**Step Down Colon Cancer Risk:**

A Pilot Intervention for Colon Cancer Risk Reduction

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**A. BACKGROUND AND SIGNIFICANCE**

Colon cancer is the third most commonly occurring cancer in men and women in the US.1, 2 Evidence linking physical activity with a reduced risk of colon cancer is consistent and convincing.3 Recent analyses suggest that nearly one third of cancer cases can be attributed to nutrition and physical activity related factors.3 Despite the benefits of physical activity, nearly 75% of the population fails to meet recommended physical activity levels.4-6

In this study, we will refine and pilot test an intervention to promote walking among individuals with a previous polyp. Our goal is to reduce risk of colon cancer by triggering changes in important biomarkers, including IL-6, PGE-2, insulin, and C-peptide through increased physical activity.

**A.1. Physical activity and colon cancer.** Observation studies consistently link physical activity with a reduced risk of colon cancer.3, 7-20 Despite the consistency of the evidence, many aspects of the relationship remain to be elucidated.

Previous studies have reported a reduced risk of colon cancer with engagement in moderate intensity activity.13, 21 Recent analyses in the Nurses’ Health Study, the largest prospective study to examine this phenomenon to date, found a significant risk reduction among women walking at least two hours per week.22 Given that walking is a commonly reported activity, and is the most common activity among middle-aged and older women23, 24, these results have important implications for prevention. The components from the biologic model of the hypothesized association between walking and colon cancer risk reduction are outlined in Figure 1.

**Figure 1. Physical activity and colon cancer**

Physical activity

Colon cancer

insulin

IL-6

PGE-2

C-peptide

+

+

+

+

+

**A.2. Biomarkers and colon cancer**

**A.2.a. Insulin and colon cancer.** Insulin is involved in cell proliferation and apoptosis. As a result, the role of insulin in carcinogenesis has been a focus of much research. Several lines of evidence support the hypothesis that hyperinsulinemia promotes the growth of colon tumors. Colon tissue has insulin receptors25 and insulin stimulates the growth of both normal and colon cancer cells in vitro.26, 27 Insulin-like growth factors may also promote colon tissue growth.28 The association seen between type II diabetes, which often results in hyperinsulinemia due to insulin resistance, and colon cancer provides additional support for the role of hyperinsulinemia in colon carcinogenesis.29-32 Animal studies also support the role of insulin in colonic carcinogenesis.33

 Observational studies have found associations between insulin and both risk of colon cancer34, 35 and risk of colon polyps, precursors to colon tumors.36-38 Individuals in the highest quartile for insulin had a twofold increased risk for colon cancer compared to those in the lowest quartile.35

C-peptide is an insulin production by-product created when proinsulin is cleaved into insulin and C-peptide. C-peptide is more stable and, therefore, a better marker of insulin secretion; levels reflect how much insulin the body is producing. Recent research39-42 has found a positive association between C-peptide levels and risk of colon cancer as well as risk of colorectal adenoma,43 further supporting the hypothesis that hyperinsulinemia may play an important role in colon carcinogenesis. Thus, it has been suggested that targeting hyperinsulinemia may be an effective colon cancer prevention strategy.

**A.2.b. Inflammation and colon cancer.** Several lines of research suggest a role for inflammation in colon carcinogenesis. Non-steroidal anti-inflammatory drugs (NSAIDs) have shown promise as chemopreventive agents, but concerns exist regarding the side effects associated with long term use.44 COX-2 specific inhibitors have shown protection against colon polyps, but have been found to have adverse cardiovascular effects.44-46 The mechanism behind the protective effect of NSAID use is hypothesized to be in part due to the inhibition of COX-derived prostaglandin E2 (PGE-2), which promotes tumor carcinogenesis.47

Prostaglandin levels are increased in COX-2 mediated inflammation (PGE-2 is a COX-2 metabolite). PGE-2 is typically released by blood vessel walls in response to infection or inflammation. PGE-2 is the most abundant prostaglandin in colorectal cancer48 and promotes tumor progression by stimulating cell proliferation and angiogenesis, inhibiting apoptosis and modulating immunosuppression.49 Thus, factors which reduce levels of PGE-2 are also hypothesized to reduce colon cancer risk.

