UNIVERSITY OF ROCHESTER CANCER CENTER

A Pilot Study of the Effects of High-Dose Oral Calcitriol and Physical Activity on Bone Health in Breast Cancer Survivors

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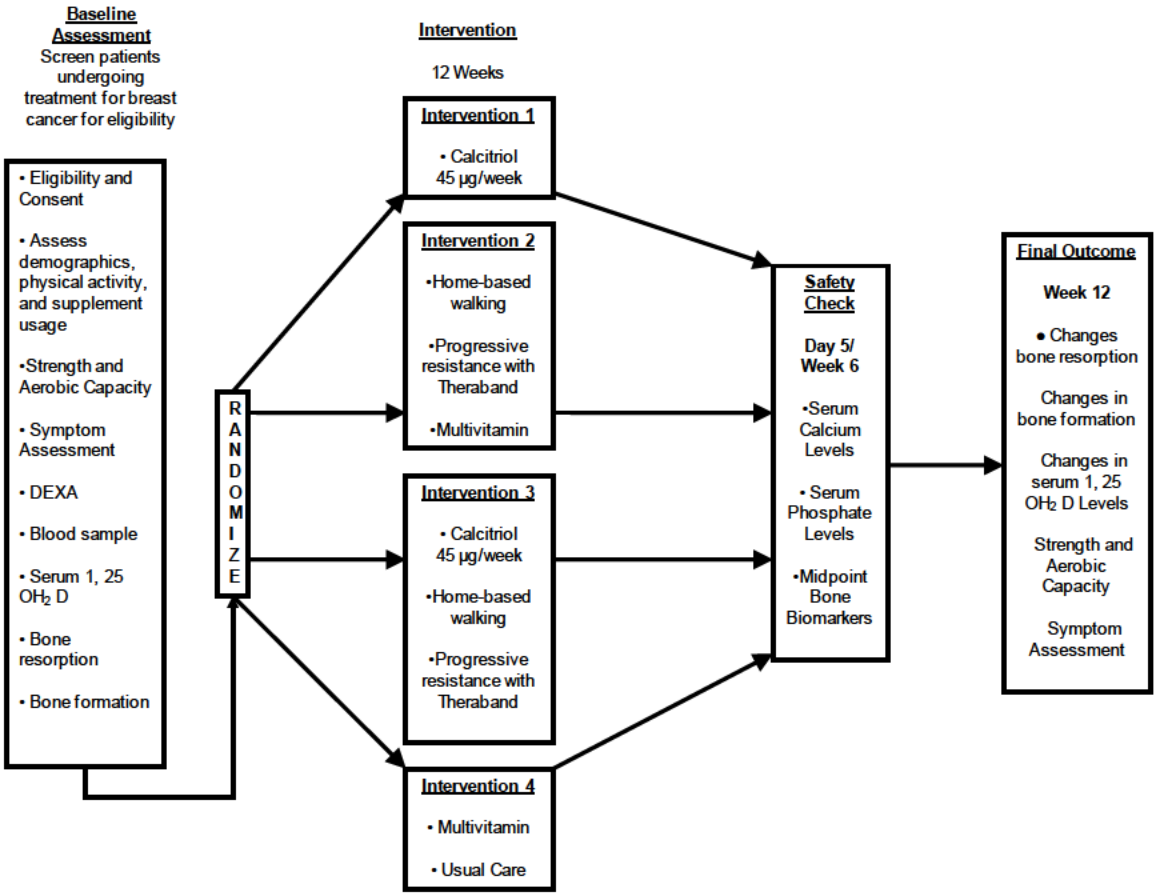
Study Schema



Both the calcitriol and exercise interventions are aimed at reducing fracture risk by maintaining proper bone density, thereby preventing osteoporotic/osteopenic conditions and increasing muscle mass. Both calcitriol and exercise are efficacious in maintaining proper bone health and muscle mass among the general population, but little research has been done on breast cancer patients and survivors. The combination of calcitriol and exercise, which function through different but similar mechanisms, could produce interactive effects in reducing fracture risk among breast cancer survivors.

Hypothesis: A combination of calcitriol 45 µg/week along with a structured home-based walking and progressive resistance exercise program will be efficacious in preventing bone resorption, as defined by NTx level, and in increasing bone formation, as defined by BAP level, among survivors of invasive breast cancer.

Primary Objective

To collect data on the efficacy and feasibility of a 12-week supplementation of calcitriol 45 µg with/without an accompanying

structured home-based walking/progressive resistance exercise program for improving bone health among breast cancer survivors.

Secondary Objectives

To collect data on the efficacy and feasibility of a 12-week supplementation of calcitriol 45 µg with/without an accompanying structured home-based walking/progressive resistance exercise program for increasing **strength** among breast cancer survivors.

To collect data on the efficacy and feasibility of a 12-week supplementation of calcitriol 45 µg with/without an accompanying structured home-based walking/progressive resistance exercise program for improving **skeletal muscle mass** among breast cancer survivors.

The primary analyses will consist of calculating mean change scores (i.e., baseline assessment minus final assessment) and standard deviations for both NTx and BAP. In addition, a paired-sample t-test will be used to calculate the differences between the baseline and end of trial values for both BAP and NTx.

1.0 Background

1.1 Incidence and Survival Rate for Invasive Breast Cancer

Breast cancer is, by far, the leading type of cancer among women in the United States, with an estimated 182,460 new cases in 2008 alone.[1] In addition to the incident cases of invasive breast cancer, 62,000 cases of cancer in situ will be diagnosed.[2] In 2008, breast cancer will claim the lives of 40,480 American women, which represents 15% of the total cancer deaths.[3] In the United States, approximately 17% of breast cancer patients are under the age of 50 (premenopausal) at time of diagnosis, while the remaining 83% of patients are 50 years of age or older.[4] The incidence rate for estrogen receptor positive (ER+) breast cancer is approximately 190 per 100,000 women, but the incidence rate for estrogen receptor negative (ER-) breast cancer is about 4 times less at 47 cases per 100,000 women. Overall, over 70% of all breast cancers display some sort of estrogen receptor activity.[5] The mortality rate for breast cancer is lower than that for other cancer sites, with an overall 5-year survival of 89% for all stages of breast cancer and 98% for localized breast cancer.[2] Due to the decreasing mortality rate of cancer, there are more than 10 million cancer survivors in the United States alone and more than 2 million breast cancer survivors.[6, 7] Because many of these survivors do not succumb to cancer, other health problems, such as bone loss, have become a concern.

1.2 Bone Health Complications in Breast Cancer Patients

We propose to conduct an efficacy and feasibility pilot of breast cancer patients studied over 12 successive weeks to determine whether breast cancer patients can safely participate in a high-dose oral calcitriol (a vitamin D analog) intervention. Additionally, we will evaluate the influence of the intervention on bone health biomarkers. Recently, the American Cancer Society joined the Canadian Cancer Society, along with 6 other health groups, in urging more vitamin D research.[8] Numerous studies have demonstrated that proper supplementation with vitamin D and its main analog (calcitriol) can improve bone health in a wide variety of populations. The majority of trials have focused on post-menopausal women, who are generally at higher risk for bone loss. Peri-menopausal women lose 3%-5% of their bone mass annually, while postmenopausal women lose approximately 2% of their bone mass annually, compared with just 0.5% annual loss in men.[9, 10] Progressive bone loss can lead to osteoporosis, a skeletal disorder characterized by diminished bone strength. Women with this condition are predisposed to increased risk of fracture, and this disorder can result in suffering and functional decline for the individual and drain health-care resources.[11]

Treatment for various types of cancer can have deleterious effects on bone health. A 1990 study was one of the first to demonstrate that those who were treated for breast cancer had lower bone mineral density compared to women without cancer of similar age.[12] Other studies have shown that both pre and postmenopausal women treated for breast cancer have a significantly lower bone mineral density than women of similar age without breast cancer.[13-15] Increased rates of bone loss and osteoporosis lead to increased fracture risk for many breast cancer survivors. A study from the Women's Health Initiative found that survivors of breast cancer were more likely to suffer an osteoporosis related fracture compared to women with no history of cancer.[16] A 1999 study in the British Journal of Cancer found that women with breast cancer were almost 5 times more likely to suffer a fracture than healthy controls.[17] The study also found women were more than 6 times more likely to suffer a fracture than controls. This evidence demonstrates that breast cancer survivors are more likely to have bone loss and fractures compared to women with no history of breast cancer.

