[Frontiers in Bioscience E4, 546-567, January 1, 2012]

Dietary supplements and natural products in breast cancer trials

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1. ABSTRACT

The association between breast cancer and modifiable health behaviors is well supported. At least one-half of all cancers are suggested to have a dietary component. It is not surprising therefore that many of the dietary agents and natural health products that have attracted the attentions of scientists and practitioners are now moving into clinical trials. In this report, we review 65 clinical intervention trials evaluating over 30 dietary supplements and natural health products for use in breast cancer. The products being tested in these trials fall broadly into the following categories: (i) vitamins, minerals, cofactors; (ii) herbal extracts; (iii) amino acids; (iv) fatty acids; (v) animal products; (vi) probiotics; (vii) phytochemicals; and (viii) combination formulations. Trial outcome measures include risk modification, efficacy testing (with dietary supplements alone or dietary supplementanticancer drug combinations), toxicity reduction, biomarker identification, symptom management, and quality of life parameters. The wide range of interests in natural product testing at the clinical trial level supports the potential utility of these agents in the breast cancer prevention, treatment, and management regimens of the future.

2. INTRODUCTION

Cancer, overall, is expected to increase in this country by as much as 45% over the next twenty years (1) Breast cancer is a particular concern. The American Cancer Society estimates that there will be well over 200,000 new cases of invasive breast cancer and over 50,000 new cases of *in situ* breast cancer in this country for the year 2010 alone. According to current statistics, 1500 Americans will die of cancer each day with a significant percentage from breast cancer (2)

Although a wide variety of treatment options are available, breast cancer remains the second leading cause of death in American women. Treatment strategies depend on the characteristics of both the tumor (including stage, grade, and molecular profile (ER, PR, ERBB2, BRCA1/2)), and the patient (age, health, menopausal status, family history) Conventional treatment options for early breast cancers (ductal carcinoma *in situ* and early invasive breast cancer) include surgery and radiation therapy with or without chemotherapy, endocrine agents, or targeted antibodies (3-5) A partial listing of standard chemotherapeutic drugs is shown in Table 1. Different drugs or therapeutic approaches are often combined in an effort to decrease the severity of side effects while maintaining or improving survival. Nevertheless, toxicity continues to be the most critical limiting factor involved in ensuring patient safety (5-6) Finding an effective treatment protocol with a favorable risk-to-benefit ratio is often the strongest obstacle to successful therapy. Adverse events from systemic therapy with cytotoxic drugs can be severe enough to cause damage to major organ systems; localized radiotherapy can lead to fibrosis, pain, edema, and irreversible changes in mobility (5-8) These problems underscore the need for safer alternatives to conventional cancer therapy (9-10) and promote interest in CAM modalities (10-12)

The use of CAMs, dietary supplements, and natural health products is believed to be high among individuals with chronic health problems. To examine the prevalence of CAM use among women who had been diagnosed with- or were at risk for developing breast cancer we surveyed the literature (13-27) We examined 15 studies conducted in 6 different countries involving over 17,000 women. The average CAM use across all 15 of these studies was approximately 72% with prevalence rates ranging from 40 to 96% (Table 2) Interest in CAMs, dietary supplements, and natural health products by consumers, health care professionals, and patients is burgeoning. It has not only fueled a tremendous expansion in our knowledge, but it is leading the way for a more integrated, multidisciplinary approach to the practice of medicine. When we ask the question of whether the effectiveness of cancer therapy can be increased by natural health products, we will be able to look to clinical trials for answers.

This review describes some of the types of dietary supplements and natural health products that are currently undergoing clinical testing. We identified 65 clinical trials that were either active or open at the time of this writing (through April of 2010) These trials are expected to accrue a cumulative total of over 9,000 women testing more than 30 natural compounds for their abilities to modify breast cancer risk, enhance treatment responses or reduce the toxicities associated with standard chemotherapy. Brief summaries of the available evidence will be provided for a portion of the dietary supplement interventions in the sections that follow. The summaries will also be correlated with the more detailed trial descriptions provided in Table 3.

3. CLINICAL TRIALS

3.1. Trial activity and enrollment

The purpose of this review was to identify the types of dietary supplements and natural health products that are currently undergoing clinical trial testing for breast cancer. Although not exhaustive, a search conducted between the February and April of 2010, produced 84 trials which met our specifications; all trials were interventional, open at the time of inquiry, and involved interventions with dietary supplements or natural health products for breast cancer. We selected 65 clinical trials from the original 84 for this review. All 65 trials centered on the use of dietary or natural products and most were aimed at measuring treatment efficacy, risk reduction, symptom management or toxicity prevention in breast cancer.

Participant enrollment was highly variable from trial to trial, ranging from 9 (trial 31) to 2,300 (trial 9), as shown in Table 3. The total projected accrual across all trials was over 9,000, with a per trial average of 139. At the time of this writing, 41 trials were actively recruiting participants, 22 trials were active but no longer recruiting while 2 of the trials were open but had not yet begun recruiting their participants. These are identified in Table 3 by green, yellow, or blue coding, respectively.

3.2. Trial Types and Phases

When we reviewed the purpose for each of the 65 trials in Table 3, four different types of trials emerged. These were: Prevention, Treatment, Supportive Care, and Basic Science (summarized in Table 4) We found that 20 trials were focused on breast cancer Prevention, 21 on Treatment, 17 were aimed at Supportive Care and 7 were involved in Basic Science. We also examined the phases designated for each of the trials.

Clinical trial testing traditionally uses the phase designations I- IV to sequentially evaluate new agents or treatments in order to prove safety, activity, and efficacy in human populations. A newer trial phase, designated phase 0, was recently developed in response to the United States Food and Drug Administration's (FDA) exploratory Investigational New Drug (IND) guidelines with the goal of streamlining the clinical evaluation process (28) Phase 0 trials are conducted with small numbers of participants to establish effectiveness and determine pharmacodynamics for further clinical development. Phase I trials test recommended doses and/or schedules needed for progression into phase II testing. Participant numbers in

Table 1. Chemotherapeutics for breast cancer (partial list[1])

Paclitaxel	Vinblastine
Docetaxel	Pralatrexate
Capecitabine	Methotrexate
Doxorubicin	Vinorelbine
Gemcitabine	Epirubicin
5-fluorouracil	Irinotecan
Ixabepilone	Cisplatin
Vincristine	Oxaliplatin

[1]also see ref. 78

Table 2. Prevalence of CAM use in the context of breast cancer

Study Objectives	Country	N =	Prevalence[1] %	Reference
Use of at least 1 CAM therapy for early stage breast cancer	US	222	58	(13)
CAM use for symptom management in women with breast cancer	Canada	1,434	80	(14)
CAM use after being diagnosed with breast cancer	China	5,046	97[1]	(15)
CAM use in breast cancer patients	US	288	84	(16)
Breast cancer patients that reported using CAMs	Australia	367	87.5	(17)
CAM use in women with metastatic stage IV breast cancer	Turkey	68	58.8	(18)
CAM use 12 to 16 weeks after breast cancer surgery	Denmark	3,343	40.1	(19)
Reported use of CAMs before/after breast cancer diagnosis	US	1,000	96.5[1]	(20)
CAM use by women at high risk for breast and ovarian cancer	US	164	78	(21)
CAM use in breast cancer survivors, 13 years after first diagnosis	US	335	59	(22)
CAM use in breast cancer survivors	US	2,022	62	(23)
CAM use in women with a diagnosis of primary breast cancer between 1990 and 1992	US	379	48	(24)
CAM use in long term breast cancer survivors, ≥5 years after diagnosis	US	608	75[1]	(25)
CAM use in disease-free breast cancer survivors, ~6.5 years after diagnosis	US	763	86.6	(26)
CAM use ≥1 year post breast cancer	US	115	69	(27)

[1] percentages shown represent the maximum prevalence

Table 3. Active clinical trials studying dietary supplements in breast cancer

1.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Soy Isoflavones and Breast Cancer Risk Reduction (NCT00204490)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double-Blind Phase II
INTERVENTION	**Soy Isoflavones** (with Multivitamins & Minerals)
PURPOSE	Changes in: serum markers of breast cancer risk, breast density, and bone mineral density after 2 years of soy isoflavones
OUTCOME MEASURES	Changes in breast density (primary); changes in bone mineral density (secondary)
PROTOCOL; COMPARATORS	Soy Isoflavones (pills with multivitamins & minerals, daily x 2 yrs) (experimental) vs. placebo (carbohydrate pills with multivitamins & minerals, daily x 2 yrs) (placebo comparator)
PARTICIPANTS	Enrollment: 200 healthy, premenopausal women between 30 and 42 y.o. with normal mammograms and regular menstrual cycles
2.TRIAL TYPE/PURPOSE/STATUS	Interventional, Diagnostic; Active, No Longer Recruiting
TITLE (ID#)	Effect of Soy Supplementation On Cellular Markers In Normal and Cancerous Breast Tissue: A Randomized Placebo Controlled Study (NCT00597532)
TYPE/PHASE	Interventional, Phase 0
INTERVENTION	**Soy Protein**
PURPOSE	To determine if certain cellular markers/gene products change after soy therapy, identify gene changes in normal and neoplastic breast tissue, and compare expression profiles
OUTCOME MEASURES	Changes in cancer tissue proliferation and apoptosis (primary); changes in the expression of cellular markers, such as HER2, tp53, cyclin D1, p27, BCL2, ER, and PR, that may be associated with breast cancer (secondary)
PROTOCOL; COMPARATORS	Soy protein (50 gm, 1/d) (experimental) vs. placebo (milk protein, 50 gm, 1/d) (placebo comparator)
PARTICIPANTS	Enrollment: 140 pre/postmenopausal women with a (+) biopsy for invasive breast cancer
3.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Soy Protein and Breast Cancer Risk Reduction (NCT00204477)
TYPE/PHASE	Interventional, Randomized, Double-Blind, Placebo-Controlled Phase II
INTERVENTION	**Soy Protein**
PURPOSE	To determine the efficacy of soy protein on ovarian steroid hormone levels in blood, urine, & breast fluid and breast density over a 2 year period
OUTCOME MEASURES	Mammographic breast density (primary outcome measure); ovarian hormone levels, bone mineral density (secondary outcome measures)
PROTOCOL; COMPARATORS	Soy protein (soy protein drink, daily x 2 yrs) (experimental) or cow's milk protein (caseinate protein drink, daily x 2 yrs) (placebo comparator)
PARTICIPANTS	Enrollment: 200 healthy, premenopausal women, 30-40 y.o., no oral contraceptives or hormone replacement, with normal mammograms and regular menstrual cycles
4.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE	The Effect of Soy Protein On Post- Breast Cancer Surgery Pain (NCT01047774)
TYPE/PHASE	Randomized, Placebo Controlled, Double Blind Phase II
INTERVENTION	**Isolated Soy Protein**
PURPOSE	To determine the effects of ingesting soy protein before breast cancer surgery on the development of chronic

