

**UNIVERSITY OF ROCHESTER CANCER CENTER**

**A Pilot Study of the Effects of High-Dose Oral Calcitriol  
on Bone Health in Breast Cancer Patients**

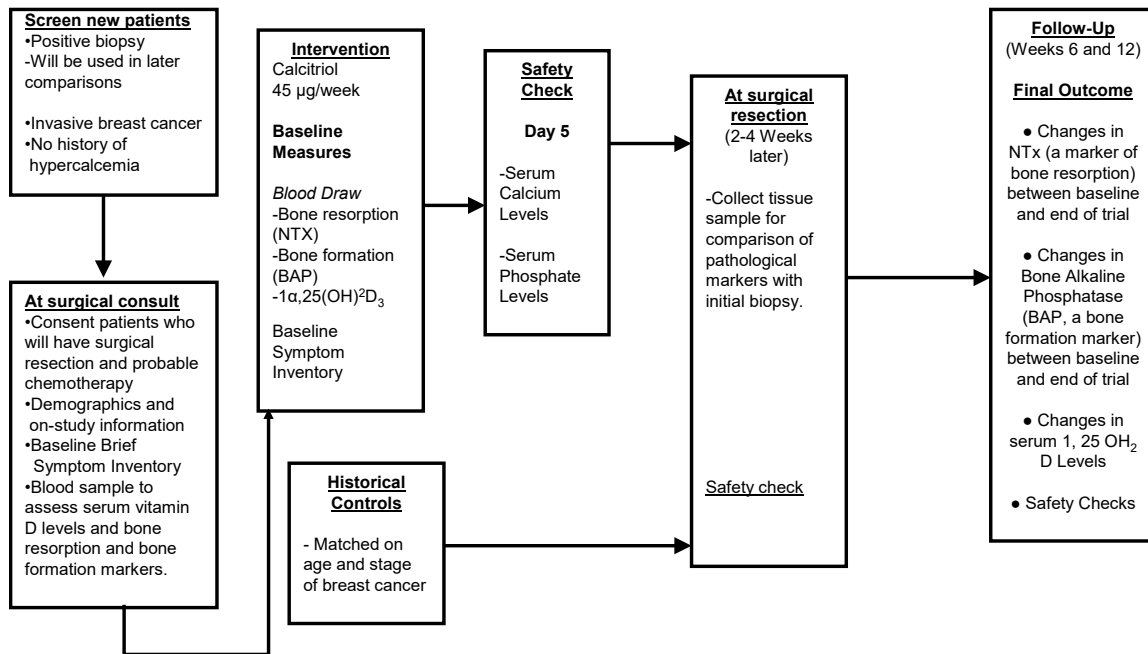
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## Study Schema



The calcitriol intervention is aimed at reducing fracture risk by maintaining proper bone density. Calcitriol is efficacious in maintaining proper bone health and muscle mass among the general population, but little research has been done on breast cancer patients. In addition, calcitriol may be effective in reducing tumor proliferation and angiogenesis, while increasing tumor apoptosis. Each of those factors could have beneficial effects on breast cancer outcomes.

**Hypothesis:** A weekly oral dose of calcitriol 45 µg will be efficacious in preventing bone loss among invasive breast cancer patients.

## Primary Objectives

To collect data on the efficacy and feasibility of Calcitriol 45 µg for maintaining proper bone health among invasive breast cancer patients for a period of 12 weeks.

To collect preliminary data on the effect of Calcitriol 45 µg on bone resorption, as measured by Cross-Linked N-Telopeptide of Type I collagen (NTx) in invasive breast cancer patients over the course of 12 weeks.

To collect preliminary data on the effect of Calcitriol 45 µg on markers of bone formation, as measured by bone-specific alkaline phosphatase (BAP) in invasive breast cancer patients over the course of 12 weeks.

