The Breast Cancer and Exercise Trial in Alberta (The BETA Trial)

Study Protocol NCT01435005

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Table of Contents

1 STUDY TITLE

The Breast Cancer and Exercise Trial in Alberta (BETA).

2 FUNDING INFORMATION

The BETA Trial is funded by the Alberta Cancer Foundation. The original grant was submitted to the Alberta Cancer Research Institute (ACRI) in November, 2008. The grant was awarded in January 2009 for $1.6 million over three years (2010-2013) and funds were requested to be released in March 2010 because of delays that occurred with the restructuring of the health regions in Alberta that occurred in April 2009. All funding is attributed to the Alberta Cancer Foundation after the restructuring of the health care regions that occurred in 2009.

3 STUDY OVERVIEW

The BETA Trial is a two-centered, two-armed randomized control exercise intervention trial conducted in Calgary and Edmonton, Alberta, Canada that includes 400 participants. The study protocol was approved by the Alberta Cancer Research Ethics Committee and the Conjoint Health Research Ethics Board of the University of Calgary and the Health Research Ethics Board of the University of Alberta.

4 OBJECTIVES

The primary aim is to compare the effects of high versus moderate volumes of aerobic exercise on specific hormonal and biological intermediate endpoints for breast cancer in a group of previously sedentary, postmenopausal women.

The primary objectives are:

- To compare the effects of these different exercise interventions on obesity levels (body mass index, percent body fat, intra-abdominal fat, subcutaneous fat) and markers of insulin resistance and obesity (insulin, glucose, leptin, adiponectin) risk factors for which there is either strong or probable evidence for an association with breast cancer, and biologic plausibility that exercise influences these mechanisms.
- To compare the effects of these different exercise interventions on sex hormone levels (estrone, estradiol, testosterone, androstenedione, SHBG) risk factors for which there is moderate evidence of an association with breast cancer and biological plausibility that exercise influences these mechanisms.

- To compare the effects of these exercise interventions on inflammatory markers (IL-6, TNF-α, CRP), biomarkers for which there is a hypothesized role in the association with breast cancer risk and biological plausibility that exercise influences these mechanisms.

The secondary aim is to evaluate the impact of the high versus moderate volumes of aerobic exercise among postmenopausal, sedentary women on psychosocial factors.

The secondary objectives are:

- To compare the effects of these exercise interventions on quality of life.
- To compare the effects of the exercise interventions on perceived stress, happiness and satisfaction with life.
- To compare the effects of the exercise interventions on sleep quality.
- To compare the effects of the exercise interventions on sedentary sitting time.
- To describe the rates and determinants of recruitment and adherence in the trial.

5 BACKGROUND

Breast cancer is a significant health risk for women in North America, particularly after age 50. Canadian women have a 1-in-9 lifetime probability of developing breast cancer [1] and in the U.S. this estimate is 1-in-8 [2]. Inadequate physical activity is a probable risk factor for postmenopausal breast cancer [3] and is one of the few known risk factors that is modifiable. Recent estimates suggest that physical inactivity accounts for nearly 20% of all postmenopausal breast cancer cases in Canada [4] and about 10% of all breast cancer cases internationally [5]. On average women with higher activity levels experience a 10-25% lower risk of breast cancer than other women [6, 7]. In postmenopausal women the hypothesized biologic mechanisms underlying the association are not well understood but might involve multiple, interrelated pathways relating to sex hormones, insulin resistance, low-grade chronic inflammation, adipokines and other factors [8] with body fat partially mediating some of these effects [9-12]. As the preventive effects of physical activity become increasingly clear, questions remain surrounding the optimal *dose* of activity that is required to reduce postmenopausal breast cancer risk.

In North America and worldwide, guidelines on physical activity and cancer prevention vary between public health agencies. With respect to aerobic activity, recommendations for adults include:

- a minimum of 150 minutes/week of moderate- or 75 minutes of vigorous-intensity activity [13, 14];
- 150 minutes/week of moderate-vigorous activity [15, 16]; and
- 210 minutes/week of moderate activity [3].

As fitness levels improve, some agencies further recommend:

- 300 [13, 14] or 420 [3] minutes/week of at least moderate activity; or

- 150 [13] or 210 [3] minutes/week of vigorous activity.