	breast pain after surgery
OUTCOME MEASURES:	Number of women with post-surgical breast pain (primary); pain intensity (acute/chronic) & quality; disability; analgesic use; anxiety & depression; adverse events; previous soy consumption, e.g. childhood/adolescence (secondary)
PROTOCOL; COMPARATORS	Isolated soy protein (30-50 gm, 1/d x 2 weeks) (experimental) vs. isolated milk protein (30-50 gm, 1/d x 2 weeks) (placebo comparator)
PARTICIPANTS	Enrollment: 220 women > 21 y.o., who are scheduled for elective breast cancer surgery and axillary lymph node dissection
5.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	Soy Protein Supplement In Treating Hot Flashes In Postmenopausal Women Receiving Tamoxifen for Breast Disease (NCT00031720)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase II
INTERVENTION	**Soy Protein Isolate**
PURPOSE	To determine the effectiveness of soy protein in reducing the number and intensity of hot flashes during tamoxifen treatment for breast cancer
OUTCOME MEASURES:	To identify changes in the number and score of hot flashes (primary outcome measures)
PROTOCOL; COMPARATORS	Soy protein isolate (oral, 1/d x 12 weeks) (experimental) vs. placebo (oral placebo, 1/d x 12 weeks) (placebo comparator)
PARTICIPANTS	Enrollment: 130 postmenopausal women with histologically confirmed breast cancer, atypical ductal hyperplasia (ADH), DCIS, LCIS, or stage I-IIa invasive adenocarcinoma, who are being treated with tamoxifen and having ≥7 hot flashes per day
6.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, No Longer Recruiting
TITLE (ID#)	Effect of Dietary Soy On Estrogens In Breast Fluid, Blood, and Urine Samples From Healthy Women (NCT00513916)
TYPE/PHASE	Interventional, Randomized Phase III
INTERVENTION	**Soy Isoflavones**
PURPOSE	To study the effects of dietary soy isoflavones on estrogens in breast fluid , blood, and urine of healthy women without cancer
OUTCOME MEASURES	Determine the effects of isoflavone dose on: estrogen levels in nipple aspirate fluid & serum, changes in 2-, 16-alpha-, and 4-hydroxy estrogen urinary metabolites, cytologic patterns of breast epithelial cells from nipple aspirates (primary outcome measures)
PROTOCOL; COMPARATORS	High dose soy isoflavones (2 servings of soy food$^{\Delta}$/d x 6 mos.) (experimental) vs. low dose soy isoflavones (≤3 servings of soy food/wk x 6 mos.) (active comparator) followed by 1 month washout and cross-over to the other intervention arm ($^{\Delta}$Soy Foods: 1/2 c tofu or ¾ c soy milk or ¼ c soy nuts)
PARTICIPANTS	Enrollement:100 healthy, 30-45 y.o. premenopausal women with regular menstrual cycles
7.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	Omega-3 Fatty Acids In Treating Women With Newly Diagnoses Carcinoma *In situ* and/or Atypical Ductal Hyperplasia (NCT00627276)
TYPE/PHASE	Interventional, Randomized, Couble-Blind Placebo-Controled, Phase II
INTERVENTION	**Omega-3 Fatty Acid** capsules 3x/d for up to 8 wks
PURPOSE	To determine the efficacy of omega 3 fatty acids in the treatment of DCIS and/or ADH
OUTCOME MEASURES	Effect of omega 3 fatty acids on markers of breast cancer progression, including specific targets identified by microarray (primary)
PROTOCOL; COMPARATORS	Omega-3 fatty acids (capsules, 3 x/d x 8 wks.) (experimental) vs. placebo (olive oil capsules, 3/d x 8 wks.) (placebo comparator)
PARTICIPANTS	Enrollment: 40 women over 21 y.o. with newly diagnosed, biopsy confirmed DCIS and/or ADH alone or with a component of invasive carcinoma
8.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, Recruiting
TITLE (ID#)	Omega-3 Fatty Acid on Joint Symptoms Induced by Aromatase Inhibitors (NCT00930527)
TYPE/PHASE	Interventional, Non-Randomized, Uncontroled, Phase II
INTERVENTION	**Omega-3 Fatty Acids**
PURPOSE	To test the safety and efficacy of omega-3 fatty acids in alleviating musculoskeletal pain and stiffness associated with postmenopausal breast cancer treatment
OUTCOME MEASURES	Serum-free and total E2 levels (primary); changes in analgesic consumption (secondary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Omega-3 fatty acids (4 gm, 1 x/d x 3 wks.)
PARTICIPANTS	Enrollment: 10 postmenopausal women with a history of non-metastatic, stage I-III, ER (+) breast cancer currently taking 3rd generation aromatase inhibitors, having joint pain/stiffness & have not taken omega 3 fatty acids for ≥6 months prior to enrollment
9.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, No Longer Recruiting
TITLE (ID#)	Omega-3 Fatty Acids In Preventing Breast Cancer In Women at High Risk for Developing Breast Cancer (NCT00114296)
TYPE/PHASE	Interventional, Randomized, Placebo Controled, No Phase Given
INTERVENTION	**Omega-3 Fatty Acids**
PURPOSE	Effect of omega-3 fatty acids on breast cancer prevention in high risk women
OUTCOME MEASURES	Effects of omega-3fatty acids on mammographic breast density (1 yr. post treatment, primary outcome measure); breast cell atypia, proliferational; plasma hormone, growth factor, and lipid peroxidation levels (secondary outcome measures)
PROTOCOL; COMPARATORS	Omega-3 fatty acids (oral, 3/d x 1 yr) (experimental) vs. pacebo (oral, 3/d x 1 yr) (placebo comparator)
PARTICIPANTS	Enrollment: 80 women at increased risk for breast cancer (criteria: 5-year Gail risk = 1.7%, BRCA1/2 mutation carrier, family history consistent with hereditary breast cancer, atypical hyperplasia, LCIS, DCIS,

	invasive stage I breast cancer, or ovarian cancer)
10.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Nutritional Supplements & Horm'l Manipulations for Breast Cancer Prevention NCT00723398
TYPE/PHASE	Interventional, Randomized, No Phase Given
INTERVENTION	**Omega-3 Fatty Acids (Lovaza)**; Raloxifene
PURPOSE	Test the chemopreventive effects of omega-3 fatty acids in combination with Raloxifene
OUTCOME MEASURES	Mammographic breast density (primary); biomarkers of oxidative stress; urinary E2 metabolites; serum levels of C-reactive protein, IL-6, IGF-1, IGFBP-3, lipids (secondary)
PROTOCOL; COMPARATORS	No intervention (control) vs. Raloxifene (oral, 60 mg, 1/d x 2 yrs.) (experimental) vs. Raloxifene (oral, 30 mg, 1/d x 2 yrs.) (experimental) vs. Lovaza (= omega-3 fatty acid supplement, 4 gm, 1/d x 2 yrs.) (experimental) vs. Lovaza (4 gm, 1/d x 2 yrs.) + Raloxifene (30 mg, 1/d x 2 yrs.) (experimental)
PARTICIPANTS	Healthy postmenopausal women, 35 to 70 y.o., undergoing routine mammographic screening with breast density >25%, not taking hormone replacement therapy
11.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Open – Not Yet Recruiting
TITLE (ID#)	Omega-3 Fatty Acids and Chemotherapy-Induced Neuropathy and Inflammation In Breast Cancer (NCT01049295)
TYPE/PHASE	Interventional, Randomized, Placebo-Controlled, Double-Blind Phase IV
INTERVENTION	**Omega-3 Fatty Acids**
PURPOSE	To determine the effects of n-3 fatty acids on taxane-induced neuropathy/inflammation in invasive breast cancer
OUTCOME MEASURES	EMG-NCV test and serum levels of IL-1, IL-6, TNF-alpha, and hs-CRP (primary outcome measures); serum levels of: DHA and EPA fatty acid (secondary outcome measures); determined before and at the end of the taxane treatment period (= 3 mos.)
PROTOCOL; COMPARATORS	Omega-3 fatty acids (640 mg oil fish pearls, 3/d x 3 mos.) (experimental) vs. placebo (corn oil pearls, 3/d x 3 mos.) (placebo comparator); each during therapy with taxanes
PARTICIPANTS	Enrollment: 52 women with invasive breast cancer not on fish oil supplementation
12.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, No Longer Recruiting
TITLE (ID#)	Gemcitabine Combined With Mistletoe In Treating Patients With Advanced Solid Tumors (NCT00049608)
TYPE/PHASE	Interventional; Phase I
INTERVENTION	**Mistletoe Extract (Viscum Album Pini)**; Gemcitabine
PURPOSE	Study effectiveness of gemcitabine-mistletoe cotreatment advanced solid tumors
OUTCOME MEASURES; OBJECTIVES:	Determinations of: a) maximum tolerated dose (mtd) of gecitabine + mistletoe;toxcity; b) pharmacokinetic effects of gemcitabine with and without mistletoe; c) tumor response; d) time to neutrophil count recovery
PROTOCOL; COMPARATORS: 0	I.V. Gemcitabine HCL (days 1 & 8, constant dose) + **Mistletoe** (s.c., escalating doses, beginning on day 8, to determine MTD) (experimental); I.V. Gemcitabine HCL (escalating doses, to determine MTD)+ Mistletoe (s.c., constant dose = MTD)
PARTICIPANTS	Enrollment: 45-51 individuals with histologically confirmed, metastatic, recurrent, or unresectable, locally advanced solid tumors of the breast (or other cancers)
13.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, No Longer Recruiting
TITLE (ID#)	Mistletoe Extreat In Early Or Advanced Breast Cancer, A Feasibility Study (NCT00176046)
TYPE/PHASE	Interventional, Randomized Phase IV
INTERVENTION	**Mistletoe (= Viscum Album Pini, Iscador® P)**
PURPOSE	To identify surrogate parameters for a randomized efficacy study using Iscador® P in patients with breast cancer
OUTCOME MEASURES	Compare changes in blood count, lymphocyte (lc) count, lc stimulation, quality of life, anxiety & depression; diurnal cortisol profiles, T-cell and NK-cell zeta chains (primary); determine local reactions, document the concomitant use of medications/therapies (secondary); 1 yr F.U.
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	Iscador® P (s.c., 0.001-20 mg, beginning on day 1, 3/wk. x 12 mos.) (experimental) vs. Iscador® P (s.c., 0.001-20 mg, beginning wk. 12, 3/wk. x 6-12 mos.) (active comparator)
PARTICIPANTS	Enrollment: 114 breast cancer patients after primary surgery during chemo- or endocrine therapy, who want additional therapy with mistletoe extract
14.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	Vitamin E and Pentoxifylline in Treating Women with Lymphedema After Radiation Therapy for Breast Cancer (NCT00022204)
TYPE/PHASE	Interventional, Double-Blind, Placebo-Controlled, Randomized Phase II
INTERVENTION	**Vitamin E** (alpha-tocopherol) + Pentoxifylline
PURPOSE	To determine the effectiveness of this combination in treating lymphedema
OBJECTIVES; OUTCOME MEASURES	Efficacy of vitamin E + pentoxifylline in reducing symptoms of lymphedema; compare normal tissue injury and quality of life in treatment vs. placebo arms at regular intervals
PROTOCOL; COMPARATORS	Vitamin E (oral, 2/d x 6 mos.)+ Pentoxifylline (oral, 2/d x 6 mos.) (experimental) vs. placebo (oral, 2/d x 6 mos.) (placebo comparator); at baseline, 3-, 6-, 9-, & 12-mos.
PARTICIPANTS	Enrollment: 100 breast cancer patients who haven't taken vitamin E for the last 3 mos. with symptomatic arm lymphedema due to previous radiotherapy (radiation fibrosis)
15.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	The Use of Pentoxifylline and Vitamin E In The Treatment of Chronic Breast Pain (NCT00188669)
TYPE/PHASE	Interventional, Non-Randomized, Uncontrolled Phase II
INTERVENTION	**Vitamin E** (alpha tocopherol) + Pentoxifylline
PURPOSE	To study the ability of vitamin E-pentoxifylline to reduce/relieve chronic breast pain 3 months to 3 years after radiation therapy in breast cancer patients
OUTCOME MEASURES	Improvement in breast pain and patient function (primary); determine: time to maximal pain improvement,