## Secondary Objective

To collect preliminary data on the effect of pre-surgical Calcitriol 45 µg therapy on tumor cell apoptosis (caspase 3 and survivin), tumor cell proliferation (Ki-67), tumor invasiveness (ER  $\alpha$ , PgR, VDR, EGFR, HER2, VEGF, and IGFR), 1 $\alpha$ ,25(OH)<sup>2</sup>D<sub>3</sub>, and Mammostrat Recurrence Score in invasive breast cancer patients.

## **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.<sup>1</sup> In addition to the incident cases of invasive breast cancer, an additional 62,000 cases of cancer in situ will be diagnosed.<sup>2</sup> In this year, breast cancer will claim the lives of 40,480 women in the United States, which represents 15% of the total cancer deaths.<sup>1</sup> 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 at the time of diagnosis.<sup>3</sup> The incidence rate for estrogen receptor positive (ER+) breast cancer is approximately 190 per 100,000 women, while 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 total breast cancers display some sort of estrogen activity.<sup>4</sup> The mortality rate for breast cancer is lower compared to other cancer sites, with an overall 5-year survival of 89% for all stages of breast cancer and 98% for localized breast cancer.<sup>2</sup> Due to the decreasing mortality rate of cancer, there are more than 10 million cancer survivors in the United States alone, with more than 2 million breast cancer survivors.<sup>5, 6</sup> 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 identify the ability to safely participate in a high-dose oral calcitriol (a vitamin D analog) intervention. Additionally, the influence of the intervention on bone health and pathological tumor markers will be evaluated. 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% in men.<sup>7, 8</sup> Progressive bone loss can lead to a condition called 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.<sup>9</sup> In 2004, there were an estimated 10 million women with osteoporosis

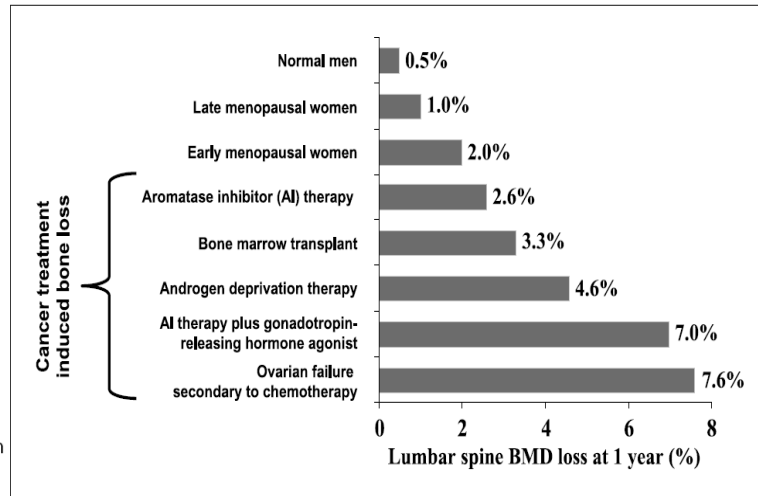
and an addition 34 million women with its precursor, osteopenia.<sup>9</sup> The effects of osteoporosis can be devastating. Every year, hip fractures are responsible for 300,000 hospitalizations.<sup>10</sup> Studies have shown that up to 25% of the elderly who fracture a hip die within one year.<sup>10</sup> Other research has found that over 30% of survivors will be permanently disabled and approximately 20% of survivors will need long-term care in a nursing home.<sup>11-14</sup> The cost attributed to hip fractures can exceed \$80,000 per person and costs the United States over \$25 billion annually, along with 550,000 years of lost life.<sup>10</sup>

### 1.3 Calcitriol and Bone Health

Calcitriol could prove to be a safe, low-cost treatment for preserving bone health in breast cancer patients. Humans obtain Vitamin D from sunlight, food, and supplementation.<sup>15</sup> Vitamin D plays a vital role in maintaining proper bone health and works in conjunction with calcium. Greater levels of vitamin D have been shown to increase the intestinal absorption of calcium.<sup>16</sup> One study demonstrated that an increase in serum vitamin D produced a 45%-65% increase in intestinal absorption of calcium.<sup>17</sup> 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.<sup>18</sup> Based on these guidelines, it is estimated more than 1 billion people worldwide and between 40%-100% of elderly U.S. residents are vitamin D deficient.<sup>19-22</sup> Further research has shown that more than 50% of postmenopausal women already being treated for osteoporosis had deficient vitamin D levels.<sup>23, 24</sup>