In 2004, there were an estimated 10 million American women with osteoporosis and an addition 34 million women with its precursor, osteopenia.[18] The effects of osteoporosis can be devastating. Every year, hip fractures are responsible for 300,000 hospitalizations.[19] Studies have shown that up to 25% of the elderly who fracture a hip die within one year.[20] Over 30% of survivors will be permanently disabled, and approximately 20% of survivors will need long-term care in a nursing home.[21-24] The cost attributed to hip fractures can exceed $80,000 per person and costs the United States between $13 and $25 billion annually, along with 550,000 years of lost life.[25]

Table 5–3. Direct Health Care Expenditures for Care of Osteoporotic Fractures Among Persons ≥45 Years of Age in the United States by Type of Service and Type of Fracture, 1995

Type of fracture	Type of service (millions of $)						
	Inpatient hospital	Emergency room	Outpatient physician	Outpatient hospital	Other outpatient*	Nursing home	Total
Hip	5576	130	67	9	90	2811	8682
Forearm	183	55	93	8	4	41	385
Spine	575	20	13	3	10	126	746
All other sites†	2259	3632	297	45	91	899	3953
Total	8594	567	470	65	194	3875	13,764

*Includes home health care, ambulance services, and medical equipment.
† Depending on age, race, and gender, from 15% to 60% of all other fractures were attributed to osteoporosis

Source: Ray et al. 1997. Reproduced from J Bone Miner Res 1997: Jan; 12(1): 24–25 with permission of the American Society for Bone and Mineral Research.

1.3 Calcitriol and Bone Health

Calcitriol could prove to be a safe, low-cost treatment for preserving bone health in breast cancer patients. Human beings obtain Vitamin D from sunlight, food, and supplementation.[26] Vitamin D plays a vital role in maintaining proper bone health and works in conjunction with calcium. Higher levels of vitamin D have been shown to increase the intestinal absorption of calcium.[27] One study demonstrated that an increase in serum vitamin D produced a 45%-65% increase in intestinal absorption of calcium.[28] Although no consensus exists on optimal vitamin D levels, most experts agree a 25-hydroxyvitamin D level of less than 20 ng per milliliter is deficient.[29] Based on this level, it is estimated more than 1 billion people worldwide and between 40%-100% of elderly U.S. residents are vitamin D deficient.[30-33] More than 50% of postmenopausal women already under treatment for osteoporosis have deficient vitamin D levels.[34, 35]

Bone health is a major concern in women undergoing treatment and who have completed treatment for breast cancer. Cancer-treatment-induced bone loss (CTIBL) is a long-term side-effect of various breast cancer treatments.[36] Chemotherapy, hormone therapy, and irradiation frequently lead, either directly or indirectly, to bone mass depletion in breast cancer patients.[37] Studies have documented accelerated bone loss in breast cancer patients, and this bone loss frequently goes undiagnosed.[38-40] Breast cancer survivors have greater bone loss than women of similar age who were not diagnosed with cancer.[41-43] Risk factors for bone loss are already present in many women prior to a breast cancer diagnosis.[44] Treating bone loss in a prophylactic manner leads to greater success than delayed treatment.[45, 46] The Women's Health Initiative (WHI) and other

studies have found that postmenopausal breast cancer survivors had increased risk of fractures.[47, 48, 49]

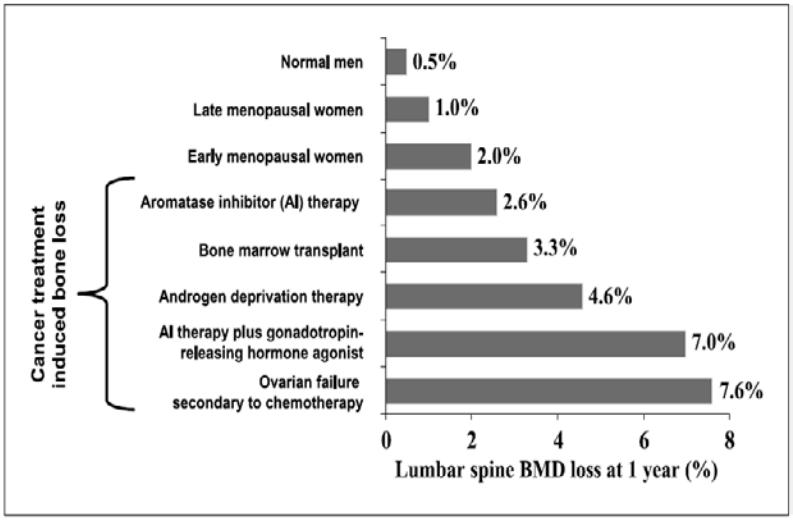


Fig. 2. Extent of bone loss due to cancer therapy. Menopausal women lose bone at a rate of 1% to 2% yearly. Cancer treatments, such as aromatase inhibitor therapy and chemotherapy, accelerate this process, leading to significant bone loss and subsequent skeletal complications (39, 75–79). Adapted from Skeletal Complications Across the Cancer Continuum CME Lecture 2005 series with permission from the Postgraduate Institute for Medicine.

The American Society of Clinical Oncology (ASCO), however, recommends pharmaceutical interventions (bisphosphonates) only after a severe amount of bone loss in patients considered osteoporotic.[50] Bisphosphonates produce a host of side effects, including poor GI absorption, nausea, and diarrhea for the oral medications.[51] Fever, flu-like symptoms, and myalgia are seen in treatment with iv bisphosphonates.[52] Among the most serious side-effects is osteonecrosis of the jaw, which can require surgical intervention.[53, 54] All of these side-effects lead to poor compliance. Studies have shown that compliance with bisphosphonate therapy is low, with 57% of patients considered non-compliant after 2 years.[55]

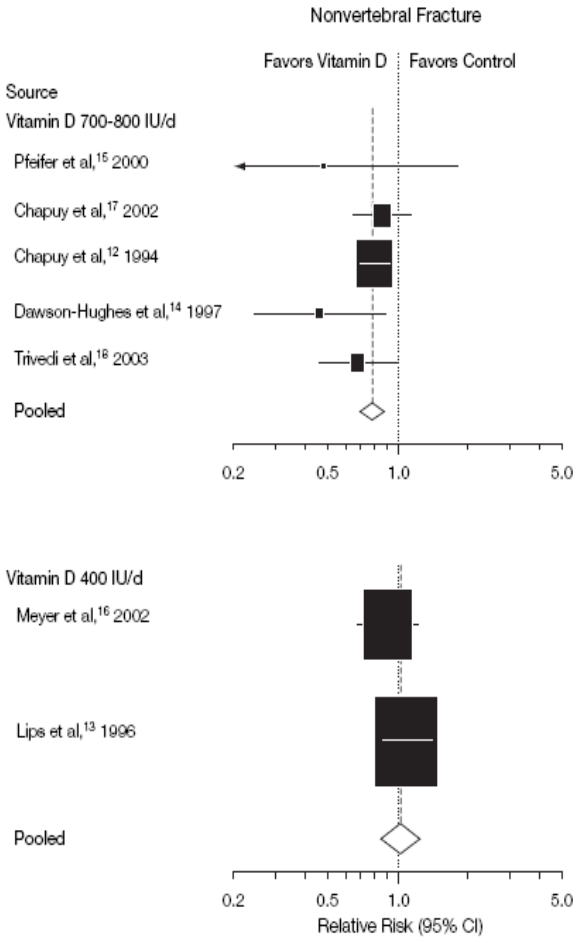
While bone loss is a significant problem for breast cancer patients and pharmaceutical interventions result in less than ideal compliance, vitamin D and calcitriol supplementation could be an effective intervention for bone health. A review of clinical trials found vitamin D supplementation had a positive effect on bone mineral density.[56] Trials that used a low-dose vitamin D intervention (≤ 400 IU/d) failed to significantly reduce bone fractures.[57, 58] In contrast, interventions that used a higher dose of vitamin D (≥ 700 IU/d) produced significant positive effects on fracture prevention.[59-63] A pooled analysis of those trials found vitamin D significantly reduced the risk of hip fracture by 26% and any nonvertebral fracture by 23%.[64] Other interventions used the active vitamin D analog, calcitriol, because of its higher efficiency and quicker absorption. These trials demonstrated calcitriol is effective in maintaining bone mineral density and reducing fractures.[65-71] A pooled analysis revealed calcitriol interventions significantly reduced the rate for nonvertebral fractures by 48% and all fractures by 48%. A comparative analysis found that calcitriol was significantly more effective at reducing bone loss and fractures than native vitamin D.[72] A pooled analysis also concluded that vitamin D analogs (calcitriol) were more effective in preserving BMD than placebo, no treatment, plain vitamin D_3 and/or calcium

alone.[73]

