders to reach consensus on codes and themes. Finally, one coder reviewed all transcripts a second time to confirm and modify codes and themes that fit, to reject codes and themes that did not fit, and to confirm that themes were saturated (i.e., no additional themes emerged).

5.3 RESULTS

5.3.1 SAMPLE

Figure 1 shows the flow of patients through the study. Patients who completed exercise logs, underwent accelerometer physical activity monitoring, or returned for follow-up measures at preoperative restaging were included in respective analyses involving each potential influence and outcome.

Figure 1. Study flow chart

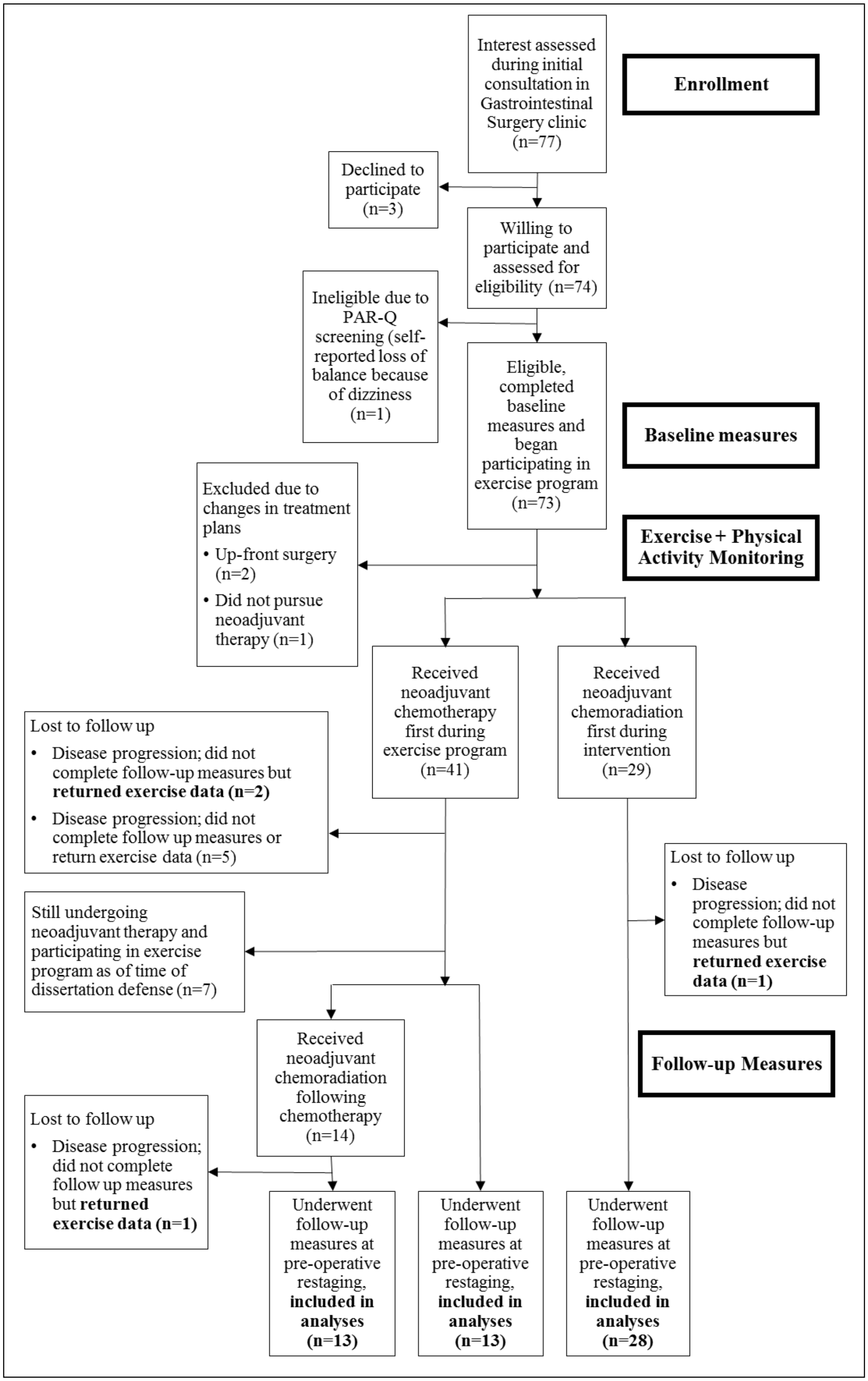


Table 1 shows clinical and sociodemographic for the 58 patients from whom adherence and follow-up data had been collected at the time of this dissertation. Patients were generally older adults, nearly 50% were female, and nearly 80% lived farther than 100 miles from the study location. Nearly 65% of patients were classified as overweight or obese at baseline (BMI≥25). Most patients had potentially resectable or borderline resectable tumors at baseline based on standard criteria for radiographic staging.[200] Half of the final sample underwent chemoradiation alone during the exercise program, while the other half underwent chemotherapy, either alone or followed by chemoradiation. On average, patients spent 14.9 weeks (SD=7.1) enrolled in the exercise program. Slightly more than half of patients had stable or improved disease following neoadjuvant treatment and underwent surgical resection, and half had progressive disease that precluded curative resection. Compared to the final sample, patients who dropped out of the study were more likely to have undergone initial chemotherapy following enrollment (p=.05), but there were no other significant differences in clinical or demographic characteristics (all p>.05).

Table 1. Clinical and sociodemographic characteristics of study sample (*N*=58)

Variable		*n*(%)	Mean(SD)
Age at enrollment (years)		-	65.8(7.7)
Sex			
	Female	28(48.3)	-
	Male	30(51.7)	-
Location of primary residence			
	≤100 miles from study location	12(20.7)	-
	>100 miles from study location	46(79.3)	-
Body mass index (kg/m^2)		-	27.4(5.3)
Radiographic stage at presentation			
	Potentially resectable	35(60.3)	-
	Borderline resectable	22(37.9)	-
	Locally advanced	1(1.7)	-
Neoadjuvant treatment course during exercise program			
	Chemotherapy alone	15(25.9)	-
	Chemoradiation alone	29(50.0)	-
	Chemotherapy followed by chemoradiation	14(24.1)	-
Exercise program duration (weeks)		-	14.9(7.1)
	During chemotherapy (weeks)	-	12.8(5.9)
	During chemoradiation (weeks)	-	4.3(2.1)
	During preoperative rest (weeks)	-	6.0(1.8)
Outcome following neoadjuvant treatment			
	Stable or improved disease; curative surgery	31(53.4)	-
	Disease progression; no curative surgery	27(46.6)	-

5.3.2 SOCIOECOLOGICAL INFLUENCES

Table 2 shows social support (baseline and preoperative restaging), neighborhood walkability (home neighborhoods and neighborhoods near MDACC), and Census tract-level sociodemographic characteristics for home neighborhoods among study participants. On average, family participation, friend participation, and the sum of these subscales were slightly higher at baseline than at preoperative restaging. However, there were no statistically significant differences in social support variables from baseline to preoperative restaging (all p>.05). On average, walkability scores were slightly higher for neighborhoods in which patients stayed while receiving care at MDACC than for home neighborhoods, but this was only among a subsample of 13 patients who stayed in alternative neighborhoods for extended treatment periods; none of these differences were statistically significant (all *p*>.05).

Table 2. Socioecological influences at baseline and preoperative restaging

Variable	Baseline [mean(SD)]	Preoperative restaging [mean(SD)]
Social support	*n*=39	*n*=39
Family participation (max 50)	28.2(12.3)	27.8(11.2)
Family rewards and punishment (max 15)	3.74(1.1)	3.74(1.2)
Friend participation (max 50)	17.5(7.7)	16.4(7.3)
Family participation + friend participation (max 100)	45.8(17.9)	44.3(16.9)
Neighborhood walkability[a]	*n*=42	*n*=13[b]
Places for walking and cycling (max 4)	2.4(.9)	2.7(1.0)
Aesthetics (max 4)	3.1(.8)	3.2(.9)
Traffic hazards (max 4)	1.7(.9)	1.8(.6)
Crime (max 4)[b]	1.4(.6)	1.0(.5)
Census tract sociodemographic characteristics	*n*=58	
Population density (people per square mile)	1244.7(1754.1)	-
Percent ≥65	15.4(10.0)	-
Percent non-Hispanic white	60.1(27.8)	-
Median household income (USD)	58144.3(25197.2)	-
Percent below poverty line	16.8(10.0)	-
Percent with at least high school education	85.3(9.1)	-

[a]Higher score denotes higher walkability for all but crime subscale.
[b]Subsample of patients who stayed near MD Anderson during chemoradiation.

5.3.3 EXERCISE ADHERENCE AND PHYSICAL ACTIVITY

Table 3 shows average weekly aerobic, strengthening, and multimodal exercise (self-reported, from daily exercise logs) and average weekly MVPA, LPA, and TPA (from accelerometers), compiled across all treatment phases. On average, self-reported weekly aerobic exercise minutes and multimodal exercise minutes exceeded program recommendations [mean(SD)=124.8(81.2) and 168.3(88.2), respectively], but self-reported weekly strengthening minutes did not reach recommendations [mean(SD)=43.3(31.8)]. Average total aerobic exercise volume was more than three times average strengthening exercise volume [mean(SD)=30.0(24.0) hours vs. 9.9(9.4) hours]. On average, accelerometer-measured MVPA was 145.8 minutes/week (SD=135.7), translating to 31.0 total hours (SD=32.0) of total MVPA volume over the entire course of the exercise program.

Table 3. Exercise adherence and physical activity

Variable	Weekly performance [min/week, mean(SD)]	Total volume [hours, mean(SD)]
Self-reported exercise adherence (*n*=52)	-	-
Aerobic exercise	124.8(81.2)	30.0(24.0)
Strengthening exercise	43.3(31.8)	9.9(9.4)
Multimodal exercise	168.3(88.2)	39.9(27.4)
Accelerometer physical activity (*n*=40)		
LPA	847.9(274.5)	187.5(109.5)
MVPA	145.8(135.7)	31.0(32.0)
TPA	993.7(342.2)	218.6(126.9)

5.3.4 ASSOCIATIONS AMONG SOCIOECOLOGICAL INFLUENCES, EXERCISE, AND PHYSICAL ACTIVITY

Table 4 shows standardized regression coefficients among socioecological influences and self-reported exercise adherence. After adjustment for age, sex, and final surgical determination, standardized regression coefficients between social support variables and self-reported exercise ranged from .01 to .56. There were statistically significant, positive associations between family participation at preoperative restaging and weekly strengthening exercise (β=.36, p=.03) and total strengthening exercise volume (β=.40, p=.02). An increase of 1 SD in family participation was associated with

11.4 additional minutes of strengthening exercise per week and 3.8 additional hours of strengthening exercise over the entire preoperative period.