In addition, muscle-strengthening exercise [13, 15] and limiting sedentary behaviour [3, 14] are advised. However it remains unproven - and even doubtful [17] - that all of these current recommendations are sufficient for lowering postmenopausal breast cancer risk. These guidelines were based partly on findings from observational studies of physical activity and overall cancer risk. With respect to breast cancer risk specifically, inverse dose-response relations with minutes/week of physical activity have been shown in pooled [18] and meta-analyses [7] of case-control and/or cohort studies. However, observational studies alone cannot inform public health guidelines due to their inherent limitations (e.g., inconsistent definitions of physical activity, physical activity measurement error, and possible confounding by other factors). A more definitive understanding of the dose-response relation can be gained using a randomized controlled trial (RCT) study design.

In the Alberta Physical Activity and Breast Cancer Prevention (ALPHA) Trial [19], we examined how a 12-month aerobic exercise prescription, compared with a usual inactive lifestyle, influenced hypothesized biologic mechanisms for breast cancer risk in 320 postmenopausal women in Alberta, Canada. The exercise group was prescribed 225 minutes/week of moderate-vigorous physical activity, five days a week, with at least half of each workout reaching 70-80% heart rate reserve. Among women assigned to the exercise arm (n=160), we observed a strong effect of exercise on the main proposed biomarkers of interest that included an effect on endogenous estrogens, insulin resistance, inflammation and body composition [19-22]. In addition, we observed favorable dose-response relations across subgroups of exercise adherence (minutes/week) with respect to 12-month changes in body weight, total body fat, and intra-abdominal fat area [20], circulating free estradiol and sex hormone-binding globulin (SHBG) levels [19], insulin and the homeostasis model assessment of insulin resistance (HOMA-IR), leptin, adiponectin:leptin [21] and high sensitivity C-reactive protein (CRP), with the strongest changes occurring when exercise exceeded 150 or 225 minutes/week. Dose-response relations were not found for androgens [19], tumor necrosis factor-alpha (TNF-α) or interleukin-6 (IL-6) [22]. Furthermore, greater improvements in quality of life variables were observed with exercise duration over 150 minutes/week (p-trend < 0.05 for seven of eight quality of life variables) [23]. Two comparable trials in postmenopausal women [10, 24] observed similar effects of an exercise intervention on hypothesized breast cancer biomarkers as well as some suggestion of a dose-response effect with stronger improvements in some biomarkers when exercise exceeded 195 minutes/week [24-26] or 130 minutes/week [12, 27] but not with others [10, 11, 28, 29]. Yet all of these findings are limited for informing breast cancer prevention guidelines due to the non-randomized, exploratory nature of the analyses (participants within the exercise arm self-selected to adherence levels) and lower statistical power for detecting significant differences in biomarker changes across strata of exercise adherence.

Other RCTs have been designed and statistically powered to compare changes across increasing durations of exercise [30-38] such as the Dose-Response to Exercise in Women (DREW) trial in over 450 postmenopausal women [33, 39-41]. The DREW trial showed favourable dose-response trends across moderate-intensity (50% VO_{2max}) exercise durations of approximately 75, 140, and 190 minutes/week and quality of life variables [41] and also weight loss [40], but not for change in waist circumference [40] or CRP levels [39]. While studies like the DREW trial

provide more convincing evidence of dose-response relations, the exercise prescriptions did not target primary cancer prevention, few breast cancer biomarkers were examined, and only some of the trials [30, 31, 33, 34] studied postmenopausal women exclusively.

Evolving from the ALPHA Trial, the Breast Cancer and Exercise Trial in Alberta (BETA) Trial will be conducted in Alberta, Canada between 2010 and 2014. The primary objective is to compare the effects of a high versus moderate volume of aerobic exercise on proposed biologic intermediate endpoints for breast cancer in previously inactive, postmenopausal women. We hypothesize that 300 minutes/week of moderate to vigorous intensity aerobic exercise will induce stronger changes in proposed breast cancer biomarker levels than would 150 minutes/week, the minimum weekly volume that is currently recommended for cancer prevention. Our specific hypotheses are that the higher volume exercise intervention will decrease adiposity levels (body mass index (BMI) (weight (kg)/height (m^2)), percent body fat, subcutaneous and intra-abdominal fat) and circulating levels of endogenous estrogens (estradiol, estrone, SHBG), insulin resistance indicators (insulin, glucose, leptin, adiponectin), and inflammatory markers (TNF-α, IL-6, high sensitivity CRP) in a dose-response manner compared to the moderate volume exercise intervention. Secondary aims are to evaluate the impact of the intervention on quality of life, perceived stress, happiness, satisfaction with life, sleep quality, and exercise adherence. Although we [23, 42, 43] and others [44-46] have assessed these secondary outcomes in previous exercise trials, very few [41, 47] were designed to identify dose-response effects. The primary intent of the BETA Trial is to determine whether a higher volume of aerobic exercise is likely to provide further reductions in breast cancer risk compared to the current moderate volume recommendations. Such information will inform public health guidelines addressing how to lower postmenopausal breast cancer risk through physical activity.

