The effects of a preoperative exercise intervention during neoadjuvant therapy in patients with pancreatic cancer

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Principal Investigator: Catherine Jankowski, PhD
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I. Hypotheses and Specific Aims:

The long-term goal of this investigation is to improve the health status of patients with pancreatic and other advanced cancers. The first specific aim will examine the feasibility of implementing a preoperative exercise intervention in patients with pancreatic cancer undergoing neoadjuvant treatment. Two additional specific aims will test the novel hypothesis that preoperative exercise during neoadjuvant treatment will maintain or improve physical fitness and function, and improve postoperative outcomes, with potential mediation by positive effects on psychological stress and systemic inflammatory status.

AIM 1: To investigate the feasibility of providing a preoperative exercise intervention during neoadjuvant therapy in patients with pancreatic cancer.

Objective: Assess the accrual rate of patients able and willing to participate in a preoperative exercise program, as well as the adherence of enrolled patients to the preoperative exercise program. Safety will be determined by non-serious and serious adverse event rate and type.

AIM 2: To investigate the effects of preoperative exercise during neoadjuvant therapy on physical fitness and function, as well as postoperative hospital length of stay and readmission.

Hypothesis 1: Preoperative exercise will result in improved or maintained physical fitness and function, during and after treatment, compared to a non-exercising control group (standard care).

Hypothesis 2: Preoperative exercise will result in reduced postoperative hospital length of stay and occurrence of readmission compared to standard care.

Exploratory AIM: To investigate how subjective and objective measures of psychological stress and systemic inflammatory markers change in response to preoperative exercise during neoadjuvant therapy and to determine relationships to postoperative outcomes.

Hypothesis 1: Measures of psychological stress and systemic inflammatory markers will decrease in response to preoperative exercise compared to standard care.

Hypothesis 2: Preoperative measures of psychological stress and systemic inflammatory markers will be positively correlated with postoperative hospital length of stay and occurrence of readmission in all participants.

II. Background and Significance:

The Problem: Interventions to improve health status in patients with pancreatic cancer are understudied. Health, as defined by the World Health Organization, is “a complete state of physical, mental, and social well-being, and not merely the absence of disease or infirmity.” Pancreatic cancer is often diagnosed at an advanced stage, which has resulted in a 5-year survival rate of less than 5%[1]. As such, most research has focused on the disease and curative components of treatment, and not the overall health status of the individual. Investigations of exercise in cancer survivors, an intervention able to address and improve most aspects of health, have specifically focused on cancer populations with high survival rates[2]. Furthermore, advances in the medical treatment of pancreatic cancer have increased 5-year survival rate to 10-30% in patients who

receive surgery[3], making this a growing clinical population in which interventions to improve health status are understudied.

The Population: Patients with pancreatic cancer undergoing neoadjuvant therapy. Pancreatic cancer is the fourth leading cause of cancer-related death in the United States, resulting in an estimated 37,390 deaths in 2012[4]. Neoadjuvant therapy (preoperative chemotherapy and radiation) is often prescribed to a subgroup of patients to improve their response to surgery, the best known treatment for the disease. This therapy, however, can reduce physical fitness and function, decreasing the health status of the patient during and after treatment. Reduced preoperative cardiopulmonary fitness may also lead to increased postoperative complications[5], resulting in further decreases in health status.

The Intervention: A preoperative exercise program during neoadjuvant treatment, which can improve patient health status during and after treatment. Preoperative exercise has been shown to be safe and effective at improving physical fitness and function, vital components of overall health, in patients with other cancer diagnoses undergoing neoadjuvant therapy[6], but has not been investigated in patients with pancreatic cancer. Therefore, a gap in the research exists surrounding interventions to improve health status in the growing clinical population of pancreatic cancer survivors. The preoperative neoadjuvant treatment period allows implementation of an exercise program likely to maintain or improve cardiovascular fitness and muscular strength, improving postoperative outcomes and health status, and improved physical function has also been associated with decreases in hospital length of stay and readmission[7]. Beneficial effects of preoperative exercise may be mediated by changes in psychological stress and systemic inflammatory markers. Both increased psychological stress and systemic inflammatory markers have been associated with accelerated disease progression and worsening health status[8,9]. Both are beneficially affected by exercise[9,10], possibly contributing to the overall effects of the exercise intervention. Regardless of effects on disease progression, the beneficial psychological effects of exercise[11] can contribute to improved health status.

Preoperative exercise is a safe intervention in patients with advanced cancer. Exercise programs, both pre and postoperative, have been safely implemented in a wide variety of cancer survivors, with few to no adverse events reported[12]. Although no studies of preoperative exercise programs for patients with pancreatic cancer have been published, postoperative exercise programs in this population have reported no adverse events[10,13]. A survey of colorectal surgeons agreed that suitable preoperative exercise programs pose no risk to elderly colorectal cancer patients[14], and a systematic review of exercise during neoadjuvant treatment stated that preoperative exercise was a safe and feasible intervention[6].

III. **Preliminary Studies/Progress Report:**

No preliminary studies have been carried out examining preoperative exercise in patients with pancreatic cancer. The preoperative exercise intervention, however, will be administered through the BFitBWell Cancer and Exercise Program at the Anschutz Health and Wellness Center. This program has successfully provided individualized exercise interventions to over 100 cancer survivors during the past two years. These interventions are led by trained cancer and exercise specialists, and have led to consistent improvements in physical fitness, physical function, and quality of life.