Research has also demonstrated a key role for interleukin-6 (IL-6) in the inflammation – colon cancer relationship. IL-6 is a pro-inflammatory cytokine secreted by T-cells and macrophages. IL-6 promotes the transition from acute to chronic inflammation.50 Emerging research indicates a predominant role for the IL-6 pathway in bowel inflammation.51 IL-6 associated genetic polymorphisms have shown an increased risk of colon cancer.52 Observational research has provided preliminary support for this model, demonstrating a positive association between serum IL-6 levels and colon cancer.53 IL-6 levels were also correlated with larger tumor size and metastasis and levels increased in a stage-related manner. Finally, there is some indication that IL-6 may be related to insulin resistance in cancer patients.54

**A.3. Physical activity and biologic markers.**

**A.3.a Physical activity (PA) and insulinemia.** PA increases insulin sensitivity 55-60 with the effects of a single exercise bout potentially lasting for several days,61, 62 resulting in decreased plasma insulin levels.60, 63-71 There is also evidence that walking, in particular, decreases insulin72, 73 and increases insulin sensitivity.74, 75 Physical activity is also inversely associated with C-peptide levels.40, 66, 76-80 However, some research suggests that vigorous physical activity may be necessary to reduce C-peptide levels.76, 78 The associations seen for vigorous physical activity may reflect that more intense physical activities are easier to recall.81 Most observational data is from cross sectional studies. Data on the effect of sustained changes in physical activity on C-peptide levels is limited.

**A.3.b. Physical activity and inflammation.** Interest in the association between physical activity and inflammation has traditionally been limited to cardiovascular research where the inflammatory factors of interest include c-reactive protein (CRP), white blood cell count (WBC) and fibrinogen.82 Population-based cross-sectional studies have generally found an inverse relation between physical activity and CRP level with similar associations for WBC and fibrinogen. 82-84

Inverse associations between self-reported physical activity and levels of other inflammatory markers have been found.85 In cross-sectional analyses, physical activity was inversely associated with IL-6.68, 86 In addition, a significant decrease in IL-6 was found following a 12-week aerobic training intervention in 24 men87 and a separate 10-week intervention in 20 men and women.88 In a 10 month study of older adults, Kohut and colleagues found that thrice weekly aerobic training, but not thrice weekly flexibility training, reduced IL-6 levels in 87 men and women.89

Less data is available on the association between physical activity and PGE-2 but given the hypothesized role in inflammatory-related colon cancer pathways noted above and the association broadly seen for physical activity and inflammation, it merits further investigation. In addition, while IL-6 is produced by visceral adipocytes, PGE-2 represents a mechanistic pathway independent of weight.

Based on the above studies, we will measure PGE-2, insulin, C-peptide and IL-6.

**A.4. Interventions to prevent colon cancer.** Numerous randomized controlled trials of lifestyle risk factors for colon cancer prevention have been conducted in recent years, but all have focused on dietary changes or taking supplements with one exception.45, 90-92 That study randomized participants to a 12 month moderate to vigorous aerobic exercise program or delayed two-month intervention and examined changes in colon cell architecture and proliferation.93, 94 Given the wealth of observational data demonstrating the large risk reductions that can occur with participation in physical activity, it is surprising that more randomized controlled trials of colon cancer prevention have not been conducted.

There is a lack of interdisciplinary research that combines theoretically driven behavior change interventions and etiologically relevant endpoints in a rigorous randomized controlled trial design for colon cancer prevention or risk reduction. This study improves on previous work by measuring PA and biomarkers. The lack of focus in the existing literature on physiologic parameters in physical activity studies, and the lack of quality interdisciplinary research, is a weakness of the existing literature. Our study is innovative and important in its ability address these multiple levels of outcomes.

**A.5.Measuring physical activity.** Despite walking being the most commonly reported physical activity,23, 24 recall of walking presents numerous challenges, including recall of occurrences, speed, and/or intensity.95-97 Thus, objective measurement tools that can detect gradations in walking behavior are useful physical activity measures.

Pedometers are easy to use, relatively low cost, reliable and accurate.98 Pedometers capture the vertical accelerations associated with normal ambulation and thus, measure the total number of steps taken over a given period of time (i.e. day, week). Most studies suggest that pedometers have acceptable validity when compared to more comprehensive objective measurement devices like accelerometers, particularly when measurement is focused on walking behaviors.99, 100

The combination of the high frequency of walking as a physical activity and their comparatively low cost makes pedometers well suited for population-based research. In addition, pedometers are non-invasive, low burden tools that are socially acceptable and practical in-vivo measures of physical activity.