There was a statistically significant, positive association between family rewards and punishment at preoperative restaging and total strengthening exercise volume (β=.57, p<.01). An increase of 1 SD in family rewards and punishment was thus associated with 5.4 additional hours of strengthening exercise over the entire preoperative period. Finally, there were statistically significant, positive associations between the sum of family and friend participation at preoperative restaging and weekly strengthening exercise (β=.35, p=.03) and total strengthening exercise volume (β=.38, p=.03). An increase of 1 SD in family and friend participation was thus associated with 11.1 additional minutes of strengthening exercise per week and 3.6 additional hours of strengthening exercise over the entire preoperative period.

There were no statistically significant associations involving baseline social support or involving aerobic or multimodal exercise after adjusting for age, sex, and surgical determination. Standardized regression coefficients between neighborhood walkability variables and self-reported exercise ranged from -.13-.39. There was a statistically significant, positive association between self-reported crime and total aerobic exercise volume (β=.35, p=.03). An increase of 1 SD in self-reported crime was thus associated with an additional 8.4 hours of aerobic exercise over the entire preoperative period. There were no statistically significant associations among Census-tract sociodemographic characteristics for patients' home neighborhoods and any self-reported exercise variables [data not shown; range of standardized regression coefficients -.48-.24].

Table 4. Standardized regression coefficients among socioecological influences and exercise adherence from linear regression models adjusted for age, sex, and final surgical evaluation.

Variable	Standardized partial correlation coefficients					
	Aerobic exercise		Strengthening exercise		Multimodal exercise	
	Min/week	Total volume	Min/week	Total volume	Min/week	Total volume
Social support						
Family participation						
Baseline	.06	.02	.16	.03	.11	.07
Preoperative restaging	.03	-.10	.36*	.40*	.14	.01
Family rewards and punishment						
Baseline	.02	.07	.09	.07	.05	.08
Preoperative restaging	.11	.08	.33	.57**	.19	.23
Friend participation						
Baseline	.01	-.09	.03	.03	.01	-.08
Preoperative restaging	.10	-.04	.27	.26	.17	.03
Family participation + friend participation						
Baseline	.05	-.03	.12	.14	.08	.01
Preoperative restaging	.06	-.08	.35*	.38*	.16	.02
Home neighborhood walkability						
Places for walking and cycling	-.06	.08	-.13	.11	-.09	.10
Aesthetics	.08	-.08	.01	-.01	.08	-.05
Traffic hazards	.04	-.07	.08	-.07	.06	-.09
Crime	.14	.35*	-.003	.13	.12	.33

*p<.05; **p<.05

Table 5 shows associations among socioecological influences and accelerometer PA. There were no statistically significant associations among social support or neighborhood walkability variables and weekly or total volumes of LPA, MVPA, or TPA (all p>.05). The ranges of standardized regression coefficients among social support and neighborhood walkability variables and accelerometer physical activity were -.22-.28 and -.30-.29, respectively. There were no statistically significant associations among Census-tract sociodemographic characteristics for patients' home neighborhoods and any accelerometer physical activity variables (data not shown; range of standardized regression coefficients -.22-.30).

Table 5. Standardized regression coefficients among socioecological influences and accelerometer physical activity from linear regression models adjusted for age, sex, and final surgical determination.

	Standardized partial correlation coefficients					
	LPA		MVPA		TPA	
	Min/week	Total volume	Min/week	Total volume	Min/week	Total volume
Social support						
Family participation						
Baseline	-.16	-.11	-.16	-.15	-.19	-.13
Preoperative restaging	.05	-.17	-.03	-.13	.03	-.18
Family rewards and punishment						
Baseline	-.14	.03	-.22	-.13	-.20	-.01
Preoperative restaging	.14	-.06	.10	.02	.15	-.05
Friend participation						
Baseline	.11	-.04	-.02	-.10	.08	-.06
Preoperative restaging	.28	.11	.06	.03	.25	.11
Family participation + friend participation						
Baseline	-.05	-.10	-.12	-.15	-.09	-.12
Preoperative restaging	.15	-.07	.01	-.07	.12	-.08
Home neighborhood walkability						
Places for walking and cycling	-.15	-.09	.15	.17	-.06	-.04
Aesthetics	.10	.02	.29	.24	.19	.08
Traffic hazards	-.08	-.30	.02	-.14	-.05	-.29
Crime	-.12	-.05	-.07	-.07	-.13	-.06

5.3.5 QUALITATIVE FINDINGS

Figure 2 shows emergent themes and representative quotes from qualitative interviews. There were 9 discrete themes regarding socioecological influences on exercise and physical activity during the exercise program. Themes were organized into two general categories: facilitators of adherence (6 themes) and barriers to adherence (3 themes). Patients widely described *disease-related motivation*, *past exercise experience*, *encouragement from physicians*, *social support from family and friends*, *neighborhood walkability and physical activity resources*, and *accountability* as important facilitators of adherence. Frequently mentioned barriers to adherence included *treatment*; *weather, logistics, and time*; and *lack of social support*.

Figure 2. Themes and quotes from qualitative interviews representing patients' perspectives regarding socioecological influences on exercise adherence and physical activity during preoperative treatment for pancreatic cancer.

Category/Theme	**Representative quotes**
Facilitators of adherence	
Disease-related motivation	"I believed in exercise, and I knew I was being attacked, and it seems like exercise was a reasonable way that I could try to make myself stronger." *–Female, 63 years old*
	"My mindset was, 'I had a month to prepare my body for surgery,' and I wanted to get as strong as I possibly could." *–Female, 63 years old*
	"You hit me at a time when all my synapses were firing like crazy. When the hospital offered me an exercise program and I had just got the death certificate that the doctors had diagnosed me with, I got quite motivated." *–Male, 71 years old*
	"I was pretty well out of shape and was getting weaker and had lost some weight. And I needed to do it to strengthen myself. To go through the chemotherapy and the radiation and eventually the surgery." *–Male, 68 years old*
	"I wanted to make sure I was in no worse shape when I got my surgery, or as good of shape as I could possibly be in for my recovery." *–Female, 65 years old*
	"I wanted rid of this disease, so that was my motivation. To get well." *–Female, 74 years old*
	"The sense of urgency and how critical it was, that helped me. The better shape I could be in coming into surgery, the quicker I was going to heal up and get over all of this." *–Male, 64 years old*
Past exercise experience	"I've always been fairly active. So, the transition wasn't hard." *–Male, 71 years old*
	"I think it certainly helped me, having been used to exercising." *–Male, 77 years old*
	"I always knew the importance of exercising, so that made it easier." *-Male, 80 years old*
Encouragement from physicians	"I really did hear the docs saying, 'The better shape you're in, the easier it's going to be for you to recover.' It motivated me." *–Male, 71 years old*
	"I think each one of the doctors stressed how important it was to stay exercising." *–Male, 77 years old*
	"I needed the support of [my surgeon] saying, 'This is pretty critical. The stronger you are going into surgery, the stronger you are when you're going to recover.'" *–Male, 77 years old*

Social support from family and friends	"My husband was like my whip. He reminded me every day that maybe I could do X, or maybe I could do Y." –*Female, 63 years old* "I'm a very fortunate person. My wife has always been exercising. The community I live in and play golf with and know, they'd kick my butt if I didn't. That encouragement really helped, because I didn't want to have to tell them why I didn't make it." *–Male, 71 years old* "My niece and my husband were after me all the time. Telling me that I had to exercise, that I had to move. That helped, because they were there for me." *–Female, 74 years old* "I've had tons of support. My family, they were the ones who hauled the exercise bike down here for me." –*Female, 74 years old* "My wife has had three mini strokes, and every single day, she gets on the treadmill, or she does pilates, and she does her yoga, without exception. For me, that was something to look up to." *–Male, 59 years old* "It would come on the edge of nagging, but you know, [my wife] was right. I begrudgingly did it, but I did do it. She is a valuable asset when it comes to getting something done." *-Male, 80 years old*
Neighborhood walkability and physical activity resources	"I like walking, and that made the walking part desirable. I live in a place that's pretty, and the walks were a nice, pleasant distraction." *–Female, 63 years old* "I remember filling out a form that asked, 'In your community, is it safe to walk in your streets?' Well, in my community, I walk right down the center line in the evenings." *–Male, 71 years old* "I'm fortunate, because I've got a gym in my neighborhood. If I had only the resistance tubes to work with, I don't know if I could have stayed with a strengthening program." *–Male, 71 years old* "I joined a gym and got a trainer, and he helped me with the exercise program. To encourage me to get it done and to give me some more accountability." *–Male, 68 years old*
Accountability	"Having to keep a log, be accountable, that was motivational." *–Female, 63 years old* "It was tremendous. The diary, the accountability, to track that stuff – it gave me some more motivation to get it done." *–Male, 68 years old* "Those relentless reports – you know, every day – you'd always have something to do. It was always on your mind, so it's not something that you can ignore. And so they helped motivate, too." *-Male, 80 years old* "It was something that had to be done. It was a job. It was a commitment. I didn't feel right unless my exercise was done." *-Male, 80 years old*

	"The phone calls I received following my progress and seeing how I was, that was motivational." *–Female, 63 years old*
Barriers to adherence	
Treatment	"I had a little trouble after the 10 days of chemo and radiation combination. I didn't have the motivation or the level that I was able to do a lot." *–Male, 77 years old*
	"On the bad days, there was no exercise. You know, 4 or 5 hours of infusions takes a lot out of you mentally, too. So I wasn't in the mood for exercising." *–Female, 65 years old*
	"Part of my chemo was the fact that I wore a pump for 3 days. I was really inactive because everything I did pulled on the catheter. The pump wasn't too heavy, but it wasn't convenient." *–Female, 65 years old*
	"After chemo and radiation, I didn't have quite as much energy, and it took a few weeks to kind of get my strength back up." *–Male, 64 years old*
Weather, logistics, and time	"It was hard to do it here in the extreme heat of summer." *–Female, 63 years old*
	"If it weren't cold out, I probably would have been a lot more involved than I was." *–Female, 65 years old*
	"What got in the way were fatigue and other tasks, other items I had to take care of during the day. Doctors' appointments, consults, and other activities." *–Male, 68 years old*
	"There were obstacles. One was travel. If you stop at a motel, you can go into that gym, if they have one, but it's limited. If you're traveling as far as I'm traveling, you'll be tired when you get there, from just sitting there, riding. *-Male, 80 years old*
Lack of social support	"I'm a social person who enjoys exercise accompanied by other people versus alone. Having my husband walk with me was good, but doing the bands alone, I just wasn't as motivated. It was harder." *–Female, 63 years old*
	"Occasionally someone encouraged me, but otherwise it was, 'Well, if you don't do it, you don't do it.' I'm not sure there was a lot of encouragement. It was probably that they thought I should be sufficiently motivated on my own." *–Female, 65 years old*
	"Friends were staying away, because they didn't want to expose me to their colds or germs or anything like that. But I'm much more motivated if I'm in a crowd." *–Female, 65 years old*

5.4 DISCUSSION

The purpose of this study was to investigate relationships among socioecological factors and exercise adherence and physical activity among patients enrolled in a home-based exercise program while undergoing preoperative treatment for pancreatic cancer. Our findings generally supported our hypotheses. We found quantitative and qualitative evidence demonstrating the influences of social support and neighborhood characteristics on program adherence. Linear regression models showed positive associations between social support from family and friends and self-reported strengthening exercise after adjusting for age, sex, and surgical determination. Linear regression models also showed a positive association between perceived neighborhood crime and self-reported aerobic exercise. In qualitative interviews, patients described social support and neighborhood walkability and physical activity resources as important influences that helped them adhere (or, in some cases, posed barriers to adherence) to exercise recommendations.