	length of response, and quality of life; examine: pain characteristics, use and feasibility of assessment techniques for determining edema, fibrosis (secondary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Vitamin E + Pentoxifylline (treatment period: 6 mos., doses not specified)
PARTICIPANTS	Enrollment: 48 patients with *in situ* (stage 0) breast cancer, treated with conservative surgery and adjuvant radiotherapy, who have chronic breast pain with or without fibrosis
16.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	Coenzyme Q in Relieving Treatment-Related Fatigue in Women with Breast Cancer (NCT00096356)
TYPE/PHASE	Interventional, Double-Blind, Placebo-Controlled, Randomized; No Phase Given
INTERVENTION	**Coenzyme Q** + **Vitamin E** vs. Placebo + Vitamin E, 3x/d 24 wks
PURPOSE	To study the efficacy of coenzyme Q in reducing chemotherapy-related fatigue, depression
OUTCOME MEASURES	Effects of coenzyme Q at baseline, 8, 16, and 24 weeks (primary); effects of coenzyme Q on quality of life, fatigue, depression at baseline, 8, 16, 24 weeks (secondary)
PROTOCOL; COMPARATORS	Beginning on day 1 of chemotherapy (anthracycline or other) coenzyme Q + vitamin E vs. placebo + vitamin E, 3x/d for 24 consecutive weeks
PARTICIPANTS	Enrollment: 236, breast cancer patients who are otherwise healthy and planning to undergo chemotherapy
17.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, Recruiting
TITLE (ID#)	Study of CoQ10 During One Cycle of Doxorubicin Treatment for Breast Cancer (NCT00976131)
TYPE/PHASE	Interventional, Randomized, Double Blind Phase I
INTERVENTION	**Coenzyme Q10**
PURPOSE	To assess the effects of coenzyme Q10 on doxorubicin metabolism
OUTCOME MEASURES	To determine the maximum tolerated dose of coenzyme Q10 that won't change the pharmacokinetics of doxorubicin
PROTOCOL; COMPARATORS	Coenzyme Q10 or placebo + doxorubicin (coenzyme Q10 capsules given at 3 dose levels: 300-, 600-, 1200-mg, 1/d x 2 weeks before cycle 4 of doxorubicin) (experimental) vs. placebo or coenzyme Q10 + doxorubicin (cycle 3 of doxorubicin with placebo, cycle 4 with coenzyme Q10; same dose levels as above) (experimental)
PARTICIPANTS	Enrollment: 18 women >21 y.o. with early stage (I, II, IIIA) breast cancer, no prior history of chemo-, radio-, or hormonal therapy, scheduled to receive ≥4 rounds of doxorubicin therapy
18.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	Pyroxidine In Preventing Hand-Foot Syndrome In Patients Who Are Receiving Capecitabine For Advanced Colorectal Cancer or Breast Cancer (NCT00559858)
TYPE/PHASE	Interventional, Randomized, Double-Blind, Placebo-Controlled, Phase III
INTERVENTION	**Pyroxidine HCL (= Vitamin B6)**; Capecitabine
PURPOSE	To determine the effectiveness of pyroxidine in preventing hand-foot syndrome in advanced cancer patients receiving Capecitabine chemotherapy
OUTCOME MEASURES	Incidence of Capecitabine toxicity-related dose modifications (primary); incidence of hand-foot syndrome, toxicity, quality of life, response to chemotherapy, progression-free survival, and changes in potentially predictive biomarkers (secondary)
PROTOCOL; COMPARATORS	Pyroxidine HCL (3/d) + Capecitabine (no dose specified) (experimental) vs. placebo (3/d) + Capecitabine (placebo comparator)
PARTICIPANTS	Enrollment: 270, patients with clinically advanced breast cancer scheduled to undergo chemotherapy with Capecitabine
19.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	Pyroxidine and Topical Urea/Lactic Acid-Based Cream In Preventing Hand-Foot Syndrome In Patients Receiving Capecitabine For Breast Cancer or Other Cancer (NCT00296036)
TYPE/PHASE	Interventional, Randomized, Double-Blind, Placebo-Controlled, Phase III
INTERVENTION	**Pyroxidine HCL (= Vitamin B6)**; Capecitabine
PURPOSE	To determine whether giving pyroxidine is more effective than applying urea/lactic acid-based cream alone or in combination
OUTCOME MEASURES	% patients with moderate hand and/or foot symptoms (primary); % patients with mild hand and/or foot symptoms, % patients with severe hand and/or foot symptoms, and mean maximum score of hand and/or foot symptoms (secondary)
PROTOCOL; COMPARATORS	Pyroxidine HCL (1/d) + topical urea/lactic acid-based cream (2/d) (experimental) vs. pyroxidine HCL (1/d) + placebo cream (2/d) (experimental) vs. oral placebo supplement (1/d) + topical urea/lactic acid-based cream (2/d) (experimental) vs. oral placebo supplement (1/d) + placebo cream (2/d) (placebo comparator) vs. topical urea/lactic acid-based cream alone (2/d) (experimental) vs. placebo cream (2 x/d) (placebo comparator); given on days 1-21, repeating every 21 days over 4 courses of treatment
PARTICIPANTS	Enrollment: 132, confirmed breast cancer patients undergoing first treatment with Capecitabine or for metastatic disease
20.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	Pyroxidine in Preventing Hand-Foot Syndrome In Patients Who Are Receiving Liposomal Doxorubicin for Recurrent Ovarian, Fallopian Tube, or Peritoneal Cancer, Metastatic Breast Cancer, or Advanced Endometrial Cancer (NCT00245050)
TYPE/PHASE	Interventional, Randomized, Double-Blind, Placebo-Controlled, Phase III
INTERVENTION	**Pyroxidine HCL (= Vitamin B6)** + Doxorubicin
PURPOSE	To compare the efficacy of pyroxidine vs. placebo in preventing hand-foot syndrome (palmar-plantar erythrodysesthesia) from doxorubicin chemotherapy
OUTCOME MEASURES	Toxicity and functional assessment for quality of life (primary outcome measures)
PROTOCOL; COMPARATORS	Doxorubicin (1h, day 1) + Pyroxidine HCL (2/d x 28d) (experimental) vs. Doxorubicin (1h, day 1) + oral placebo (2/d x 28d) (placebo comparator); repeats @4 wks, 6 courses
PARTICIPANTS	Enrollment: 34 women with metastatic breast cancer (or other cancer) scheduled for chemotherapy with Doxorubicin HCL liposome

21.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, No Longer Recruiting
TITLE (ID#)	Study of Pralatrexate In Female Patients with Previously-Treated Breast CancerNCT01118624)
TYPE/PHASE	Interventional, Phase II
INTERVENTION	**Vitamin B12** (1 mg, I.M), **Folic Acid** (1-1.25 mg, oral), Pralatrexate (I.V.)
PURPOSE	To determine the efficacy of pralatrexate + vitamin B12 + folic acid in advanced metastatic breast cancer patients who have failed other chemotherapy regimens
OUTCOME MEASURES	Objective response rate (primary); duration of response, overall survival, adverse events, pharmacokinetics (secondary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Vitamin B12 (I.M., 1 mg x 10 wks. prior to pralatrexate, every 8-10 wks of study, and again 30 days after) + folic acid (oral, 1-1.25 mg, 1/d x 7d prior to Pralatrexate, throughout study, + 30 days after) + Pralatrexate (I.V., days: 1 & 15, 4 week cycles)
PARTICIPANTS	Enrollment: 30 women with previously treated advanced or metstatic breast cancer
22.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Open – Not Yet Recruiting
TITLE (ID#)	High Dose Cholecalciferol In Premenopausal Women at High Risk for Breast Cancer (NCT01097278)
TYPE/PHASE	Interventional, Randomized, Double-Blind, Placebo-Controlled, Phase II
INTERVENTION	**Cholecalciferol**
PURPOSE	To study how well cholecalciferol works in the prevention of premenopausal breast cancer
OUTCOME MEASURES	Changes in mammographic breast density: baseline vs. 12 mos. (primary); Ki-67 in breast epithelial cells from biopsies, biomarker expression, serum hormone levels (secondary)
PROTOCOL; COMPARATORS	Cholecalciferol (= high dose vitamin D3, 20,000 IU, 1/wk. x 12 mos.) + vitamin D (1/d x 1 yr) (experimental) vs. placebo (1/wk. x 1 yr.) + vitamin D (1/d x 1 yr.) (placebo comparator)
PARTICIPANTS	Enrollment: 200 premenopausal women, 18 – 50 y.o., with an elevated breast cancer risk
23.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Study of Vitamin D For Premenopausal Women at High Risk for Breast Cancer (NCT00976339)
TYPE/PHASE	Interventional, Non-Randomized; No Phase Given
INTERVENTION	**Vitamin D (= Vitamin D3 = Cholecalciferol)**
PURPOSE	Pilot feasibility study using 2 different doses of vitamin D3 supplementation for 1 year to see if risk factors for breast cancer change
OUTCOME MEASURES; OBJECTIVES	Changes in mammographic breast density; changes in biomarkers in breast biopsies; and toxicity evaluations from blood samples (primary objective); identification of the biologic effects of vitamin D3 on normal breast tissue (secondary objective)
PROTOCOL; COMPARATORS: 0	Vitamin D (30,000 IU 1/wk. x 1yr.) (experimental) vs. Vitamin D (20,000 IU 1/wk. x 1yr.) (experimental)
PARTICIPANTS	Enrollment: 20 premenopausal women with greater than normal risk for breast cancer
24.TRIAL TYPE/PURPOSE/STATUS	Interventional, Other; Active, Recruiting
TITLE (ID#)	Gene Expression Profile of Breast Cancer Samples After Vitamin D Supplementation (NCT00926315)
TYPE/PHASE	No Phase Specified
INTERVENTION	**Calcitrol**
PURPOSE	To evaluate the effects of calcitrol on the proliferation of tumor cells and gene expression profiles of biopsy samples from postmenopausal women with breast cancer
OUTCOME MEASURES	Tumor dimensions; Ki-67 (for proliferation); gene expression profiles before and after 1 mo. calcitrol supplementation (primary); follow-up – 5 years later (secondary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Calcitrol (0.25 mcg, 2/d x 1 mo.) (experimental); calcitrol (0.50, 1/d x 1 mo.) (expt'l)
PARTICIPANTS	Enrollment: 60 postmenopausal women, 40 y.o, scheduled for invasive breast cancer surgery
25.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Calcitrol, Physical Activity, and Bone Health In Cancer Survivors (NCT00904033)
TYPE/PHASE	Interventional, Randomized, Phase II
INTERVENTION	**Calcitrol**, Exercise, Multivitams
PURPOSE	To collect data on the efficacy and feasibility of calcitrol supplementation on bone health and muscle mass in survivors of breast cancer
OUTCOME MEASURES	Determinations of bone resorption, bone formation, and serum calcium (primary outcome measures); evaluation of strength and muscle mass (secondary outcome measure)
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	Calcitrol (no dose specified, 1/wk. x 12 wks.) (experimental) vs. exercise (progressive x 12 wks.) (experimental) vs. calcitrol (no dose specified, 1/wk. x 12 wks.) + exercise (progressive x 12 wks.) (experimental) vs. multivitams (1/d x 12 wks.) (active comparator)
PARTICIPANTS	Enrollment: 54 premenopausal breast cancer survivors who are within 5 years of diagnosis and who had previously received chemo-, radiation-, or hormonal therapy
26.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Study of The Effect Of Glutamine Supplementation On Chemotherapy-Induced Toxicities In Breast Cancer Patients (NCT00772824)
TYPE/PHASE	Interventional, Randomized, Placebo-Controlled, Phase IV
INTERVENTION	**Glutamine**; Chemotherapy
PURPOSE	To evaluate the effect of glutamine supplementation, either orally or intravenously, on toxic side effects (like peripheral neuropathy) of chemotherapy in breast cancer patients
OUTCOME MEASURES	Toxicity reduction (primary); serum creatine kinase and LDH levels (secondary)
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	Chemotherapy (30 cycles) + PLACEBO (no invention arm) vs. glutamine (I.V., 50 ml x 20% glutamine before chemotherapy) (active comparator) vs. glutamine (oral, 1gm/kg body weight, 2/d x 5d) (experimental)
PARTICIPANTS	Enrollment: 30 women, between 18 and 85 y.o. with breast cancer who are/have had chemotherapy with stage I-, subclinical-, or surgery-induced neuropathy