**A.5.a. Average Daily Pedometer Step Counts:** A review of 32 observational and intervention studies suggests that daily step counts range from: (1) 7-13,000 steps per day for healthy younger adults; (2) 6-8,500 steps per day for healthy older adults; and (3) 3,500-5,000 steps per day for sedentary individuals and those with disabilities of chronic illness.101 Recent research has attempted to derive a step count recommendation associated with a 30-minute interval of activity (the current American College of Sports Medicine (ACSM) physical activity recommendation for moderate intensity physical activity5). These studies have yielded varying results, but have suggested step counts in the range of 3000- 4000 steps are accumulated during 30-minutes of walking.102, 103

**A.5.b. Use of Pedometers as Health Promotion Tools:** Evidence is emerging that pedometers, in particular, are effective physical activity promotion tools as they can provide immediate feedback in the form of step counts, thereby facilitating individual-level behavior modification.102, 104-106 For example, a study by Croteau found that a minimal contact, self-managed, pedometer-based intervention resulted in a significant increase in the average daily steps of participants from 8565 (+/- 3121) to 10538 (+/- 3681) at follow-up in 37 men and women.105

**A.5.c. The 10,000 Steps Per Day Goal:** For pedometers to be successfully implemented in physical activity promotion interventions, they must be paired with clear and empirically-meaningful step count recommendations. The 10,000 steps per day recommendation has become increasingly popular with the public, media, and interested corporations (including recent marketing efforts by McDonald’s and Kellogg cereals).107 Existing pedometer-based physical activity promotion studies have also adopted this intervention message. While there has been empirical support for the 10,000 steps per day goal in clinical and monitored populations,101, 108, 109 the goal may initially be too ambitious for sedentary and older adult populations, who may take as few as 3,500 – 5,500 steps per day.101 A 10,000 steps per day goal for these individuals then, amounts to a two- to three-fold increase in daily physical activity – a recommendation that is very likely to promote attrition.110 Given that there is some evidence to suggest that a single 10,000 steps per day goal may in fact be an ineffective physical activity promotion strategy, particularly among the largely sedentary populations who could benefit most from increases in their physical activity patterns, interventions that employ stepwise physical activity goals and incorporate other ways of promoting physical activity in addition to step count recommendations may be most effective.

1. **SPECIFIC AIMS**

To design and evaluate the feasibility of a pilot version of a colon cancer prevention intervention focused on walking. Individuals (n=20) with a polyp found on screening colonoscopy in the last six months (i.e., a colonoscopy to detect polyps or adenocarcinoma) will be enrolled and randomized to an evidence-based intervention recommending one of two physical activity recommendations (30 or 60 minutes). Participants in both conditions will receive the First Step intervention, which has previously been tested and found to be efficacious for increasing physical activity in clinical populations. First Step recommends walking most days of the week using a daily step count goal to monitor and motivate behavior change.111, 112 Outcomes will be measured at one month and three months post baseline. We anticipate larger changes in the primary outcomes in the Plus group than the standard intervention group.

Primary Outcomes: Blood levels of insulin, C-peptide, IL-6, and PGE-2

Secondary Outcome: Change in physical activity level as measured by blinded pedometer.

The specific aims are:

**Primary Aim:** To conduct a dose response pilot trial of low (30 min/day) or high (60 min/day) dose exercise in men and women at increased risk of colon cancer. The major outcomes are changes in serum levels of four risk-related biomarkers: insulin, C-peptide, IL-6 and PGE-2.

 Hypothesis 1: Exercise will decrease serum markers in a dose response manner.

**Secondary Aim.** To compare changes in the secondary outcome of physical activity over three months.

Hypothesis 2: Participants in the 60 minute intervention will have significantly higher physical activity levels than those in the 30 minute intervention at three months.