In addition to regulating bone health, vitamin D also protects against falls and helps maintain muscular strength.[74, 75] A meta-analysis of 5 randomized clinical trials reported a 22% reduction in falls in those receiving vitamin D supplementation.[76] Similarly, calcitriol protects against falls. One trial found those supplemented with calcitriol, in addition to having adequate calcium intake, had a 55% reduction in falls.[77] A 2001 intervention trial reported a significant reduction in the number of falls for those treated with calcitriol compared to placebo.[78] A recent comparative meta-analysis concluded that calcitriol was more effective at preventing falls than native vitamin D.[79]

1.4 Calcitriol Dosing

To date, the maximum tolerated dosage of vitamin D has not been clearly established. Many clinical trials have failed to produce protective bone health effects from vitamin D because the supplementation level was too low.[80, 81] Some researchers have suggested that interventions should use high, intermittent doses of vitamin D to increase serum levels and overcome low adherence.[82] Trials that supplemented with ≥ 700 IU/d of vitamin D were able to show protection against bone loss.[83-87] In both North America and Europe, the upper limit for vitamin D intake is considered to be 2,000 IU/d.[88, 89] However, many researchers, even government committees, believe numerous individuals are vitamin D deficient and this upper limit is too low.[90-92] These recommendations were formulated out of concern for safety and to prevent toxicity such as hypercalcemia.[93] However, many clinical trials have administered vitamin D doses well above the upper limit. One trial administered 100,000 IU of vitamin D every four months for five years without reports of toxicity.[94] Another intervention administered 50,000 IU/d of vitamin D for a period of 8 weeks without a change in serum calcium.[95] A long-term trial was able to administer 18,000 IU/d (9 times higher than the upper limit) of vitamin D for a period of 5 years without evidence of adverse events.[96] A review of these trials shows that vitamin D is not toxic at intakes much greater than previously considered unsafe.[97]



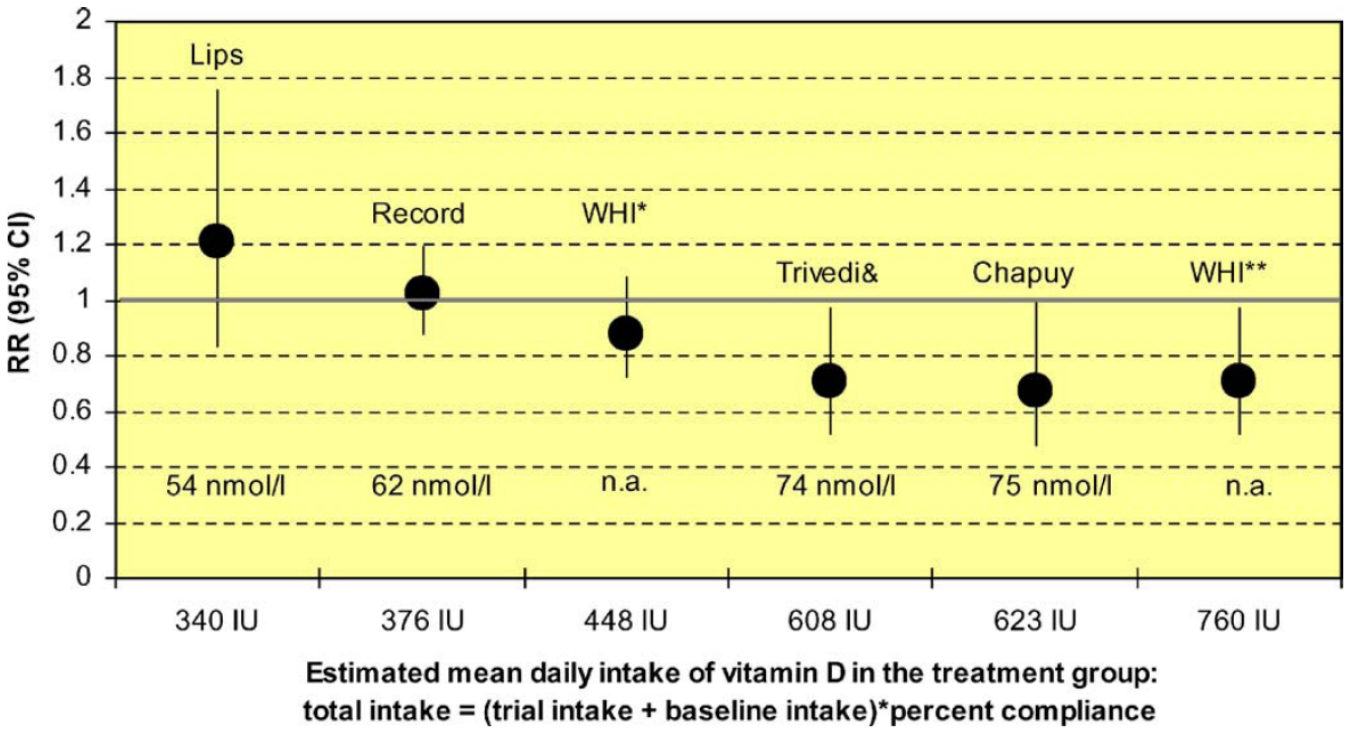


Fig. 1 Hip fracture efficacy by total estimated vitamin D intake (all trials used oral cholecalciferol) considering adherence to treatment. Compliance in the different trials was reported as follows: Lips (400 IU per day)=85% [36], Record (800 IU per day)=47% [13], WHI* intent-to-treat analysis (400 IU per day plus additional reported mean vitamin D intake of 360 IU)=59% [14], Trivedi (100,000 IU every 4 months equals 820 IU per day)=76% (&includes hip plus forearm fractures) [38], Chapuy (800 IU per day)=84% [57], WHI**-compliant women (400 IU per day plus additional reported mean vitamin D intake of 360 IU)=100% [14]. In most studies, being compliant was defined as taking 80% or more of the study medication. The x-axis gives the DiaSorin equivalent 25(OH)D levels in nmol/l achieved in the treatment arm of the trials. #For the Record trial a HPLC method has been used for 25(OH)D measurement with an unknown DiaSorin equivalent value. In the WHI trial, 25(OH)D levels have not been measured at follow-up in the study population (n.a. = not available) 98

The pattern is similar in terms of dosing for calcitriol. Higher doses of calcitriol were typically not possible when given on a daily dosing schedule because of the development of hypercalcemia and hypercalcuria.[99, 100] In recent years, researchers discovered that a less frequent dosing schedule allowed them to circumvent dose-limiting toxicities.[101, 102] A weekly administration of high-dose oral calcitriol was shown to be safe in cancer patients.[103, 104] The dosage was not limited by toxicities, but rather by nonlinear pharmacokinetics.[105] Subsequent studies have shown substantial dose escalation was possible when calcitriol was administered once a week.[106-113] Trump et al. were able to administer 12 µg of calcitriol daily for three consecutive days (36 µg/week) without any dose-limiting toxicities.[114] A trial of prostate cancer patients found that 60 µg/week of calcitriol was well tolerated .[115] Recently, 7 separate clinical trials were able to administer 45 µg/week (or 0.5 µg/kg/week) of calcitriol to patients undergoing adjuvant cancer therapy.[116-122] In the larger trials, participants remained on calcitriol for one year or longer.[123, 124] These studies demonstrated that this dose was well tolerated, and adverse events were extremely rare. In fact, a number of studies have demonstrated the safety of doses much greater than 45 µg/week. A phase I study in patients with cancer found calcitriol was well tolerated at a dose of 165 µg/week.[125] Another phase I trial administered calcitriol at doses up to 38 µg/d

for three consecutive days (114 μg/week) without dose-limiting toxicity.[126] These trials established intermittent oral dosing of calcitriol as a method of significant dose escalation and produced potentially therapeutic levels.[127] Additionally, calcitriol enhances the effects of radiation, chemotherapy, hormone therapy, and other antineoplastic treatments.[128-131] Based on previous trials, the 45 μg/week of calcitriol is an ideal dose to elicit positive effects and should pose only a minimal risk to the subject enrolled in this study. Nonetheless, potential toxicities related to calcitriol will be closely monitored.