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.<sup>25</sup> Chemotherapy, hormone therapy, and radiation treatment frequently lead to, either directly or indirectly, to bone mass depletion in breast cancer patients.<sup>26</sup> Studies have documented accelerated bone loss in breast cancer patients, and this bone loss frequently goes undiagnosed.<sup>6, 27, 28</sup> Research shows that breast cancer survivors have greater bone loss than women of similar age who were not diagnosed with cancer.<sup>29-31</sup> Researchers believe that risk factors for bone loss are already present in many women preceding a breast cancer diagnosis.<sup>29</sup> Treating bone loss in a prophylactic manner leads to greater success than delayed treatment.<sup>32, 33</sup> The accelerated bone loss seen in these patients in all likelihood will lead to a higher rate of falls and fractures.<sup>34, 35</sup>

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.



However, the American Society of Clinical Oncology (ASCO) recommends pharmaceutical interventions (e.g. bisphosphonates) only after a severe amount of bone loss in patients considered osteoporotic.<sup>36</sup> A host of side effects exist for patients taking bisphosphonates. For those taking the oral medication, poor GI absorption, nausea, and diarrhea are all common effects.<sup>37</sup> Those on IV bisphosphonates commonly experience fever, flu-like symptoms, and myalgia.<sup>38</sup> Among the most serious side-effects is osteonecrosis of the jaw, which can require surgical intervention.<sup>39, 40</sup> All of these side-effects tend to lead to poor compliance.<sup>41</sup> A review of bisphosphonate compliance found that patients were between 18% and 78% compliant with the medication.<sup>42</sup>

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.<sup>43</sup> Trials that used a low-dose vitamin D intervention ( $\leq 400$  IU/d) failed to find significant prevention of fractures.<sup>20, 44</sup> In contrast, interventions that used a higher dose of vitamin D ( $\geq 700$  IU/d) found significant positive effects on fracture prevention.<sup>45-49</sup> A pooled analysis of those trials found vitamin D significantly reduced the risk of hip fracture by 26% and any nonvertebral fracture by 23%.<sup>50</sup> Other interventions used the active vitamin D analog, calcitriol, because of its higher efficiency and quicker absorption in humans. These trials demonstrated calcitriol is effective in maintaining bone mineral density and reducing fractures.<sup>51-57</sup> 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.<sup>58</sup>

In addition to regulating bone health, vitamin D also protects against falls and helps maintain muscular strength.<sup>59, 60</sup> A meta-analysis of 5 randomized clinical trials reported a 22% reduction in falls by those receiving vitamin D