The BFitBWell program has provided exercise interventions for six patients with pancreatic cancer. Pre- and post-program measures of physical fitness were collected in two of these patients, both showing improvement. Measures of strength and physical function improved in the majority of patients and 4 of 6 patients reported measurable decreases in fatigue.

Based on discussions with physicians at the University of Colorado Cancer Center, approximately 100 patients are diagnosed and treated there each year who would be potential participants in the proposed study.

IV. Research Methods

A. Outcome Measure(s):

Physical fitness and function outcomes:
The primary outcome of physical fitness and function will be the *400-meter walk time,* which is a validated measure of cardiorespiratory fitness and mobility. The test assesses the time it takes a participant to independently walk 400 meters[15]. This test was developed to assess functional walking and exercise capacity in older adults, as distance was found to be more motivating than time (compared to the 6 minute walk test). This test has been associated with the development of cardiovascular disease and functional limitations[16], and has been used to assess functional walking and exercise capacity in cancer populations[17].

Secondary measures of physical fitness and function include:

Lean muscle mass and body composition. This will be assessed utilizing a dual-energy x-ray absorptiometry (DXA) scan. This is the gold standard measure of body composition and commonly used in studies of exercise interventions in cancer survivors[18]. The potential preservation of lean muscle is an important assessment in this population as improved muscle quantity and quality has been associated with improved postoperative outcomes in patients with pancreatic cancer undergoing surgery[19].

Gait speed is an easily implemented measure linked to a variety of functional outcomes in multiple populations[20]. It will be measured during the middle 4 meters of a 10 meter course where participants will be instructed to walk at a normal pace and as quickly, but safely as possible. Participants will perform one practice trial and two test trials for each pace, with the fastest trial recorded, according to NIH guidelines[21].

The *Timed Up and Go (TUG)* times participants as they rise from a chair, walk 3 meters, turn around, and return to the chair and sit[22]. One practice trial is performed, followed by two test trials. The two test trials are averaged for the final time. This is an easily implemented test that has shown good sensitivity and specificity for predicting falls in older cancer patients[23], as well as predicting surgical complications following cardiac and colorectal procedures[24].

The *Stair Climb Test (SCT)* records the time taken to ascend and descend a single flight of stairs. It correlates with the TUG[25], but as a higher level task, reduces possibilities of a ceiling effect during data processing and has been utilized in previous studies of cancer survivors[18]. One trial is performed.

The *Single Limb Stance (SLS)* test records how long participants can balance on one leg, with a cap at 30 seconds. Participants are given two attempts with the best time recorded. This is a valid and reliable measure of balance and postural stability[26].

The *30 sec Sit-to-Stand (30StS)* test is associated with strength and function of the lower extremities and records the number of times participants can go from a seated position to a standing position in 30 seconds[27]. It is a valid and reliable test that has been used previously to assess strength and function in cancer survivors[18].

Grip strength will be assessed on both the dominant and non-dominant hands using grip dynamometry. This is a valid and reliable measure[28] that has been associated with physical function, health, gross strength, and survival in cancer survivors[29].

Average daily step count (ADSC) will be assessed using pedometers. Pedometers will be given to participants for 7-day periods and participants will record their daily step count in a paper journal at the end of each day, prior to resetting the pedometer. Participants will also record any periods of time that the pedometer was not worn. *ADSC* will be assessed as average step count per day worn.

Postoperative outcomes:
Hospital length of stay will be collected from medical records and be defined as the number of days from surgical admission to hospital discharge.

Hospital readmission will be assessed as whether a patient is rehospitalized in an unplanned response to a surgical complication within 30 days of hospital discharge. Planned rehospitalizations will not be assessed as a hospital readmission.

Hospital physical function will be assessed using the AM-PAC test of inpatient physical activity and basic mobility[30].

Questionnaire/Psychological Outcomes Assessment:

Fatigue will be assessed using the Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-Fatigue), a validate measure of fatigue in cancer survivors[31].

Health-related Quality of Life (HRQOL) will be assessed with the Functional Assessment of Cancer Therapy-General form (FACT-G)[32]. This form provides information on the physical, social, emotional, and functional well-being of patients with cancer.

Subjective psychological stress will be assessed with the Perceived Stress Scale (PSS)[33], which assesses *perceived stress* based on individual and environmental stressful events, focusing on experiences in the last month. *Depression* will be assessed using the Center for Epidemiologic Studies Depression Scale (CES-D)[34].

Prior physical activity level will be assessed with the Godin Physical Activity Questionnaire. This measure is a self-report estimate of leisure physical activity for the prior month. Prior physical activity level will be compared between groups and considered as a potential factor to control for in statistical analyses. This will only be collected at the first assessment.