1.5 Exercise and Bone Health

Exercise and physical activity, in general, have beneficial effects on bone health. Several clinical trials demonstrate that various exercise interventions have positive effects on bone mineral density.[132-138] These trials found that exercise was beneficial in postmenopausal women, who are those at the highest risk for osteoporosis. A pooled analysis found a mean difference of 1.79 ($p<0.01$) in spinal bone mass density when an exercise intervention was compared to controls.[139] In terms of specific exercises, walking interventions are effective in preventing bone loss.[140-142] Interventions examining the effect of exercise on bone health in breast cancer patients have been limited. Nevertheless, exercise interventions in breast cancer patients are also protective against bone loss.[143, 144] One single-arm clinical trial in breast cancer patients found a combination exercise and vitamin D had significant effects on bone health.[145] In addition to the benefits of aerobic exercise on bone health, resistance training has also been shown to be effective.[146-149] A pooled analysis revealed a weighted mean difference of 2.50 ($p=0.02$) in spinal bone density when resistance training was compared to placebo.[139] The literature shows that improvements in bone mineral density for resistance training were greater with a higher resistance/lower repetition regimen in older populations.[150-152] Therefore, it is recommended that women at higher risk for osteoporosis (e.g. breast cancer patients) train with higher resistance and fewer repetitions, which is the regimen that this protocol will follow.[153]

1.6 Summary

We propose to conduct a feasibility and efficacy pilot in breast cancer patients studied over 12 weeks to identify the ability to participate in a high-dose oral calcitriol and exercise intervention and to investigate the subsequent effects on bone health. The study will accrue 54 patients and is intended to provide pilot data for a later grant submission. The anticipated results could provide important information with clinical and methodological applications. Acquiring a better understanding of treatments capable of preserving bone health in breast cancer patients could lead to a higher quality of life and functional independence for these survivors.

2.0 Objectives

Both the calcitriol and exercise arms are aimed at reducing fracture risk by maintaining proper bone density, thereby preventing osteoporotic/osteopenic conditions and increasing muscle mass. Both calcitriol and exercise are efficacious in maintaining proper bone health and muscle mass among the general population, but little research has been done on breast cancer patients and survivors. The combination of calcitriol and exercise, which function through different but similar mechanisms, could produce interactive effects in reducing fracture risk among breast cancer survivors.

Hypothesis: A combination of calcitriol 45 μg/week along with a structured home-based walking and progressive resistance exercise program will be efficacious in preventing bone resorption, as defined by NTx level, and in increasing bone formation, as defined by BAP level, among survivors of invasive breast cancer.

2.1 Primary Objective

2.1.1 To collect data on the efficacy and feasibility of a 12-week supplementation of calcitriol 45 μg with/without an accompanying structured home-based walking/progressive resistance exercise program for improving bone health among breast cancer survivors.

2.2 Secondary Objectives

2.2.1 To collect data on the efficacy and feasibility of a 12-week supplementation of calcitriol 45 μg with/without an accompanying structured home-based walking/progressive resistance exercise program for increasing **strength** among breast cancer survivors.

2.2.2 To collect data on the efficacy and feasibility of a 12-week supplementation of calcitriol 45 μg with/without an accompanying structured home-based walking/progressive resistance exercise program for improving **skeletal muscle mass** among breast cancer survivors.

3.0 Subject Eligibility

Inclusion Criteria:

3.1 Must be female.

3.2 Women of child-bearing potential (i.e. women who are pre-menopausal or not

surgically sterile) must use acceptable contraceptive methods (abstinence, intrauterine device (IUD), or double barrier device) and must have a negative serum or urine pregnancy test within 1 week prior to beginning treatment on this trial. Contraceptive use needs to be continued at least 1 month after the trial has ended.

3.3 Must provide informed consent.

3.4 Must be willing to discontinue use of calcium and/or vitamin D supplements.

3.5 Participants must have an ionized serum calcium level within normal limits (1.19-1.29mmol/L) and a total corrected serum calcium of < 10.2mg/dl.

3.6 Must have a functional capacity rating of ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) performance status when assessed at baseline.[154]

3.7 Must have the approval of their treating physician (or physician's nurse practitioner or physician's assistant) to participate in sub-maximal physiological fitness testing and a low to moderate home-based walking and progressive resistance exercise program and to receive the 12-week supplementation of calcitriol 45 μg. Participants assigned to either of the calcitriol treatment arms will be instructed to stop taking calcium and/or vitamin D supplements.

3.8 Must be less than five years from the diagnosis of breast cancer and have received chemotherapy, radiation therapy, and/or hormonal therapy. Chemotherapy and radiation therapy, if received, must have been completed prior to study enrollment. Hormonal therapy may be ongoing.

Exclusion Criteria:

3.9 Subjects with life-threatening conditions that would preclude them from breast cancer treatment including chronic cardiac failure, which is unstable despite medication use, uncontrolled hypertension, uncontrolled diabetes mellitus, or unstable coronary artery disease.

3.10 Patients who had a myocardial infarction within the past year.

3.11 Patients with severe metabolic disorders, which includes phenylketonuria (PKU), homocystinuria, and Fabry's disease, that would preclude them from taking calcitriol.

3.12 Patients with impaired renal function (CRCL < 60 mL/min) or who had kidney stones (calcium salt) within the past 5 years.

3.13 Patients with hypercalcemia (corrected serum Ca > 10.2 mg/dl) or a history of

hypercalcemia or vitamin D toxicity.

3.14 Patients currently taking calcium supplements or aluminum-based antacids must be willing to discontinue their use if they are to enroll in the study.

3.15 Patients currently taking vitamin D supplements must immediately discontinue their use if they are to enroll in the study.

3.16 Patients with a known sensitivity to calcitriol.

3.17 Women who are pregnant or lactating.

3.18 [redacted]

3.19 [redacted]

3.20 Patients not capable of participating in an exercise intervention due to severe knee arthrosis or ligament/cartilage injuries of the lower extremities.

3.21 Women currently using oral contraception.

3.22 Women with malabsorptive syndromes (i.e. cystic fibrosis, chronic pancreatitis) or taking medications that decrease the absorption of fat soluble vitamins (i.e. Orlistat, Questran).

3.23 [redacted]

4.0 Treatment Assignment

4.1 All patients who meet the eligibility criteria, sign the patient informed consent form, obtain physician consent, and complete baseline assessments will immediately be randomized to one of four treatment arms. Randomization will be determined by means of a computer-generated random number table.

4.1.1 This study will use a block-randomized scheme with block sizes of 8 to ensure an equal distribution among the four arms.

4.1.2 A total enrollment of 72 patients is planned (18 in each treatment arm).

4.1.3 Treatment sequence in the four trial arms will be as follows:

Treatment Arm	**Condition**
1	*Calcitriol 45 μg:* Patients will be given 45 μg/week of calcitriol beginning at baseline for a period of 12 weeks.
2	*Home-Based Exercise:* Patients will be given a progressive walking and resistance band exercise treatment and a daily multivitamin for a period of 12 weeks.
3	*Calcitriol 45 μg and Home-Based Exercise:* Patients will be given 45 μg/week of calcitriol along with a progressive walking and resistance band exercise treatment for a period of 12 weeks.
4	*Usual Care:* A daily multivitamin plus standard care monitoring.

5.0 Treatment Protocol

5.1 This will be a four-arm clinical trial of an intervention examining the feasibility and efficacy of calcitriol 45 μg alone, a structured home-based walking/progressive resistance exercise program alone, along with the combination of calcitriol 45 μg and a structured home-based walking/progressive resistance exercise program for the maintenance of proper bone health among invasive breast cancer survivors.

5.2 Potentially eligible subjects at Strong Memorial Hospital will be approached by their physician either at a regularly scheduled oncology appointment or by standardized letter in the mail. The initial contact will assess whether the patient has any interest in participating in a clinical trial to preserve bone health. If interested, patients will be invited to call or come to our research center for screening to determine their eligibility for the study. If the patient is eligible, study personnel will explain the details of the study and obtain informed consent from patients who agree to participate.