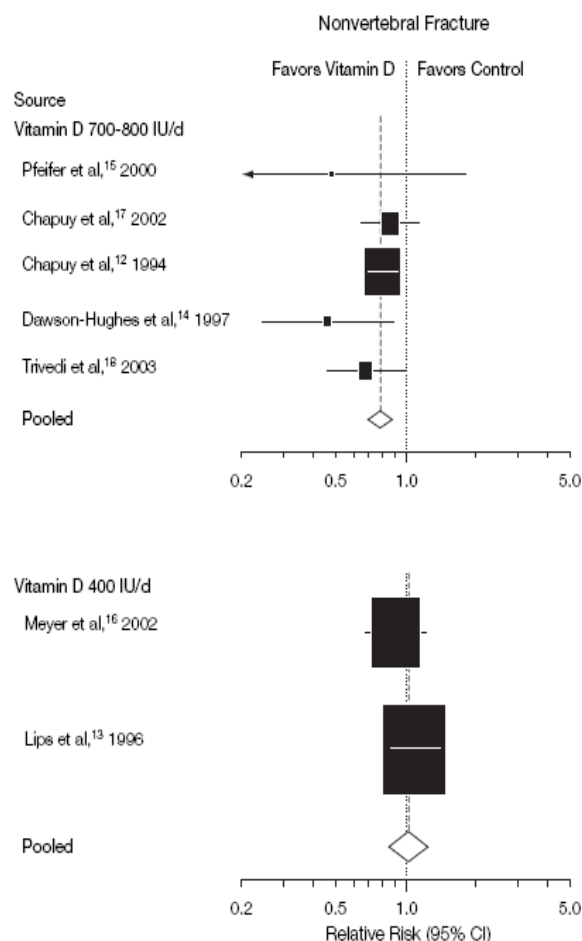
supplementation.<sup>61</sup> Similarly, calcitriol has been shown to protect against falls. One trial found those supplemented with calcitriol, in addition to having adequate calcium intake, had a 55% reduction in falls.<sup>62</sup> A 2001 intervention trial reported a significant reduction in the number of falls for those treated with calcitriol compared to placebo.<sup>54</sup> A recent comparative meta-analysis concluded that calcitriol was more effective at preventing falls than native vitamin D.<sup>63</sup>

#### 1.4 Other Effects of Calcitriol

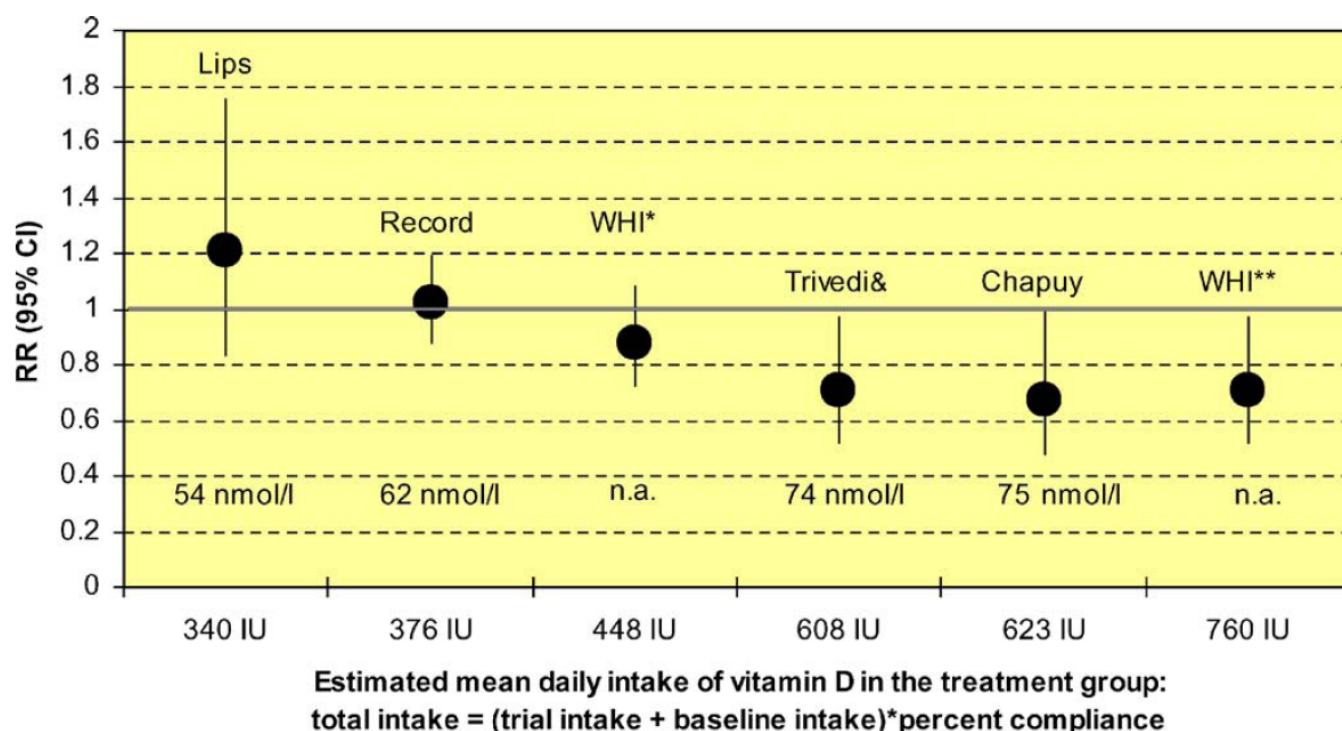
Research during the past 10 years has demonstrated that appropriate intakes may provide greater benefits than previously known.<sup>64</sup> Vitamin D exerts numerous effects on cellular growth and regulation through both genomic and non-genomic mechanisms.<sup>65</sup> The effects are mediated through the vitamin D receptor (VDR), which has been found in both neoplastic and non-neoplastic tissues of the breast, pancreas, colon, brain, lymph nodes, among other sites.<sup>66-68</sup> Tumor regression or growth reveals the balance between cellular proliferation and cellular death.<sup>69</sup> Reducing tumor cellular proliferation drives towards tumor regression, as apoptosis outpaces proliferation.<sup>70</sup> Both in vitro and in vivo studies have demonstrated calcitriol is extremely effective at reducing breast cancer cell proliferation.<sup>71-75</sup> Additional research has found that calcitriol is also extremely efficient at inducing apoptosis in breast cancer cells.<sup>76-79</sup> Angiogenesis is the formation of new blood vessels and is usually a hallmark in tumor metastasis.<sup>80</sup> High-dose calcitriol has exhibited the ability to significantly limit the angiogenic potential of breast tumors.<sup>81-83</sup>