Objective Stress Assessment:

Heart rate variability (HRV) will be used as an objective measure of stress, both physiologic and psychological. HRV will be assessed in four different conditions. Electrocardiography (ECG) will be recorded during a 10 minute baseline period (seated), a 5 minute orthostatic challenge (sit-to-stand), a 5 minute cognitive dissonance period (standard Stroop Task), and a 5 minute cancer-salient dissonance period (cancer-related Stroop Task)[35]. The standard Stroop Task involves naming the color a word is printed in. The words are usually a color word (e.g. “Red”, “Blue”) and sometimes do not match the color the word is printed in. The cancer-related Stroop Task also requires participants to name the color a word is printed in, except words will either be neutral words or words related to cancer (e.g. “Malignancy”, “Chemo”). Participants will be told prior to performing either task that the tasks are designed to be challenging and possibly evoke emotion. The standard Stroop and cancer-related Stroop will be performed in a random order between participants, but kept constant across Visits within participants, and separated by a 5 min rest period. Both time and frequency domain HRV measures will be calculated from the ECG signal for each period offline, quantifying overall autonomic tone (assessed by average heart rate and the total spectral power of HRV), parasympathetic tone (the high frequency component of HRV), and changes from baseline for each condition.

Biomarker Assessment:

Systemic markers of inflammatory status will be assessed by measuring pro-inflammatory cytokines: serum C-reactive protein, associated with postoperative outcomes in patients with pancreatic cancer[36], interluekin-6, potentially involved in the development and progression of cachexia[37], and soluble tumor-necrosis factor receptor 1, a possible indicator of exercise-induced changes in systemic inflammatory status[38], and an anti-inflammatory cytokine, interleukin-10, involved in exercise-induced pathways[39]. Blood samples will be drawn at the same time as other blood draws performed as part of standard care at the University of Colorado Cancer Center, to reduce patient burden. If these routine blood draws do not occur within a one week window of the assessment, blood draws will be performed at the Clinical and Translational Research Center on the Anschutz Medical Campus, where all sample analyses will be performed.

B. Description of Population to be Enrolled

The potential participant population will be individuals who receive a diagnosis of borderline-resectable pancreatic cancer (adenocarcinoma), being treated at the University Hospital Cancer Center. These inclusion and exclusion criteria will apply to participants in both groups.

Inclusion Criteria: Recent (< 4 week) first diagnosis of a borderline-resectable pancreatic adenocarcinoma, assigned to receive neoadjuvant therapy and surgery at University of Colorado Cancer Center, physician clearance to participate in exercise program, and age 21-80 years.

Exclusion Criteria: Any significant comorbid conditions that would interfere with or preclude participation in an exercise intervention, including orthopedic conditions such as advanced osteoarthritis, mobility-limiting amputations or chronic injuries, or mobility-limiting acute orthopedic injuries; advanced rheumatoid arthritis; widespread chronic pain conditions such as fibromyalgia; pulmonary conditions such as chronic obstructive pulmonary disease, emphysema, interstitial lung disease, use of supplemental oxygen; known cardiovascular disease, uncontrolled hypertension, or new cardiac event within the past 6 months. Participants with a second cancer diagnosis at the time of enrollment will be excluded.

Sample size estimation: No studies have previously investigated the effects of preoperative exercise in patients with pancreatic cancer. In patients with lung cancer, a preoperative exercise program reduced hospital length of stay by 4 days compared to usual care[40]. Based on this difference, with a SD of 3, 12 participants would be required in each the experimental and control groups ($\alpha = 0.05$, $\beta = 0.90$[41]). To account for overall attrition, groups will be increased by 3 participants each, based on a study of preoperative exercise after neoadjuvant treatment in patients with rectal cancer showing an overall attrition of 28%[42]. A total of **30 participants (15 per group)** will be recruited for this study.

C. Study Design and Research Methods

This is a prospective, non-randomized, parallel group, intervention control trial, patterned on a similar pilot study in patients with rectal cancer[42].

Recruitment: Participants will be recruited from the University Hospital Cancer Center. Patients with a recent diagnosis (< 4 weeks) of pancreatic cancer will be given information on the study by their treating physicians and asked if they would be interested in participating. If yes, physicians will have patients complete a HIPAA A form to provide study personnel with their name. Study personnel will access the patients' medical records to evaluate the inclusion/exclusion criteria. If these criteria are met, research personnel will meet with the

potential participant at the University of Colorado Cancer Center to provide information about the study. If patients are still interested in participating, the familiarization and possibly first visit will be scheduled. Participants will have the option of combining the familiarization session and Visit 1. All data collected during screening will be destroyed and recollected after obtaining written consent in patients choosing to participate. If the inclusion/exclusion criteria are not met after review of the health record, the patient will be contacted and the exclusion decision will be explained.

Group Assignment: Volunteers meeting the inclusion and exclusion criteria and willing to participate in the exercise intervention will be assigned to the exercise group. The standard of care, non-exercise control group will comprise volunteers who meet the inclusion and exclusion criteria but are unable to commit to participation in the exercise intervention for practical reasons (e.g. barriers in transportation or home location). The use of a non-randomized study design is to maximize patients participating in the exercise program to determine accrual rate, program adherence, and safety while still allowing a non-exercise control group.