6 STUDY POPULATION

6.1 Inclusion and Exclusion Criteria

All eligibility criteria are outlined in Table 1, below.

Women are eligible for this trial if they:

- Are 50-74 years of age.
- Are postmenopausal.
- Had no previous cancer diagnosis (except for non-melanoma skin cancer) or other major co-morbid condition (e.g. diabetes, cardiovascular disease, arthritis, emphysema) or had recently undergone major reconstructive surgery.
- Are sufficiently physically fit to be able to participate in the exercise program and able to maintain acceptable heart and lung function during a sub-maximal treadmill test.
- Have a BMI between 22 and 40.
- Are moderately inactive as determined by the baseline physical activity and fitness assessments.
- Have no external factors influencing estrogen metabolism, i.e., were non-users of exogenous hormones or drugs related to estrogen metabolism and breast tissue growth.

- Are non-smokers.
- Do not consume more than two drinks of alcohol/day.
- Are English-speaking and able to complete questionnaires and follow instructions in English.
- Are residents of Calgary or Edmonton and able to attend the fitness facility regularly.
- Are not intending to be away for more than four weeks consecutively and eight weeks in total during the year of intervention.
- Are not currently on a weight loss program or planning to start one.

6.2 Study Recruitment

A number of strategies will be used to recruit participants for this study.

- The primary method of recruitment will be through the Calgary and Edmonton centers of *Screen Test*, the Alberta Breast Cancer Screening Program. This method was chosen because it provided access to an appropriate study population that is similar in education and ethnicity to women of the same age in the general Alberta population and had been used successfully previously in the ALPHA Trial [20]. All women in the Screen Test database who are between the ages of 50-74, living in Calgary and Edmonton and have attended Screen Test for a mammogram within the previous two years, from 2008 to 2010, will be sent letters of invitation directly from the Screen Test Chief Radiologist. Using Screen Test is advantageous because the invitation is endorsed by an authorized custodian of their information and comes from an organization in which they already had an established relationship. These letters of invitation will be followed up with individual phone calls to determine eligibility and to invite interested individuals to an information session. Up to six phone calls will be made to each selected Screen Test participant.

- Additional participant recruitment will be done through media campaigns conducted in both cities twice during the trial.

- Recruitment will also be done in collaboration with physicians who are members of the Alberta Family Physicians Research Practice Network and who agree to display study materials in their offices and clinics.

All women who are invited or contacted by our study centers will undergo preliminary screening for eligibility (using the Participant Eligibility Questionnaire; see Table 1) by telephone. Women who remained eligible and interested will be invited to attend an information session at either the Tom Baker Cancer Center in Calgary or the University of Alberta in Edmonton. At the information session, the study rationale, methods, intervention and follow-up will be explained in detail and the roles and responsibilities of the study participants will be clearly outlined. If these women remain interested in the study, informed consent will be obtained and baseline questionnaires will be completed at the information session.

Table 1. Participant eligibility criteria and assessment methods in the BETA Trial, Alberta, Canada

Reason for criterion	Assessment methods	Timing of assessment
Appropriate target group for breast cancer risk reduction		
Female	*Screen Test*[1] database	Before contacting participant/immediately upon contact
Age 50-74 years at baseline	*Screen Test* database or PEQ[2]	Before contacting participant
Postmenopausal	PEQ	After participant indicates interest
No previous breast cancer diagnosis	PEQ	After participant indicates interest
Fit to undertake exercise program		
No major co-morbidities	Screening questionnaires and blood tests	After participant indicates interest
No previous invasive cancer	PEQ	After participant indicates interest
Passes the self-completed Physical Activity Readiness Questionnaire	PEQ	After participant indicates interest
Obtains physician approval to participate	PARmed-X [3]; approval to do 60 minutes of aerobic exercise ("unrestricted physical activity – start slowly and build up gradually") five times/week for 12 months	After *Information Session*
Acceptably healthy heart and lung function during fitness test	Sub-maximal treadmill test	After blood sample and obtaining physician approval
Risk profile amenable to change with exercise intervention		
Body mass index 22.0-40.0	PEQ (screening) and objective measurement of height and weight	After participant indicates interest (PEQ) and after exercise tester approval (height and weight)
Moderately sedentary lifestyle (no more than 3 days/week of moderate-intensity recreational activity lasting a maximum of <30 minutes/session). Or, no more than 120 minutes of moderate-intensity recreational activity/week.	PEQ (screening) and PYTPAQ[4] (comprehensive)	After participant indicates interest (PEQ) and at *Information Session* (PYTPAQ)