27.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	Randomized Placebo-Controlled Trial Of Glutamine for Breast Cancer Patients with Peripheral Neuropathy (NCT001915013)
TYPE/PHASE	Interventional, Randomized, Placebo-Controlled, Double-Blind Phase IV
INTERVENTION	**Glutamine**
PURPOSE	To improve mild peripheral neuropathy in paclitaxel-treated breast cancer patients
OUTCOME MEASURES	Assess ability of glutamine to reduce the signs and symptoms of peripheral neuropathy; to determine whether glutamine correlates with changes in nerve growth factor or insulin like growth factor in the presence and absence of symptom reduction; and to identify the potential for oral glutamine to interfere with the pharmacokinetics of paclitaxel
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	Placebo (oral, 10 gm, 3/d x 4 d) (placebo comparator) vs. glutamine (oral, 10 gm, 3/d x 4d) (experimental)
PARTICIPANTS	Enrollment: 50 women with breast cancer (stage i-iv), receiving or have recently received weekly paclitaxel and have treatment-associated peripheral neuropathy (≥grade I)
28.TRIAL TYPE/PURPOSE/STATUS	Interventional, Basic Science; Active, Recruiting
TITLE (ID#)	The Potential for Oral Diindolylmethane (DIM) Supplementation to Increase the Production of the BRCA1 Protein In BRCA1 Mutation Carriers (NCT01022333)
TYPE/PHASE	Interventional, Non-Randomized, Phase I
INTERVENTION	**DIM, Diindolylmethane**
PURPOSE	To determine that DIM has the potential to increase normal BRCA1 protein production in women who are BRCA1 mutation carriers.
OUTCOME MEASURES	To see if oral DIM can increase BRCA1 mRNA and protein levels in BRCA1 mutation carriers (primary); to determine whether oral DIM causes favorable changes in estrogen metabolism in BRCA1 mutation carriers (secondary)
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	DIM (BRCA1 mutation carriers: oral, 300 mg, 1 x/d x 6 wks.) (experimental) vs. no intervention (BRCA1 mutation carriers) vs. no intervention (not BRCA1 mutation carriers but have ≥1 family member with a BRCA1 mutation) (general control group)
PARTICIPANTS	Enrollment: 300 women, 25-45 y.o., who are (+) for the BRCA1 mutant gene or have ≥1 BRCA1 mutation (+) family member
29.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE	Use of Organic Germanium or Placebo For The Prevention of Radiation Induced Fatigue (NCTOO651417)
TYPE/PHASE	Interventional, Randomized, Double-Blind Phase II
INTERVENTION	**Organic Germanium**
PURPOSE	To test whether Organic Germanium can reduce fatigue and to see how well fatigue reduction correlates with quality of life factors
OUTCOME MEASURES	To assess the efficacy of o. germanium in fatigue reduction (primary); to determine: the peak time and duration of fatigue, tolerability and toxicity of germanium dosing schedule, and associated changes in mood (secondary); assessments will be made before o. germanium, after 1 month of o. germanium, and 3 months later
PROTOCOL; COMPARATORS	Organic germanium tablets (oral, 5 /d x 1 mo.) (active comparator) vs. placebo (oral, 3-5 /d x 1 mo.) (placebo comparator), beginning on day 1 of radiation therapy
PARTICIPANTS	Enrollment: 101 patients with localized breast or other cancer scheduled to undergo external beam radiation therapy
30.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, Recruiting
TITLE (ID#)	Glucosamine and Chondroitin for Aromatase Inhibitor Induced Joint Symptoms in Women with Breast Cancer (NCT00691678)
TYPE/PHASE	Non-Randomized, Phase II
INTERVENTION	**Glucosamine Chondroitin**
PURPOSE	To determine whether glucosame + chondroitin can reduce/relieve joint pain and stiffness resulting from therapy with aromatase inhibitors
OUTCOME MEASURES	Pain, function, and the patient's global assessment of disease (primary outcome measure)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Glucosamine (500 mg, 3/d x 24 wks.) + chondroitin (400 mg, 3/d x 24 wks.) (expt'l)
PARTICIPANTS	Enrollment: 53 postmenopausal women with stage I, II, or IIIA hormone receptor (+) breast cancer without metastasis
31.TRIAL TYPE/PURPOSE/STATUS	Treatment; Active, No Longer Recruiting
TITLE (ID#)	Docetaxel Plus Garlic In Treating Patients With Locally Advanced or Metastatic Breast Cancer (NCT00079170)
TYPE/PHASE	Interventional, No Phase Given
INTERVENTION	**Garlic** + Docetaxel
PURPOSE	Assess garlic + docetaxel in the treatment of locally advanced or metastatic breast cancer
OUTCOME MEASURES	To determine the pharmacokinetic behavior and toxicity of docetaxel in the presence and absence of cotreatment with garlic (primary); to identify enzyme- and transporter polymorphisms in trial participants (secondary)
PROTOCOL; COMPARATORS: 0	Docetaxel (I.V., days: 1, 8, & 15) + garlic tablets (2/d, days: 5-17); repeats @ 28 d
PARTICIPANTS	Enrollment: 9-12 patients with incurable locally advanced or metastatic breast cancer suited for docetaxel chemotherapy
32.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Limonene Study In Women With Breast Cancer (NCT01046929)
TYPE/PHASE	Interventional, Phase I
INTERVENTION	**Limonene**
PURPOSE	To evaluate limonene distribution in breast tissue and determine biomarkers of activity after 2 to 4 weeks of

	dosing in women with a recent diagnosis of breast cancer
OUTCOME MEASURES	To determine the level of limonene in the breast tissue (primary); to determine markers of drug effect in breast tissue and serum (secondary); >2-4 weeks of dosing
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Limonene (oral, 2 gm, 1/d x 2-6 wks.)
PARTICIPANTS	Enrollment: 40, women who have elected to undergo excision surgery for breast cancer
33.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care ; Active, Recruiting
TITLE (ID#)	Saftey Assessment of Lactobacillus Fermented Extract In Cancer Patients Undergoing Chemotherapy (NCT00606970)
TYPE/PHASE	Randomized, Placebo-Controlled, Double-Blind Phase 0
INTERVENTION	**Seigen Alpha EV (= Lactobacillus Fermented Extract)**
PURPOSE	Effects of lactobacillus on nutritional depletion and immune functioning during chemotherapy in patients with breast and other cancers
OUTCOME MEASURES	Changes in self-rated symptoms (primary); changes in treatment results (secondary)
PROTOCOL; COMPARATORS	Seigen alpha EV (oral, 1 packet = 6 gm, 3/d x 3 mos.) (experimental) vs. placebo (oral, 1 packet = 6 gm, 3/d x 3 mos.) (placebo comparator)
PARTICIPANTS	Enrollment: 30 breast cancer patients with at least 1 month of chemotherapy remaining
34.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	A Phase II Biomarker Trial of Gelatin Encapsulated Extract of American Ginseng Root (LEAG) In Breast Cancer (NCT00631852)
TYPE/PHASE	Interventional, Non-Randomized Phase II
INTERVENTION	**American Ginseng Root (= Panax Quinquefolium)**
PURPOSE	To investigate the antitumor effects of American ginseng supplementation in breast cancer patients
OUTCOME MEASURES	Identification of proliferation and cytotoxicity markers (primary); correlation between ginsenosides and inflammatory mediators in the serum (secondary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	American ginseng root (250 mg tablet, 1/d x 5-14 days before surgery) (experimental)
PARTICIPANTS	Enrollment: 50 women with invasive or non-invasive (DCIS) breast cancer (≥1 cm)
35.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, No Longer Recruiting
TITLE (ID#)	Green Tea Extract In Treating Women With Hormone Receptor-Negative Stage I, Stage II, or Stage III Breast Cancer (NCT00516243)
TYPE/PHASE	Randomized, Placebo Controlled, Double-Blind Phase I
INTERVENTION	**Polyphenon E (Poly E = Green Tea Catechin Extract)**
PURPOSE	Assess polyphenon E safety in women with hormone receptor (-) breast cancer; to determine the efficacy of polyphenon E in modulating secondary outcome measures
OUTCOME MEASURES	Determine maximum tolerated dose & toxicity (primary); Ki-67, p53, EGFR, caspase 3, & ER expression in healthy, contralateral breast; mammographic breast density; serum hormone metabolites; urinary eicosanoids; biomarkers of oxidative damage; quality of life; green tea extract activity relative to COMT genotype of participants (secondary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Polyphenon E (1 of 3 doses-200 mg EGCG caps given: 2 x/d x 6 mos., 3/d x 6 mos., or 4/d x 6 mos.) (experimental) vs. placebo (2, 3, or 4 placebo caps, 2/d x 6 mos.) placebo comparator
PARTICIPANTS	Enrollment: 40 women, 21-65 y.o., with stage I-III, receptor (-) breast cancer
36.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	A Pilot Study of Chemoprevention of Green Tea In Women With Ductal Carcinoma *In situ* (NCT01060345)
TYPE/PHASE	Interventional, Non-Randomized, No Phase Given
INTERVENTION	**Polyphenon E (= Green Tea Extract)**
PURPOSE	To evaluate the impact of green tea on biomarkers of proliferation, inflammation, and angiogenesis in DCIS breast cancer
OUTCOME MEASURES	Percent change in Ki67 staining (primary); lesion reduction; % staining of: CD68, CD31, & VEGF in breast tissue; change in serum IGF-1; safety of green tea ingestion (secondary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Polyphenon E (three 200 mg capsules, 1 x/d x 4 wks. prior to surgery) (experimental)
PARTICIPANTS	Enrollment: 50 women with ductal carcinoma *in situ*, DCIS
37.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Green Tea In Breast Cancer Patients (NCT00949923)
TYPE/PHASE	Interventional, Non-Randomized, Phase I
INTERVENTION	**Green Tea Extract**
PURPOSE	To determine proliferative/apoptotic changes associated with EGCG in breast cancer
OUTCOME MEASURES	Level of proliferation reduction, increased apoptosis (primary outcome measure)
PROTOCOL; COMPARATORS: 0, PARALLEL ASSIGNMENT	Green tea (3 capsules, 1/d x 3 wks.) (active comparator) vs. no intervention (control)
PARTICIPANTS	Enrollment: 20 postmenopausal women diagnosed with incident breast cancer (on diagnostic biopsy) who are not green tea drinkers
38.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Green Tea and Reduction of Breast Cancer Risk (NCT00917735)
TYPE/PHASE	Randomized, Placebo Controlled, Double Blind, Phase II
INTERVENTION	**Green Tea Extract**
PURPOSE	To study how well green tea works, relative to placebo, in the prevention of breast cancer
OUTCOME MEASURES	Mammographic breast density; serum: E1, E2, androstenedione, SHBG, IGF-1, IGFBP-3; effects of COMT genotype (primary); urinary estrogen metabolites, serum- & urinary catechin levels, circulating F2-

	isoprostanes-systemic oxidative stress marker (secondary)
PROTOCOL; COMPARATORS	Green tea extract (2 capsules, 2/d x 12 mos.) (experimental) vs. placebo (2 capsules, 2/d x 12 mos.) (placebo comparator)
PARTICIPANTS	Enrollment: 800 healthy, postmenopausal women 50-70 y.o. with heterogenously dense or extremely dense breasts who are willing to avoid green tea consumption for 12 months
39.TRIAL TYPE/PURPOSE/STATUS	Interventional, Basic Science; Active, Recruiting
TITLE (ID#)	A Study of the Effect of Polyphenon E (Green Tea Extract) on Breast Cancer Progression (NCT00676793)
TYPE/PHASE	Interventional, Phase II
INTERVENTION	**Polyphenon E (Green Tea Extract, EGCG)**
PURPOSE	To determine changes in biomarkers of breast cancer and cancer progression
OUTCOME MEASURES; OBJECTIVES:	To determine the effect of daily polyphenon E on C-MET Expression and phosphorylation (primary objective); to assess the effects of polyphenon E on signaling pathways and markers of breast cancer progression; to evaluate the safety and tolerability of polyphenon E in trial participants (secondary outcome measures)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Polyphenon E (200 mg capsule, 1/d x 4-6 wks. prior to surgery)
PARTICIPANTS	Enrollment: 25 women > 21 y.o. with stage I-III breast cancer requiring surgical resection
40.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	IH636 Grape Seed Extract In Preventing Breast Cancer In Postmenopausal Women At Risk of Developing Breast Cancer (NCT00100893)
TYPE/PHASE	Interventional, Phase I
INTERVENTION	**IH636 Grape Seed Proanthocyanidin Extract**
PURPOSE	Identify side effects and best IH636 grape seed extract dose for breast cancer prevention
OUTCOME MEASURES	Estrogen suppression (serum E2, E1, E1-S, SHBG) at 1, 2, 4, & 12 weeks (primary); androgenic-, lipid-, bone metabolic-, insulin regulatory-, and pharmacokinetic- effects at designated intervals (secondary)
PROTOCOL; COMPARATORS: NONE	Placebo (1 or 2/d on days -14 to 0) followed by IHS636 grape seed proanthocyanidin extract (1 or 2/d on days 1-85) (experimental); cohorts of 6 are receive 1 of 4 dose levels
PARTICIPANTS	Enrollment: 24 women, ages 40 – 75 y.o., at risk of developing breast cancer
41.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	The Effect of Grape Seed Extract On Estrogen Levels of Postmenopausal Women (NCT00566553)
TYPE/PHASE	Interventional, Randomized, No Phase Given
INTERVENTION	**Grape Seed Extract**
PURPOSE	To conduct a pilot, dose-finding study of procyanidins in grape seed extract
OUTCOME MEASURES	To document decreases in plasma levels of E1, E2, and E1-conjugates and increases in precursor androgen levels associated with grape seed extract supplementation (primary); to identify the most effective, well-tolerated doses in achieving the primary outcome measures in the participant population (secondary)
PROTOCOL; COMPARATORS: 0, PARALLEL ASSIGNMENT	Grape seed extract (200 mg pills, 1/d x 12 wks.) (active comparator) vs. grape seed extract (two 200 mg pills, 1/d x 12 wks.) (active comparator) vs. grape seed extract (three 200 mg pills, 1/d x 12 wks.) (active comparator) vs. grape seed extract (four 200 mg pills, 1/d x 12 wks) (active comparator)
PARTICIPANTS	Enrollment: 40 healthy, postmenopausal women, 55-75 y.o., with no history of cancer
42.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	IH636 Grape Seed Extract In Treating Hardening of Breast Tissue In Women Who Have Undergone Radiation Therapy For Early Breast Cancer (NCT00041223)
TYPE/PHASE	Randomized, Placebo Controlled, Double Blind, Phase II
INTERVENTION	**IH636 Grape Seed Proanthocyanidin Extract**
PURPOSE	To evaluate the effectiveness of IH636 grape seed proanthocyanidin extract in reducing breast tissue fibrosis associated with prior radiation therapy
OUTCOME MEASURES; OBJECTIVES:	To determine the efficacy of IH636 grape seed proanthocyanidin extract in treating radiation-induced fibrosis associated with previous radiotherapy for breast cancer
PROTOCOL; COMPARATORS	IH636 grape seed proanthocyanidin extract (oral, 3/d x 6 mos.) (experimental) vs. placebo (oral, 3/d x 6 mos.) (placebo comparator)
PARTICIPANTS	Enrollment: 72 women with early breast cancer or breast cancer history, no evidence of recurrence, and palpable induration due to prior radiotherapy
43.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Studying The Effect of Freeze-Dried Table Grape Powder on Blood Estrogen Levels in Postmenopausal Women (NCT00611104)
TYPE/PHASE	Interventional, No Phase Given
INTERVENTION	**Standardized Freeze-Dried Table Grape Powder**
PURPOSE	Assess effect of table grape powder on blood estrogen in postmenopausal women
OUTCOME MEASURES	Determine E1, E2, E1 conjugates, & E1 sulfate serum levels and bioavailability of freeze dried table grape powder supplement in the trial participants (primary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Freeze-dried table grape powder (oral, 1/d x 42 d)
PARTICIPANTS	Enrollment: 25 postmenopausal women, participants of the Mayo Mammography Study
44.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active Recruiting
TITLE (ID#)	Evaluation of The Safety And Efficacy of THL-P in Metastatic Breast Cancer (NCT00976365)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase II
INTERVENTION	**THL-P, Extract of Several Natural Herbs**
PURPOSE	To assess the efficacy of THL-P in patients with metastatic breast cancer
OUTCOME MEASURES	Determine global health/ quality of life (primary); CBC with platelet and differential counts, blood enzymes, uric acid, and creatinine levels (2ndary), baseline-posttreatment