1. **RESEARCH DESIGN AND METHODS**

**C.1. Overview of research design and study.** The overall objective of this study is to compare two doses of physical activity delivered through existing walking intervention paradigm in 20 individuals at increased risk for colon cancer and evaluate the dose of activity necessary to change colon cancer risk related serum biomarkers. This 12-week two-arm randomized controlled trial will administer the First Plus walking program prescribing two different doses (30 minutes vs 60 minutes) of physical activity.111, 112 This study builds on previous physical activity interventions with cancer outcomes where 12 week interventions are common.113-118 The subjects in the study will be recruited from the gastroenterology practice at Barnes Jewish Hospital / Washington University School of Medicine (BJH/WUSM). The gastroenterology practice sees approximately 4000 patients per year for colonoscopy. Of these, half present for screening or surveillance procedures and approximately 20% of these present with adenomatous polyps. The patients are representative of the larger patient population at BJH/WUSM, with half being female and one third African American. Children are not screened for colon cancer and are thus not included in this study. The study will be coordinated and intervention delivered by Cindi Inman, MS, RD, LD and overseen by Dr. Wolin. Ms. Inman has a master’s degree in exercise physiology and extensive experience managing health promotion research studies. Angela Tanner will assist with data collection and management under Dr. Wolin’s supervision. A study schema (Figure 2) is provided below.

Eligibility screening

Blinded pedometer protocol & accelerometer protocol (n=20)

Baseline assessment

* Fasting blood draw (insulin, C-peptide, IL-6, PGE-2)
* Height and weight
* PPAQ
* Social support
* Self efficacy
* Safety
* IPAPS
* HINTS benefits of physical activity
* Social norms
* Sociodemographics (age, race/ethnicity, gender, education, occupation, income)
* Cancer risk factors (family history, tobacco, hormones, diet)

Phase I assessment:

Baseline assessment minus sociodemographic and cancer risk factor questions

**PLUS**

Pedometer & accelerometer data download

Phase I assessment:

Baseline assessment minus sociodemographic and cancer risk factor questions

**PLUS**

Pedometer & accelerometer data download

randomization

60 minute dose

(n=10)

30 minute dose

(n=10)

Week 12

Week 5

Pedometer data download

**Figure 2. STUDY SCHEMA**

Week 10

**C.2. Recruitment**

**C.2.a. Screening procedures.** The first 20 interested and eligible patients will be enrolled. To identify patients, staff in the BJH/WUSM gastroenterology practice have agreed to review practice records to identify individuals meeting eligibility criteria (see below). These individuals will be sent a letter from their gastroenterologist inviting them to participate in Dr. Wolin’s study. Individuals may contact study staff to opt out of the study. Individuals who do not contact study staff to opt out will be contacted by the Recruitment Enhancement Core (REC) of the ICTS to invite them to participate and determine eligibility.

REC staff will screen interested individuals for a history of cancer, diagnosis of familial polyposis syndromes, ulcerative colitis, Crohn’s Disease and medical indications that counter-indicate exercise. Participants will answer a brief questionnaire (based on the BRFSS) to determine current physical activity levels and participants’ current use of NSAIDs. Staff will explain the overall study design to eligible individuals. Specifically, potential participants will be told that the study is a randomized behavior change intervention for colon cancer recurrence where that participants will be assigned by chance to one of two physical activity interventions. Staff will detail the length of the study and that participants may be required to do any or all of the following: (1) attend a thirty- to sixty-minute behavior change sessions at the BJH/WUSM once a week for a month, (2) answer weekly telephone-based questionnaires, (3) complete evaluations at BJH/WUSM every four to for three months, including an evaluation at the study end.

Participants will be made aware that by enrolling in the study they may be subject to an in person health evaluation and that all participants must return to BJH/WUSM in three months to complete additional assessments.

**C.2.b. Eligibility.** Eligibility is based on the following criteria: (1) aged 50 to 80; (2) no personal cancer history; (3) found to have an adenomatous polyp upon colonoscopy at BJH/WUSM in the previous six months; (4) no contraindications to beginning an exercise program; (5) no previous diagnosis of familial polyposis syndromes; (6) no previous diagnosis of ulcerative colitis or Crohn’s disease;

**Additional Exclusion Criterion: NSAID use.** Participants who are regular NSAID users will be excluded as this may interfere with the measurement of inflammatory marker outcomes. Regular use is defined as taking 80mg or more per day of aspirin, ibuprofen, naproxen or other NSAID 5 or more days of the week.

**Additional Inclusion Criterion: Sedentary.** Individuals who report 30 or more minutes of moderate intensity physical activity five or more days per week or 20 or more minutes of vigorous intensity physical activity three or more days per week will be considered physically active and thus, ineligible. Participants will be administered the Behavioral Risk Factor Surveillance System (BRFSS) physical activity questionnaire as it is a brief screening tool useful for this purpose. This instrument asks participants to report on physical activity of at least moderate intensity performed in bouts of at least 10 minutes during the previous week. Individuals who report having been diagnosed with Type 1 or Type II diabetes will be included.