Estimated $VO_{2max} \leq 34.5$ mL/kg/min. If VO_{2max} was between 34.6 and 37.0 mL/kg/min, accelerometer count <10,000 steps/day over seven days.	Sub-maximal treadmill test; seven-day accelerometry (Actigraph GT3Xplus®) if VO_{2max} 34.6-37.0 mL/kg/min	After physician approval
No other outside factors to influence estrogen metabolism		
Not currently, previously (<6 months) or planning to take drugs related to estrogen metabolism or breast tissue growth	PEQ	After participant indicates interest
Not a current smoker, or excessive drinker Smoker = needs to have quit for at least 6 months Drinking maximum = no more than 14 drinks/week	PEQ	After participant indicates interest
Not currently or planning to undertake a weight control/loss program or taking weight loss medications	PEQ	After participant indicates interest
Logistics		
Lives in Calgary or Edmonton	*Screen Test* database and PEQ	Before contacting participant and after participant indicates interest
English-speaking	Initial contact with participant and PEQ	After participant indicates interest (telephone recruiters will ascertain)
Not planning to be out of Calgary/Edmonton area more than 4 consecutive weeks during the subsequent 18 months or more than 8 weeks during the entire year.	PEQ	After participant indicates interest

[1]Screen Test: The Alberta Breast Screening Program
[2]PEQ: Participant Eligibility Questionnaire
[3]PAR-medX: Physical Activity Readiness Medical Examination
[4]PYTPAQ: Past Year Total Physical Activity Questionnaire

6.4 Randomization

Randomization will be stratified by:

- Study center (Edmonton or Calgary)
- Baseline BMI (< or ≥28.8)

This randomization approach will ensure balance between the two arms with respect to study sites (i.e., potential differences in the participant populations) and the proportion of obese participants.

Blocking will be used within strata with blocks of four or six to ensure balance between the two arms with respect to the number of participants.

The random allocation sequence will be generated by user-defined functions in R software (version 2.11). The allocations will be concealed in numbered envelopes prepared by a staff member unrelated to the study team. Randomization will be performed only for women who were eligible for the study and have completed all baseline measurements. Each participant will be randomly assigned to either the HIGH volume (300 minutes/week) aerobic exercise intervention group or to the MODERATE volume (150 minutes/week) aerobic exercise control group. Participants and exercise trainers, by necessity, will be unblinded to the intervention assignment.

7 LOCATION OF ASSESSMENTS

The locations of study assessments will be as follows.

7.1 Edmonton

- *Health-related fitness assessments:* Cross Cancer Institute and the Behavioral Medicine Fitness Center at the University of Alberta.
- *Full body dual energy X-ray absorptiometry (DXA) scans:* Human Nutrition Centre, University of Alberta.
- *Computed tomography (CT) scans:* Cross Cancer Institute in Edmonton.
- *Supervised exercise sessions:* Behavioural Medicine Fitness Centre at the University of Alberta.

7.2 Calgary

- *Health-related fitness assessments:* Faculty of Kinesiology, Human Performance Laboratory at the University of Calgary.
- *Full body dual energy X-ray absorptiometry (DXA) scans:* Human Performance Laboratory, Faculty of Kinesiology, University of Calgary.
- *Computed tomography (CT) scans:* Foothills Medical Centre

- *Supervised exercise sessions:* Westside Recreation Centre.

8 EXERCISE AND CONTROL INTERVENTION

The two exercise groups will be determined by doubling the duration of each exercise session for the HIGH versus MODERATE group. Both groups will complete the same frequency (five days/week) and intensity (moderate-to-vigorous) of aerobic exercise. The targets will be 60 minutes/session, totaling 300 minutes/week for the HIGH group, and 30 minutes/session, totaling 150 minutes/week for the MODERATE group.

9 DATA COLLECTION AND MEASUREMENTS

9.1 Questionnaires

9.1.1 Baseline Health

Baseline health characteristics and other demographic information will be collected through a self-administered questionnaire. Questions will be asked regarding marital status, education, employment as well as medical, menstrual and reproductive history. Additional questions will address history of vitamin, medication and exogenous hormone use.

9.1.2 Physical Activity and Sedentary Behavior

Physical activity from the previous 12 months will be self-reported at baseline and 12 using the *Past Year Total Physical Activity Questionnaire* (*PYTPAQ*) [48]. This questionnaire, developed by our study team, measures all types of occupational, household and recreational physical activity and transportation to perform work as well as the duration, frequency and intensity of these activities. The questionnaire has been shown to have acceptable reliability and validity [48]. All reported activities are coded and converted into MET-hours/week/year using the *Compendium of Physical Activities* developed by Ainsworth and colleagues [49-51]. This measure of total physical activity, which includes activities performed outside the intervention, will be used to characterize our study population.