PROTOCOL; COMPARATORS	THL-P (20 ml, 3/d x 24 wks.) (experimental) vs. THL-p (sugar 'pill', 20 ml, 3/d x 24 wks.) (placebo comparator)
PARTICIPANTS	Enrollment: Sixty 20-80 y.o. women with clinically confirmed metastatic breast cancer
45.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active Recruiting
TITLE (ID#)	Acetyl-L-Carnitine In Preventing Neuropathy In Women With Stage II, Stage II, or Stage IIIa Breast Cancer Undergoing Chemotherapy (NCT00775645)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase III
INTERVENTION	**Acetyl-L-Carnitine HCL**
PURPOSE	To see how well Acetyl-L-Carnitine works in lessening neuropathy associated with chemotherapy in stage I-III breast cancer
OUTCOME MEASURES	To identify changes in taxane-neurotoxicity (primary); fatigue; functional status; prevalence of neuropathy; NGF levels; genetic markers of taxane metabolism; taxane schedule, concurrent medications, dietary supplements, CAMs (secondary)
PROTOCOL; COMPARATORS	Acetyl-L-Carnitine HCL (oral, 3/d x 24 wks.) (experimental) vs. placebo (oral, 3/d x 24 wks.) (placebo comparator)
PARTICIPANTS	Enrollment: 380 women with Iary invasive adenocarcinoma (stages I-III) who have undergone surgery and are planning to receive taxane-based systemic chemotherapy
46.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	L-Carnitine L-Tartrate In Preventing Peripheral Neuropathy Caused By Chemotherapy In Women With Metastatic Breast Cancer (NCT00754767)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind, No Phase Given
INTERVENTION	**L-Carnitine L-Tartrate**
PURPOSE	To see how well L-Carnitine L-Tartrate works in peripheral neuropathy prevention caused by chemotherapy for metastatic breast cancer
OUTCOME MEASURES	Vibratory threshold; sensitivity to light touch; motor & sensory neuropathy; toxicity; tumor response & time to response; survival (primary outcome measures)
PROTOCOL; COMPARATORS	L-Carnitine L-tartrate (oral, 2/d, beginning on day 2 and through 4 courses of chemotherapy) (experimental) vs. placebo (oral, 2/d, beginning on day 2 and through 4 courses of chemotherapy) (placebo comparator)
PARTICIPANTS	Enrollment: 20 women scheduled to receive chemotherapy for metastatic breast cancer
47.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, No Longer Recruiting
TITLE (ID#)	Herbal Therapy In Treating Women With Metastatic Breast Cancer (NCT00028977)
TYPE/PHASE	Interventional, Phase I-II
INTERVENTION	**Herba Scutellaria Barbata (Chinese Herbal Extract)**
PURPOSE	To study the effectiveness of this herb in treating metastatic breast cancer
OUTCOME MEASURES; OBJECTIVES	To evaluate tumor response to scutellaria barbata (efficacy); to determine: safety, toxicity, feasibility of therapy, time to progression, overall survival, quality of life, bioavailability, and pharmacokinetics associated with herba scutellaria barbata
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Herba scutellaria barbata (oral, 2/d x 12 mos.)
PARTICIPANTS	Enrollment: 25 women: histologically confirmed breast cancer + metastatic involvement
48.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, No Longer Recruiting
TITLE (ID#)	A Phase I/II Clinical Trial Assessing Safety And Efficacy of BZL 101 For Metastatic Breast Cancer (NCT00454532)
TYPE/PHASE	Interventional, Non-Randomized, Phase I/II
INTERVENTION	**Herba Scutellaria Barbata Extract (Bezielle®, BZL 101)**
PURPOSE	To evaluate toxicity, maximum tolerated dose, safety, and efficacy of BZL 101 in the treatment of advanced metastatic breast cancer
OUTCOME MEASURES	Toxicity and response to evaluation criteria in solid tumors, RECIST, Phase 2 (primary)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	BZL 101 (freeze dried powder mixed with liquid, 1/d x 1-2 mos.)
PARTICIPANTS	Enrollment: 100 histologically confirmed breast cancers with evidence of metastasis
49.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, Recruiting
TITLE (ID#)	Flaxseed in Treating Postmenopausal Women with Hot Flashes Who Have a History of Breast Cancer or Other Cancer or who do Not Wish to Take Estrogen Therapy (NCT00956813)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase III
INTERVENTION	**Flaxseed**
PURPOSE	Assess efficacy of flaxseed in treating postmenopausal hot flashes, no estrogen therapy
OUTCOME MEASURES; OBJECTIVES	Hot flash scores (primary); toxicity, mood, general menopausal symptoms, hot flash-related daily interference level (secondary)
PROTOCOL; COMPARATORS	Flaxseed **(**oral flaxseed bar, 1/d x 6-12 wks.) (experimental) vs. placebo (oral placebo bar, 1/d x 6-12 wks.) (placebo comparator)
PARTICIPANTS	Enrollement: 210 postmenopausal women (+/-a history of non-malignant breast or other cancer) who are bothered by hot flashes and want to avoid estrogen therapy
50.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Flxseed In Preventing Breast Cancer In Premenopausal Women At Risk of Developing Breast Cancer (NCT00794989)
TYPE/PHASE	Interventional, Randomized, No Phase Given
INTERVENTION	**Flaxseed**
PURPOSE	To evaluate how well flaxseed works in preventing premenopausal breast cancer in high risk women
OUTCOME MEASURES; OBJECTIVES:	Develop consistent methods for: sample collection, optimization of cellular yield, IHC, and qRT-PCR; determine whether ground flaxseed ingestion can prevent the development of primary breast cancer or modify:

	proliferation, apoptosis, intermediate biomarkers, estrogen-regulated genes, or serum IGF-1 and IGFBP-3 levels (primary objectives); prepare for future chemoprevention trials; evaluate feasibility and tolerance of long flaxseed consumption and factors that diminish compliance (secondary objectives)
PROTOCOL; COMPARATORS	ground flaxseed (oral, w/ food, 1/d x 6 mos.) (intervention) vs. no flaxseed (observation)
PARTICIPANTS	Enrollment: 60 premenopausal, 21- 50 y. o. who: a) are scheduled for prophylactic mastectomy for unilateral tumors or (b) have a history of atypical ductal/lobular hyperplasia, lobular carcinoma, DCIS, or previously treated stage I breast cancer
51.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	Flaxseed And/Or Anastrozole In Treating Postmenopausal Women Undergoing Surgery For Newly Diagnosed Stage I or Stage II Breast Cancer (NCT00635908)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind, No Phase Given
INTERVENTION	**Flaxseed**; Anastrozole
PURPOSE	To determine how well flaxseed works with or without anastrozole in treating postmenopausal women with newly diagnosed stage I-II breast cancer prior to surgery
OUTCOME MEASURES	Changes in: growth and signaling factors, markers of proliferation and apoptosis; mammostat antibody panel; steroid and growth hormone profiles (primary)
PROTOCOL; COMPARATORS	Placebo (oral, 1/d x 2 wks.) (placebo comparator) vs. flaxseed + placebo (oral, ground flaxseed, 1/d x 2 wks.) (active comparator) vs. anastrozole (oral, 1/d x 2 wks.) (active comparator) vs. flaxseed + anastrozole (as above) (active comparator)
PARTICIPANTS	Enrollment: 100 postmenopausal women newly diagnosed with resectable primary or invasive, ER (+) breast cancer, scheduled for surgery
52.TRIAL TYPE/PURPOSE/STATUS	Interventional, Basic Science; Active, Recruiting
TITLE (ID#)	Flaxseed, Aromatase Inhibitors and Breast Tumor Characteristics (NCT00612560)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase 0
INTERVENTION	**Flaxseed**; Anastrozole
PURPOSE	To examine the effect of flaxseed compared to anastrozole in treating ER (+) breast cancer and to gain clinical information for future studies
OUTCOME MEASURES; OBJECTIVES:	To assess tumor cell: proliferation and apoptosis as well as ER, PR, and HER2 expression (primary); to determine serum levels of steroid- and growth hormones (secondary)
PROTOCOL; COMPARATORS	Flaxseed (flaxseed, 25 mg pills, 1/d) + PLACEBO (placebo pills, 1/d) (experimental) vs. flaxseed (flaxseed, 25 mg pills, 1/d) + anastrozole (1 mg pills, 1/d) (experimental) vs. placebo (placebo pills, 1/d) (placebo comparator) vs. anastrozole (1 mg pills, 1/d) (experimental); given in the interval between biopsy and surgery
PARTICIPANTS	Enrollment: 100 postmenopausal women with newly diagnosed incident, primary, invasive, ER (+) clinical stage II or lower, breast cancer
53.TRIAL TYPE/PURPOSE/STATUS	Intervention, Treatment; Active, Recruiting
TITLE (ID#)	Coriolus Versicolor Extract In Treating Women With Stage I, Stage II, or Stage III Breast Cancer Who Have Finished Radiation Therapy (NCT00680667)
TYPE/PHASE	Interventional, Phase I
INTERVENTION	**Coriolus Versicolor Extract**
PURPOSE	To identify side effects and best dose for use in the treatment of stages I-III breast cancer patients who have completed radiation therapy
OUTCOME MEASURES	Determine: maximum tolerated dose (primary); evaluate: quality of life, fatigue, toxicity, % NK cell activity (+ other immunologic measures), differential blood counts
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	Coriolus versicolor extract (oral, 2/d x 6 weeks)
PARTICIPANTS	Enrollment: 24 women who have been treated with chemotherapy and surgery (within the last 12 months) for infiltrating ductal adenocarcinoma of the breast (stages I-III)
54.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	Yunzhi As Dietary Supplement in Breast Cancer, Yunzhi-BC (NCT00647075)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase IV
INTERVENTION	**Coriolus Versicolor (= Yunzhi Extract)**
PURPOSE	Evaluate traditional Asian mushroom Yunzhi, as an adjuvant for breast cancer treatment
OUTCOME MEASURES:	Mean change in signs & symptoms; treatment adherence; adverse events; adherence to chemotherapy schedule; need for blood transfusion (primary outcome measures)
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	Yunzhi extract (3.5 gm, 1 x/d x 6 mos.) (experimental) vs. placebo (starch, 1 x/d x 6 mos.) (placebo comparator)
PARTICIPANTS	Enrollment: 60 breast cancer patients undergoing adjuvant/neoadjuvant chemotherapy
55.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, Recruiting
TITLE (ID#)	Zoledronate, Vitamin D, and Calcium with or without Strontium 89 or Samarium 153 in Preventing or Delaying Bone Problems in Patients with Bone Metastases From Prostate Cancer, Lung Cancer, or Breast Cancer (NCT00365105)
TYPE/PHASE	Interventional, Randomized Phase III
INTERVENTION	**Calcium (+ Vitamin D)**; Zoledronate
PURPOSE	To determine how well zoledronate + calcium + vitamin D work compared to zoledronate, calcium, vitamin D and either strontium89 or samarium 153 in preventing/delaying bone problems in breast and other cancer patients with bone metast.
OUTCOME MEASURES	Time to development of malignant skeletal-related events (primary); rate of development, overall survival, and quality of life, pain (secondary)
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	Zoledronate (I.V., 1/mo.) + calcium (oral, 1/d) + vitamin D (oral, 1/d) (active comparator) vs. zoledronate (I.V., 1/mo.) + calcium (oral, 1/d) + vitamin D (oral, 1/d) + strontium 89 or samarium 153 (single dose) (experimental)
PARTICIPANTS	Enrollment: 352 (total) patients with histologically confirmed cancers of the breast (lung, or prostate) and bone