#### 1.5 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.<sup>20, 44</sup> Some researchers have suggested that interventions should use high, intermittent doses of vitamin D to increase serum levels and overcome low adherence.<sup>84</sup> Trials that supplemented participants with  $\geq 700$  IU/d of vitamin D were able to show protection against bone loss.<sup>45-49</sup> In both North America and Europe, the upper limit for vitamin D intake is considered to be 2,000 IU/d.<sup>85, 86</sup> However, many researchers, even government committees, believe numerous individuals are vitamin D deficient and the upper limit is too low.<sup>43, 87, 88</sup> These recommendations were formulated out of concern for safety and to prevent toxicity, such as hypercalcemia.<sup>64</sup> However, a growing number of clinical trials



have given vitamin D doses many times the upper limit. One trial administered 100,000 IU of vitamin D every four months for five years without reports of toxicity.<sup>49</sup> Another intervention administered 50,000 IU/d of vitamin D for a period of 8 weeks without a change in serum calcium.<sup>89</sup> 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.<sup>90</sup> A review of these trials shows that vitamin D is not toxic at intakes much greater than previously considered unsafe.<sup>64</sup>



**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)

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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.<sup>91, 92</sup> In recent years, researchers discovered that a less frequent dosing schedule allowed them to circumvent potential dose-limiting toxicities.<sup>93, 94</sup> A weekly administration of high-dose oral calcitriol was shown to be safe in cancer patients.<sup>95, 96</sup> The dosage was not limited by toxicities, but rather by nonlinear pharmacokinetics.<sup>97</sup> Subsequent studies have shown substantial dose escalation was possible when calcitriol was administered once a week.<sup>98-105</sup> Trump et al. were able to administer 12 µg of calcitriol three consecutive days (36 µg/week) without any dose-limiting toxicities.<sup>106</sup> A trial of prostate cancer patients found that 60