Similarly, participants will be asked at baseline and 12 months to report how much time they spend in sedentary activities over the past year using a sedentary behaviour questionnaire called the *SIT-Q*. This questionnaire was recently developed by one of our study investigators and has since undergone psychometric testing and shown to be a reliable and valid tool for sedentary behaviour assessment [52]. Given that sedentary behavior has been linked to many of the same breast cancer biomarkers as physical activity [53, 54], we will explore in our analyses how sedentary behaviour changes with our exercise intervention.

9.1.3 Diet

Dietary intake for the 12 months prior to the study will be reported at baseline and at 12 using the self-administered Canadian version of the US National Cancer Institute's *Diet History Questionnaire* [55].

Study participants will be asked not to change their dietary intake during the study. Hence, we are interested in verifying if dietary intake was changed since the primary purpose of this study is to examine the independent effect of physical activity on breast cancer biomarkers. In addition, given that energy intake impacts body weight, and because dietary composition might impact proposed biomarkers of risk [56-59], diet will be considered as a potential confounder (although the randomization reduces the chances of this) in our statistical analyses.

9.2 Blood Collection and Analysis

9.2.1 Baseline

A 60 mL blood sample will be taken at baseline after a minimum 10 hour fast and complete abstinence from exercise and alcohol for 24 hours. From the 60 mL, 20 mL were used for eligibility screening to assess for underlying medical conditions that would preclude participation.

Screening tests will include:

- complete blood count
- lipid panel
- fasting glucose
- creatinine
- alanine aminotransferase
- thyroid stimulating hormone.

Each test will be required to be within normal reference ranges for the participant to be eligible for the study. If the woman is under 55 years of age and has not had a bilateral oophorectomy or is uncertain of her menopausal status, a follicle stimulating hormone (FSH) test will also be done.

The additional 40 mL of blood from the baseline blood draw will be saved for analysis of endogenous sex and metabolic hormones and other biomarkers.

If the participant does not begin the exercise intervention within eight weeks of the initial blood test, a repeat 40 mL, non-screening blood draw will be required to ensure true baseline values of the various biomarkers being examined.

9.2.2 Six Months

A 40 mL blood sample will be taken at six months and saved for analysis.

9.2.3 Twelve Months

A 40 mL blood sample will be taken at twelve months and saved for analysis.

9.2.4 Blood Storage and Tracking

- All blood samples will be stored in -86 ºC freezers in the Alberta Cancer Research Biorepository in Calgary.
- Freezerworks® Unlimited software (version 6.02) will be used to track and manage the location and quantity of all collected samples.

9.2.5 Blood Assays

The blood samples will be batched so that each participant's baseline, six and 12 month samples are in the same batch and an equal number of MODERATE and HIGH exercise volume bloods are in the same batch. Blind duplicates are included in and between batches to estimate coefficients of variation. All lab personnel will be blinded to the intervention assignment.

9.2.5.1 Estradiol and Estrone

Estradiol and estrone will be measured by radioimmunoassay with preceding organic solvent extraction and Celite column partition chromatography steps. The assay sensitivities are 2 pg/ml and 4 pg/ml, respectively, and the interassay coefficients of variation (CVs) are 9-14%.

9.2.5.2 SHBG, Insulin and High Sensitivity CRP

SHBG, insulin and high sensitivity CRP will be measured by solid-phase, two-site chemiluminescent immunometric assays on the Immulite analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). The assay sensitivities are 1 nmol/L, 2 μIU/ml, and 0.02 mg/dL, respectively, and the interassay CVs are <10%.

9.2.5.3 Glucose

Glucose will be quantified by a standard analytical procedure using the Vitros Chemistry System.

9.2.5.4 Additional Biomarkers of Interest

Ten additional biomarkers will be quantified using three different multiplex assays:

- the Human Adipokine panel
- the Human Circulating Cancer panel
- the Human High Sensitivity panel

These assays will be performed at Eve Technologies (Calgary, AB, Canada) using the Bio-Plex™ 200 system (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

The Human Adipokine panel assesses adiponectin and resistin with assay sensitivities ranging from 2.2-11 pg/mL, the Human Circulating Cancer panel contains leptin, FGF2, prolactin and VEGF with sensitivities ranging from 3.6-42.8 pg/mL, and the Human High Sensitivity panel contains IL-4, IL-6, IL-10 and TNF-α; with sensitivities ranging from 0.11-1.12 pg/mL. Appropriate quality control samples will be used to monitor the reliability of each assay.