	metastases
56.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Clinical Trial of Vitamin D3 to Reduce Cancer Risk In Postmenopausal Women, CAPS (NCT01052051)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase III
INTERVENTION	**Vitamin D; Calcium**
PURPOSE	To determine whether vitamin D3 + calcium can decrease cancer risk
OUTCOME MEASURES	Cancer incidence (5 years; primary outcome measure); cancer type: breast and others; other health conditions (5 years; secondary outcome measures)
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	Calcium (oral, 1200 mg, 1/d x 5 yrs.) (active comparator) vs. vitamin D (oral, 2000 I.U./d x 5 yrs.) + calcium (oral, 1200 mg, 1/d x 5 yrs.) (experimental)
PARTICIPANTS	Enrollment: 2,300 (total no.) Healthy, postmenopausal women who are at least 55 y.o.
57.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, No Longer Recruiting
TITLE (ID#)	High Dose Vitamin D Musculoskeletal Symptoms and Bone Density in Anastrozole-Treated Breast Cancer With Marginal Vitamin D Status (NCT00263185)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind, No Phase Given
INTERVENTION	**Vitamin D; Calcium Carbonate**
PURPOSE	To determine see if vitamin d (+ calcium) reduces muscle stiffness /joint tenderness in anastrozole-treated breast cancer patients
OUTCOME MEASURES	To determine the effects of high vs. Standard dose vitamin D + calcium on musculoskeletal (M-S) pain (primary); to determine: the prevalence of vitamin D deficiency in anastrozole treated breast cancer patients with M-S pain; whether vitamin D & PTH levels correlate with bone loss & M-S symptoms; the effects of high vs. standard dose vitamin D on bone density in these participants (secondary)
PROTOCOL; COMPARATORS	Vitamin D (oral, 400 I.U., 1/d x 8 wks.) + calcium carbonate (oral, 1000 mg, 1/d x 8 wks.) (treatment) vs. calcium carbonate (oral, 1000 mg, 1/d x 8 wks.) + vitamin D (oral, 400 mg, 1/d x 8 wks.) (placebo comparator) vs. vitamin D (50,000 I.U., 1/d x 16 weeks) + no intervention (observation)
PARTICIPANTS	Enrollment: 60 postmenopausal women with hormone receptor (+) invasive (stage I-IIB) breast cancer or DCIS
58.TRIAL TYPE/PURPOSE/STATUS	Interventional, Diagnostic; Active, No Longer Recruiting
TITLE (ID#)	Bone Mineral Density in Postmenopausal Women with Primary Breast Cancer Who Are Receiving Treatment On Clinical Trial CAN-NCIC-MA27 (NCT00354302)
TYPE/PHASE	Interventional, Phase III
INTERVENTION	**Calcium Carbonate, Calcium Citrate, Cholecalciferol**
PURPOSE	To study bone mineral density in this participant population
OUTCOME MEASURES	Change in bone mineral density 2 years post treatment (L1-4, hip; primary outcome measures); % change in BMD from baseline; mean % bone mineral density change (1, 3, 5 years); # patients w/o osteopenia/osteoporosis who develop low bone mineral density or fracture; % patients with osteopenia/osteoporosis + improved bone mineral density with fracture (2 years); change in bone biomarkers; treatment safety & tolerability (secondary outcome measures)
PROTOCOL; COMPARATORS	Calcium (calcium carbonate, citrate, or gluconate, oral, 1 x/d x 5 yrs. , no dose specified) + cholecalciferol (vitamin D, oral, 1 x/d x 5 yrs.) with or without bisphonates (oral Risedronate or Alendronate, doses were not specified)
PARTICIPANTS	Enrollment: 226 postmenopausal women ≥45 y.o. with primary breast cancer who are receiving treatment on clinical trial CAN-NCIC-MA27
59.TRIAL TYPE/PURPOSE/STATUS	Interventional, Supportive Care; Active, No Longer Recruiting
TITLE (ID#)	Combination Chemotherapy After Surgery with or without Chinese Herbal Therapy to Treat Symptoms in Women With Breast Cancer (NCT00028964)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase I/II
INTERVENTION	**Chinese Herbal Therapy**; Cyclophosphamide, Doxorubicin HCL
PURPOSE	To examine the effectiveness of herbs used in traditional chinese medicine in attenuating the toxic side effects of chemotherapy in women who have had surgery for breast cancer
OUTCOME MEASURES; OBJECTIVES:	Determine: safety and toxicity of chinese herbal therapy when in a setting of adjuvant chemotherapy; compliance & feasibility of daily treatment/documentation; patient preferences & concerns; preliminary efficacy (primary objectives)
PROTOCOL; COMPARATORS	Adjuvant chemotherapy (I.V., doxorubicin + I.V. cyclophosphamide, days: 0, 21, 42, & 63) + chinese herbal therapy (oral, 3 x/d, days: -10 to 105) (experimental) vs. adjuvant chemotherapy (I.V. doxorubicin + I.V. cyclophosphamide, days: 0, 21, 42, & 63) + placebo (oral, 3 x/d, days: -10 to 105) (placebo comparator)
PARTICIPANTS	Enrollment: 60 women with histologically confirmed breast cancer (stage I-early III), without metastases, recommended for adjuvant chemotherapy
60.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, No Longer Recruiting
TITLE (ID#)	Effect of A Natural Health Product On Urinary Estrogen Metabolites (NCT01089049)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase I/II
INTERVENTION	**FemMED Breast Health Formula™**
RATIONALE/HYPOTHESIS	The phytochemicals in this formula may differentially act as weak estrogen mimics
PURPOSE	Determine whether consumption of the FemMED breast health formula beneficially alters the ratio of urinary estrogen metabolites
OUTCOME MEASURES	To determine the urinary ratio of 2-hydroxyestrone:16-alpha-hydroxyestrone (days 0 & 28; primary); to determine the blood levels of enterolactone (days 0 & 28; secondary)
PROTOCOL; COMPARATORS: PARALLEL ASSIGNMENT	FemMED Breast Health Formula™ (oral, 2 capsules, 1 x/d x 28d, pre-menopausal participants) (experimental) vs. FemMED Breast Health Formula™ (oral, 2 capsules, 1/d x 28d, post-menopausal participants) (experimental)
PARTICIPANTS	Enrollment: 100 healthy, pre- and postmenopausal women
61.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting

TITLE (ID#)	Docetaxel with or without A Phytochemical In Treating Patients with Breast Cancer (NCT00852332)
TYPE/PHASE	Interventional, Randomized Phase II
INTERVENTION	**Phytochemical** (origin: unidentified)
PURPOSE	To study the effectiveness of first or second-line combination therapy with docetaxel + phytochemical compared with docetaxel alone in breast cancer
OUTCOME MEASURES	Response rate assessed by recist criteria (primary); overall clinical benefit, time to progression, and overall survival assessed by RECIST; and safety (secondary)
PROTOCOL; COMPARATORS	Docetaxel (I.V. , 1 x on day 1, repeats every 3 wks. for 6 courses) (experimental) vs. docetaxel (I.V. , 1 x on day 1, repeats every 3 wks. for 6 courses) + dietary phytochemical (2 x on day 1, repeats every 3 week for 6 courses) (experimental)
PARTICIPANTS	Enrollment: 100 participants with (a) histologically/cytologically confirmed, locally advanced, metastatic (no bone lesions), HER2 (-) breast cancer or (b) locoregional recurrence not amenable to surgery or radiotherapy but suitable for taxane chemotherapy
62.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	Broccoli Sprout Extract In Treating Women With Newly Diagnosed Ductal Carcinoma *In situ* and/or Atypical Ductal Hyperplasia (NCT00843167)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase II
INTERVENTION	**Broccoli Sprout Extract (Sulforaphane)**
PURPOSE	To determine how effective broccoli sprout extract is in treating newly diagnosed DCIS and/or atypical ductal hyperplasia (ADH)
OUTCOME MEASURES	To determine: isothiocyanate levels in blood, urine, and nipple fluid aspirates; changes in apoptosis or prognostic biomarkers, Ki67, H3, H4, HDAC (primary); to assess: safety, toxicity, and treatment compliance (secondary)
PROTOCOL; COMPARATORS	Broccoli sprout extract (oral, 3/d x 2-8 wks.) (experimental) vs. placebo (oral, 3/d x 2-8 wks.) (placebo comparator)
PARTICIPANTS	Enrollment: 66 women >21 y.o., with newly diagnosed, biopsy confirmed DCIS and/or ADH
63.TRIAL TYPE/PURPOSE/STATUS	Interventional, Prevention; Active, Recruiting
TITLE (ID#)	Study To Evaluate The Effect of Sulforaphane In Broccoli Sprout Extract On Breast Tissue (NCT00982319)
TYPE/PHASE	Interventional, Randomized, Placebo Controlled, Double Blind Phase II
INTERVENTION	**Broccoli Sprout Extract (Sulforaphane)**
PURPOSE	Monitor tumor proliferation, intermediate markers of breast cancer risk, and compliance
OUTCOME MEASURES	Decrease in mean proliferative rate, Ki67%, 14d (primary); increases in mRNA and protein levels of cytoprotective, sulforaphane-modulated enzymes; qualitative morphologic changes in DCIS- and adjacent normal tissue specimens
PROTOCOL; COMPARATORS	Broccoli sprout extract (oral, in mango juice + cruciferous-free diet x 14d) (experimental) vs. mango juice (no extract, x 14d) (placebo comparator)
PARTICIPANTS	Enrollment: 28 pre- or post-menopausal women with a biopsy-confirmed diagnosis of DCIS, not on hormone replacement therapy, scheduled for definitive surgery
64.TRIAL TYPE/PURPOSE/STATUS	Interventional, Basic Science; Active, Recruiting
TITLE (ID#)	Proof of Principle Trial To Determine If Nutritional Supplement Conjugated Linoleic Acid (CLA) Can Modulate The Lipogenic Pathway In Breast Cancer Tissue (NCT00908791)
TYPE/PHASE	Interventional, Phase 0
INTERVENTION	**Conjugated Linoleic Acid, CLA**
PURPOSE	To determine if CLA suppresses markers of lipogenesis in breast cancer tissue and whether adipose tissue can serve as a surogate marker for tumor tissue
OUTCOME MEASURES	To determine if CLA suppresses markers of lipogenesis in breast cancer tissue (2 y.; primary); to determine: if CLA suppresses markers of lipogenesis in adipose tissue, CLA blood levels, and the relationship between CLA levels and markers of lipogenesis (2 y.; secondary outcome)
PROTOCOL; COMPARATORS: 0, SINGLE GROUP ASSIGNMENT	CLA (3.25 gm Clarinol™ capsules; 2 x/d x 10-28d) prior to surgery
PARTICIPANTS	Enrollment: 24 women with histologically confirmed, invasive, resectable adenocarcinoma of the breast, stage I-II
65.TRIAL TYPE/PURPOSE/STATUS	Interventional, Treatment; Active, Recruiting
TITLE (ID#)	Natural Supplements and a Special Diet in Eliminating Growth Hormones Made Outside The Body in Patients with Early-Stage Prostate Cancer, Breast Cancer, or Uterine Cancer (NCT00910884)
TYPE/PHASE	Interventional, Randomized Phase I
INTERVENTION	**Natural Supplements**[Π] **(**[Π]Indole-3-Carbinol, Perillyl Alcohol, Glucuronic Acid, Flavonoids)
PURPOSE	To determine how well natural supplements[Π] + special diet work to eliminate growth-promoting hormones in early stage breast- and other cancers
OUTCOME MEASURES; OBJECTIVES	Evaluate exogenous estrogen sequestion/elimination, suppression of proliferation, reduction of secondary bonding, maintenance of normal metabolic functions (primary)
PROTOCOL; COMPARATORS	Natural supplements[Π] + whole foods containing indole-3-carbinol + special diet (daily x 12 mos.) (experimental) vs. no supplements or special diet (no intervention)
PARTICIPANTS	Enrollment: 300 individuals with early stage cancers of the breast (prostate or uterus) with or without concurrent chemo- or radiation therapy

Iscador® P: standardized, aqueous extract of all parts of the Viscum album plant; participants are over 18 years old if no age is given; EGCG: epicatechins, epigallocatechin, epicatechin gallate, epigallocatechin gallate; Enrollment: projected accrual ; FemMED, Breast Health Formula™: vitamin D, milk thistle, schizandra, stinging nettle, calcium, hydroxymatairesinol; Zoledronate: a bisphosphonate for osteoporosis treatment; BMD: bone mineral density; I.V.: intravenous; s.c.: subcutaneous; I.M: intramuscular; /d: per day; mo.: month; y.o.: years old; E1: estrone; E2: estradiol; F.U.: follow-up; CAMs: complementary and alternative medicines.

phase I trials are generally small and the doses tested are considered subtherapeutic. This allows accrual to be achieved rapidly while preserving safety (29) Phase I/II clinical trials are designed to obtain data for more definitive phase II level testing. In phase II trials endpoints including toxicity, biologic activity, plasma concentrations, and target interactions are often tested. Efficacy and safety are also evaluated in these trials but they do so with much larger participant numbers over a greater length of time. Phase III trials have the power to explore the effectiveness of a given agent on risk reduction, disease incidence and symptom occurrence. In addition they monitor side effects and evaluate a range of safety and efficacy-related parameters. Phase IV, trials are typically described as post-marketing or safety surveillance trials, aimed at increasing the knowledge surrounding a given agent or treatment and identifying any late effects or long term consequences that may emerge. Many of these designations have become blurred in dietary agent trials or trials investigating drug-dietary agent combinations.