Protocol:

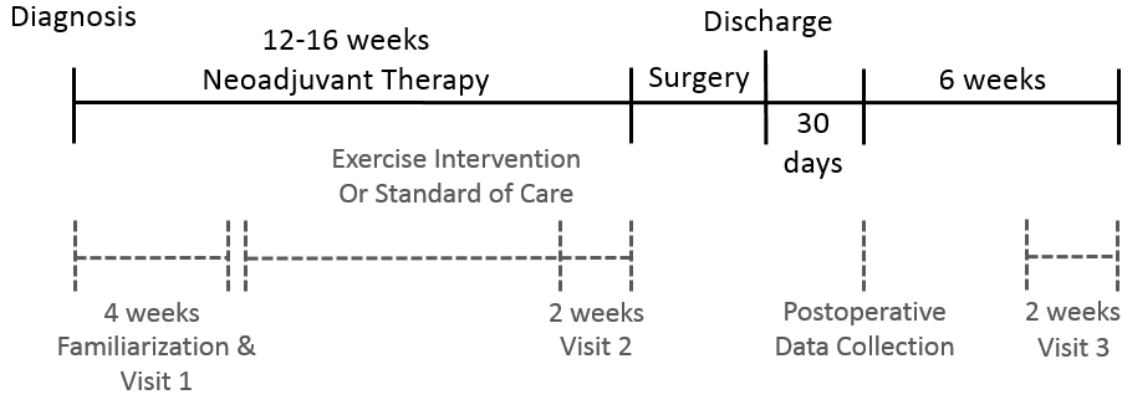

Figure 1

Figure 1 shows the event timeline of the study, with time points of visits and intervention in relation to diagnosis and surgery. Written informed consent will be obtained by a study investigator during a familiarization period, where participants will have assessments and the exercise investigation explained in-depth. There will be four time points for data collection: pre-intervention (Visit 1), post-intervention and preoperative (Visit 2), 30-day postoperative (data retrieved from electronic health record), and follow-up (Visit 3).

Assessments: All assessments will be performed at the Anschutz Health and Wellness Center. Participants will also complete the Godin Physical Activity Questionnaire during Visit 1 only. The following assessments will be completed at visits 1, 2, and 3.

A total body DXA scan will be performed to determine body composition. The scan takes approximately 3 minutes, but 15 minutes is allocated for data entry and positioning the patient.

HRV assessments will be performed prior to functional testing, to avoid the potential impact of physical activity on heart rate measures. This assessment will be performed in a private examination room and will take approximately 30 min.

Physical fitness and function assessments will then be performed. These assessments will be performed in the same order at every assessment, with the most fatigueing assessments performed at the end of the session. The order will be: SLS, TUG, grip strength, 30StS, SCT, gait speed, 400MWT. All tests will be performed by the same investigator at all time points.

This investigator is a licensed physical therapist with experience performing functional tests in medically involved or functionally limited populations. A secondary tester, blinded to participant group, will be present at all sessions to provide any necessary assistance and insure lack of testing bias. Participants will also be given the activity tracker to assess ADSC, with instructions on how to use the device and how to return the device in one week. The functional assessment period will take approximately 1 hour.

Questionnaire data will be collected using REDCap software. Participants will have two options for completing questionnaire data at each assessment: 1) completion of questionnaire data via emailed REDCap survey at the Health and Wellness Center via provided computer or tablet, 2) completion of printed questionnaires provided at the functional assessment. Data obtained from participants completing printed questionnaires will be entered in the REDCap system by two study investigators independently to insure accuracy, following which hardcopies will be destroyed.

If participants will not receive a standard blood draw as part of their medical care within a one-week window of the visit, they will be transported to the CTRC where the necessary blood draw will be performed.

Thirty days after hospital discharge, the participants' electronic health record will be reviewed to retrieve data about initial hospital length of stay and 30-day unplanned hospital readmission. Visit 3 will be performed at approximately 6 weeks post hospital discharge. This is the time at which some patients may begin more chemotherapy or radiation treatment (adjuvant therapy), and Visit 3 will be performed prior to this to avoid confounding effects of the therapy.

Exercise Intervention: Participants will start the exercise program within four weeks of their diagnosis and decision to undergo neoadjuvant treatment and continue until surgery. Participants will continue to receive the standard medical care (described below) provided at UCCC. Individual exercise sessions in this program implement a "whole body" approach and consist of a 10-min cardiovascular warm-up and 50 minutes of cardiovascular endurance, resistance, and flexibility exercises (session components). Typical cardiovascular endurance exercises include walking on an indoor track or treadmill, stationary cycling, and stationary rowing. Resistance training includes exercises using body weight, free weights, and weight machines targeting increased strength of the large upper and lower extremity muscle groups and core stability. Flexibility exercises target major muscle groups activated during the exercise. Target intensity of exercise will be based on the American College of Sports Medicine (ACSM) recommendations for cancer survivors[2]: 40-85% heart rate reserve for cardiovascular endurance exercises; 60-70% one repetition maximum for resistance exercises; and a rate of perceived exertion of 12-16 on a 6-20 Borg scale for all activities.