9.3 Health Related Fitness Measures

Only participants who successfully pass the baseline blood screening criteria will be invited for health-related fitness assessments (Figure 1).

Health-related fitness assessments will include:

- Measurements of resting heart rate and blood pressure assessment
- Submaximal fitness test
- Anthropometric and body composition measurements.

All fitness assessments will be performed by a Canadian Society for Exercise Physiology Certified Exercise Physiologist (CSEP:CEP®) and one assistant exercise trainer.

The same testing protocols and equipment will be used at both study centers.

All measurements will be taken at baseline and at 12 months.

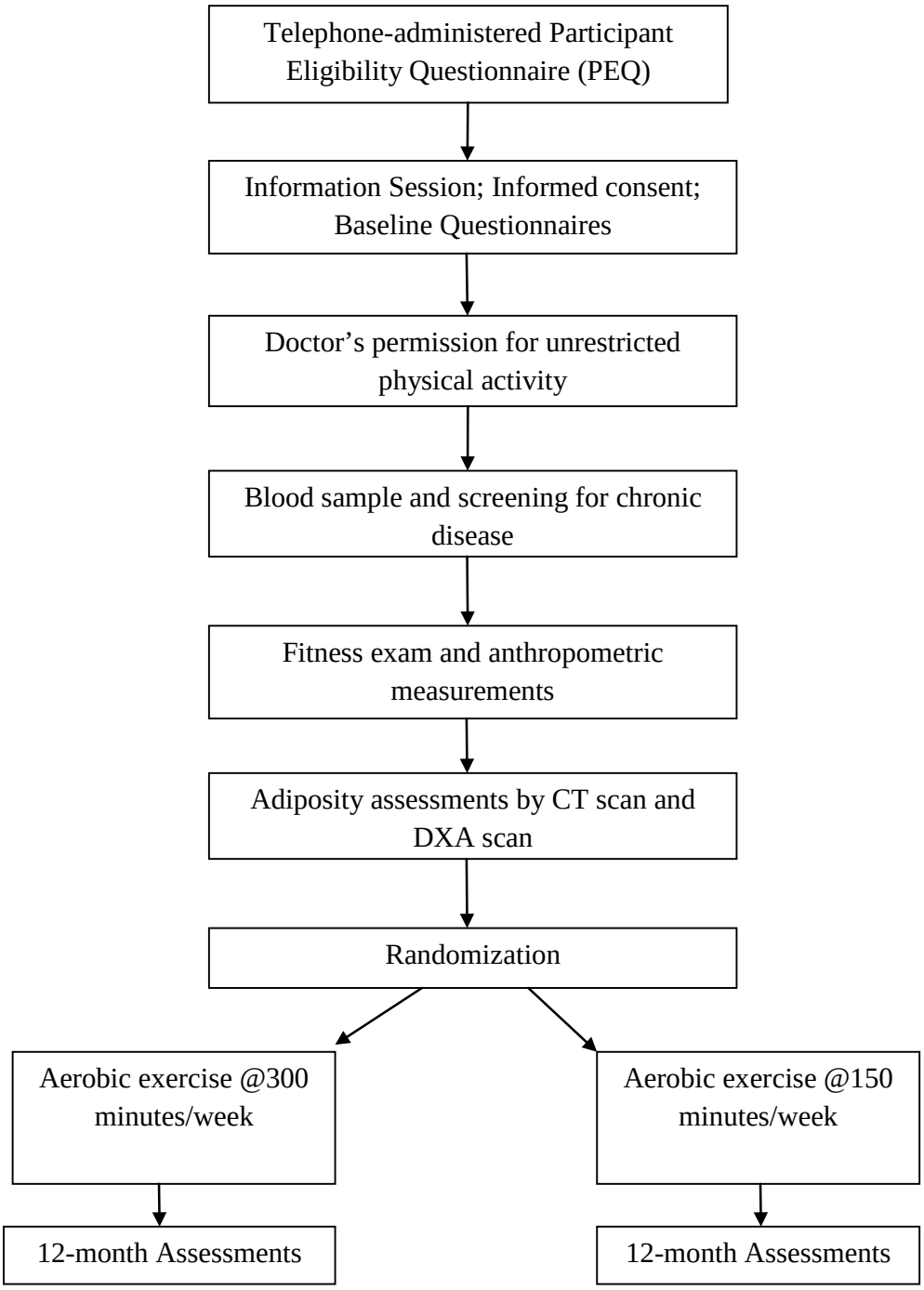

Figure 1. Participant flow chart for the BETA Trial, Alberta, Canada

9.3.1 Heart Rate and Blood Pressure

Following standard procedures, [60] participants will be instructed to sit quietly for five minutes before measurements are taken.