µg/week of calcitriol was well tolerated with docetaxel, as the patients did not show signs of hypercalcemia.<sup>107</sup> Recently, 7 separate clinical trials were able to successfully administer 45 µg/week (or 0.5 µg/kg/week) of calcitriol to patients undergoing adjuvant cancer therapy.<sup>108-114</sup> In the larger trials, participants were able to remain on calcitriol for one year or longer.<sup>115,116</sup> These studies demonstrated this dose was well tolerated and adverse events were extremely rare. In fact, a number of studies have shown that doses much greater than can be safely administered. A phase I study in patients with cancer found calcitriol was well tolerated at a dose of 165 µg/week.<sup>117</sup> Another phase I trial administered calcitriol at doses up to 38 µg/d for three consecutive days (114 µg/week) without dose-limiting toxicity.<sup>118</sup> It is these trials which that established intermittent oral dosing of calcitriol as a method of significant dose escalation and produced potentially therapeutic levels.<sup>119</sup> Additionally, calcitriol enhances the effects of radiation, chemotherapy, hormone therapy, and other antineoplastic treatments.<sup>120-123</sup> 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.

### 1.6 Summary

We propose to conduct a feasibility and efficacy pilot in breast cancer patients studied over 12 weeks to identify the ability to safely participate in a high-dose oral calcitriol intervention and to investigate the subsequent effects on bone health. The study will accrue 25 patients and is intended to provide pilot data for a later grant submission. The anticipated results could serve as 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**

The calcitriol intervention is aimed at reducing fracture risk by maintaining proper bone density. Calcitriol is efficacious in maintaining proper bone health and muscle mass among the general population, but little research has been done on breast cancer patients. In addition, calcitriol may be effective in reducing tumor proliferation and angiogenesis, while increasing tumor apoptosis. Each of those factors could have beneficial effects on breast cancer outcomes.

**Hypothesis:** A weekly oral dose of calcitriol 45 µg will be efficacious in preventing bone loss among invasive breast cancer patients.

## **2.1 Primary Objectives**

- 2.1.1 To collect data on the efficacy and feasibility of Calcitriol 45 µg for maintaining proper bone health among invasive breast cancer patients for a period of 12

weeks.

- 2.1.2 To collect preliminary data on the effect of Calcitriol 45 µg on bone resorption, as measured by Cross-Linked N-Telopeptide of Type I collagen (NTx) in invasive breast cancer patients over the course of 12 weeks.
- 2.1.3 To collect preliminary data on the effect of Calcitriol 45 µg on markers of bone formation, as measured by bone-specific alkaline phosphatase (BAP) in invasive breast cancer patients over the course of 12 weeks.

## **2.2 Secondary Objective**

- 2.2.1 To collect preliminary data on the effect of pre-surgical Calcitriol 45 µg therapy on tumor cell apoptosis (caspase 3 and survivin), tumor cell proliferation (Ki-67), tumor invasiveness (ER α, PgR, VDR, EGFR, HER2, VEGF, and IGFR), 1α,25(OH)<sup>2</sup>D<sub>3</sub>, and Mammostrat Recurrence Score in invasive breast cancer patients.

## **3.0 Subject Eligibility**

### **Inclusion Criteria:**

- 3.1 Must be female.
- 3.2 Must have pathologically confirmed incident, primary invasive breast cancer.
- 3.3 Must be awaiting surgical resection.
- 3.4 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.
- 3.5 Must provide informed consent.
- 3.6 Must be willing to discontinue use of calcium and/or vitamin D supplements other than multivitamin supplementation.
- 3.7 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.

### **Exclusion Criteria:**

- 3.8 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.
- 3.9 Patients with severe metabolic disorders, which includes phenylketonuria (PKU), homocystinuria, and Fabry's disease, that would preclude them from taking calcitriol.
- 3.10 Patients with a previous history of any other cancer except non-melanomous skin cancer within the past 5 years.
- 3.11 Patients with impaired renal function (CRCL < 60 mL/min) or who had kidney stones (calcium salt) within the past 5 years.
- 3.12 Patients with hypercalcemia (corrected serum CA > 10.2 mg/dl) or a history of hypercalcemia or vitamin D toxicity.
- 3.13 Patients currently taking calcium supplements or aluminum-based antacids must immediately discontinue their use if they are to enroll in the study.
- 3.14 Patients currently taking vitamin D supplements must immediately discontinue their use if they are to enroll in the study.
- 3.15 Patients with a known sensitivity to calcitriol.
- 3.16 Women who are pregnant or lactating.
- 3.17 Women on antiresorptive drugs (e.g. bisphosphonates) within the past year.
- 3.18 Women currently using oral contraception.
- 3.19 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).
- 3.20 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.