Exercise Adaptations: Prior to the start of exercise sessions, participants will be questioned on significant changes in symptoms or the presence of new symptoms (such as nauseau or fever), which will used to modify the exercise session (intensity and components) for that day to allow maximum symptom-limited participation. Participants will be encouraged to complete three sessions per week for at least eight weeks during neoadjuvant therapy. Exercise intensity, components, and time will be recorded for each exercise session to guide the exercise specialist in making appropriate exercise adjustments (progression, maintenance, or reduction). Exercise programs have been found to be safe in cancer survivors, even during life-threatening treatments[2], but safety has not been investigated specifically in the current population. Common risks may include muscular fatigue and soreness, as well as transient increases in treatment-related symptoms. Rarer risks include the possibility of injury due to unknown bone metastases or acute cardiac events. Intensity and acute changes in symptoms will be closely monitored to decrease these risks.

Participants will schedule their sessions with the exercise specialists administering the program, typically taking place between 8AM and 4PM, Monday through Friday, at the

Anschutz Center for Health and Wellness. Adherence will be measured as the percent of scheduled sessions attended. Exercise sessions will also be individualized to participants on a day to day basis, with time and intensity not exceeding that listed above. Prior to the start of exercise sessions, participants will be questioned on significant changes in symptoms or presence of new symptoms (such as nauseau or fever), which will be used to modify the exercise session for that day. Exercise intensity, type, and time will be recorded for each exercise session.

Standard Care: Participants in the Standard Care group will receive no exercise intervention, but will continue to receive standard follow-ups, treatments and services from their oncology team. The services that participants receive as standard care include their medical care, symptom control, social worker support, and nutrition.

Participants in all groups will receive $50 reimbursement for each Visit completed, totalling $150.00 for all three Visits.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Risks of exercise and assessments: Certain risks are associated with performing exercise in any population, as well as specifically in cancer survivors. The likely risks of exercise include muscular fatigue and/or soreness, acute increase in fatigue, joint stiffness or soreness, and possible acute increase in treatment- or cancer-related symptoms. The more serious risks include fracture associated with unknown bone metastases, development of ventricular arrhythmia, myocardial infarction, cardiac arrest, and death.

Justifications and Protection: For adults in the general population and for cancer survivors in particular the benefits of exercise training outweigh the risks. Exercise interventions have been shown to be safe in multiple cancer survivor populations[12]. The discomforts of exercise training and testing will be explained to the participants. Participants will be informed that they can choose to withdraw or not participate in some or all portions of the study at any time for any reason. Before, during, and at the conclusion of each exercise training and testing session, study personnel will ask participants about new or worsening signs and symptoms. Every exercise session will be supervised by qualified study personnel who are versed in exercise training for clinical populations and BLS-certified. Exercise intensity and types of exercise will be adapted for each individual participant to match their capacity throughout the study. Exercise tests and training will be of submaximal intensity. Exercise intensity will be monitored by study personnel to decrease likelihood of an acute cardiac event, and participants will be monitored for symptoms including chest pain, acute shortness of breath at rest, or dizziness. Patients will be instructed to stay well-hydrated, and will be monitored for symptoms of dehydration including headache, confusion, tachycardia, significantly increased respiratory rate, and changes in skin elasticity. Patients with diabetes will be monitored for symptoms of hypoglycemia, encouraged to bring snacks to assessments and exercise sessions, and snacks and juice will also be stocked by research personnel.

After providing written informed consent, each participant will be asked to provide clinical provider contact information. In the event of an emergency, study personnel will call 9-1-1, according to the protocol of the Anschutz Health and Wellness Center and outpatient clinics on the AMC. AEDs are available throughout the Wellness Center. The PI will contact the designated clinical provider if an emergency arises (after first responders are summoned) or a participant exhibits or reports exacerbation of symptoms. In the case of a medical emergency, the participant must be cleared for exercise by their clinical provider before resuming exercise training or testing.

The risks of the venipuncture are momentary discomfort from the needle stick, excessive bleeding, light-headedness with insertion of needle, and infection or hematoma at the site of

the blood draw. The risks of hematoma and infection will be minimized by having trained clinical personnel perform the procedures using sterile techniques.

The risks of DXA (to assess body composition) involves exposure to ionizing radiation. The DXA scans at 3 times during the study involve a total effective radiation exposure of about 3 mrems. DXA involves <1% of the annual maximum non-therapeutic radiation exposure to the whole body recommended by the FDA (5000 mrem/year). This risk is minimized by having trained DXA technicians administer the procedure, thereby reducing the likelihood of needing repeat assessments.

The risk of the heart rate variability (HRV) testing is a possible brief increase in perceived stress and physiologic arousal induced by the cognitive difficulty of the Stroop Task. Participants will be warned of this possible increase in stress and arousal. The change will be no different than that occurring while performing difficult cognitive tasks on a daily basis. The Stroop Task has been previously used to effectively and safely evaluate HRV changes[43]. The ECG electrode adhesive may cause localized skin redness and discomfort.

Confidentiality and privacy: The use of questionnaires and collection of personal medical information poses a risk to confidentiality and privacy and may cause embarrassment.

These risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting interviews and collection of personal information in a private setting. Direct data entry into a secure website using REDCap software will be coded with a unique participant number.