Heart rate will be monitored using a Polar® FT4 heart rate monitor (©Polar Electro, Canada). Resting blood pressure will be measured using a sphygmomanometer (WelchAllyn®) and stethoscope (3M™ Littmann®).

A blood pressure reading of 144/94 mmHg or lower will be required for the participant to undergo the fitness test.

9.3.2 Body Composition and Anthropometry

Anthropometric data on standing height, weight, waist and hip circumference will be measured using standardized methods and equipment at the time of the fitness tests.

9.3.2.1 Waist circumference

Waist circumference will be measured using the National Institutes of Health protocol and hip circumference was measured using the World Health Organization procedure with an anthropometric measuring tape [61].

9.3.2.2 Dual Energy X-ray Absorptiometry (DXA) Scans

Full body DXA scans will be taken using a Hologic DXA system in Calgary and a General Electric Lunar iDXA in Edmonton to assess overall percent body fat, total lean body mass, total fat mass and bone mineral density.

9.3.2.2 Computed tomography (CT) Scans

Computed tomography (CT) scans will be taken at the level of the umbilicus to measure subcutaneous and intra-abdominal adiposity. Three single slices will be taken at the L5 vertebrae These data will then be transferred to our study radiologist (Dr Aalo Duha) at the Cross Cancer Institute in Edmonton who will review each scan individually using a software program (Aquarius Intuition by Terarecon, Inc.) which will quantify the amount of subcutaneous and intra-abdominal fat at this level of the abdomen.

Because of the high cost associated with both the DXA and CT scans, only participants who complete all screening stages and are considered eligible for the study will be given these scans at baseline.

9.3.3 Cardiorespiratory Fitness

All participants will complete a sub-maximal cardiorespiratory testing to assess their aerobic fitness and determine eligibility (Table 1; Figure 1). The multistage, modified Balke treadmill test protocol will be used [62] in which a speed of 3.0 mph is maintained throughout the test and the grade is gradually increased every three minutes by 2.5% starting at 0%. The test is completed when the participant finishes the stage in which she reaches 85% of her age predicted maximum heart rate or reaches volitional exhaustion. The participant's predicted VO_2 max will be estimated using the multistage model and the American College of Sports Medicine metabolic equations for estimating maximum oxygen consumption [63].

To be eligible for the BETA Trial, a minimum of two stages of the test will need to be completed and the estimated VO_2 max must be $\leq$ 34.5 mL/kg/min (Table 1). If the estimated VO_2 max is between 34.6 mL/kg/min and 37 mL/kg/min, additional assessments of their activity levels will be requires. In these individuals additional step count data from the accelerometer devices (Actigraph GT3X+® and *activPAL*™) that all participants were required to wear for seven days will need to be retrieved. If it is determined that, on average, these participants walked <10,000 steps/day they will be eligible for the study. Any woman with an estimated VO_2max greater than 37 mL/kg/min is ineligible for the study.

A modified version of the fitness test will be repeated at 3, 6, and 9 months post-randomization for external verification of reported adherence to the exercise prescription and as a means to adjust the prescription. Randomization into the study will only occur after all health related fitness tests have been completed including the DXA and CT scans (Figure 1).

9.4 Objective Measures of Physical Activity and Sedentary Behavior

An accelerometer and inclinometer will be worn by participants at three time points during the trial to complement self-reported physical activity and sedentary behavior in the *PYTPAQ* and *SIT-Q*, respectively.

All participants will be asked to wear both devices simultaneously for seven days immediately after their fitness tests. As mentioned above, the step counts on the Actigraph GT3X+® will also used to determine eligibility in any woman with an estimated VO_{2max} that was deemed potentially too high. Additionally participants will be required to record, in a daily activity log, when the devices were worn each day and which activities they were doing when not wearing the device, e.g., showering or swimming since only non-sleep activity was recorded.

The devices will be worn at:

- Baseline
- Six months
- Twelve months

9.4.1 ActiGraph GT3X+® accelerometer

The ActiGraph GT3X+® accelerometer (Actigraph, LLC, Pensacola, FL) will be used to assess moderate-vigorous physical activity since the GT3X+ model is particularly suitable for measuring upright moderate-vigorous intensity movement.

The accelerometers are to be worn on the hip with an elastic belt and will record the duration, frequency and intensity of movement.