5.3 Consent Process and Initial Assessments

5.3.1 Cancer survivors less than 5 years removed from the diagnosis of breast cancer who meet the eligibility criteria including approval from their physician will be invited to participate in the trial.

Upon consent, with help from the study coordinator, the patient will complete an On-Study Data Form, a Clinical Record Form, and a Medication Form, providing clinical and demographic data. Questions concerning the patient's sun exposure history, medical history, supplement usage history, exercise history, and baseline brief symptom inventory are also included. The study coordinator will obtain information necessary to complete these three forms from the patient's medical records when the patient is unable to provide this information in sufficient detail (e.g., staging, Karnofsky Performance Scale, surgical procedures, types and doses of treatments). Additionally, patients will be evaluated on vitals (Resting Heart Rate, Height, Weight & Blood Pressure), aerobic capacity (VO2max Treadmill Test and Resting Metabolic Rate (RMR) test) muscular strength (Handgrip Dynamometry and 7-10 repetition maximum test), skeletal muscle mass (Bioelectrical Impedance Analysis), and physical activity. (Note: Baseline measures of physical activity involve fitting each participant with a Pedometer for a 5-day baseline assessment). Patients will also provide a blood sample at this time.

5.3.2 Patients will be randomized to one of four treatment arms. Study medication and instructions for calcitriol 45 μg will be given and reviewed with all patients. Arm 2 and arm 3 patients will also receive instructions and an Exercise Kit for the home-based walking and progressive

resistance exercise program.

5.3.2.1 Patients assigned to Treatment Arm 1 will receive a 12-week supply of calcitriol, which consists of twelve 45μg pills of calcitriol to be taken once a week (QW).

5.3.2.2 Patients assigned to Treatment Arm 2 will receive a 12-week supply of daily multivitamins and a home-based walking and progressive resistance exercise regimen to follow for a total duration of 12 weeks.

5.3.2.3 Patients assigned to Treatment Arm 3 will receive a 12-week supply of calcitriol, which consists of twelve 45μg pills of calcitriol to be taken once a week (QW) and a home-based walking and progressive resistance exercise regimen to follow for a total duration of 12 weeks.

5.3.2.4 Patients assigned to Treatment Arm 4 will receive a 12-week supply of daily multivitamins but will not receive an exercise regimen to follow during the study period.

5.4 Physiological and Psychological Assessments

5.4.1 Blood sampling at four time points (baseline, day 5, week 6, and week 12) will be done to estimate bone resportion and formation and as a safety check for hypercalcaemia. Measures of bone pathology will be performed through the Associated Regional and University Pathologists (ARUP) Laboratories. Pre and post-intervention tests for Cross-linked N-teleopeptide of type I collagen (NTx), a specific indicator of bone resorption will be performed. In addition, pre and post-intervention tests for bone-specific alkaline phosphatase (BAP), an indication of bone formation, will be performed.

5.4.2 The blood draws for estimation of NTx and BAP will use 2 red top tubes for serum.

5.4.3 All blood draws will occur in the General Clinical Research Center (GCRC) and the blood will be drawn by research personnel in the GCRC. The time of day will be noted, with future assessments at approximately the same time of day during post-testing and follow-up.

5.4.4 All patients will be given a measure of physical activity (Aerobics Center Longitudinal Physical Activity Questionnaire (ACLS)), fatigue

(Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-F); Brief Fatigue Inventory (BFI); Multidimensional Fatigue Symptom Inventory (MFSI)), QOL (Functional Assessment of Chronic Illness Therapy with Fatigue (FACIT-F)), to complete at home at the appropriate times (i.e. during baseline and post-testing). (Note: Pilot use of the questionnaire packet indicates an average completion time of ≤ 30 minutes).

5.4.5 All patients will be evaluated on aerobic capacity (VO2max Treadmill Test), muscular strength (handgrip dynamometry, 7-10 repetition maximum test), gait (tandem walk test), and skeletal muscle mass (bioelectrical impedance). All physiological fitness testing will be administered according to the Guidelines for Exercise Testing and Prescription (GETP) as outlined by the American College of Sports Medicine (ACSM).

5.5 Calcitriol 45 μg Arms 1 & 3

5.5.1 The calcitriol 45 μg arms 1 & 3 will follow the guidelines listed below:

5.5.1.1 The calcitriol 45 μg pills will be supplied by Roswell Park Cancer Institute and the State University of New York at Buffalo. The pills will be placed in a tamper-proof blister pack. Research subjects will be instructed to take the calcitriol on an empty stomach, 1 to 2 hours prior to or after any meal. Subjects will also be advised to increase their intake of water by 4 cups on the day of taking the pill and the day after. Subjects will take 1 capsule 1 day a week for a duration of 12 weeks. Subjects will be supplied with the full 12 weeks of capsules that will be dispensed by the University of Rochester Medical Center pharmacy.

5.5.1.2 [redacted]

5.5.1.3 The study coordinator will contact each subject on the day she is scheduled to take calcitriol 45 μg as a reminder. The study coordinator will use this opportunity to assess any potential complications or toxicities due to the intervention.

5.5.1.4 Because of improved calcium absorption from the gastrointestinal tract caused by calcitriol, most participants may be maintained on a lower calcium intake. Most patients on calcitriol require only dietary sources of calcium and need no supplementation. Therefore, participants must not take multivitamin or calcium supplementation while on the study medication. In addition, ingestion of large amounts of foods containing dairy products should be avoided. Participants assigned to calcitriol who are routinely taking a multivitamin supplement may continue the supplement as long as the amount of vitamin D in the supplement is not in excess of the RDA (recommended daily allowance) of 400 IU or 10 μg. If they are not taking a multivitamin supplement, they will be asked to not start supplementation while on study.

5.5.2 Toxicity Monitoring:

After the first dose of calcitriol is administered on day 0, the patients will return for blood collection on day 5. On day 5, any patient displaying any grade ≥ 3 toxicity related to the study drug will be removed from the study. The patients will return at 6 weeks and 12 weeks for blood collection. These visits will be coordinated with surgical oncology visits, medical oncology visits, or radiation oncology visits, when possible, to reduce patient burden. Following her appointment, the patient will proceed directly to phlebotomy.

Removal from study: Patients will be removed from the study for any of the following reasons:

1. Any grade ≥ 3 toxicity related to the study drug.
2. A grade 2 toxicity that persists for more than 2 weeks.
3. Withdrawal of consent.

For any clinically adverse event, the toxicity grading scale established by the FDA will be used. It is as follows:

Grade 1 toxicity (Mild): No interference with activity
Grade 2 toxicity (Moderate): Some interference with activity not requiring medical intervention.
Grade 3 toxicity (Severe): Prevents daily activity and requires medical intervention.
Grade 4 toxicity (Potentially Life Threatening): ER visit or hospitalization.

For hypercalcemia, the FDA toxicity grading scale specific to serum calcium will be used:

Grade 1 toxicity (Mild): 10.3-11.0 mg/dL
Grade 2 toxicity (Moderate): 11.1-11.5 mg/dL
Grade 3 toxicity (Severe): 11.6-12.0 mg/dL
Grade 4 toxicity (Potentially Life Threatening): > 12.0 mg/dL

The FDA toxicity grading scale will be used for determining all adverse events.

In addition to blood safety checks throughout the study, a research coordinator will call each patient at on the day of the week she is scheduled to take calcitriol 45 μg to ensure compliance and assess side effects. The nurse will record any adverse events (AE) and/or serious adverse events (SAE). Any patient who reports an AE or SAE will be scheduled for a clinical visit. In addition, the research coordinator will inquire as to any change in over the counter supplement usage. Reports regarding potential toxicities, patient safety, and outcomes will be submitted to the University of Rochester Medical Center Research Subjects Review Board (RSRB). The potential risks and side effects of calcitriol include:[155]

Because calcitriol is the active analog of vitamin D, adverse effects are similar to those found with excessive vitamin D intake. Because of the short biological half-life of calcitriol, elevated serum calcium levels normalize within a few days, much more quickly than with native vitamin D supplementation.