Data Safety and Monitoring: Research personnel will monitor safety concerns on an ongoing basis as data is collected and analyzed. The study PI will review the safety of the protocol at least monthly and submit an annual report. A medical safety officer (Dr. Kessler), who is not an investigator on the study, will review the safety of the study after enrollment of every 10 participants and submit a report at least annually. Study participants will be informed that they can choose to stop the study (exercise intervention or assessments) at any time. If study personnel deem that the participant is no longer physically capable of performing the exercise intervention or assessments, the participant will be discontinued from the study. The overall protocol will be discontinued if the PI, research team, and safety officer agree that participants in the exercise group are experiencing significant negative outcomes, not experienced in the non-exercise (control) group, attributed to the exercise intervention or testing.

The PI will report all unanticipated problems and adverse events to COMIRB within 5 days of occurrence. Unanticipated problems and adverse events are defined as by COMIRB.

E. Potential Scientific Problems:

Potential Problems and Solutions: Given that no previous studies of preoperative exercise programs exist in patients with pancreatic cancer, the power analysis for the current study was based on the outcomes of a study of preoperative exercise in patients with lung cancer. It is possible that the estimated sample size here will not provide enough power to detect differences in postoperative outcomes. Regardless of statistical significance, outcomes from this study will provide the basis to allow future studies in this population that are adequately powered. Study groups will not be randomized, resulting in a potential selection bias and baseline differences. The decision to design the study as a non-randomized trial was made to improve recruitment for the target patient population and the short duration of the funding period. Analysis of the number of participants who are willing and able to participate in an exercise intervention at the AHWC will determine if a randomized trial is feasible and allow a better estimate of a realistic enrollment period. We will interpret our enrollment activity as

follows: if less than 70% of anticipated enrollment is achieved, we will conclude that additional study sites will be needed to enroll sufficient numbers of patients treated with neoadjuvant therapy for pancreatic cancer for formal hypothesis testing in a RCT.

The individualized nature of the exercise program precludes rigorous control of exercise components between participants. An individualized exercise program may increase adherence and will allow adaptability to acute changes in the patients' health status due to treatment- or disease-related symptoms. The neoadjuvant therapy period will vary between participants, resulting in a variable duration of the exercise intervention. The duration of exercise must remain variable to avoid deconditioning that would be caused by a long lapse between the end of the exercise intervention and surgery. Most patients complete 16 weeks of neoadjuvant therapy before surgery, which will result in a typical exercise intervention lasting 12 weeks. We will record the duration of exercise training and neoadjuvant therapy and test these factors as covariates in the analyses of the fitness, function, and stress outcomes.

F. Data Analysis Plan:

The timeline for this protocol is estimated at 2 years. Data collection (participant recruitment and intervention) is estimated at 1 - 1.5, after which data will be analyzed and manuscripts prepared.

Data Analysis and Anticipated Outcomes: Groups will be compared on demographic variables such as age and gender. Variables that differ significantly will be included in planned analyses as covariates. Statistical significance will be defined as $\alpha \leq 0.05$, however, results will be interpreted cautiously as is warranted for pilot studies[44]. As we expect to be underpowered to test for statistical interactions, multiple tests will be used to assess differences in baseline measures, change scores, and postoperative outcomes between groups. Change scores will be calculated as the difference between Visit 2 and Visit 1. Groups will be compared using non-parametric exact k-sample permutation tests, which are well suited for small sample sizes as they do not rely on typical normal-theory methods[45].

Aim 1: The feasibility of implementing this intervention will be assessed by quantifying the accrual rate of patients willing and able to participate in the preoperative exercise intervention and individual patients' adherence to the prescribed exercise program (percentage of scheduled sessions attended). Safety will be determined by the number of non-serious and serious adverse events and relatedness of the events to exercise, as described by COMIRB.

Aim 2: Hypothesis 1 – Baseline physical fitness and function measures and change scores will be compared between groups using exact k-sample permutation tests. We anticipate a significant difference in the changes from Visit 1 to Visit 2, with the Exercise group demonstrating maintained or improved physical fitness and function compared to the Control group, with no differences in baseline measures. A secondary analysis will be used to describe the trajectory of changes in physical function from visits 1, 2, and 3.

Hypothesis 2 – Postoperative outcomes will be compared with exact k-sample permutation tests (hospital length of stay) or Fisher's exact tests (hospital readmission) between the Exercise and Control groups. We anticipate the Exercise group to have a significantly lower hospital length of stay and occurrence of hospital readmission compared to the Control group.

Exploratory Aim: Hypothesis 1 – Baseline psychological stress and systemic inflammatory status measures and change scores will be compared between groups using exact k-sample permutation tests. We anticipate a significant difference in change scores, with the Exercise group demonstrating decreased (improved) psychological stress and improved systemic inflammatory status (decreased CRP, IL-6, sTNFR1 and IIS; increased IL-10) compared to the Control group, with no differences in baseline measures.

Hypothesis 2 – Spearman correlations will be performed between preoperative measures of psychological stress and systemic inflammatory status and postoperative variables. We

anticipate a significant negative correlation between psychological stress and systemic inflammatory status and postoperative outcomes, with lower levels of stress and inflammation associated with improved outcomes in all participants.

G. Summarize Knowledge to be Gained:

Aim 1: The feasibility of future, larger scale implementation of the preoperative exercise program will be assessed primarily by patient adherence to the program, demonstrating patients' ability and willingness to complete the program. The future study of the intervention will be assessed through the measurement of patient accrual, which will provide a reference for the necessary time frame of future studies.