This is the first study to examine socioecological influences on exercise adherence and physical activity among patients with pancreatic cancer and among patients with cancer participating in a structured, preoperative exercise program. We found evidence of positive associations between family participation in physical activity, as reported by patients at preoperative restaging (following the exercise program), and self-reported strengthening exercise. There was also evidence of positive associations between family rewards and punishment for physical activity and total volume of strengthening exercise. Finally, there was evidence of positive associations between the sum of family and friend participation in physical activity and strengthening exercise. Our findings regarding social support are in agreement with previous studies involving older adults[41] and a recent study involving breast cancer survivors.[174] Interestingly, positive associations involving social support were only evident for strengthening exercise variables. This, coupled with the difficulty patients had adhering to the strengthening exercise recommendations in this exercise program, suggests that social support may be particularly important for strengthening exercise. Future exercise interventions with strengthening components among patients with pancreatic cancer should further examine the support roles of family and friends. For example, simply including caretakers or family members in exercise recommendations, providing them with their own exercise logs, and including them in exercise demonstrations may help improve patients' adherence to the exercise recommendations.

The positive association that we observed between neighborhood crime and total aerobic exercise volume was unexpected, but somewhat reflective of the inconsistent nature of relationships between perceived neighborhood characteristics and physical activity. It is unlikely that neighborhood crime actually posed a barrier to strengthening exercise adherence in this study, as strengthening exercises could be performed safely within patients' homes using the portable resistance tube sets provided to all patients. It is also possible that some patients who reported higher neighborhood crime regularly used gyms or fitness centers to perform strengthening exercises.

We found no evidence of associations between social support and aerobic exercise or any objectively-measured physical activity variables. In the context of patients undergoing preoperative treatment for pancreatic cancer, it is possible that disease- and treatment-related motivation or barriers were more influential than social support in determining aerobic exercise. The lack of evidence for associations involving accelerometer physical activity may be attributable to measurement limitations, as accelerometers may not capture moderate-intensity strengthening exercise reliably.[37] The degree of hip movement that occurred while patients were conducting strengthening exercises using the upper or lower extremities may not have been extensive enough to contribute significantly to LPA or MVPA counts during periods of accelerometer wear.

The themes that emerged from qualitative interviews aligned with our hypotheses and previous research involving social support and physical activity among cancer survivors and older adults.[41,203] Patients widely described the importance of social support in helping them adhere to the exercise program. Most patients described social support as a positive influence, with family or friends providing emotional or instrumental support for exercise. However, two female participants described a lack of social support as a barrier to adherence. Interestingly, social support from outside of patients' circles of friends and family emerged as an important physical activity influence among interviewees. Patients regularly described the encouragement they received from physicians and the support and accountability they felt in completing exercise logs that were regularly reviewed by study staff as important drivers of program adherence.

Perhaps unique to this context, patients emphasized that disease-related motivation was an important influence of adherence during this exercise program. When patients were enrolled in this exercise program, they were facing several weeks of difficult treatment, but they also seemed to recognize that they had limited timeframes in which to optimize their health to prepare for potentially curative surgery. Therefore, disease-related motivation may have been one of the most significant drivers of exercise adoption and maintenance during preoperative treatment.

One limitation of this study was wide variability in the exact types of treatment patients received and in the duration of preoperative therapy courses. While these issues reflect the true nature of clinical care for patients with pancreatic cancer in this context, they provide methodological and statistical issues that future studies should strive to control using stratification. Completion of daily exercise logs was also inconsistent and variable across patients, and patients may have over-reported time spent exercising at moderate intensity, as is frequently the case with self-reported exercise measures. Although qualitative interviews elicited patients' input and themes emerged regarding exercise motivation, we did not include a measure to study motivation specifically. Our findings suggest that disease- and treatment-related motivation may be particularly important in this context, so future studies should measure exercise motivation specifically and provide variable support based on patients' needs.

This is one of few studies examining socioecological influences on exercise adherence and physical activity among patients with cancer. We included self-reported and objective measures of exercise adherence and physical activity, and we measured social support and neighborhood characteristics using a mix of self-reported, objective, and qualitative methods. Further, this was the first known study to examine socioecological influences in the specific context of a preoperative exercise program for patients undergoing simultaneous, neoadjuvant treatment. We showed that social support from family, friends, and even from physicians and program staff may be important influences on exercise adherence, particularly involving strengthening exercise. Future intervention efforts should incorporate additional program components to capitalize upon patients’ existing resources for social support or supplement with additional support for patients who may lack social support at home.

5.5 CONCLUSION

Social support may be an important influence on physical activity and exercise adherence (particularly strengthening exercise) among patients participating in a home-based exercise program during preoperative treatment for pancreatic cancer. Given the hypothesized benefits of strengthening exercise in this context, it is important for future interventions to include components to increase and capitalize upon social support. Qualitative findings suggest that a significant portion of exercise motivation may stem from patients’ goals involving completing treatment successfully and recovering from surgery in this context.

CHAPTER 6

MANUSCRIPT 3: RELATIONSHIPS AMONG PHYSICAL ACTIVITY, HEALTH-RELATED QUALITY OF LIFE, INFLAMMATION, AND SKELETAL MUSCLE IN PATIENTS PARTICIPATING IN A HOME-BASED EXERCISE PROGRAM DURING NEOADJUVANT TREATMENT FOR PANCREATIC CANCER

6.1 INTRODUCTION

Pancreatic cancer is one of the leading causes of cancer-related death in United States. Curative surgery can improve long-term survival for patients with resectable pancreatic cancer, but the complexity of surgery requires robust preoperative health and performance status. Patients with pancreatic cancer are generally older adults and increasingly undergo neoadjuvant chemotherapy and chemoradiation that may diminish functional status. Therefore, it is important to develop strategies to optimize health and wellbeing during this window of neoadjuvant treatment to improve readiness for surgery and potentially accelerate postoperative recovery.

Current consensus is that healthcare providers should develop and improve their understanding and incorporation of physical activity in cancer survivorship.[49] Preoperative exercise programming, or *prehabilitation*, is an increasingly common strategy to improve outcomes in cancer care and has been linked to improvements in improved fitness, physical functioning, and postoperative recovery among patients with various cancer diagnoses. To date, no studies have examined potential outcomes related to preoperative exercise among patients with pancreatic cancer.

Health-related quality of life (QOL) is an important, patient-reported outcome in cancer survivorship, and it is a frequent target for exercise interventions for cancer survivors. QOL includes physical, functional, emotional, and social wellbeing. A meta-analysis of exercise interventions among cancer survivors demonstrated that they lead to statistically significant and clinically meaningful improvements in QOL.[66] Physical activity-associated improvements in QOL have been studied extensively in the contexts of longer-term survivorship and post-treatment settings for survivors of breast, prostate, endometrial, and colorectal cancer.[64,66] Recent, preoperative exercise interventions have shown improvements in QOL among patients with colorectal and liver cancer.[204,205] Impairment in QOL is prevalent among patients with pancreatic cancer upon diagnosis,[206] and anxiety and low QOL have been shown to be associated with fear of cancer recurrence postoperatively.[22] Patients undergoing preoperative treatment for pancreatic cancer may benefit from exercise-related improvements in QOL, and the relationships among exercise program adherence, physical activity, and QOL thus warrant investigation.

Sarcopenia, or progressive loss of skeletal muscle frequently associated with aging, is prevalent among patients with pancreatic cancer and associated with poor prognosis.[108] Sarcopenia frequently accompanies neoadjuvant treatment for pancreatic cancer,[12] potentially placing patients at increased risk for adverse outcomes including reduction of mobility, loss of physical functioning, and mortality.[106,107] Physical activity interventions have also shown the ability to mitigate sarcopenia.[103] Resistance exercise has shown promise in reversing sarcopenia during endocrine therapy for breast cancer[109] and among older patients undergoing prehabilitation prior to surgery for gastric cancer,[110] but research examining associations between exercise and sarcopenia among cancer survivors is generally limited. There exists important potential for exercise programming to mitigate loss of skeletal muscle among patients undergoing preoperative treatment for pancreatic cancer.[12]

Inflammation is an important prognostic indicator among patients with pancreatic cancer, with lower inflammation associated with longer survival.[24,25,207] Patients undergoing neoadjuvant treatment for pancreatic cancer have shown increases in neutrophil-to-lymphocyte ratio that are inversely associated with survival following pancreatectomy.[136] Exercise training has been shown to reduce inflammatory biomarkers in healthy older adults.[208] A recent review identified inflammation as an important target for exercise to improve oncologic, recurrence, and survival outcomes among patients with cancer,[139] and exercise shown potential to improve some mediators of inflammation among breast cancer survivors.[138] There exists theoretical basis for preoperative exercise to reduce systemic inflammation among patients with cancer, but scientific evidence to date is inconclusive.[26] It is important to determine whether preoperative exercise interventions can help reduce inflammation among patients undergoing preoperative treatment for pancreatic cancer.

The purpose of this study was to investigate relationships among exercise adherence, physical activity, and health-related quality of life, skeletal muscle, and inflammation among patients enrolled in a home-based exercise program while undergoing preoperative treatment for pancreatic cancer. We hypothesized that exercise adherence and physical activity would be positively associated with changes in health-related quality of life, skeletal muscle, and inflammation among these patients. Further, we hypothesized that changes in skeletal muscle would be favorable among patients participating in the exercise program compared to historical controls who did not participate in a formal exercise program.

6.2 METHOD

6.2.1 STUDY SETTING

Recruitment occurred at the University of Texas MD Anderson Cancer Center (MDACC), a comprehensive cancer center in Houston, TX. The MDACC Internal Review Board approved all study activities, and analyses of de-identified data were approved by the Committee for the Protection of Human Subjects at the University of Houston.