**C.3. Measures**

**C.3.a. Objective physical activity measurement.** Within two weeks of their baseline assessment all participants will come in to complete the consent and be fitted with a blinded pedometer with instructions on placement and wear. Participants will be instructed to wear the device for the 7 days prior to their baseline visit. All pedometers will be blinded to minimize behavior change in response to the assessment. Logs will be collected at the baseline visit. Log data will be used to determine days and hours of wear. At the baseline visit, pedometers will be collected and data will be downloaded to the study computer and processed using manufacturer software. Participants will also be provided with an accelerometer during this period for assessment of total physical activity levels. Participants will also provide objective physical activity data at follow-up as outlined below.

**C.3.a.1 Pedometer.** We will use the Omron HJ 720IT pedometer in this study. This pedometer displays seven days of step count data (when not blinded and sealed), but can store up to 41 days of step count data in the memory for later download. Research has suggested that the Omron pedometer technology may have superior accuracy among elderly and obese individuals.119, 120 Given the high prevalence of obesity in the general population121 and the age range of our eligibility criteria, we believe it is prudent to use the Omron device. Participants will complete logs and record daily hours of wear.

**C.3.a.2. Accelerometer.** We will use the Actigraph brand accelerometer in this study. The accelerometer will allow us to estimate the participants’ total physical activity level including minutes of moderate or vigorous intensity physical activity as well as a summary indicator of physical activity that accounts for both intensity and duration, expressed as metabolic equivalent (MET) minutes per week. Finally, it will allow us to estimate the participants’ energy expenditure.

Accelerometers are generally recognized as a “gold-standard” approach for the objective measurement of physical activity. Accelerometers record the g-forces common to movement and translate them into data that reflect the frequency and intensity of movement, sampled at set intervals. With accelerometry the duration time spent at defined intensities of activity can be determined, which allows for the more valid assessment of physical activity. In interventions of physical activity behavior change, accelerometers provide the most valid estimates of change in energy expenditure.

**C.3.b. Physiologic assessment.** At the baseline and follow-up visit, all participants will undergo a fasting blood draw. Staff will also measure participants’ weight and height.

**C.3.b.1. Serum marker measurement.** Blood will be collected after a 12 hour fast. Participants will also be instructed not to consume alcohol for 18 hours prior to the blood draw or take NSAIDs for 24 hours prior to blood draw. Because daily physical activity is part of the intervention message, participants will not be asked to terminate physical activity, but limit it. Specifically, participants will be asked not to participate in vigorous physical activity for 12 hours prior to the blood draw and not to participate in any moderate or vigorous intensity physical activity for three hours prior to the blood draw.

The Center for Clinical Studies (CCS) will oversee the physiologic assessment, including sample collection, processing, and storage. Samples will be processed in order to allow subsequent analysis of levels of insulin, C-peptide, IL-6 and PGE-2. Blood will be processed and stored as serum, EDTA plasma, and red blood cells. Each participant’s baseline and follow-up blood samples will be assayed in the same batch. In addition, an equal number of samples from each study arm will be included in each batch.

**C.3.b.2. Body composition assessment.** Body weight and height will be measured in duplicate using a digital scale and tape measure constructed specifically for research quality measures. We will also measure waist and hip circumference.

**C.3.c. Questionnaire.** Following the physiologic assessment and pedometer return, participants will be provided a questionnaire that includes physical activity, potential confounder and sociodemographic information. Measures are summarized in Table 2 and are described in detail below.

**C.3.c.1. Self-reported physical activity.** As a supplement to the step count data, participants will complete a physical activity questionnaire. We will use the Paffenbarger Physical Activity Questionnaire (PPAQ) which assesses moderate and vigorous intensity physical activity with distinct items to measure walking.95, 122 The PPAQ also allows measurement of both leisure time only and total (leisure time plus occupational and transport) physical activity. This validated instrument was selected because it provides an assessment of total physical activity while also employing several detailed walking items. The information in the PPAQ supplements that provided by the accelerometer and pedometer by providing information about context/domain of physical activity.