When we examined the phase designations for trials under consideration here, we found that they spanned nearly all phases of investigation (Tables 3-4) If we excluded those trials that were without specified phases, we found that over 70% of the Treatment trials consisted of phase I and phase II activities while 70% of the Supportive Care trials were in phases II and III. By contrast, approximately 55% of the phase-specified trials in the Prevention category were at the phase II level while 50% of those in the Basic Science group were in phase 0. Notably, there were no phase 0 trials in either the Prevention or Treatment groups; only one phase 0 trial was found in the Supportive Care category (Table 4)

4. NATURAL HEALTH PRODUCTS IN CURRENT CLINICAL TRIALS

We found that a variety of CAMs, dietary supplements and natural health products were being evaluated alone or in combination with anticancer agents. There has been an unprecedented increase in the growth in natural product use for health maintenance, disease prevention and cancer control. The acronym CAM has grown to encompass a vast number of treatment modalities – well beyond those reviewed here. In addition, many of the health approaches that had previously been considered complimentary are now being integrated into medical practices considered to be 'conventional'. This progression is reflected in the term 'Integrative Medicine' which is described further elsewhere (30)

The dietary supplements and natural products identified in the 65 clinical trials shown in Table 3 include vitamins, minerals, trace elements and cofactors (vitamins: B6, B12, D, and E; calcium; germanium and coenzyme Q10); herbal extracts (mistletoe, grapeseed, broccoli sprout, green tea, coriolus vesicolor and herba scutellaria barbata); amino acids and amino acid derivatives (l-carnitine-l-tartrate, l-acetyl-l-carnitine and glutamine), fatty acids (omega-3-fatty acids and conjugated linoleic acid); animal products (glucosamine chondroitin); probiotics (lactobacillus); phytochemicals (flaxseed, soy, garlic, d-limonene, diindolylmethane and ginseng); and proprietarial combinations (FemMED®, THL-P and Chinese Herbals) We will provide a brief summary for some of the dietary and natural health products and describe how they are being evaluated in clinical trials at this time. For each of the following correlations, the reader is referred to Table 3.

4.1. Vitamins, minerals, and cofactors in breast cancer trials4.1.1. Vitamin D

Vitamin D has been shown to inhibit the proliferation of mammary tissue and promote its differentiation (31-33) Moreover, there is evidence that the vitamin D signaling pathway plays a role in breast tissue remodeling and homeostasis (34) Whether vitamin D signaling becomes dysregulated in mammary cancer is not known. Results from the National Health and Nutrition Examination Survey (NHANES) and from the Nurses' Health Study (35-36) provide support for the role of vitamin D in reducing the risk of developing breast cancer. Alternatively, the Women's Health Initiative (WHI) failed to demonstrate an association between breast cancer risk and vitamin D intake (37) Despite the mixed results in the literature, most experts agree that vitamin D adequacy is a key factor in the quality of life for women with breast cancer (38-41) The active form of vitamin D_3 is calcitriol or 1,25 dihydroxyvitamin D_3 (40) Other forms such as cholecalciferol and calcidiol are also referred to as 'vitamin D'. Cholecalciferol is an inactive precursor of calcidiol (25-hydroxyvitamin D) Calcidiol itself is a prehormone which must undergo hydroxylation for conversion to the biologically active form of vitamin D: calcitriol (1,25-dihydroxyvitamin D_3) The enzyme required for this conversion is 1-alpha-hydroxylase. The kidneys produce this rate-limiting enzyme and are thus responsible for putting the active form of vitamin D into the circulation (42) Although optimum vitamin D levels are not clearly defined for breast cancer patients, the current evidence suggests that maintaining adequate vitamin D levels before, during and after therapy may result in better symptom management, improved bone health, lower treatment toxicity and reduced rates of recurrence (38-45) Members of the vitamin D family are being examined in several of the trials in this report. Most focus on dosing, prevention, potential treatment efficacy (given prior to surgery), and bone health (see trials 22-25, Table 3) Vitamin D and calcium are also being examined together (trials 55-58) in order to assess risk reduction or to test efficacy in delaying bone metastasis, reducing bone loss or improving musculoskeletal symptoms associated with aromatase inhibitor (endocrine) therapy.

4.1.2. vitamin B6 (pyroxidine)

Vitamin B6 or pyroxidine is being evaluated in combination with the chemotherapeutic drugs doxorubicin (trials 17 and 20) and capecitabine (trials 18-19) for efficacy in preventing palmar-plantar erythrodysthesia and to determine maximum tolerated doses, MTDs (Table 3) Palmar-plantar erythrodysthesia, also referred to as hand-foot syndrome, is a side effect of capecitabine and other drugs used in chemotherapy.

Table 4. Clinical trial summary

Trial No.[1]	Dietary Supplement[2] (alternate name)	Trial Type and Phase (total)				Trials (total)	Participants (total)
		Basic Sci.[3]	Prevention	Treatment	Supportive Care		
35-39	Green Tea (Polyphenon E)	Phase II (1)	No Phase (1) Phase II (1)	Phase I (2)	---	5	135
12-13	Mistletoe (Viscum album pini)	---	---	Phase I (1) Phase IV (1)	---	2	165
26-27	Glutamine	---	Phase IV (1)	Phase III (1)	---	2	80
22-25	Vitamin D	No Phase (1)	Phase II (2) No Phase (1)	---	---	4	334
28	DIM	Phase I (1)	---	---	---	1	300
18-20	Pyroxidine (B6)	---	---	---	Phase III (3)	3	436
34	Ginseng Root	---	---	Phase II (1)	---	1	50
33	Lactobacillus	---	---	---	Phase 0 (1)	1	90
32	Limonene	---	Phase I (1)	---	---	1	40
31	Garlic	---	---	No Phase (1)	---	1	10
30	Glucosamine/Chondroitin	---	---	---	Phase II (1)	1	53
29	Org. Germanium	---	Phase II (1)	---	---	1	101
21	Vitamin B12/Folic Acid	---	---	Phase II (1)	---	1	30
14-15	Vitamin E	---	---	Phase II (1)	Phase II (1)	2	148
16-17	Coenzyme Q10	---	---	---	No Phase (1) Phase I (1)	2	254
7-11	Omega-3 Fatty Acids	---	No Phase (2)	Phase II (1)	Phase II (1) Phase IV (1)	5	554
53-54	Yunzhi (Coriolus Versicolor)	---	---	Phase I (1) Phase IV (1)	---	2	84
49-52	Flaxseed	Phase 0 (1)	No Phase (1)	No Phase (1)	Phase III (1)	4	470
1-6	Soy	Phase 0 (1)	Phase II (3) Phase III (1)	---	Phase II (1)	6	990
47-48	H. Scuterria Barbata	---	---	Phase I/II (2)	---	2	125
45-46	Carnitine[4]	---	---	---	No Phase (1) Phase III (1)	2	400
40-43	Grape Seed Extract[5] (IH636)	---	Phase I (1) No Phase (1)	No Phase (1)	Phase II (1)	4	161
44	THL-P Extract	---	---	Phase II (1)	---	1	60
55-58	Calcium/VitD	Phase III (1)	Phase III (1[6])	No Phase (1)	Phase III (1)	4	2,938
59	Chinese Herbal Therapy	---	---	---	Phase I/II (1)	1	60
62-63	Broccoli Sprout/Sulphor.	---	Phase II (1)	Phase II (1)	---	2	94
65	Natural Supplements[7]	---	---	Phase I (1)	---	1	300
61	Phytochemical[8]	---	---	Phase II (1)	---	1	100
60	FemMED® Breast[9]	---	Phase I/II (1)	---	---	1	100
64	Conjug. Linoleic Acid	Phase 0 (1)	---	---	---	1	24
TOTALS		7	20	21	17	65	8,811

[1]Correspond to trial numbers on Table 3; [2]Note the term 'Dietary Supplement' as used here, includes vitamins, minerals, natural health products (amino acids and derivatives, phytochemicals, herbals, probiotics) and combinations; [3]Basic Sci.: Basic Science; [4]includes: L-Carnitine L-Tartrate and Acetyl-L-Carnitine; [5]includes: grape seed (proanthocyanidin) extract and freeze dried table grape powder; [6]trial enrolls breast- and other cancer types; [7]refers to: indole-3-carbinol, perillyl alcohol, glucuronic acid, flavonoids; [8]unspecified constituents; [9]contains: vitamin D, milk thistle, schizandra, stinging nettle, calcium, hydroxymatairesinol.

4.1.3. Vitamin B12 (cobalamin)

The efficacy of vitamin B12 and folate in combination with pralatrexate is described in trial 21 (Table 3) which is enrolling patients with advanced metastatic breast cancer. Pralatrexate is an antifolate anticancer drug which has shown greater clinical activity than methotrexate (46)

4.1.4. Vitamin E

Vitamin E, an antioxidant, is being studied in two of the trials reviewed here (trials 14 and 15, Table 3) with pentoxifylline, for the efficacy of this combination to lessen the symptoms of radiotherapy, particularly radiation-induced fibrosis. Pentoxifylline is derived from a hemorrheologic methylxanthine. This drug is of interest in

radiation oncology because it has shown the potential to enhance tumor oxygenation and promote radiosensitivity. Radiation-induced fibrosis is a late and generally irreversible consequence of radiotherapy (47) which is believed to respond to pentoxifylline-vitamin E cotreatment than to treatment with pentoxifylline alone. Previously published findings support the efficacy of this combination in attenuating the symptoms associated with fibrosis induced by radiation (47-48)

4.1.5. Coenzyme Q10

Coenzyme Q10 is a ubiquinone which is structurally similar to vitamin K. It is a natural component of living cells and can be synthesized in the body (49) Coenzyme Q10 functions as a cofactor in the mitochondrial electron transport chain and is essential to the ATP production. Coenzyme Q10 has antioxidant, neuroprotective and cardioprotective activities – qualities which are being exploited to reduce toxicities associated with anthracycline chemotherapy (50) Coenzyme Q10 is being given to participants enrolled in trials 16 and 17 with chemotherapeutic drugs like doxorubicin to determine the MTD or to evaluate the efficacy of this combination plus vitamin E (Coenzyme Q10-doxorubicin-vitamin E) in relieving treatment-related fatigue (Table 3)

4.2. Herbal extracts in breast cancer trials

Extracts of mistletoe, grapeseed, broccoli sprouts, green tea (polyphenon E), coriolus vesicolor (yunzhi) and herba scutellaria barbata are currently being examined in the breast cancer trials reviewed here.

4.2.1. Mistletoe extract (viscum album pini; iscador P)

Mistletoe (viscum album) is one of the most widely studied CAM therapies for solid cancers in Europe. Mistletoe extract contains lectins, viscotoxins, oligo- and polysaccharides. The lectins in mistletoe extract have demonstrated immune-modulating properties. Iscador P® is an extract of mistletoe that has been prescribed to cancer patients in Germany for years (51) The FDA in this country has approved mistletoe extract for cancer treatment studies. This review includes two interventional trials that are examining mistletoe extract, trials 12 and 13. In trial 12, it is given in combination with gemcitabine (a chemotherapeutic drug) in order to identify the MTD, tumor response and toxicity during metastatic breast cancer treatment. In trial 13, the study participants are given mistletoe extract (Iscador P) during chemo- or hormonal therapy to identify surrogate parameters of efficacy. For greater detail, see Table 3.