Approximately 100 patients with technically resectable pancreatic ductal adenocarcinoma (PDAC) receive care from Gastrointestinal (GI) Center physicians at MDACC annually. Neoadjuvant therapy consisting of chemotherapy, chemoradiation, or a sequence of both represents the standard of care at MDACC and is increasingly used for patients with localized pancreatic cancer.[8,12,21,34] The typical duration of preoperative treatment is approximately 2-6 months, providing an important timeframe for optimizing health and wellbeing preoperatively.

6.2.2 ELIGIBILITY AND ENROLLMENT

Patients presenting to the MDACC GI Surgery Clinic with technically resectable PDAC between February, 2015 and January, 2017 were targeted for enrollment. Eligibility requirements included intended pancreatectomy for biopsy-proven PDAC; treatment plan including at least 2-6 weeks neoadjuvant chemotherapy and/or chemoradiation followed by rest before final surgical evaluation; English fluency and telephone access; and willingness to engage in follow-up calls every 2 weeks and maintain daily exercise logs. Patients who had underlying and unstable cardiac or pulmonary disease or symptomatic cardiac disease (New York Heart Association functional class of III or IV), acute musculoskeletal injury or fracture that affected exercise ability, intense pain (numeric rating ≥7 out of 10), or other disease that limited physical function were excluded.

Following recommendation and approval from attending medical oncologists or surgeons at initial consultations, patients completed the Physical Activity Readiness Questionnaire (PAR-Q)[178] and the Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function 12a Short Form[179] screener question ("Can you walk 25 feet on a level surface, with or without support?"). Self-reported loss of balance, chest pain, dizziness, or loss of consciousness during physical activity, and inability to walk 25 feet on a level surface were grounds for exclusion. Patients who reported potential for bone or joint problems to worsen with physical activity required clearance from a physician in Physical Medicine and Rehabilitation. Patients who reported heart conditions, current prescriptions for hypertension or other heart problems, or recommendations to only perform physical activity upon doctors' recommendations required clearance from a physician in Internal Medicine. Patients who reported needing to be cautious about physical activity for any other reasons required clearance from at least one physician who was a co-Principal Investigator on the study.

6.2.3 EXERCISE PROGRAM

The exercise program was modelled after recommendations for cancer survivors from the American Cancer Society and the American College of Sports Medicine.[53,54] However, as these organizations have recommended,[53,54] exercise prescriptions were attenuated to accommodate the circumstances of enrolled patients (i.e., older age and simultaneous neoadjuvant treatment). Patients were encouraged to engage in home-based, multimodal exercise throughout neoadjuvant therapy (chemotherapy and/or chemoradiation and preoperative rest). The intervention period thus spanned from enrollment until final surgical evaluation (Figure 1). Study staff exercise prescriptions and provided instruction on proper form for all strengthening exercises during clinic visits at enrollment. Study staff called patients via phone at least once every two weeks to encourage adherence and monitor for adverse events.

Aerobic exercise component. The aerobic exercise recommendation was ≥20 min/day of preferred aerobic exercise (e.g., brisk walking, elliptical trainers, or stationary bicycles) on ≥3 days/week. Patients were also encouraged to begin and conclude aerobic exercise sessions with ≥5 minutes of stretching. Patients received Borg Rating of

Perceived Exertion (RPE) scales[180] and were instructed exercise at a moderate intensity that allowed them to carry on conversations speaking in short sentences. Patients received pedometers (Digiwalker SW-200, Yamax Inc.) and were instructed to wear them daily and record daily step counts in exercise logs.

Strengthening component. The strengthening exercise recommendation was ≥30 min/day of structured, full-body strengthening exercises on ≥2 days/week. Patients underwent detailed instruction demonstrating each strengthening exercise upon enrollment. Patients also received video and written/photo guides demonstrating each exercise. Prescribed exercises engaged all major muscle groups and included sitting and standing options when possible accommodate various levels of balance and improve comfort. Nineteen different strengthening exercises were provided in guides. For a given strengthening exercise session, patients were encouraged to select eight different exercises (1-2 for abdominal muscles, 3-4 for upper body, and 3-4 for lower body) and to perform three sets of 8-12 repetitions for each exercise. Patients received portable resistance tube sets (Stackable Resistance Band Set, Black Mountain Products, Inc.) to perform all recommended strengthening exercises. However, if patients were familiar with and preferred to use weights or strengthening machines to perform comparable exercises, they were encouraged to do so. Patients were encouraged to begin strengthening sessions with five minutes of stretching and five minutes of warmup exercises, and to conclude strengthening sessions with five minutes of stretching. As with aerobic exercise, patients were instructed to maintain moderate exercise intensity.

6.2.4 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Sociodemographic and clinical characteristics were collected from the MDACC electronic medical record. These characteristics included age at enrollment, sex, distance of residence from MDACC (≤100 miles from study location vs. >100 miles from study location, confirmed by zip code using Google Maps), body mass index (BMI, kg/m^2), radiographic stage at presentation (potentially resectable, borderline resectable, or locally advanced), neoadjuvant treatment course during the exercise program (chemotherapy alone, chemoradiation alone, or chemotherapy followed by chemoradiation), exercise program duration (overall and separately by phase), and outcome following neoadjuvant treatment (stable or improved disease; curative surgery or disease progression; no curative surgery).

6.2.5 PHYSICAL ACTIVITY AND EXERCISE ADHERENCE

Exercise adherence. Patients were instructed to complete daily exercise logs each night, just before bed, throughout the exercise program. Logs were available to patients in paper format or via daily emails using the Research Electronic Data Capture (REDCap) system (Vanderbilt University, 2015). Patients recorded daily aerobic and strengthening exercise minutes separately. For each 7-day period from enrollment to preoperative restaging, weekly totals of aerobic, strengthening, and multimodal (aerobic plus strengthening) exercise (aerobic + strengthening) were computed. Weekly exercise minutes were summed to compute total exercise volumes (converted from minutes to hours to improve interpretability). Average weekly aerobic, strengthening, and multimodal exercise minutes were then computed by dividing total volumes for each variable by the total weeks of program enrollment (rounded to the nearest full week).

Objective physical activity. ActiGraph GT3X+ accelerometers (ActiGraph Corp, 2011) were used to monitor physical activity objectively. Patients underwent two-week accelerometer wear protocols at the approximate midpoint of each preoperative phase. For example, a patient who underwent chemotherapy followed by chemoradiation and then preoperative rest underwent three 14-day accelerometer wear protocols (one in each phase). Patients received accelerometers with elastic belts and were instructed to wear them with devices positioned over their right hips during all waking hours. The basis of 2-week wear protocols was the potentially cyclical nature of fatigue and side effects from chemotherapy regimens in which patients receive one treatment every several days.[201] Patients received instruction regarding accelerometer placement and recording wear periods in daily accelerometer logs at enrollment. When possible, accelerometers were provided to and collected from patients during appointments at MDACC to provide repeat instruction. However, devices were mailed with instructional packets and prepaid and addressed return envelopes when necessary. Patients received phone calls 1-2 days before intended wear periods to ensure that they had received the devices and to provide additional follow-up instruction. Accelerometer physical activity measurement was implemented after the first 20 patients had completed the study; therefore, these patients are not included in analyses involving objective physical activity.

Accelerometers were initialized to collect data at 60 Hz with counts processed in 1-minute epochs.[181] Ten hours (minimum) of wear time on each of 8 days (minimum) were required to include a wear period in analyses. Freedson adult (1998) cutpoints were used to provide weekly estimates of light physical activity (LPA), moderate-to-vigorous physical activity (MVPA), and total physical activity (TPA, MVPA+LPA) for each wear period.[199] Accelerometer physical activity for each intensity was averaged across each treatment phase for each patient to compute weekly averages of each physical activity intensity. Weekly minutes during a given preoperative phase were multipled by the number of weeks the patient spent in that phase, and then the products for each phases were added to compute total volumes of accelerometer physical activity.

6.2.6 OUTCOMES

Health-related quality of life. Patients completed the Functional Assessment of Cancer Therapy – Hepatobiliary questionnaire (FACT-Hep) at baseline and preoperative restaging to assess QOL.[68] The FACT-Hep consists of the 27-question FACT-General (FACT-G) subscale and the 18-question hepatobiliary subscale. The FACT-G measures wellbeing in four domains: physical, social/family, emotional, and functional. The hepatobiliary subscale (HS) measures the severity of hepatobiliary-specific symptoms and consists of 18 questions designed to evaluate the severity of hepatobiliary cancer-specific symptoms. All questions are scored on a Likert scale from 0 (“Not at all”) to 4 (“Very much”). A higher score on the FACT-G subscale indicates higher QOL, and a higher score on the hepatobiliarly subscale indicates lower disease-related symptoms. The instrument has shown strong validity, consistency, and reliability.[68] Data were processed per standard protocols to provide scores for the general QOL (FACT-G subscale alone) and disease-specific QOL (FACT-Hep; sum of FACT-G and hepatobiliary subscales). The FACT-Hep has shown acceptable validity and reliability.[68]

Skeletal muscle. Cross-sectional areas of skeletal muscle tissue at the L3 vertebral body midpoint were measured on computed tomography (CT) images using SliceOMatic v5.0 software (Tomovision, Magog, Canada). CTs were identified from patients’ work ups at baseline/enrollment and preoperative restaging. Skeletal muscle cross-sectional areas were standardized to the square of each patient's height (m^2). Sarcopenia was defined as SKM ≤38.9 cm^2/m^2 for women and ≤55.4 cm^2/m^2 for men.[22] Body mass index (BMI) at each time point was calculated using weights and heights (kg/m^2) recorded in the MDACC electronic medical record and coinciding with CT scan dates. CT scan dates were used to compute the time between scan dates (months), CT scans at equivalent, relative time points were processed using the same method for a sample of patients (*n*=127) who underwent neoadjuvant treatment and surgical resection for PDAC at MDACC between 2009 and 2012 but were not enrolled in a formal exercise program. These results (historical controls) were included for comparisons involving skeletal muscle changes with patients who were enrolled in the exercise program.

Inflammation. Inflammation was measured using the ratio of C-reactive protein (CRP) to albumin in blood serum[25] for a convenience sample of exercise program patients among whom complete data was available (*n*=17). CRP (in mg/dL) and albumin (in g/dL) were read and recorded in the EMR from blood draws taken during restaging workups by trained laboratory technicians. Dates of blood draws coincided with workups that also included the CT scans that were used to measure skeletal muscle cross-sectional areas. Values for CRP and albumin were reported separately and in a ratio of CRP/albumin (CRP/alb) for interpretability.