**C.3.c.2. Modifying mechanisms.** We will also collect information related to the intervention constructs using validated published scales whenever possible. Self-efficacy for physical activity will be measured using the Exercise Confidence Survey.123 Social support for physical activity will be measured using the Sallis Social Support Scale.124

|  |  |  |
| --- | --- | --- |
| **Table 2. Survey measures** |   |   |
| **Construct** | **Measure** | **Baseline** | **Follow up** |
| Self-reported physical activity | Paffenbarger Questionnaire | X | x |
| Sociodemographic | Age | X |  |
|  | Marital Status | x |  |
|  | Race/ethnicity  | X |  |
|  | Gender | X |  |
|  | Education | X |  |
|  | Income | X |  |
|  | Occupation | X |  |
|  | Immigrant status | X |  |
| Other cancer risk factors | Family history of colorectal cancer | X | x |
|  | Current and past tobacco use | X | x |
|  | Hormone use (women only) | X | x |
|  | Diet (Willett Questionnaire) | X | x |
| Self efficacy | Exercise Confidence Survey | X | x |
| Social support | Sallis Social Support Scale | X | x |
| Neighborhood safety | Day/Night; Home/work | X | x |
| Benefits of physical activity | HINTS questions | X | x |
| Neighborhood walkability and access | IPAPS self administered module  | X | X |
| Length of residence |  | X |  |
| Perceived neighborhood disorder |  | X | X |
| Depression | CES-D | X | X |
| Perceived Stress |  | X | X |
| Coping strategies | Brief COPE | X | X |
| Urban life stress | Urban Life Stress Scale | X | X |

**C.3.c.3. Other factors potentially related to physical activity**. We will measure the perceived benefits of physical activity using the HINTS survey items.125 This instrument asks participants: (1) As far as you know, does physical activity or exercise increase the chances of getting some types of cancer, decrease the chances of getting some types of cancer, or does it not make much difference? (2) Can exercise help to lower the chances of getting some types of cancer or does exercise not make much difference? We will also administer the International Physical Activity Prevalence Study environmental module which queries participants about their neighborhood and its walkability as well as access to physical activity and recreation facilities. We will assess perceived neighborhood safety by asking participants, “how safe is the neighborhood you live in during the daytime?” We will also ask about the safety of the neighborhood they live in at night and the neighborhood they work in. Response options will be “safe”, “a little unsafe” and “not at all safe”. In previous work by the research team, these questions were associated with daily step count.126 Additional items on stress 127-131, neighborhood environment 132, 133, depression134, and coping mechanisms135 will also be included on the questionnaire.

**C.3.c.3. Other measures.** The baseline and follow-up questionnaires will also query sociodemographic variables (age, race/ethnicity, gender, education, household income, current occupation), family history of colon cancer, current and past tobacco use, diet and supplement use (using the Willett food frequency questionnaire) and use of hormones (in women).

**C.4. Randomization.** Following the baseline assessment, study staff will assign participants to an intervention condition using a random numbers program. An equal number of individuals will be assigned to each condition (10 low dose, 10 high dose). Staff doing the randomization will not participate in the eligibility screening or baseline assessment and will not have access to information about participants.

**C.5. Intervention.** Following the baseline assessment, participants will be randomly assigned to one of two doses of physical activity delivered through the First Step program.

**C.5.a. First Step Program.** The First Step Program (also published as Manpo-Kei111) is a theoretically-based two phase intervention that aims to promote adoption of physical activity, specifically walking, and adherence to the newly adopted behavior.112 The program draws on social cognitive theory and the Transtheoretical Model of behavior change. The first phase lasts one month and is comprised of four weekly facilitated group meetings. The group meeting covers individual progress reports, brief group walk of increasing duration, group strategy discussion, and individual goal setting for the following week. Participants use pedometers and logs to monitor their progress. Between the weekly sessions, participants wear pedometers to monitor their daily steps. Participants log their goals and daily step counts. The program addresses self-efficacy, outcome expectations and social support in line with social cognitive theory and moves participants through the phases (precontemplation, contemplation, preparation, action and maintenance) of the Transtheoretical Model. In the second phase, lasting eight weeks, participants receive weekly phone contact. The First Step Program aims to progress participants to a steps per day goal. The First Step Program has successfully increased physical activity in several diabetic patient populations.136, 137 The First Step Program has resulted in significant changes in waist girth.137, 138 Studies have found mixed results for changes in weight.137, 138 Changes have not been seen for waist to hip ratio137, or insulin.136.