9.4.2 *activPAL*™ inclinometer

The *activPAL*™ inclinometer (PAL Technologies Ltd, Glasgow, Scotland) will be used to measure duration and frequency of time spent sitting, standing and stepping (light ambulation), and number of postural changes. The *activPAL*™ inclinometer is considered the most accurate device for assessing sedentary time in adults [64].

The inclinometers will be adhered to the upper thigh area using Cover-Roll® stretch adhesive.

9.5 Patient Reported Outcomes

Participants will be asked to complete self-administered questionnaires at baseline and 12 months to assess quality of life, sleep quality, perceived stress, satisfaction with life, and happiness; psychosocial factors that have been associated with exercise in some intervention trials [23, 45, 46, 65] and observational studies [66, 67] and therefore might improve with increasing exercise dose.

9.5.1 Quality of Life

Quality of life will be measured using the *RAND SF-36* [68] which includes 36 questions and uses eight subscales to assess physical and social functioning, pain, mental health. Questions will also asked about stress using the *Perceived Stress Scale* [69] and sleep using the *Pittsburgh Sleep Quality index* [70]. Happiness and satisfaction with life will be assessed using the Happiness Measure [71] and the Satisfaction with Life Scale [72], respectively.

9.6 Determinants of Physical Activity

The social cognitive determinants of physical activity will be assessed at baseline and 12 months, through participant-administered questionnaires that follow the standard questions based on the Theory of Planned Behavior [73]. This theory assesses attitude, subjective norm, perceived behavioral control, intentions and planning. At the end of the study, the participants will also be asked to complete a *Participant Satisfaction Questionnaire* to assess their attitudes and barriers towards exercise.

10 SAMPLE SIZE

Sample size calculations were based on a standard two-sample mean comparison formula using $\alpha = 0.05$ (two-sided). Taking a conservative approach, the means of 12-month outcomes (log-transformed, with adjustment for baseline values) were compared. Results from the ALPHA Trial provided estimates of standard deviations and 'yardstick' intervention effects that might be expected. A sample size of 150 participants/group was chosen, providing 80% power to detect anticipated changes of 12% in insulin resistance and inflammatory outcomes (leptin, insulin, adiponectin) at 12 months and 99% power to detect changes as low as 2% in all body fat outcomes. While an initial group size of 165 was planned it was later increased 200 per group without incurring extra resource requirements. The increase in sample size created an improvement in power, on average, and adequately accounted for an anticipated 10% loss-to-follow up and more modest exercise adherence that we postulated might occur with the higher demands associated with the exercise intervention in the HIGH volume arm of the trial.

11 STATISTICAL ANALYSIS

The trial analysis will follow the intention-to-treat principle, as such all participants who were randomized (n=400) will be included regardless of their adherence to the study. After initial descriptive and graphical examination of the response measurements (with a consideration of transformation), we will examine correlations among markers within each of the hypothesized pathways that are being examined between physical activity and breast cancer risk. This approach will guide us to a hypothesis-driven pathway-based evaluation of intervention effects. Specifically, the correlation analysis will explore if consistent patterns supportive of a simultaneous evaluation of multiple markers in each pathway is warranted. As a formal evaluation approach, we will apply the linear mixed effects model methodology to compare the changes from the baseline to 12-month follow-up in levels of estrogens, markers of obesity, insulin resistance and inflammation and also in our psychosocial outcomes of interest. The mixed model evaluation will be considered for both individual markers (univariate outcomes) and pathway-based multiple markers (multivariate outcomes), of which we propose the latter to be our primary evaluation scheme.

The analysis will be performed with and without covariate adjustments, initially without any adjustment based on the randomized design, followed by adjustment for covariates in which substantial imbalances between the two groups were observed. Rates of recruitment and adherence to the intervention as well as maintenance of exercise behaviour will be estimated and examined in association with the study participant characteristics.

12 DATA MANAGEMENT

12.1 Data Entry

12.1.1 TELEform®

Most questionnaires will be created using TELEform®, an optical character recognition software program that allows scanning and verification of the data and automatic transfer into tables within the final database to be used in the study, the Structured Query Language (SQL) Server.

All data entering the databases in this or any other manner are hand-checked for accuracy and completeness by a research assistant before scanning and verification of the data occurs.

12.1.2 Blaise®

Blaise® survey software will be used to complete the Participant Eligibility Questionnaire (PEQ) as well as the Physical Activity Questionnaire (PAQ).

12.2 Project Databases

Multiple Microsoft Office Access® databases will be created for tracking and storing participant information and data through all stages of the study. All electronic information is kept in secured database files, and is listed only by participant study ID number, without any identifying information.

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