<u>Early signs and symptoms of vitamin D intoxication:</u> Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, metallic taste, anorexia, abdominal pain, or stomach ache.

<u>Late signs and symptoms of vitamin D intoxication:</u> Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis, pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN,

albuminuria, hypercholesterolemia, elevated SGOT and SGPT, ectopic calcification, nephrocalcinosis, hypertension, cardiac arrhythmias, dystrophy, sensory disturbances, dehydration, apathy, arrested growth, urinary tract infections, and, rarely, overt psychosis.

This protocol requests a Comprehensive Metabolic Profile (Panel 14) from the GCRC. Of main concern is serum calcium, specifically hypercalcemia. A serum calcium level between 8.4 and 10.2 mg/dL is considered normal. Any level > 10.2 mg/dL or < 8.4 mg/dL is considered outside the safety range and the investigators should be notified.

5.5.3 **Adverse Events**

5.5.3.1 An **adverse event (AE)** is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

5.5.3.2 A **serious adverse event** (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent

one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

5.5.3.3 An **unexpected adverse event** is any drug experience, the specificity or severity of which is not consistent with the risk information described in the investigators brochure or general investigational plan (see section 5.91). Unexpected as used in this definition refers to an adverse drug event that has not been previously observed rather than from the perspective of such experience not having been anticipated from the pharmacological properties of the drug.

5.5.4 Adverse Event Reporting

University of Rochester Medical Center Reporting - Serious adverse events that are associated with the study and occur while a subject is on study until 14 days after the date the subject goes off study must be reported in writing to the Strong Memorial Hospital IRB within 10 working days. They are also reported to the Data Safety Monitoring Committee within the same time frame. Adverse events that are both **unexpected fatal or life-threatening events** must be reported immediately to the IRB.

5.5.5 Data Safety Monitoring Plan

Investigators will conduct continuous review of data and patient safety. The review will include for each treatment arm level: the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. The Investigator will submit twice yearly summaries of this data to the Clinical Trials Monitoring Committee for review.

Clinical Trials Data Safety Monitoring Committee: The Director of the Cancer Center delegates responsibility for continued review and monitoring of all clinical trials conducted by the URCC to the Clinical Trials Data Safety Monitoring Committee. This committee provides oversight of study progress and safety by review of accrual and adverse events at annual meetings. Any adverse event requiring expedited review per protocol will be submitted to the Data Safety Monitoring Committee (DSMC) for determination as to whether further action is required. The study PI and the study medical monitor determine if the adverse event

requires expedited review. Interim meetings are scheduled, as needed, to address specific issues that require immediate attention to assure patient safety.

The Committee:

a) Reviews assigned clinical trials conducted at the URCC for progress and safety.

b) Reviews all adverse events requiring expedited reporting as defined in the protocol.

c) Reviews reports generated by the URCC data quality control review process.

d) Submits recommendations for corrective actions to the Protocol Review Committee and the PI

e) In general, outcome data is not made available to individuals outside of the DSMC until accrual has been completed and all patients have completed their treatment. At this time, the DSMC may approve the release of outcome data on a confidential basis to the trial PI for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMC's recommendation for general dissemination of results must be reviewed and approved by the DSMC.

Safety Coordinator: The Medical Director of the Cancer Center Clinical Trials Office appoints the Safety Coordinator. The Safety Coordinator monitors adverse event rates utilizing the URCC Clinical Trials database. If any assigned study has had two or more of the same SAEs reported in a month or more than six of the same SAEs in six months, the DSMC will review the summary of SAEs, discuss events with the Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

5.5.6 All study drugs will be dispensed and all biological specimens will be collected at the University of Rochester Medical Center.

5.5.7 There will be no cost to the patient for the study medication, the pathological tests, blood tests, or bone health tests. All costs will be paid from funds controlled by Dr. Gary R. Morrow within the James P. Wilmot

Cancer Center.

5.6 Walking and Progressive Resistance Exercise Arms 2 & 3

5.6.1 The Home-Based Walking and Progressive Resistance Exercise Program is designed by an Exercise Scientist certified by the American College of Sports Medicine (ACSM) and is in accordance with the guidelines for exercise testing and prescription as set forth by the ACSM.

5.6.2 The Home-Based Walking and Progressive Resistance Exercise Program will follow the guidelines listed below.

5.6.2.1 The Home-Based Walking Prescription will be based on a patient's baseline pedometer assessment. [redacted]

5.6.2.2 The Home-Based Progressive Resistance Prescription will be based on a patient's optimal level of challenge. Patients will be instructed on the proper use of resistance bands. [redacted]

5.6.2.3 The study coordinator will talk with each patient on a weekly basis by telephone as a reminder to take calcitriol.

He/she will also answer any questions the patient may have regarding the exercise program in order to facilitate proper adherence and compliance to the exercise intervention.

5.6.3 All Walking and Progressive Resistance Exercises will be performed off-site from the University of Rochester Cancer Center in a home-based patient-selected environment.

5.6.4 There will be no costs to the patient for the physiological assessments (e.g. serum collection and muscular strength), resistance bands, pedometers, or Home-Based Walking and Progressive Resistance Exercise Prescription. All costs will be paid from funds controlled by Dr. Gary Morrow in the Behavioral Medicine Unit within the James P. Wilmot Cancer Center.

5.7 Commencement of a low to moderate walking and progressive resistance exercise program is not associated with any severe side effects and risks are minimal for individuals with no cardiopulmonary, orthopedic, or age-identified high risk factors as determined by the patient's treating physician (or designee). The chance of a cardiac event is rare once coronary disease has been excluded with reasonable certainty. Approximately 1 death per 15,000-20,000 healthy men per year occurs during jogging; this risk is much lower in women. A transient increase in blood pressure may occur with all types of exercise. Although unlikely, the risks involved in a low to moderate walking and progressive resistance exercise program are musculoskeletal— possibly mild muscle soreness, a muscle strain, or related injuries such as tripping. Overall, the risk level for participation in a low to moderate Home-Based Walking and Progressive Resistance program is minimal. Risks associated with a 6-minute walk test are similar to participation in a low to moderate walking exercise program and are minimal for individuals with no cardiopulmonary, orthopedic, or age-identified high risk factors as determined by the patient's doctor. 7-10 Repetition maximum tests for strength may cause minor stiffness and/or tenderness in muscles for a few days following testing. The nature of these assessments will require a level of exertion causing temporary changes such as an increase in heart rate and blood pressure, both of which are normal responses to moderate exercise. There is a small risk of irritation to the skin from the electrodes used for the BIA analysis. Lying under the canopy for resting metabolic testing creates a risk for some subjects to feel anxious or claustrophobic. Every effort will be made to minimize the risks for all study procedures through the approval of the treating physician to enter the study, supervision of all testing and exercise prescription by an American College of Sports Medicine certified Health and Fitness Instructor or a physician (or physician's designee) when necessary according to American College of Sports Medicine Guidelines, the use of standardized guidelines for exercise testing and prescription provided by the American College of Sports Medicine and resting metabolic rate testing and bioelectrical impedance analysis. Regarding the risks for resting metabolic testing, if patients feel claustrophobic during the resting metabolic test it will be stopped. Electrodes will be removed

immediately after the bioelectrical impedance test by the patient to minimize skin irritation. Risks will also be minimized by following the documented and approved procedures for the tests that are performed in the NIH-funded and approved University of Rochester General Clinical Research Center, and trained staff will perform these tests.

5.8 Multivitamin Arm

5.8.1 New Formula Centrum®

Study participants assigned to arm #4 will receive a daily multivitamin and mineral supplement. They will be instructed to take one (1) tablet of New Formula Centrum® (Wyeth Consumer Healthcare) daily for the duration of the intervention. The supplement contains: Vitamin A 3500 IU (70% Daily Value (DV), Beta-Carotene 25 µg, Vitamin C 90 mg (150% DV), Vitamin D 10 µg (100% DV), Vitamin E 30 IU (100% DV), Vitamin K 25 µg (31% DV), Thiamin 1.5 mg (100% DV), Riboflavin 1.7 mg (100% DV), Niacin 20 mg (100% DV), Vitamin B_6 2 mg (100% DV), Folic Acid 500 µg (125% DV), Vitamin B_{12} 6 µg (100% DV), Biotin 30 µg (10% DV), Pantothenic Acid 10 mg (100% DV), Calcium 200 mg (20% DV), Iron 18 mg (100% DV), Phosphorus 109 mg (11% DV), Iodine 150 µg (100% DV), Magnesium 100 mg (25% DV), Zinc 11 mg (73% DV), Selenium 55 µg (79% DV), Copper 0.9 mg (45% DV), Manganese 2.3 mg (115% DV), Chromium 35 µg (29% DV), Molybdenum 45 µg (60% DV), Chloride 72 mg (2% DV), Potassium 80 mg (2% DV), Boron 150 µg, Nickel 5 µg, Silicon 2 mg, Tin 10 µg, Vanadium 10 µg, Lutein 250 µg, and Lycopene 300 µg. Patients will be provided with the first 6 weeks worth of multivitamins at the start of the trial and the remainder of the multivitamins at the week 6 visit. There are no dietary restrictions for participants assigned to this arm. Participants assigned to this arm who normally use calcium supplementation are free to continue.