**C.5.b. Dose.** To date, the First Step Program has administered a single dose recommendation of 30 minutes of walking and 10,000 steps per day. This is in line with the current federal physical activity guidelines for health.6 Research in colon cancer survivors suggests that 60 minutes of physical activity is needed to prevent recurrence and improve survival. This is also the amount of activity indicated as necessary to maintain a healthy weight. Thus, we will compare the First Step Program as previously delivered in diabetics, with a modified version that delivers a higher dose of physical activity (60 minutes of walking, 13,000 steps per day).

**C.6. Intervention evaluation and outcome measurement**

**C.6.a. Objective physical activity.** One week prior to the conclusion of the study, participants will come into receive a blinded sealed pedometer to wear for seven days. Participants will again be given an Actigraph device to wear for seven days. At the end of the seven day period, all participants will return to Washington University for their study conclusion evaluation visit. Data from the devices will be processed as at the baseline visit. Participants will complete a questionnaire and undergo a final physiologic examination and blood draw.

**C.6.b. Physiologic measures.** Participants will undergo physiologic measurement identical to baseline at the end of the study. We will measure height and weight, as well as insulin, C-peptide, IL-6 and PGE-2 levels. Blood will be processed and stored as serum, EDTA plasma, and red blood cells.

**C.6.c. Questionnaire.** Following the physiologic assessment and pedometer return, participants will be provided a questionnaire identical to that used at baseline that includes items querying physical activity, potential confounder and sociodemographic information.

**C.7. Incentives.** All study participants will receive $50 each for completing the baseline assessment as well as $50 for attending the 3 month (study end) visit. Participants will also be allowed to keep their study pedometers.

**C.8. Retention strategies.** To ensure high retention rates of study participants, we will employ several strategies including providing detailed information on risks associated with study participation to build trust, accessing participant information through their physician to help reinforce the clinical support for the study program, and the use of incentives. In addition, at enrollment we will collect multiple sources of contact information from participants including home, work and mobile phone numbers as well as email addresses where available. We will also request the name and contact information for a friend or family member who can be contacted in the event the participant relocates. Our regular phone contact will help participants feel connected to and invested in the study.

**C.9. Sample size and power considerations for primary outcomes.** Schmitz et al found baseline insulin in the control group to be 4.46 (+/- 0.59) uU/ml and in intervention subjects to be 5.18 (+/- 0.54) uU/ml in an exercise study.67 Over 39 weeks of exercise intervention, insulin increased an average of 1.16 uU/ml in the control group and 0.05 uU/ml in the intervention group, for a net intervention effect of 1.1 uU/ml. Using this data, the sample size to achieve 85% power for the primary comparison of insulin change over 12 months between the intervention and control groups using a Bonferroni correction with two-sided 0.05/2 = 0.025 and an estimated correlation over 39 weeks for insulin of 0.5 is n = 2σ2change (Z0.9875 + Z0.85)2/ Δ2

where σ2change = 2 σ2baseline (1 – ρ) = 123.63, σ2baseline = 0.592, ρ = 0.5, Z0.9875 = 2.24, Z0.85 = 1.035, and Δ = 1.1 This yields a sample size of 6 subjects per group.

The estimates of change for insulin are comparable to the difference between the highest and lowest quintiles of physical activity in the Nurses’ Health Study (difference = 1.37 μU/ml) and the Health Professionals’ Follow-up Study (difference = 2.4 μU/ml).68 The difference in C-peptide between highest and lowest quintile of physical activity among women in the Nurses’ Health Study was 0.44 ng/mL. The mean level at baseline was 1.92 +/- 0.91 ng/mL. In the Health Professionals Follow-up Study, the within person correlation for C-peptide over four years was 0.57. This yields a sample size of 79 subjects per group. We can assume the within person correlation over one year is higher. If the correlation rises to 0.73, the sample size is 50 subjects per group.

In a 12-week exercise study of lean men, Dekker et al reported a mean IL-6 level of 2.8 +/- 0.6 pg/mL at baseline and of 1.9 pg/mL at study end for a mean change of 0.9 pg/mL.87 Assuming a correlation of 0.85, this yields a sample size of 3 subjects per group. If the correlation drops to 0.5, the sample size increases to 10 subjects per group.