6.2.7 QUALITATIVE INTERVIEWS

Program satisfaction and perceived outcomes related to participation were examined qualitatively through structured interviews with a subsample of patients (*n*=10). Primary questions and probing questions for qualitative interviews focused on the following constructs: perceived impacts of exercise adherence on aerobic fitness and strength, treatment tolerance, and physical and emotional wellbeing; satisfaction with the exercise program; and suggestions for improvement. The interview guide included four primary and 11 potential probing questions covering these topics, all of which were open-ended and non-leading. Interviews were conducted approximately 1-2 months following surgery to minimize study burden on patients during neoadjuvant treatment and post-operative recovery. Interviews lasted approximately 30 minutes and were conducted via telephone, recorded, and transcribed by the first author, experienced in conducting qualitative interviews. Transcriptions were compared with audio recordings for accuracy.

6.2.8 ANALYSES

Quantitative analyses. Descriptive statistics were used to quantify sociodemographic, disease, and treatment characteristics; self-reported exercise, accelerometer physical activity; and QOL, skeletal muscle, and inflammation at baseline and preoperative restaging. Due to their non-normal distributions, Wilcoxon signed rank tests were used to compare QOL and CRP/alb from baseline to preoperative restaging. Paired t-tests were used to compare skeletal muscle and BMI from baseline to preoperative restaging. Independent t-tests were used to compare skeletal muscle, BMI, and changes in both outcomes between exercise program patients and historical controls.

Linear regression models were used to measure associations among exercise and physical activity and outcome measures. Separate models were used to measure the associations between exercise or physical activity and each outcome measure, which included preoperative restaging and change scores (preoperative restaging – baseline) for each outcome. Linear regression models were also fit with baseline values for outcome measures (QOL, skeletal muscle, and inflammation) predicting exercise adherence and physical activity to assess potential effects of baseline health status on program adherence All linear regression models were adjusted for age, sex, and final surgical determination (yes/no) based on theoretical basis and evidence suggesting differences in exercise or physical activity based on these covariates. Models involving skeletal muscle at preoperative restaging and change in skeletal muscle from baseline to preoperative restaging were also adjusted for exercise program duration. Linear regression models were also used to compare change in skeletal muscle between exercise program patients and historical controls. This model was adjusted for age, sex, baseline BMI, and preoperative duration. Because of the arbitrary scale of the outcomes measures (except the model comparing skeletal muscle change), standardized coefficients were interpreted to describe the associations among predictor and outcome variables. All analyses were performed using SPSS Statistics Version 24 (IBM Corp., 2016).

Qualitative analyses. Two members of the research staff, including the first author, were trained in qualitative analyses and used NVivo software version 10 (QSR International, 2015) to code qualitative interviews. Coders used a constant comparison approach,[202] first creating *a priori* codes and themes and coding 5 interview transcripts independently. During initial coding, each coder added emergent codes and themes to the list and rearranged *a priori* codes that fit emerging themes. The coders then met to review first 5 interview transcripts together, reaching consensus on the list of codes and themes by discussing similarities and discrepancies. This process was repeated for interviews 6-10. Finally, one coder reviewed all transcripts a second time to modify and confirm codes and themes that fit, eliminate and reject duplicate codes or codes and themes that did not fit, and to confirm that themes were saturated (i.e., no additional themes emerged).

6.3 RESULTS

6.3.1 SAMPLE

Figure 1 provides a flow chart of patients through the study. Patients who completed and returned exercise logs, underwent objective physical activity monitoring with accelerometers or returned for follow-up measures at preoperative restaging were included in respective analyses.

Figure 1. Study flow chart

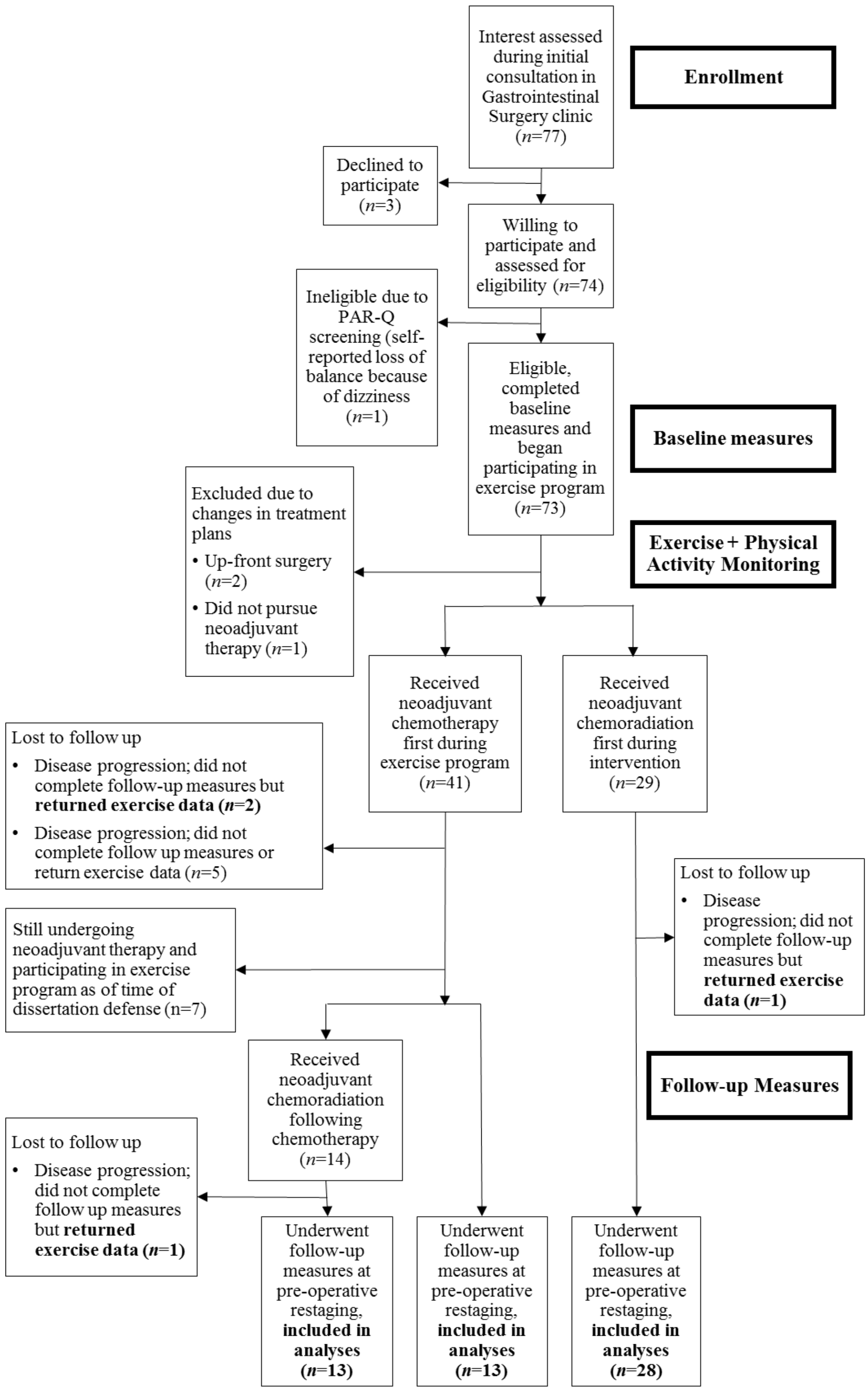


Table 1 shows sociodemographic and clinical characteristics among the 58 patients who had returned adherence and follow-up data at the time of this dissertation. Patients' average age was 65.8(SD=7.7), and nearly 50% were female. The majority of patients (80%) lived ≥100 miles from the study location. Average BMI was in the overweight classification [mean(SD)=27.4(5.3)], with approximately 65% of patients were overweight or obese at baseline (BMI≥25). Most patients had potentially resectable or borderline resectable tumors, based on radiographic staging criteria.[200] Fifty percent of patients underwent chemoradiation alone during the exercise program. Approximately 26% of patients underwent chemotherapy alone, and approximately 24% of patients underwent chemotherapy and chemoradiation during the exercise program. The average duration of the exercise program among patients was 14.9 weeks (SD=7.1). Approximately 53% of patients underwent surgical resection with curative intent after showing stable or improved disease at preoperative restaging. Disease progression occurred among forty seven percent of patients, and these patients did not undergo surgery. Compared to the final, included sample, patients who were lost to follow up were more likely to have undergone initial chemotherapy following enrollment (p=.05). There were no other significant differences in clinical or demographic characteristics (all p>.05).

Table 1. Clinical and sociodemographic characteristics of study sample (N=58)

Variable		*n*(%)	Mean(SD)
Age at enrollment (years)		-	65.8(7.7)
Sex			
	Female	28(48.3)	-
	Male	30(51.7)	-
Location of primary residence			
	≤100 miles from study location	12(20.7)	-
	>100 miles from study location	46(79.3)	-
Body mass index (kg/m^2)		-	27.4(5.3)
Radiographic stage at presentation			
	Potentially resectable	35(60.3)	-
	Borderline resectable	22(37.9)	-
	Locally advanced	1(1.7)	-
Neoadjuvant treatment course during exercise program			
	Chemotherapy alone	15(25.9)	-
	Chemoradiation alone	29(50.0)	-
	Chemotherapy followed by chemoradiation	14(24.1)	-
Exercise program duration (weeks)		-	14.9(7.1)
	During chemotherapy (weeks)	-	12.8(5.9)
	During chemoradiation (weeks)	-	4.3(2.1)
	During preoperative rest (weeks)	-	6.0(1.8)
Outcome following neoadjuvant treatment			
	Stable or improved disease; curative surgery	31(53.4)	-
	Disease progression; no curative surgery	27(46.6)	-

6.3.2 EXERCISE ADHERENCE AND PHYSICAL ACTIVITY

Table 2 shows weekly averages for self-reported aerobic, strengthening, and multimodal exercise from daily exercise logs and for LPA, MVPA, and TPA from accelerometers. Table 2 also shows total volumes for all exercise and physical activity variables.compiled across all treatment phases. Average self-reported aerobic and multimodal exercise were 124.8 (SD=81.2) and 168.3 (SD=88.2), respectively. Both of these weekly averages exceeded program recommendations. However, average strengthening exercise did not meet the program recommendation [mean(SD)=43.3(31.8)]. Total aerobic exercise volume was more than three times average strengthening exercise volume, on average [mean(SD)=30.0(24.0) hours vs. 9.9(9.4) hours]. Average weekly, accelerometer-measured MVPA was 145.8 minutes/week (SD=135.7). This translated to total MVPA volume of 31.0 hours (SD=32.0) over the entire course of the exercise program.