6.0 Treatment Evaluation

6.1 Measures

6.1.1 Bone health

6.1.1.1 Levels of bone resorption will be measured by **Cross-linked N-teleopeptide of type I collagen (NTx).** NTx is a specific indicator of bone resorption. It is generated from bone by osteoclasts as a degradation product of type I collagen, and it can easily be measured in urine or serum. NTx is a valid and reliable measure of bone resorption.[156] Researchers believe that markers of bone resorption are superior to markers of bone formation and more accurately predict changes in bone mass.[157] Bone resorption markers are also able to predict failing bone health in advance of BMD. Laboratory assay methods of NTx levels are well

established and considered reliable.[158]

6.1.1.2 Levels of bone formation will be measured by **bone-specific alkaline phosphatase (BAP)**. Bone formation markers, specificially (BAP), are also considered a valid measure of bone health.[159, 160] Although BAP is a valid measure of bone health, measures of bone resorption tend to be better predictors of bone health. Laboratory assay methods of BAP levels are well established and considered reliable.[161]

6.1.2 **Physical activity** will be assessed subjectively using the Aerobic Center Longitudinal Study Physical Activity Questionnaire and questions on the daily journal. In addition, objective assessments of physical activity will be obtained via the pedometer.

6.1.2.1 The **Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)** is a measurement instrument that includes assessment of lifestyle physical activity. The questionnaire requests that participants report their engagement (frequency, intensity and duration) in fourteen different physical activities over the last three months. Estimates of energy expenditure are calculated using the following equation: (sessions/week) * (min/session)* (hour/min) * MET [Note: MET = metabolic energy expenditure rate] for each activity and then summed to provide total MET hours of energy expenditure for a week. The index of walking, jogging, and running predicted treadmill performance time $\beta = 0.31$ and there is a moderate relationship between energy expenditure estimates and treadmill performance ($r = 0.41$). The accuracy and reliability of the ACLS has been previously demonstrated.[162]

6.1.2.2 The **Pedometer** device will be used to assess duration of physical activity via steps walked during the time out of bed. [Note: Participants NOT assigned to the exercise arm will give back their pedometer after the 5-day baseline measure and will have the pedometer reissued for the 5-day measure at the end of the trial.]

6.1.2.3 The **Daily Journal** is designed to track daily physical activity. The participant will be asked to complete the journal each night immediately prior to sleeping and record steps and miles walked, caloric expenditure, and a Rating of Perceived Exertion.

6.1.3 Aerobic capacity will be assessed using a **VO2max Treadmill Test** as a measure of compliance using a modified "Branching Treadmill Protocol". Participants begin at a normal walking speed (2.5 mph) and 0% grade.

After 2 min. the speed is increased to a faster walking speed (3.0 mph) and 0% grade. After 2 min, the speed is increased to 3.5 mph and 2% grade. Thereafter, only the grade is increased by 2% every 2 min. Oxygen consumption (VO2), carbon dioxide production (VCO2), and flow rate will be measured continuously. The test is ended when the participant wants to stop. An MD is available onsite in the hospital during all tests as outlined by the ACSM fitness testing guidelines. In preparation for the exercise treadmill test, subjects will be instructed to fast for 4 hrs prior to the test and they will be asked to rest quietly on a bed in a quiet room for 30 minutes under a clear canopy which is placed over their head. During this 30 minute period, they will have their resting metabolic rate measured for 30 minutes using continuous, computerized open-circuit indirect calorimetry (Sensormedics® Vmax). A 6-Minute walking test may be substituted for the treadmill test in the event the person is not able to complete it. This is a sub maximal measurement using a 6 minute walk protocol. Participants are given a short warm up and cool down walking protocol in the test walking area in the University of Rochester. Participants walk for a total of 6 minutes and cover as much distance as they can during this time. Upon completion of the test, the total distance walked is used to calculate an estimate of aerobic capacity (VO2max:Maximal Oxygen Consumption).

6.1.4 **Muscular fitness** will be assessed using two measures: a handgrip dynamometer test and a 7-10 repetition maximum strength test.

6.1.4.1 The **Handgrip Dynamometer Test** is a grip strength test used to assess the maximal voluntary contraction generated by the arm muscles. The test is administered with the patient standing in anatomical position, the elbow joint angle will be held constant at 180 degrees with the medial distal humeral epicondyl held 2 inches from the torso. Trials will be performed in an alternating bilateral sequence for a total of six attempts (three with each arm). The best score of the three trials will be used for right and left limbs to calculate static strength. The surgically involved arm(s) will be noted for data analysis. The handgrip dynamometer test has been previously used in a number of URCC CCOP protocols and has shown to be a reliable clinical method of assessing strength.[163]

6.1.4.2 The standard **7-10 Repetition Maximum Dynamic Strength Testing Protocol** will be used to estimate patients' 1-repetition maximums for the leg extension (quadriceps) and bench press (pectoralis and deltoid). The patients will receive a full orientation to the fixed resistance machines and proper lifting form by a certified (ACSM) exercise testing professional. Participants will perform a light warm up consisting of 8 lift repetitions employing the lightest weight on the machine. After the warm up, patients

will be given a 2-3 minute rest break. A weight will be selected by the exercise testing staff based on the ease or difficulty of completing the warm up for each patient, and this weight will be lifted until subjective fatigue. Alternating rest breaks (2-3 minutes) and lifting bouts will continue with the resistance weight adjusted by the exercise testing staff until the patient reaches a level of resistance that results in subjective fatigue between 7-10 repetitions. Established algorithms employing the weight lifted and the number of repetitions completed will then be used to estimate the patients' 1-repetition maximum.[164] The 7-10 Repetition Maximum Dynamic Strength Testing Protocol has been previously used in a number of URCC CCOP protocols and is used by ACSM as a method of assessing strength.[165]

6.1.5 Skeletal muscle mass is assessed using the following measure:

6.1.5.1 The **RJL Bioelectrical Impedance System** is a non-invasive, easy-to-administer and safe method of assessing lean body mass. BIA involves passing a small electrical current through the body and evaluating the reactance and resistance to flow, which are related to fat-free mass (FFM) and total body water. Prediction of lean body mass from BIA is as reliable as skin-fold measurements and hydrostatic weighing. Participants need to be 4-hours fasted, abstained from physical exercise for 12 hours, abstained from alcohol and diuretics (unless prescribed) for 48 hours, well hydrated (water only), and voided completely prior to assessment. Participants lie supine on a flat surface for approximately 5 minutes prior to the test to ensure a resting metabolic state. Electrodes are attached to the right hand (distal end of the 3rd and 4th metacarpal and distal end of the ulnar and radius) and the right foot (distal end of the 3rd and 4th metatarsal and distal end of the tibia and fibula). Skeletal muscle mass will then be calculated from the lean body mass.[166] BIA is considered an accurate and reliable test in determining skeletal muscle mass among the general population, including older adults.[167-169]

6.1.6 For the resting metabolic rate, subjects will be instructed to fast for 4 hrs prior to the test, and they will be asked to rest quietly on a bed in a quiet room for 30 minutes under a clear canopy which is placed over their head. During this 30 minute period, they will have their resting metabolic rate measured for 30 minutes using continuous, computerized open-circuit indirect calorimetry (Sensormedics® Vmax).