4.2.2 grape seed extract (IHS636)

Grape seed extract contains a number of procyanidins which have been attributed with antioxidant, anti-inflammatory, cytoprotective, and antitumor properties. In preclinical studies, grapeseed extract has been shown to protect cell membranes from oxidative damage and from the protein and lipid oxidation caused by cytotoxic drugs or radiation. Clinical trials testing the efficacy of IHS636 grape seed extract in reducing or reversing induration caused by high dose radiation therapy in breast cancer patients have produced mixed results (52) Nevertheless, it is currently being tested (trial 42) as a potential strategy against fibrotic tissue changes associated with prior radiation therapy. Grape seed extract interventions enrolling healthy, high and low risk participants, are also being conducted for risk reduction, dose finding and serum marker evaluation, in trials 40, 41, and 43 (Table 3)

4.2.3. Green tea extract (polyphenon E extract)

Green tea, rich in bioactive compounds, has been referred as both drug and beverage, (53) The bioactive compounds of interest are the catechins: EGCG, EGC, ECG, and EC ((-) epigallocatechin-3-gallate, (-) epigallocatechin, (-) epicatechin-3-gallate, and (-) epicatechin, respectively). The literature has consistently shown an association between these bioactive agents and chemoprevention (54) Findings from a prospective cohort study conducted in Japan have shown that 10 or more cups of green tea per day (the equivalent of 2.5 grams of green tea extract) can significantly decrease the relative risk of cancer incidence and delay onset (55-57) The results of a recent review point to an inverse relationship between green tea consumption and breast cancer recurrence (58) Polyphenon E is a Japanese product which consists of decaffeinated catechins (200 mg EGCG, 37 mg EGC, 31 mg EC) and other polyphenols (59) Current clinical testing is being conducted using polyphenon E (trials 35, 36 and 39) or green tea extract (trials 37 and 38) in order to assess a variety of factors, including markers of breast cancer progression, MTDs, and risk reduction (Table 3)

4.2.4. Coriolus vesicolor extract (yunzhi extract)

Coriolus vesicolor is a fungus derived from the Asian mushroom yunzhi. Yunzhi has been shown to act as both a radio- and immunoprotectant; it has been used as a restorative or safeguard to reverse or limit tissue damage caused by radiation treatment for cancer (60) It is currently being evaluated for efficacy as an adjuvant during chemotherapy for breast cancer, protection against treatment-induced toxicity, and MTD determinations in trials 53 and 54 (Table 3)

4.2.5. Herba scutellaria barbata (chinese herbal extract, BZL101)

Herba scutellaria barbata or Bezielle (BZL101™) is an oral botanical designed to target cancer cells. It has been tested in preclinical studies (61) and is currently undergoing phase I/II efficacy and safety testing in women with histologically confirmed, metastatic breast cancer (trials 47-48) Various pharmacokinetic parameters including toxicity and MTDs and tumor responses are being evaluated (Table 3)

4.3. Amino acids and derivatives in breast cancer trials

4.3.1. Carnitine (acetyl-l-carnitine)

Acetyl-l-carnitine has been shown to be both neurotrophic and neuroprotective (62-63) Current evidence suggests that that acetyl-l-carnitine promotes the regeneration of injured nerve fibers, decreases oxidative stress, regulates acetyl CoA levels, modulates the acetylation of critical cellular proteins, enhances

mitochondrial DNA synthesis, and increases intraneuronal levels of nerve growth factor, NGF (62-63) Moreover, acetyl-l-carnitine has demonstrated efficacy and tolerability in patients with chemotherapy-induced peripheral neuropathies**;** overall it is thought to play a protective role in patients suffering with treatment-induced neuropathy associated with paclitaxel or cisplatin chemotherapy (64-65) A current intervention trial (trial 45) is being conducted to examine the efficacy of oral acetyl-l-carnitine with taxane chemotherapy for the prevention or reduction of treatment-induced fatigue and peripheral neuropathy in breast cancer; similar studies are also being conducted with l-carnitine-l-tartrate in trial 46 (Table 3)

4.3.2. Glutamine

Glutamine is a nonessential amino acid which serves as an energy source for rapidly dividing cells; it can become depleted during stress, advanced cancer or during anticancer treatment regimens. Studies support the role of glutamine as a neuroprotectant. Glutamine is currently undergoing phase IV testing (trials 26 and 27) It is administered to breast cancer patients orally or intravenously to determine efficacy in reducing chemotherapy-induced peripheral neuropathy associated with taxane treatment (Table 3)

4.4. Fatty acids

4.4.1. Omega-3-fatty acids

Omega-3 polyunsaturated fatty acids (n-3) are essential fatty acids necessary for human health and well being. Moreover, n-3 fatty acids have demonstrated antitumor activities in preclinical studies and epidemiologic studies suggest that high n-3 levels may lower cancer risk (66) We have identified five clinical trials that are actively testing omega-3-fatty acids, trials 7-11 (Table 3) These trials are using omega-3-fatty acid supplements to reduce breast cancer risk in high risk women, evaluate mammographic breast density and biomarker expression during endocrine therapy with raloxifene, identify markers of breast cancer progression, reduce the musculoskeletal and neuropathic symptoms of taxane-induced toxicity during chemotherapy.

4.5. Phytochemicals

4.5.1. Garlic

Studies to determine the therapeutic potential of garlic (allium sativum) and its chemical constituents (diallyl disulfide, S-allylcysteine and ajoene) in patients with breast and other cancers are relatively new despite a vast amount of knowledge regarding its medicinal properties which dates back for centuries (67-68) Early evidence for the anti-cancer effects of garlic from population-based case-control studies provided the impetus for laboratory testing. Garlic constituents were shown to have bioactivity against chemically induced cancers and favorable effects on carcinogen metabolism in animal models and to cause growth inhibition, apoptosis, and cell cycle arrest in tumor cells (69-72) Currently, as shown in trial 31, garlic tablets are being given to patients with incurable or metastatic breast cancer during chemotherapy with docetaxel. The main objective is to assess changes in the pharmacokinetics and toxicity profile of docetaxel in the presence of garlic (Table 3) in order to achieve a more favorable outcome.

4.5.2. d-Limonene

d-Limonene, a constituent of many citrus oils, is a monocyclic monoterpene and solvent of cholesterol (73) Therapeutically, it has been used to dissolve gallstones, relieve gastric acidity, and treat gastroesophageal reflux disease, GERD (73-74) d-Limonene has also demonstrated chemopreventive activity in a number of cancers (75) Early clinical trials of breast and colorectal cancer showed modest responses to d-limonene (76) Trial 32 is recruiting women with breast cancer who will take d-limonene orally for 2 to 6 weeks prior to surgery during which time biomarkers of activity and the tissue distribution will be determined (Table 3)

4.6. Other natural health products currently undergoing clinical trial testing

Other dietary supplements and natural health products that are also undergoing current clinical trial testing, but which are not discussed here, include the following: organic germanium; broccoli sprout extract (sulforafane); conjugated linoleic acid; soy isoflavones, soy protein; diindolylmethane (DIM); flaxseed; freeze-dried table grape powder; American ginseng; THL-P Extract; Chinese herbal therapy; a natural supplement combination consisting of indole-3-carbinol, perillyl alcohol, glucuronic acid, and flavonoids; lactobacillus; and the FemMED™ Breast Health Formula. These are shown in Tables 3-4.

5. COMPLEMENTARY AND CONVENTIONAL THERAPY COMBINATIONS

In several of the clinical trials reviewed here, dietary agents and natural health products are being evaluated in combination with chemotherapeutic drugs, endocrine agents, or radiation.

5.1. Natural health products and chemotherapeutic drugs

The following dietary/natural product - chemotherapeutic drug combinations are currently being tested in cotreatment trials: (i) omega-3-fatty acids, garlic, l-acetyl-l-carnitine or various phytochemicals with taxanes such as paclitaxel and docetaxel (trials 11, 31, 45, 61); (ii) coenzyme Q10, vitamin B6 or Chinese herbals with doxorubicin (trials 17, 20, 59); (iii) mistletoe extract with gemcitabine (trial 12); and (iv) vitamin B6 with capecitabine (trials 18-19) In a number of other trials the use of mistletoe extract, vitamin B12, glutamine, lactobacillus, l-carnitine-l-tartrate or yunzhi extract (coriolus vesicolor) is being explored in the context of more than one chemotherapeutic drug given concurrently or using chemotherapeutic drugs that were not specified (trials 13, 21, 26-27, 33, 46, 54) All trials are described further in Table 3.

5.2. Natural health products and endocrine agents

The dietary agents and natural health products that are being given in combination with endocrine therapies including antiestrogens (tamoxifen, raloxifene)

and aromatase inhibitors (letrozole, anastrozole) include: (i) soy protein isolate with tamoxifen (trial 5); (ii) omega-3-fatty acids with raloxifene (trial 10); (iii) omega-3-fatty acids, glucosamine-chondroitin sulfate or flaxseed with the aromatase inhibitor anastrazole (trials 8, 30, 51, 52), as shown in Table 3.

5.3. Natural health products and radiation therapy

Currently, organic germanium, grape seed extract, and coriolus vesicolor are being examined during or after radiation therapy (trials 29, 42, 53)

6. CLINICAL TRIALS TESTING NATURAL HEALTH PRODUCTS IN HEALTHY WOMEN

Twenty-three percent of all the trials reviewed here are enrolling healthy women with no prior diagnosis of cancer. About half of these include trials investigating the efficacy of various dietary and natural compounds for risk reduction in women with higher than normal risk for developing breast cancer. These include women with mutated BRCA1/2 genes, those having more than one family member with these gene mutations, or other positive family history factors. . Trials 9, 22-23, 28, 40, 43, and 50 are currently evaluating the effects of omega-3-fatty acids, cholecalciferol, DIM, grapeseed extract or freeze-dried powder, and THL-P (an extract of several natural herbs) on risk reduction in women who are at higher than normal risk for developing breast cancer. Trials that are enrolling healthy women without risk factors were also included for comparison; these are trials 1, 3, 6, 38, 41, 56, and 60. Most of these trials are designed to assess changes in surrogate markers relevant to breast cancer such as changes in serum, tissue, and molecular markers; hormone and hormone metabolite levels; and mammographic breast density. Trial interventions included: soy isoflavones, soy protein, green tea extract, grape seed extract, calcium with or without vitamin D, and the FemMED™ Breast Health Formula (a proprietarial combination of vitamin D, milk thistle, schizandra, stinging nettle, calcium and hydroxymatairesinol) For greater detail, see Table 3.

7. SUMMARY AND PERSPECTIVES

There is a critical need to identify natural compounds with low toxicity and high utility in breast cancer (77) This report describes 65 open clinical intervention trials testing a range of dietary supplements and natural health products. Vitamins and minerals, herbal extracts, amino- and fatty acids, probiotics and phytochemicals were among the compounds being tested. Outcome measures included markers of risk (in high risk women), MTDs, efficacy (alone and in combination with standard anticancer drugs), toxicity and symptom management (in breast cancer patients) In addition, breast cancer markers (molecular, tissue, and serum), mammographic breast density were also incorporated into the design of many of the trials. Although definitive analyses will have await trial completion, data from these trials can be anticipated to improve treatment strategies in the future, and to produce toxicity profiles and tumor responses that are compatible with long term survival.

8. ACKNOWLEDGEMENTS

We gratefully acknowledge Wendi Rodgers Wilson, MLIS, for her technical assistance during the writing of this manuscript.

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Abbreviations: CAMs: complementary and alternative medicines; NHANES: national health and nutrition examination survey; WHI: women's health initiative; MTDs: maximum tolerated doses; ER: estrogen receptor; PR: progesterone receptor; FDA: food and drug administration; IND: investigational new drug; EGCG: (-)epigallocatechin-3-gallate; EGC: (-)epigallocatechin; ECG:(-)epicatechin-3-gallate; EC: epicatechin; NGF: nerve growth factor; GERD: gastrointestinal reflux disease; DCIS: ductal carcinoma *in situ*; LCIS: lobular carcinoma *in situ*; ADH: atypical ductal hyperplasia; y.o.: year old; IL: interleukin; IGF: insulin-like growth factor; IGFBP: insulin-like growth factor binding protein 3; gm: grams; mg: milligram; HCL: hydrochloride; FU: follow up; s.c.: subcutaneous; IV: intravenous; IM: intramuscular; VEGF: vascular endothelial growth factor.

Key Words: Dietary supplements, antioxidants, phytochemicals, CAMs, natural health products, clinical trials, breast cancer, chemoprevention, vitamins and minerals, vitamin D, mistletoe extract, Iscador P, grapeseed extract, coriolus vesicolor, scutellaria barbata, natural health product-chemotherapy combinations, endocrine therapy, complementary-conventional therapy combinations, green tea polyphenols

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