Table 2. Exercise adherence and physical activity

Variable	Weekly performance [min/week, mean(SD)]	Total volume [hours, mean(SD)]
Self-reported exercise adherence (n=52)	-	-
Aerobic exercise	124.8(81.2)	30.0(24.0)
Strengthening exercise	43.3(31.8)	9.9(9.4)
Multimodal exercise	168.3(88.2)	39.9(27.4)
Accelerometer physical activity (n=40)		
LPA	847.9(274.5)	187.5(109.5)
MVPA	145.8(135.7)	31.0(32.0)
TPA	993.7(342.2)	218.6(126.9)

6.3.3 HEALTH-RELATED QUALITY OF LIFE, ANTHROPOMETRICS, AND INFLAMMATION

Table 3 shows QOL, anthropometrics (skeletal muscle and BMI), and inflammation (CRP, albumin, and CRP/alb) at baseline and preoperative restaging. Average scores for both FACT-G and FACT-Hep were higher at preoperative restaging than at baseline among exercise program patients [mean(SD) 86.7(14.3) vs. 85.2(14.4) and 144.4(21.7) vs. 140.2(20.8), respectively]. The increase in FACT-Hep was statistically significant (p=.01), but the increase in FACT-G was not statistically significant (p=.19).

Average skeletal muscle was slightly higher at preoperative restaging vs. baseline among exercise program patients [mean(SD) 46.2(8.5) vs. 46.1(98.0)], but the increase was not statistically significant. Among historical controls, average skeletal muscle was slightly lower at preoperative restaging vs. baseline [mean(SD) 25.6(6.0) vs. 26.5(4.7)], but the decrease was not statistically significant. On average, skeletal muscle decreased by .03 cm^2/m^2 (SD=3.0) among exercise program patients, and by .44 cm^2/m^2 (SD=3.5) among historical controls. However, the difference in skeletal muscle change between exercise program patients and historical controls was not statistically significant (test not shown; $p>.05$). Average BMI was significantly lower at preoperative restaging compared to baseline among both exercise program patients [mean(SD) 26.7(4.8) vs. 27.5(5.4)] and historical controls [mean(SD) 25.6(6.0) vs. 26.5(4.7)] (both $p<.05$). There were no significant differences between exercise program patients and historical controls in skeletal muscle or BMI at either time point or in change from baseline to preoperative restaging for either outcome (test not shown; all $p>.05$).

Average CRP increased from baseline to preoperative restaging among exercise program patients [mean(SD) 8.9(15.0) vs. 13.5(19.4)], but the increase was not statistically significant ($p=.09$). There was a statistically significant decrease in average albumin from baseline to preoperative restaging [mean(SD) 4.1(0.4) vs. 3.8(0.6)] ($p=.001$). Average CRP/alb was higher at preoperative restaging than baseline [mean(SD) 3.4(5.1) vs. 2.2(3.7)], but the increase was not statistically significant among the subsample ($n=17$) patients with complete data at both time points. Average increase in CRP/alb from baseline to preoperative restaging was 1.7(SD=3.8).

Table 3. Health-related quality of life, anthropometrics, and inflammation at baseline and preoperative restaging

Variable	Baseline		Preoperative restaging		Tests for differences		
	n	mean(SD)	*n*	mean(SD)	*N*	*Z or t*[a]	*p*
Health-related quality of life							
FACT-G (max 108)	56	85.2(14.4)	54	86.7(14.3)	53	-1.3	.19
FACT-Hep (max 180)	56	140.2(20.8)	54	144.4(21.7)	53	-2.6	.01
Anthropometrics							
Skeletal muscle (cm^2/m^2)							
Exercise program patients	57	46.1(9.0)	58	46.2(8.5)	57	.07	.95
Historical controls	126	46.5(8.8)	124	46.2(8.3)	123	1.4	.17
BMI (kg/m^2)							
Exercise program patients	58	27.5(5.4)	58	26.7(4.8)	58	3.3	.002
Historical controls	127	26.5(4.7)	127	25.6(6.0)	127	2.4	.02
Inflammation							
CRP (mg/dL)	32	8.9(15.0)	28	13.5(19.4)	18	-1.7	.09
Albumin (g/dL)	57	4.1(0.4)	56	3.8(0.6)	55	-3.2	.001
CRP/alb	32	2.2(3.7)	27	3.4(5.1)	17	-1.6	.10

[a]Paired t-test used to test differences between time points for skeletal muscle and BMI; Wilcoxon signed rank tests used for all other variables.

6.3.4 ASSOCIATIONS AMONG EXERCISE, PHYSICAL ACTIVITY, AND OUTCOMES

Table 4 shows standardized regression coefficients between self-reported exercise adherence or accelerometer physical activity variables and QOL among exercise program patients after controlling for age, sex, and final surgical determination (yes vs. no). There were no significant associations between baseline QOL and any self-reported exercise or accelerometer physical activity variables (all $p > .05$). There were statistically significant, positive associations between weekly LPA minutes and both FACT-G and FACT-Hep at preoperative restaging (*ß*=.43, $p = .01$ and *ß*=.35, $p = .04$, respectively). An increase of 1 SD in weekly LPA minutes (274.5 minutes) was thus associated with increases of 6.1 points on the FACT-G subscale and 7.6 points on the FACT-Hep, respectively. There were also statistically significant, positive associations between weekly TPA minutes and both FACT-G and FACT-Hep at preoperative restaging (*ß*=.41, $p = .01$ and *ß*=.35, $p = .03$, respectively). An increase of 1 SD in weekly TPA minutes (342.2 minutes) was thus associated with increases of 5.9 points on the FACT-G subscale and 7.6 points on the FACT-Hep, respectively.

Table 4. Standardized regression coefficients between exercise adherence or physical activity and health-related quality of life among exercise program patients after controlling for age, sex, and final surgical determination

Variable	Baseline		Preoperative restaging		*Change from baseline to preoperative restaging*	
	FACT-G	FACT-Hep	FACT-G	FACT-Hep	FACT-G	FACT-Hep
Aerobic exercise						
Weekly	-.14	-.18	-.01	-.04	.12	.10
Total volume	-.17	-.27	.04	-.02	.18	.18
Strengthening exercise						
Weekly	-.06	.04	-.10	-.01	-.01	-.003
Total volume	-.09	-.08	-.05	.03	.03	.08
Multi-modal exercise						
Weekly	-.15	-.15	-.05	-.04	.10	.09
Total volume	-.18	-.26	.02	-.01	.16	.18
MVPA						
Weekly	.16	.24	.22	.21	.06	.01
Total volume	.14	.16	.20	.17	.06	.03
LPA						
Weekly	.24	.16	.43*	.35*	.18	.20
Total volume	.12	-.04	.27	.19	.11	.18
TPA						
Weekly	.25	.23	.41*	.35*	.16	.16
Total volume	.14	.002	.28	.20	.11	.16

*p<.05

Table 5 shows standardized regression coefficients between self-reported exercise adherence or accelerometer physical activity variables and skeletal muscle among exercise program patients after controlling for age, sex, final surgical determination (yes vs. no), and exercise program duration. There were no significant associations between baseline skeletal muscle and any self-reported exercise or accelerometer physical activity variables (all p>.05). There was a statistically significant, positive association between weekly LPA minutes and skeletal muscle at preoperative restaging (*ß*=.31, p=.05). An increase of 1 SD in weekly LPA minutes (274.5 minutes) was associated with having an additional 2.6 cm^2/m^2 of skeletal muscle at preoperative restaging. There were statistically significant, positive associations between both weekly aerobic exercise minutes and weekly multimodal exercise minutes and change in skeletal muscle from baseline to preoperative restaging (*ß*=.32, *p*=.02 and *ß*=.32, *p*=.03, respectively). An increase of 1 SD in weekly aerobic exercise (81.2 minutes) or an increase of 1 SD in weekly multimodal exercise minutes was associated with gaining 1.7 cm^2/m^2 of skeletal muscle from baseline to preoperative restaging.

Table 5. Standardized regression coefficients between exercise adherence or physical activity and skeletal muscle among exercise program patients after controlling for age, sex, final surgical determination, and exercise program duration.

Variable	Baseline skeletal muscle (cm^2/m^2)	Preoperative restaging (cm^2/m^2)	Change from baseline to preoperative restaging
Aerobic exercise			
Weekly	.00	.12	.32*
Total volume	.12	.15	.27
Strengthening exercise			
Weekly	-.11	-.06	.02
Total volume	.10	.08	.09
Multi-modal exercise			
Weekly	-.04	.09	.32*
Total volume	.14	.16	.28
MVPA			
Weekly	.049	.13	.29
Total volume	.06	.13	.26
LPA			
Weekly	.37	.31*	.05
Total volume	.22	.21	.07
TPA			
Weekly	.32	.29*	.15
Total volume	.20	.21	.13

**p*<.05

Linear regression showed no significant association between being enrolled in the exercise program (with historical controls as the reference group) and change in skeletal muscle from baseline to preoperative restaging after adjusting or age, sex, duration of preoperative period, and baseline BMI (B=.81, *p*=.12).

Table 6 shows standardized regression coefficients between self-reported exercise adherence or accelerometer physical activity variables and inflammation among exercise program patients after controlling for age, sex, and final surgical determination (yes vs. no). There were no significant associations between inflammation at baseline and any self-reported exercise or accelerometer physical activity variables (all $p>.05$). There was a statistically significant, positive association between total volume of strengthening exercise and inflammation at preoperative restaging (*ß*=.43, *p*=.05). An increase of 1 SD in total strengthening volume (9.4 hours) was associated with having a CRP/alb that was 2.2 points higher at preoperative restaging. There was also a statistically significant, positive association between weekly strengthening exercise minutes and change in inflammation from baseline to preoperative restaging (*ß*=.74, *p*=.007). An increase of 1 SD in weekly strengthening exercise (31.8 minutes) was associated with an increase of 2.8 in CRP/alb from baseline to preoperative restaging.

Table 6. Standardized regression coefficients between exercise adherence or physical activity and skeletal muscle among exercise program patients after controlling for age, sex, and final surgical determination.

Variable	Baseline	Preoperative restaging	Change from baseline to preoperative restaging
Aerobic exercise			
Weekly	.10	.14	.21
Total volume	.03	.06	.19
Strengthening exercise			
Weekly	-.20	.42	.74**
Total volume	-.15	.43*	.44
Multi-modal exercise			
Weekly	.04	.27	.38
Total volume	-.006	.15	.26
MVPA			
Weekly	-.08	-.12	-.40
Total volume	-.08	-.05	-.33
LPA			
Weekly	.07	-.12	-.40
Total volume	.10	-.11	-.32
TPA			
Weekly	.02	-.13	-.42
Total volume	.06	-.10	-.33

*p<.05
**p<.01

6.3.5 QUALITATIVE FINDINGS

Figure 2 shows emergent themes and representative quotes from qualitative interviews. There were 5 discrete themes regarding perceived outcomes from exercise and physical activity during the exercise program. Patients widely described *reduced fatigue*, *improved strength and fitness*, *improved emotional wellbeing*, *improved general health*, *accelerating postoperative recovery*. Patients also expressed *overall satisfaction* with the exercise program.

Figure 2. Themes and quotes from qualitative interviews representing patients' perspectives regarding outcomes from xercise exercise during preoperative treatment for pancreatic cancer.