#### **4.0 Treatment Assignment**

- 4.1 All patients who meet the eligibility criteria, sign the patient informed consent

form, and complete baseline assessments will immediately be assigned to the treatment Arm.

4.1.1 This is a single sequence study with one trial arm, and patients will be assigned to the intervention arm as follows:

<b><u>Treatment Arm</u></b>	<b><u>Condition</u></b>
1	<i>Calcitriol 45 µg</i> : Patients will be given 45 µg/week of calcitriol beginning prior to surgical resection for a period of 12 weeks.

## **5.0 Treatment Protocol**

5.1 This will be a one-arm clinical trial examining the feasibility and efficacy of a Calcitriol 45 µg regimen for the maintenance of bone health among invasive breast cancer patients.

### **5.2 Consent Process and Initial Assessments**

#### **5.2.1**



5.2.1.1 Patients will be evaluated by their treating physician approximately once a month while enrolled in this study.

5.2.2 Upon consent, the patient will complete an On-Study Data Form providing demographic data. Questions concerning the patients' sun exposure history, medical history, supplement usage history, along with baseline brief symptom inventory are also included. Additionally, patients will be evaluated on vitals (Resting Heart Rate, Height, Weight & Blood Pressure). Patients will proceed to phlebotomy to give a blood sample. They will then proceed to the University of Rochester Medical Center pharmacy to receive their study medication.

5.2.3 Any woman of childbearing potential will have a pregnancy test. If the woman is not pregnant, she may proceed with the study. The women must also agree to practice barrier methods of contraception for the duration of the study.

5.2.4 All patients 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 Bone Health Biomarkers and Pathological Markers

5.3.1 Measures of bone pathology will be performed through ARUP Medical Laboratories. Pre and post-intervention tests for Cross-linked N-telopeptide of type I collagen (NTx), a specific indicator of bone resorption will be performed. In addition, pre and post-intervention test for bone-specific alkaline phosphatase (BAP), an indication of bone formation will be performed.

5.3.2



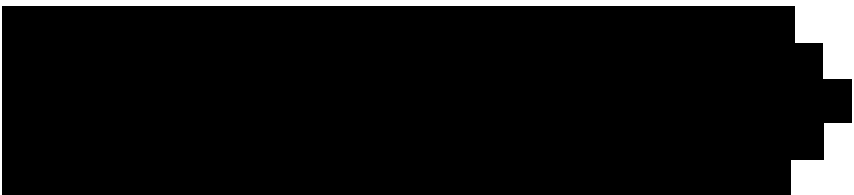
### 5.4 Calcitriol 45 µg Intervention

5.4.1 The Calcitriol 45 µg intervention will be monitored and directed by a team of professionals including: Dr. Luke J. Peppone, Research Assistant Professor of Radiation Oncology at the University of Rochester Medical Center, Dr. Gary R. Morrow, Professor of Radiation Oncology at the University of Rochester Medical Center; Dr. Kristen Skinner, Chief of Surgical Oncology at the University of Rochester Medical Center; Dr. Mary Reid, Research Scientist at Roswell Park Cancer Institute; and Dr. David G. Hicks, Director of Surgical Pathology at the University of Rochester Medical Center.

5.4.2 The Calcitriol 45 µg intervention will follow the guidelines listed below:

5.4.2.1 The Calcitriol 45 µg intervention is based on previous trials of Calcitriol 45 µg conducted among cancer patients.<sup>125-133</sup>

5.4.2.2



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 5.4.3 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  $\geq 3$  toxicity related to the study drug will be removed from the study. **Toxicities resulting from the study drug or removal from the study will not result in a delay of surgical resection.** Patients will also have a safety check during their pre-surgical workup. 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 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  $\geq 3$  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  $\mu$ g 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:<sup>134</sup>

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 quicker than with native vitamin D supplementation.