Aim 2: The analyses performed in this aim will reveal 1) how a preoperative exercise intervention affects physical fitness and physical function prior to and after surgery, and 2) whether a preoperative exercise program is associated with improved postoperative outcomes in patients with pancreatic cancer undergoing neoadjuvant treatment. These analyses will also illustrate typical changes in measures of physical fitness and physical function through analysis of the Standard Care group.

Exploratory Aim: The analyses performed in this aim will reveal 1) how a preoperative exercise intervention effects subjective and objective measures of psychological stress, autonomic function, and systemic inflammation prior to and after surgery, and 2) whether these preoperative measures predict postoperative outcomes in patients with pancreatic cancer undergoing neoadjuvant treatment. These analyses will also illustrate typical changes in measures of physical fitness and physical function through analysis of the Standard Care group. Results from this aim may also lead to the development of novel interventions, if measures are predictive of outcomes but not adequately changed by exercise.

Outcomes from this study will add to the growing body of literature on the effectiveness of preoperative exercise programs in cancer survivors, as well as demonstrate the potential effectiveness of an exercise intervention in patients with pancreatic cancer, where there is limited evidence. By examining potential mediators in the effectiveness of exercise on postoperative outcomes, it allows future studies to tailor exercise program components to focus on the mediators most strongly associated with positive outcomes.

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COMIRB
APPROVED
For Use
31-Mar-2016
08-Mar-2017

Principal Investigator: Catherine Jankowski, PhD
COMIRB No: 15-2266
Version Date: 3-16-16

Study Title: Effects of a preoperative exercise intervention during neoadjuvant therapy in patients with pancreatic cancer

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You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about whether the effects of providing a personalized exercise program to patients recently diagnosed with pancreatic cancer can improve their health and tolerance to cancer treatment. The exercise program will take place before surgery, while you are receiving chemotherapy and radiation therapy to improve your response to surgery. We anticipate that the exercise program will improve your fitness, ability to move, and response to surgery.

You are being asked to be in this research study because you have recently been diagnosed with pancreatic cancer and plan on receiving neoadjuvant treatment and surgery at the University of Colorado Cancer Center.

Other people in this study

Up to 30 people from your area will participate in the study. This study is not being performed in any other locations.

What happens if I join this study?

If you join the study, you will receive physical fitness and function testing at several times (now, before surgery, and 6 weeks after surgery). These tests are performed only as a part of this research study and are not typically performed as part of standard care. You will need to travel to the Anschutz Health and Wellness Center for 1 visit at each assessment time (totaling 3 assessment visits). There will also be a familiarization session, which may or may not be combined with the first assessment. At the familiarization session, we will go over the study in detail and you will fill out an additional questionnaire with demographic and medical history information.

There are four components to each assessment: questionnaires, heart rate variability testing, functional testing, and body composition testing.

 Initials_____

The questionnaires at each assessment can be filled out in one of two ways: on a computer or tablet at the Wellness Center, or on a provided paper copy at the Wellness Center. If completed at home (on a device or paper), this must be done within one week of the functional testing (and returned to the Center if on paper). It will take about 20 minutes to complete the questionnaires.

During heart rate variability testing we will attach small plastic electrodes to the center of your chest or over your ribs in order to record your heart beat. We will record your heart beat while you are quietly sitting, standing, or performing cognitive tasks for 5-10 minute periods of time. The cognitive tasks require you to identify the color of words on a screen. Sometimes the words will be different color name, random objects, or medical terms related to cancer. These tasks are designed to be difficult and evoke some emotion.

During functional assessments, you will perform tasks designed to measure how well you can move and perform daily tasks. These include: balancing on one leg, rising from a chair and sitting in a chair, gripping a force measuring device as hard as possible, going up and down stairs, and walking (short, timed walking in 10 meter intervals, and one timed 400 meter [a quarter mile] walk). You will also be given an activity monitor that is worn on your upper arm during this session. We will ask you to wear this monitor for a week and then return it. It will measure how many steps you take each day.

To assess body composition, we will perform up to 3 DEXA scans. There will be 1 DEXA scan per assessment visit. DEXA is a way of looking inside the body by using X-rays. X-rays are a type of radiation. We will pay for these scans, you will not be charged.

Finally blood will be drawn either during a routine clinical care or on the medical campus on the day of your functional assessment. This will be done to assess the inflammatory status in your body. If we do draw blood during the assessment, we will need to get about 1 teaspoon of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

As a part of the study, you will join a preoperative exercise program or continue to receive standard care if you cannot join the exercise program. The exercise program consists of 60-minute sessions with a cancer exercise specialist that is based on a “whole-body” approach to exercise. Sessions will include aerobic (walking, treadmill, bike, rowing machine), resistance (machines, free weight, and body weight), and flexibility (stretching) exercises. You will wear a heart rate monitor and activity monitor during these sessions to help monitor the intensity of your exercise. These sessions will be scheduled for 2-3 times a week from initiation of the program to your date of surgery, and you will be required to travel to the Wellness Center for these sessions. Sessions need to be scheduled between 8AM and 4PM.

Initials_____

What are the possible discomforts or risks?