6.1.7 Gait and balance is assessed using the following measure:

6.1.7.1 The **Tandem Walk Test** (TWT) is a non-invasive, easy-to-administer, and safe method of assessing gait. The TWT involves

testing a woman's ability to walk with the heel of her front foot touching the big toe of her rear foot.[170, 171] The scores for this test are: 1=able to do four consecutive tandem steps; 2=unable to do four consecutive tandem steps without stepping off or touching the examiner's arm; 3=unable or unwilling to put feet in tandem position. Women who use walking assistance and do not take the test will be assigned a score of 4.

7.0 Statistical Considerations

7.0 Primary measures and analyses:

7.0.1 Bone Resorption: NTX
7.0.2 Bone Formation: BAP

Since the primary objective of this pilot study is to gather preliminary efficacy and feasibility data for the development of a planned career development grant application, the primary analyses will consist of calculating mean change scores (i.e., baseline assessment minus final assessment) and standard deviations for the two variables above. In addition, a paired-sample t-test will be used to calculate the differences between the baseline and end of trial value for both BAP and NTX. An independent t-test will be used to calculate the difference between the baseline and end of trial value for both BAP and NTx between the trial arms. Lastly, ANCOVA models will be used for BAP and NTx with the addition of relevant covariates collected during the study. Results of these two analyses will be interpreted cautiously because of the limited sample size.

7.1 Secondary measures and analyses:

7.1.1 Physical Activity: ACLS and Pedometer
7.1.2 Aerobic Capacity: VO2max Treadmill Test
7.1.3 Muscular Fitness: Handgrip Dynamometer and 7-10 Repetition Maximum
7.1.4 Muscle Mass: Bioelectrical Impedance Analysis

7.1.5 Since the secondary aims relating to physical activity, aerobic capacity, muscular fitness, and muscle mass, respectively, are intended to gather preliminary efficacy data for the development of a planned K07 submission, the secondary analyses will consist of calculating mean change scores (e.g., baseline assessment subtracted from the final assessment, and baseline subtracted from the follow-up assessment), standard deviations, and correlations on these variables for the two study arms. Additional exploratory analyses will use mixed effects models, to compare mean bone health within the four treatment arms during the intervention time and follow-up period of the study. The mixed effects

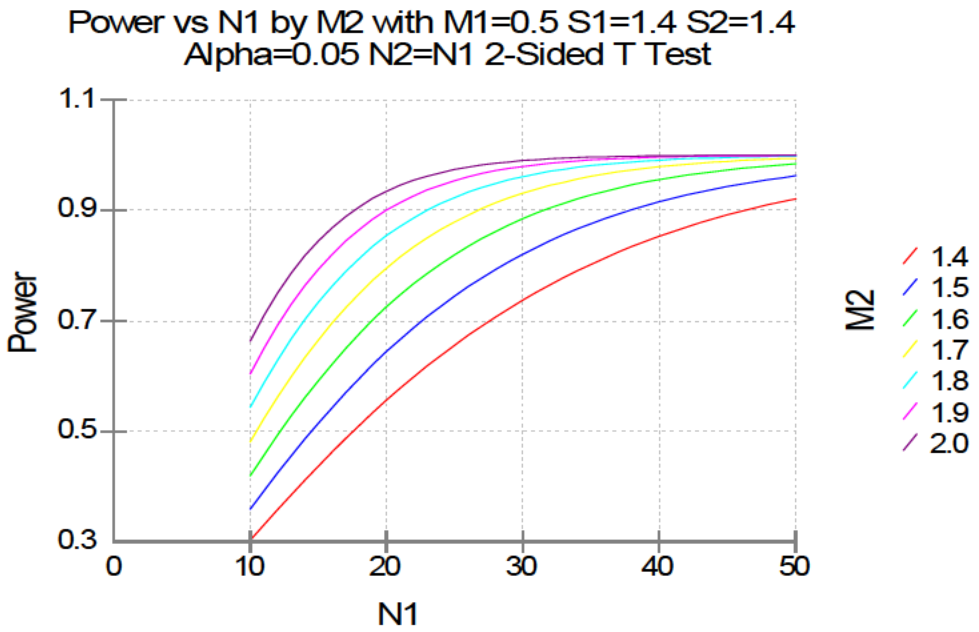
models will use the change in bone health levels (NTx, BAP) during the study and during follow-up as the outcomes. The subject will be included as a random effect, and treatment arms, time, their interactions, hormone therapy, and baseline bone health levels will be included as fixed effects. Individual trial arms will be compared to each other and the interaction term between treatment and time is used to investigate whether the benefit of the intervention changes with time. **Because of the small sample size and the resulting low statistical power, these secondary analyses will be interpreted very cautiously and only used to aid in the design of a study for our future K07 application.**

7.1.6 Additional analyses will examine between group differences in the other outcome measures. These will include Physical Activity (ACLS and Pedometer), aerobic capacity (VO2max treadmill test), muscular strength (handgrip dynamometry and 7-10 repetition maximum), and muscle mass (Bioelectrical Impedance).

7.2 Sample Size

7.2.1 Seventy-two women (18 women per treatment arm) were selected as an adequate size to provide pilot data for subsequent studies.

7.2.1.1 Based on the enrollment numbers above, the study will be able to detect a 40% difference in effects size between bone resorption and formation with 80% statistical power between the groups. Below is a graph of various effect sizes and the corresponding statistical power.



7.2.2 Based on a discussion with breast cancer clinicians at the University of Rochester Medical Center about patient volume and projecting an accrual rate of 50%, it will take approximately ten months to enroll 72 women.

8.0 Records to be Kept

Schedule of Clinical Visits, Data and Specimen Collection				
	Time Since Randomization			
Procedure	0	5 Days	6 Weeks	12 Weeks
Eligibility Interview	+			
Informed Consent	+			
Medical History	+		+	+
Assess Supplement Use	+	+	+	+
Blood CBC Levels	+	+	+	+
Serum 1, 25 OH_2 D_3 Levels	+	+	+	+
Bone Biomarkers	+		+	+
On Study Data (Demographics and Clincal Data)	+			+
Phone call reminders	Weekly	Weekly	Weekly	Weekly
Toxicity monitoring	+	+	+	+
Daily Diary	Daily	Daily	Daily	Daily
Functional Assessment of Chronic Illness Therapy (FACIT) (28-item QOL measure & 13-item fatigue subscale)	+			+
Brief Fatigue Inventory (BFI) (Severity of fatigue and level of interference in activities of daily living - 9 items)	+			+
Symptom Inventory (13-item symptom rating scale)	+			+
VO2max Treatmill Test	+			+
Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS) (15-item physical activity history measure)	+			+
Pedometer	+			+
Tandem Wallk Test (TWT)	+			+
Handgrip Dynamometer	+			+
7-10 Maximum Repetition	+			+
Bioelectrical Impedance Analysis	+			+

8.1 All hardcopy research records will be stored onsite in the University of Rochester Medical Center, in the Behavioral Medicine Unit of the James P. Wilmot Cancer Center. The Cancer Center is secured by electronic key cards. Offices within the Cancer Center are again secured by key and data is kept in locked file cabinets. Electronic research records are stored on the University of Rochester Medical Center's password secured and firewall protected networks. These are the same methods of security used for patient medical records. Human serum samples and biopsy samples are stored in locked freezers, within locked and alarmed laboratories that are accessible by key codes and electronic card swipes. All study data will be kept for a period of 10 years after the study and all reports and publications are complete.

8.2 All data (information, human blood samples, and human tissue samples) collected for the current study will be used in post hoc analyses as appropriate. No blood or biopsy samples will be banked. The patient is provided the opportunity to be contacted for future research studies in the informed consent. The patient's individual research record will not be shared with their treating physician, unless they provide consent or the patient's treating physician is a study physician, in

which case they will have access to study data as a study co-investigator. Overall study results will be presented to participants, faculty and staff at the University of Rochester Medical Center after completion of the study. Study results will be presented at professional meetings and published.

8.3 The study coordinator will assign a numerical Study ID to each participant once they have signed the consent form. All study forms and questionnaires will use this number and the participant's first, middle, and last initials as identifiers, to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with study ID, name, and contact information will be maintained separately. This linkage information will only be accessible to the study coordinator, study investigators, and the individual responsible for maintaining the database.

9.0 Patient Consent and Peer Judgment

9.1 Current, state, federal, and institutional regulations concerning informed consent will be followed.

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