Category/Theme	Representative quotes
Reduced fatigue	"I'd feel real fatigued and I knew exercise would help, if I forced myself to do it, and I'd try to do that." *–Female, 65 years old*
	"Before the exercise, I felt weak and tired. Then I started the exercise, and it was different. I felt like I could do things. I wasn't exhausted all the time." *–Female, 74 years old*
	"I saw the results. It made me feel good at the end of the day. I felt so much better when I had exercised and I could move around and do things." *–Female, 74 years old*
	"I'd be lying there with some fatigue, and then I'd finally go, 'Get out there and do something!' And then I'd feel so good afterwards that I could actually sit up and knit. Because I had actually done some exercising." *–Female, 65 years old*
Improved strength and fitness	"I could see a difference in my body from the resistance exercises, the strengthening exercises. And I was seeing the results in my golf game. Even though I was under treatment and not feeling good, my golf game got better, and my drive got longer. There was more power in my swing." *–Male, 71 years old*
	"At that point [after radiation], I was doing the bands nearly every day, and I was walking every day, and I was doing everything I could do to make myself stronger." *–Female, 63 years old*
	"If I could have done a little more strength exercise with the bands, that would have helped me out more." *–Male, 64 years old*
Improved emotional wellbeing	"I'm thoroughly convinced that it helped release serotonin and things that helped with my mood and helped keep me from becoming depressed." *- Female, 63 years old*
	"When my wife saw me getting down, letting [treatment side effects] affect me, she would kick my butt and get me back to a place where I started feeling like some form of exercise and getting through it." *-Male, 71 years old*
	"I think it kept my mind off my challenges coming up. It kept my mind off the worries of the world." *–Male, 68 years old*
	"It helped me a lot, because I wasn't just sitting there or laying there. I wasn't just feeling sorry for myself—I didn't really have time." *–Female, 74 years old*

	"I enjoyed the feeling of accomplishment every day when I finished exercising. It gave me something to focus on and gave me an inside look at what I'm about. It helped a lot with self-esteem. Self-esteem and just overall joy. It gave me a feeling of happiness." *–Male, 59 years old* "It can help you emotionally and psychologically, knowing that, 'Hey, I'm in better shape.' I'm going to tackle this surgery better. I'm going to come out strong on the other side. I'm going to heal quicker." *–Male, 64 years old*
Improving general health	"I recognize, especially over this last year during the exercise program, that the more exercise I can do, the less medications I'm going to need to feel good. So, I'm exercising with the purpose of having my blood flow, having lots of oxygen in my blood. You know, things that docs are very happy to give you medication to help you with. I know a healthy body is what will carry me through any new adventures I have." *-Male, 71 years old* "I do think the exercise was helping. It contributed to not feeling nasty and not being out of breath and not saying, you know, 'I can't do that.'" *–Female, 65 years old* "It helped, it really helped. I have a friend who has cancer also, and she was not in the program. And for her it's very different. All she does is stay at home, never does anything. So hers is very different from mine. I think that's what helped me, the exercise. Because if I didn't have that, I would have probably been like her." *–Female, 74 years old* "My back problems are getting better now because of the workouts. And so I think it's both a physical and emotional or mental state. But more physically. If I don't feel good, as soon as I go walk a mile, I feel energized." *–Male, 59 years old* "There are three or four reasons I'm here today, and sticking to the program is one of the reasons. I love surgeons. I know two of them that have saved my life. But as much, exercising has saved my life." *-Male, 71 years old*
Accelerating postoperative recovery	"It's so much easier to recover if you're healthier going in." *-Male, 71 years old* "I think I got through the surgery recovery pretty quickly." *–Female, 74 years old* "I had the strength to recover. And at no time did I feel that I could *not* do it. And the way I was going to do it was through that strength training." *-Male, 80 years old* "Surgery limited me from doing the resistance and stuff. But it didn't stop me from walking. I found ways to work around it. I was told that after surgery, no more than lifting a gallon of milk. And so, when I'd buy milk for the kids, I'd lift my gallon!" *–Male, 59 years old* "If you want to come out on the backside of this healthy and strong and have a better chance of getting well, I would highly, highly encourage you to get in as good a shape as you can and get your muscle tone up, your cardiovascular aerobics, and lungs, and everything in as good of shape as you can. I mean, this deal, this surgery is major." *–Male, 64 years old*

	“I think it benefited me in getting through this very tough operation. Because I was up the next day, and I was walking around. And although I had the little thing with the feed bags on it, pulling it, I really was walking alone. I could walk alone the first day, without any support from anybody. And I think that, without the strength training and that motivation, I think it would be somewhat hard to get up and do that.” -*Male, 80 years old*
Overall satisfaction	“The exercise program kept me motivated and kept me focused, and I’m thoroughly convinced that I was in better shape and stronger – both mentally and physically – from having done it.” – *Female, 63 years old* “There are a lot of things I’m very, very thankful for. And the exercise program is right up near the top of the list.” -*Male, 71 years old* “I was very satisfied. Having all the techniques and the information was great. Just having the motivation and the willpower to make it happen was the more challenging aspect of it.” –*Male, 68 years old* “I didn’t enjoy exercising, but I knew I had to do it.” –*Female, 74 years old* “Exercising was vital to my survival. And it continues to be. And getting through that surgery now, and recovery. My surgery was three hours longer than what’s typical, but I feel so good today.” –*Male, 59 years old* “It was something that I needed. What I had been doing [before the program] was not very effective, because I wasn’t doing it on a regular basis. So, what your program did was put me in a system wherein it was a structured thing.” -*Male, 80 years old*

6.4 DISCUSSION

The purpose of this study was to investigate relationships between self-reported exercise adherence and objective physical activity and potential outcomes among patients enrolled in a home-based exercise program while undergoing preoperative treatment for pancreatic cancer. Our findings generally supported our hypotheses. We found quantitative and qualitative evidence demonstrating favorable relationships among exercise adherence or physical activity and QOL and maintenance of skeletal muscle tissue. Patients who participated in the exercise program had improved QOL at preoperative restaging compared to baseline and generally maintained skeletal muscle over the same time frame. Linear regression models showed positive associations between weekly minutes of objective-measured LPA and TPA during the exercise program and QOL and skeletal muscle at preoperative restaging. Linear regression models also showed positive associations between self-reported weekly aerobic and multimodal exercise and change in skeletal muscle from baseline to preoperative restaging. In qualitative interviews, patients described a variety of perceived benefits of participating in the exercise program during preoperative treatment, including improved ability to tolerate treatments and recover following surgery; improved physical, emotional, and general health; and general satisfaction with the program.

The improvements we observed in QOL among patients undergoing preoperative treatment for pancreatic cancer generally agree with previous findings regarding exercise during various stages of cancer survivorship.[63] Surgical resection itself has been shown to be positively associated with improvements in QOL among patients with resectable pancreatic cancer,[209,210] but in this study we showed that patients' QOL improved prior to final surgical consideration, during a combination of preoperative therapy and exercise. Future research efforts should parse the independent effects of preoperative therapy and exercise in improving QOL for patients in this context. Improving perioperative QOL using preoperative exercise has been identified as an intervention target for colorectal cancer survivors,[211] and given our findings, the same target should be applied for pancreatic cancer surivors. That LPA and TPA (and not MVPA or self-reported exercise adherence) were positively associated with QOL in this study suggests that patients undergoing preoperative treatment for pancreatic cancer may benefit from simple recommendations or programming that help them avoid being sedentary.[212]

Several exercise variables were positively associated with skeletal muscle at preoperative restaging and with change in skeletal muscle from baseline to preoperative restaging. In a previous study involving patients undergoing preoperative treatment for pancreatic cancer, there was a significant loss of skeletal muscle from baseline to preoperative restaging.[12] Average skeletal muscle remained stable from baseline to preoperative restaging in the current study, demonstrating that exercise may help mitigate detrimental changes in body composition that tend to occur during preoperative treatment. Furthermore, we demonstrated that this relationship may be dose-dependent, in that performing more exercising more may be more beneficial in reversing expected muscle loss. Although it was not statistically significant, the association between exercise program enrollment and change in skeletal muscle (compared to historical controls) was in the favorable direction. Differences between the two groups in disease or treatment characteristics may have confounded differences in skeletal muscle observed between them. For example, all of the historical controls were patients who underwent surgical resection, whereas only 53.4% of exercise program patients underwent surgical resection.

The positive associations we observed between strengthening exercise and increased inflammation were unexpected. Although reducing inflammation is a theoretical mechanism explaining exercise-related improvements in cancer-related fatigue, relationships among exercise and inflammation among cancer survivors are not yet well understood.[88] Furthermore, inflammation in this sample was exceptionally high at both baseline and preoperative restaging compared to established, prognostic cutpoints.[213] Disease- and treatment-related inflammation may simply be too high during preoperative treatment for pancreatic cancer for exercise to bring about measurable or meaningful benefits. Without a more rigorous design, it is difficult to draw meaningful conclusions about relationships between exercise and inflammation.

Findings from qualitative interviews mirror those found quantitatively involving QOL and skeletal muscle. Patients widely reported improvements in QOL, specifically involving improvements in strength and fitness, ability to tolerate preoperative treatment and recover from surgery, and emotional wellbeing. Patients also expressed general satisfaction with participating in the exercise program. These findings are similar to those among cancer survivors in the cancer rehabilitation context and following treatment.[214,215] Our findings are novel in that they pertain to preoperative exercise interventions, which are an increasingly prioritized area for improving outcomes in cancer survivorship. In qualitative interviews, patients generally highlighted the importance of both strengthening and aerobic exercise in improving their health and wellbeing during the preoperative period. However, none of the favorable associations we observed among exercise, physical activity and outcomes in this study involved strengthening exercise. It will be important to improve adherence to recommendations for strengthening exercise, such as by increasing social support or self-efficacy, and to further investigate its specific role in improving perioperative outcomes, because the theoretical basis for its benefits is clear.

This study's strengths included its inclusion of both self-reported and objective exercise data to quantify program adherence and general physical activity. Objective monitoring with accelerometers helped to validate self-reported adherence data, which is widely known to be subject to recall and favorability biases.[32,33] We also used valid and precise methods to measure skeletal muscle, which, through use of CT scans acquired for disease restaging workups, imposed no additional burden on patients.

There was wide variability in treatment courses and durations among patients in this study, reflecting the actual nature of clinical care in the context of patients with resectable pancreatic cancer. However, this variability imposed statistical limitations that future studies should attempt to control with advanced matching techniques and stratification. Further, we had access to only a small subsample of patients with complete data regarding inflammation over the preoperative time frame. Future studies should ensure more complete data availability when examining change in inflammation as a potential exercise outcome.