Discomforts you may experience while in this study include muscle fatigue and soreness, acute increase in fatigue, or joint stiffness or soreness. These are commonly associated with any exercise program and exercise intensity will be monitored to decrease these symptoms as much as possible. Any of these discomforts may be experienced in response to assessments, as well as exercise sessions. It is very important that you inform whoever you are with if you have any change in symptoms during assessments and exercise sessions. If getting blood drawn as part of the study, you may feel a momentary sharp pain.

The DEXA scan for measuring your muscle and fat uses x-ray and exposes you to radiation. Your natural environment has some radiation in it. Each DEXA scan will give you about the same amount of radiation that you would get from your environment in 6 days.

The heart rate variability test requires concentration and may cause emotional distress. You will be seated at a computer with words presented on the screen. You will need to identify either the word or the color of the font the word is printed in as they are presented to you. This task is designed to be difficult, possibly resulting in distress. Sticky patches will be placed on your chest to measure your heart rate activity during the test. The patches may cause redness or soreness of the skin.

Rare risks include:
Exercise testing and assessment: 1) acute cardiovascular event, 2) musculoskeletal injury, 3) dehydration, 4) excessive bleeding, and 5) possible fracture due to unknown bone metastasis.

Blood draw risks are possible light-headedness with insertion of needle during blood draw, and possible infection or bruising at the site of the blood draw.

Careful monitoring of the intensity of exercise sessions as well as any symptoms experienced will be done to minimize the occurrence of associated rare risks. When a blood draw is performed sterile procedures will be used to minimize the risk of infection.

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

You may not be in this study if you are pregnant, the particular treatment or procedures involved in the study may involve risks to the embryo or fetus which are currently unclear.

The study may include risks that are unknown at this time.

 Initials_____

Optional Future Research

I give my permission to be contacted with information about future studies conducted in the Anschutz Health and Wellness Center for which I may qualify. These studies would be related to exercise during and after cancer treatment. I can withdraw my permission to be contacted at any time by contacting study personnel either by phone (303-724-7383), email (catherine.jankowski@ucdenver.edu), or in writing at the address listed below for Dr. Catherine Jankowski. Contact for future studies will not occur after one year from the date I consent to be in this study.

_____YES _____NO _____Initials

I give my permission for my data to be stored in a registry at the Anschutz Health and Wellness Center for future use by the study investigators. I can withdraw my permission to be contacted at any time by contacting study personnel either by phone (303-724-7383), email (catherine.jankowski@ucdenver.edu), or in writing at the address listed below for Dr. Catherine Jankowski.

1. I give my permission for my data to be kept for use in future research to learn more about the effects of exercise during and after cancer treatment.

   _____YES _____NO _____Initials

2. I give my permission for my data to be used for research about other health problems (for example: causes of heart disease, osteoporosis, diabetes).

   _____YES _____NO _____Initials

What are the possible benefits of the study?

This study is designed for the researcher to learn more about how fitness and function change after a diagnosis of pancreatic cancer, and if these can be changed with an exercise program. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study, which are described above.

Who is paying for this study?

This research is funded by the Anschutz Health and Wellness Center and the University of Colorado Cancer Center.

Will I be paid for being in the study?

You will be paid $50.00 for each assessment visit in this. This will add up to a total of $150 if you complete all of the visits. If you leave the study early, or if we have to

take you out of the study, you will be paid only for the visits you have completed. If you are in the exercise group, you will not be paid for session attendance, but will receive the necessary gym membership and exercise sessions for free.

It is important to know that payments for participation in a study is taxable income.

Will I have to pay for anything?

It will not cost you anything to be in the study.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled. If you leave this study, you will still receive your normal medical care.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should contact the PI, Catherine Jankowski, immediately. Her phone number is 303-724-7383.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Dr. Catherine Jankowski. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call her at 303-724-7383. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

 Initials_____

Who will see my research information?

The University of Colorado Anschutz Medical Campus (UC-AMC) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.
The institutions involved in this study include:

- University of Colorado Anschutz Medical Campus
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UC-AMC and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Catherine Jankowski
University of Colorado College of Nursing
Mail Stop C288-19
13120 East 19th Ave.
Aurora, CO 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:.

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study team.
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

 Initials_____

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study is completed..

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Psychological and mental health tests
- Blood samples and the data with the samples.

What happens to Data, Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data collected from you during this study are important to this study and to future research. If you join this study:

- The data given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data collected from you.
- If data are in a form that identifies you, CU-AMC or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

Initials_____

HIPAA Authorization for Optional Future Contact

In this form, you were given the option to agree to additional, optional research procedures. You must also give us your permission, under HIPAA rules, to use and disclose the information collected from these optional procedures, as described above.

If you decline to give us permission to use and disclose your information, you cannot take part in these optional procedures, but you can still participate in the main study. Please initial next to your choice:

_____ I give permission for my information, from the optional procedures I have agreed to above, to be used and disclosed as described in this section.

_____ I **do not** give permission for my information for any optional procedures to be used and disclosed; I understand that I will not participate in any optional procedures.

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature:_____ Date:_____

Print Name:_____

Consent form explained by:_____ Date:_____

Print Name: _____

Investigator: _____ Date: _____
Investigator must sign within 30 days