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

Late signs and symptoms of vitamin D intoxication: 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). 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.

#### 5.4.4 Adverse Events

5.4.4.1 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.

5.4.4.2 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.

5.4.4.3 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.

#### 5.4.5 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.

#### 5.4.6 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.

- 5.4.7 All study drugs will be dispensed and all biological specimens will be collected at the University of Rochester Medical Center.
- 5.4.8 The principal investigator and/or the study coordinator will be present at all participant study visits. Checklists for study procedure elements will be used to ensure compliance.
- 5.4.9 The data is collected by either the study coordinator or the principal investigator. The paper files that may contain identifying information are kept in a locked file within the locked study coordinators office. When the data is entered into the computer, no identifying information is used and only available to staff within the Behavioral Medicine Unit of Radiation Oncology. Computer records with identifying information are kept in locked files only accessible by the data manager, the PI, and study coordinator, and will be password protected.

Numerous mechanisms are in place to ensure the data integrity and validity. The study uses the exact same procedures as the University of Rochester Community Clinical Oncology Program (CCOP) uses. The University of Rochester serves as a research base for CCOP, which is an NCI sponsored collection of clinical centers for the conduct of multi-center clinical trials, which has been sponsored for more than 25 years. All the methods of data collection and the instruments have been previously validated and have been used in numerous trials conducted at the University of Rochester.

- 5.4.10 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.

## **6.0 Treatment Evaluation**

### **6.1 Measures**

### 6.1.1 Bone health biomarkers

6.1.1.1 Levels of bone resorption will be measured by **Cross-linked N-telopeptide 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 has been shown to be a valid and reliable measure of bone resorption.<sup>135</sup> Researchers believe that markers of bone resorption are superior to markers of bone formation and more accurately predict changes in bone mass.<sup>136</sup> Bone resorption markers are also able to predict failing bone health in advance of BMD.

6.1.1.2 Levels of bone formation will be measured by **bone-specific alkaline phosphatase (BAP)**. Bone formation markers, specifically (BAP), are also considered a valid measure of bone health.<sup>137, 138</sup> Although BAP is a valid measure of bone health, measures of bone resorption tend to be better predictors of bone health.

6.1.2 Breast tumor prognostic markers will be assessed using a number of markers specific to malignancies.



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.1.2.2

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 6.1.3 Cancer symptoms

6.1.3.1 The effects of breast cancer will be measured by the **Symptom Inventory**. The Symptom Inventory is a list of 13 symptoms modified from measures created at MD Anderson and Memorial-Sloan Kettering Cancer Centers. Patients are asked to rate the severity of several symptoms, such as pain, nausea and fatigue. Responses are anchored using an 11 point scale ranging from 0 to 10 (Not Present At All to As Bad As You Can Imagine).

## **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:

[REDACTED]

7.1.7

[REDACTED]

7.1.8



## 7.2 Sample Size

7.2.1 Twenty-five women will constitute an adequate size to provide pilot data for subsequent studies.

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 25%, it will take approximately one year to enroll 26 women.



## 8.0 Records to be Kept

Schedule of Clinical Visits, Data and Specimen Collection					
Procedure	Time Since Randomization				
	0	5 Days	2-4 weeks	6 Weeks	12 Weeks
Eligibility Interview	+				
Informed Consent	+				
Medical History	+			+	+
Assess Supplement Use	+	+		+	+
Blood CBC Levels	+	+	+	+	+
Plasma Vitamin D Levels	+	+	+	+	+
Bone Biomarkers	+			+	+
Symptom Inventory	+				+
Phone call reminders	Weekly	Weekly	Weekly	Weekly	Weekly
Toxicity monitoring	+	+	+	+	+
Surgical Resection			+		

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 samples or biopsy samples will be banked and data will not be used for future studies without prior consent of the patient. 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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