In this study, we provided important, initial evidence of benefits patients may reap from exercise while undergoing preoperative treatment for pancreatic cancer. Through a simple, home-based exercise program, we showed that exercise can potentially contribute to important improvements in perioperative health and wellbeing among patients with pancreatic cancer.

6.5 CONCLUSION

Participating in a multimodal exercise program may help improve QOL and mitigate skeletal muscle loss among patients undergoing preoperative treatment for pancreatic cancer.

Cancer clinicians should continue to explore the feasibility of exercising programming among patients undergoing preoperative treatment for pancreatic cancer. Establishing formal programs to encourage preoperative exercise may help improve important perioperative outcomes for these patients. It is important for future examinations to include more complete inflammation data and to further explore the potential for exercise to confer preoperative benefits through comparisons between exercising and non-exercising patients.

CHAPTER 7

7. SUMMARY, STRENGTHS AND LIMITATIONS, AND FUTURE DIRECTIONS

7.1 SUMMARY

Pancreatic cancer and preoperative treatment provide a context in which patients, many of whom are older adults with age-related comorbidities, can have difficulties in maintaining physical and functional health and well-being.[12,22] Surgery for pancreatic cancer, due to its anatomical complexity and the arduous recovery and perioperative risks associated with it, requires that patients exhibit optimal preoperative performance status.[4] While preoperative exercise shows great promise in improving clinical and quality of life outcomes among patients with other cancer diagnoses, no studies prior to this one have examined formal prehabilitation programs among patients with pancreatic cancer. Accordingly, there were no previous scientific findings quantifying the physical activity patients with pancreatic cancer are able to perform during preoperative treatment or exploring the influences of socioecological supports and barriers on physical activity during formal exercise programming. Finally, there were no scientific findings regarding clinical, health, or quality of life outcomes outcomes or the health and quality of life outcomes through which patients may benefit from participation in pancreatic cancer prehabilitation.

This dissertation project fulfilled three important aims: 1) Determining the feasibility of aerobic and strengthening exercise among patients undergoing preoperative treatment for pancreatic cancer; 2) Measure associations among socioecological supports (social support for exercise and neighborhood walkability) and exercise adherence among patients undergoing preoperative treatment for pancreatic cancer; and 3) Measure associations among exercise adherence and clinical and quality of life outcomes among patients undergoing preoperative treatment for pancreatic cancer.

7.1.1 FEASIBILITY OF EXERCISE AMONG PATIENTS UNDERGOING PREOPERATIVE TREATMENT FOR PANCREATIC CANCER

Findings from this dissertation project indicated that exercise is feasible among patients undergoing preoperative treatment for pancreatic cancer. On average, patients reported exceeding the weekly recommendation for self-reported aerobic exercise and performing nearly 75% of the weekly recommendation for strengthening exercise. Findings regarding objectively-measured, moderate-to-vigorous physical activity mirrored the findings regarding aerobic exercise performance. The difference in adherence to aerobic and strengthening guidelines supports the notion that patients may need additional support or motivation to achieve strengthening recommendations.

Contrary to hypotheses, there were no statistically significant differences in exercise adherence or physical activity by treatment phase. These results held after adjusting for the interactions of self-reported daily fatigue and treatment-related side effects by treatment phase. The absence of significant differences implies that exercise is feasible in each treatment phase, and programs aiming to improve perioperative fitness and quality of life among patients with pancreatic cancer should target the entire preoperative treatment course. Exercise motivation may be particularly high for patients in this context. This presents a prime opportunity to capitalize on this motivation and start patients on exercise programs as soon as possible, despite the difficult treatment regimens they may be undergoing.

7.1.2 SOCIOECOLOGICAL INFLUENCES ON EXERCISE AND PHYSICAL ACTIVITY AMONG PATIENTS UNDERGOING PREOPERATIVE TREATMENT FOR PANCREATIC CANCER

Given the home-based nature of the exercise program on which this dissertation project focused, it was important to examine potential socioecological influences on exercise adherence and physical activity. Quantitative and qualitative evidence from this project demonstrated that social support from friends and family were important influences on program adherence, especially regarding performance of strengthening exercise. These findings, along with the difficulty patients showed adhering to strengthening recommendations relative to aerobic exercise recommendations, indicate that involving family and friends in preoperative exercise programs may be important to encourage adherence. Qualitative evidence provided insights involving social support and accountability beyond those that could be measured by the survey employed in this study. For example, patients highlighted conversations with physicians and other healthcare providers during clinic visits and follow up calls from program staff as important social interactions that increased their accountability and improved adherence to program recommendations. Qualitative evidence also indicated that neighborhood walkability and access to convenient resources were important influences on program adherence; ensuring that patients have access to and encouraging them to utilize resources such as walking trails and fitness facilities may also improve adherence.

7.1.3 CLINICAL AND QUALITY OF LIFE OUTCOMES RELATED TO EXERCISE AMONG PATIENTS UNDERGOING PREOPERATIVE TREATMENT FOR PANCREATIC CANCER

Findings from this dissertation project demonstrated that exercise may help improve important perioperative outcomes for patients undergoing preoperative treatment for pancreatic cancer. Quantitative evidence demonstrated that exercise may have helped patients improve quality of life and maintain skeletal muscle tissue in the preoperative period. In qualitative interviews, patients described perceived benefits in quality of life and strength and fitness that corroborated quantitative findings. Further, patients emphasized that exercising improved their abilities to tolerate treatments and recover following surgery.

7.2 STRENGTHS AND LIMITATIONS

This dissertation project contributes novel findings to the evidence base involving exercise and cancer survivorship. This was the first known study to include both self-reported and objective measures to quantify adherence to home-based exercise programs, and the agreement between self-reported aerobic exercise and objectively-measured MVPA provide important evidence that exercise is feasible in this context. This study also included a variety of measures to evaluate influences and outcomes that may be related to preoperative exercise among patients with pancreatic cancer. Indeed, this was the first study to examine socioecological influences on physical activity among patients participating in preoperative exercise programs. Given the increasing focus on this specific area within exercise and cancer survivorship, this provides an important example to examine and consider facilitators and barriers patients may face when provided with recommendations to exercise preoperatively. Finally, patients in this study were undergoing chemotherapy and chemoradiation that can be difficult to tolerate, and the duration of this exercise program was considerably longer for many patients than previously tested preoperative exercise programs among patients preparing for cancer surgery. Given these details, retention of patients in this exercise program was strong. This may be attributed to the relatively simple nature of the program and its recommendations and frequent and positive communication between patients and exercise program staff.

There was wide variability in treatment courses and durations among patients in this study that created statistical limitations. While these circumstances reflect the true context of clinical care for pancreatic cancer, future studies should attempt to account for potentially confounding factors using stratification or matching with suitable concurrent or historical controls or comparison groups. Completion of daily exercise logs was also variable among patients in this study, and this may have introduced bias in the compilation of self-reported aerobic and strengthening exercise. While we used a strategy that addressed this potential bias conservatively, future studies may be able to prioritize or incentivize exercise log completion to provide a more accurate picture of exercise adherence.

This is the first study to examine the feasibility of preoperative exercise among patients with pancreatic cancer. Patients with pancreatic cancer are generally older adults and increasingly undergo preoperative treatment. Feasibility in this context may therefore generalize to a variety of other contexts in preoperative cancer care in which patients may be younger, less sick, or not undergoing simultaneous cancer treatment.

7.3 FUTURE DIRECTIONS

This dissertation project has important implications for research, policy, and practice. It will be important for future studies to include larger numbers of patients and rigorous study designs to control for potential confounding effects of treatment plans. Further, future studies should utilize matching among exercising patients and historical controls or other comparison groups who did not participate in formal exercise programs to examine potential exercise-related differences in clinical and quality of life outcomes. It will also be important to further explore potential associations among exercise in this context and more rigorous measures of aerobic and functional fitness, as well as longer-term outcomes involving treatment and survival. Finally, future research efforts should investigate differences in and strategies to improve social support, motivation and exercise self-efficacy. These strategies may be particularly important for encouraging adherence to strengthening exercise recommendations.

Important policy and practice implications for clinical cancer care stem from this project. Appendix 1 provides a list of lessons learned and best practices that researchers, clinicians, and hospital administrators may find helpful when planning to implement formal exercise programs for patients preparing for cancer surgery. It is important for clinical services to develop protocols and workflows to formalize physical activity assessment, which is increasingly being recognized as a vital sign for health. Moreover, solely recommending and encouraging exercise may not be sufficient for patients undergoing preoperative cancer treatment. Adherence to exercise recommendations may require consistent follow-up and reassessment, which in turn require time and resources. Clinicians should not only encourage exercise, but also ensure that there are mechanisms in place to follow up and improve accountability. Furthermore, some of the most valuable resources for getting patients to exercise and adhere to recommendations may be sitting right next to them during clinic appointments. It may be important for clinicians to directly involve caretakers, family and friends in exercise programs and recommendations to facilitate adherence.

Taken together, the findings from this dissertation project indicate that exercise is feasible among patients undergoing preoperative treatment for pancreatic cancer and may confer important benefits for patients' perioperative health and quality of life. Future research projects and efforts to formalize clinical exercise prescription for patients with pancreatic cancer assess and account for potential socioecological influences on exercise and physical activity in order to maximize adherence.

Appendix 1

Lessons learned and best practices for implementing home-based exercise programs for patients undergoing preoperative cancer treatment

- Capitalize on potentially high motivation to exercise and optimize health and well-being among patients with difficult cancer diagnoses.

- Recommendations to exercise are not enough! Exercise adherence may increase with follow-up from clinicians and research staff. Patients may be more likely to adhere to exercise recommendations if they feel accountable to medical providers.

- If recommendations involve multimodal exercise (i.e., aerobic and strengthening exercise), patients may need more instruction and support to perform strengthening exercises safely and confidently. It is important to keep strengthening recommendations simple and to allow patients to slowly progress in adding volume and complexity to strengthening programs.

- Patients may benefit from increased accountability from family members, friends, and other caretakers. Whenever possible, these individuals should be involved in instructional sessions involving exercise recommendations and encouraged to provide instrumental or emotional support to cancer survivors in order to increase adherence.

- Social support for exercise does not come from friends and family alone. Clinicians and research staff should provide social support to improve accountability and increase adherence. Patients trust and rely heavily on information and advice from medical providers, and providing frequent and intentional encouragement to exercise may help increase adherence.

- Patients may benefit from tracking and monitoring their progress and results. This can be accomplished using daily exercise logs, or providing patients with scores from tests of physical functioning and fitness during follow-up visits.

- Patients may benefit from variety. Explore options for patients to join or access local gyms, parks, or fitness centers where they can safely and conveniently perform aerobic and strengthening exercises.

- Explain clearly to patients that exercise may help them deal with fatigue from chemotherapy and chemoradiation. By building up an “energy reserve” and improved strength and fitness, patients are making themselves more robust and possibly stronger to handle side effects from these treatments.

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