Thus, based on our estimates, we estimate that 20 subjects per group is sufficient to detect differences in several of our outcomes, but not all. 50 subjects per group will provide sufficient power to detect differences in all our markers. However, as this is a pilot project we are not concerned with obtaining sufficient power in our outcomes and we will enroll 20 subjects (10 per group). We realize that participant drop out may prohibit our ability to detect differences in some outcomes, but as noted above, **this is a pilot feasibility study**.

**C.11. Data analysis**.

**C.11.a. Primary Aim:** To conduct a dose response pilot trial of low (30 min/day) or high (60 min/day) dose exercise in men and women at increased risk of colon cancer. The major outcomes are changes in serum levels of four risk-related biomarkers: insulin, C-peptide, IL-6 and PGE-2.

Hypothesis 1.1: First we will evaluate randomization success by comparing the two intervention groups on demographic and health factors. We will then evaluate intervention effects by differences in biomarker levels at study end between intervention groups using linear regression. We will compare differences in mean change in each of the biomarkers from baseline to three months between intervention groups. The analysis is based on change over three months using mixed effects regression models with PROC MIXED of SAS. The model is:

 Yit = α + β1t + β2Xi1 + β3Xi1t + β4tYi0 + eit

 where Yit = biomarker for subject i at time t, where t = 0 for baseline, t = 1 for 3 months.

 Xi1 = 1 if ith subject is in the Plus intervention group, = 0 otherwise; eit ~ N(0, σ2)

Of primary interest is β3 = mean difference in biomarker level change between intervention groups. The coefficient β2 allows for mean differences in level between groups at baseline. The coefficient β4 allows the change in biomarker to depend on initial level. We will conduct unadjusted analyses because of the randomization design but will also examine the effects of adjusting for sociodemographic factors, and family history of colon cancer. We will conduct outcome analyses based on assigned treatment at randomization regardless of adherence (intent to treat analysis). Throughout our analyses missing data will be imputed.139

**C.11.b. Secondary Aim: To compare changes in the secondary outcome of physical activity over three months.**

Hypothesis 2.1: We will evaluate the intervention effectiveness at changing physical activity levels by comparing change in average step count recorded on blinded pedometers from baseline to follow up between the intervention groups. Mixed effects regression will be used to account for the longitudinal design. The outcome variable will be the average steps per day for the measurement period. The measurement period at baseline and follow-up is the seven day period participants were required to wear the blinded pedometer. Only days where the participant wore the pedometer for at least eight hours will be counted and the average will be based on the number of full days of wear. The analysis is based on change using mixed effects regression models similar to that outlined in Aim 1. We will also examine the percentage of intervention participants meeting the 10,000 and 13,000 steps per day goals at the study conclusion based on data recorded on the pedometer. We will use the last seven days of the phase. We will also examine the percent of participants adhering to their study arm prescription (defined as completing 90% of required physical activity) at three months. We will examine whether sociodemographic factors, overall physical activity level, or family history of colon cancer are associated with meeting the intervention step count requirement. Finally, we will examine whether the intervention changed total physical activity levels by comparing baseline and follow-up total physical activity levels (as measured by the PPAQ) in the intervention groups and by comparing change in those levels between the intervention groups using the general estimating equation modification to linear regression.

**D. Data Safety and Monitoring**

Participants will be identified in data records by a study ID code to protect data. Identifiable information will be kept separate from study data and will be locked in a study file cabinet. Electronic files will not contain identifiable participant information. Identifiable information will be destroyed at the end of the study.

All investigator-level staff members have completed the NIH human subject’s certification as required. All study field staff, investigators, and others involved with participants and/or data collection and handling will have completed the NIH human subjects’ certification as required. Human subjects concerns will be a standard agenda item for project meetings. We will participate in a standard continuing review process. All adverse events reported to study staff or investigators will be discussed by the investigators. Investigators will evaluate the potential risk to other participants.

The principal investigator will review all patient data at least every six months, and provide a semi-annual report to the QASM Committee. This report will include

1. the protocol title, IRB protocol number, and the activation date of the study.
2. the number of patients enrolled to date
3. the date of first and most recent patient enrollment
4. a summary of all adverse events regardless of grade and attribution
5. a response evaluation for evaluable patients
6. a summary of any recent literature that may affect the ethics of the study.

The study principal investigator and study coordinator will monitor for toxicities/adverse events on an ongoing basis. Once the principal investigator or study coordinator becomes aware of a serious adverse event, the SAE will be reported to the HRPO and QASM Committee within 10 working days.

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