ARTICLE

Pilot Evaluation of Flaxseed for the Management of Hot Flashes

Sandhya Pruthi, MD, Susan L. Thompson, RN, MS, Paul J. Novotny, MS, Debra L. Barton, RN, PhD, Lisa A. Kottschade, RN, MSN, CNP, Angelina D. Tan, BS, Jeff A. Sloan, PhD, Charles L. Loprinzi, MD

The objective of this study was to evaluate, in a phase 2 pilot study, tolerability and the effect of 6 weeks of flaxseed therapy on hot flash scores in women not wishing to receive estrogen therapy. Eligibility included 14 hot flashes per week for at least 1 month. In the baseline week, participants took no study medication and documented the characteristics of their hot flashes. Thereafter, crushed flaxseed was administered at 40 g daily. Participants provided weekly toxicity reports and health-related quality of life information. The primary end point was a change in hot flash score prospectively reported in a daily hot flash diary. Thirty women were enrolled between June 17 and November 8, 2005. The mean decrease in hot flash scores after flaxseed therapy was 57% (median decrease 62%). The mean reduction in daily hot flash frequency was 50% (median reduction 50%), from 7.3 hot flashes to 3.6. Fourteen of the 28 participants (50%) experienced mild or moderate abdominal distention. Eight participants (29%) experienced mild diarrhea, one experienced flatulence, and six (21%) withdrew because of toxicities. This study suggests that dietary therapy decreases hot flash activity in women not taking estrogen therapy. This reduction is greater than what would be expected with placebo.

Key words: *flaxseed, hot flashes, linseed, menopause*

A hot flash is described as a sudden sensation of intense warmth that involves the face, chest, and upper body and may spread to the rest of the body. The experience of heat may be accompanied by sweating, flushing, and, for some women, cold spells. These episodes may occur from less than once a day to every hour, and they may continue during sleep. Hot flash duration varies and is often brief, but a hot flash may last several minutes. Related symptoms that may accompany hot flashes include sleep deprivation, anxiety, and irritability. It is estimated that well over half of the women who experience these menopausal symptoms seek medical treatment.[1]

Effective treatment of hot flashes has become more problematic for postmenopausal women in recent years because of changes in the acceptance of hormonal treatment, given the concerns about an increased risk of heart disease, breast cancer, stroke, and thromboembolism.[2] Estrogen therapy has been the effective hot flash treatment most commonly used. However, women are seeking nonestrogenic options for alleviating hot flashes. Various nonestrogenic agents have been studied in the past several years, and some of these agents have been shown to have moderate benefit in efficacy and tolerability.[3]

Currently, the most effective nonestrogenic therapy for hot flashes is progestational agents, such as megestrol acetate and medroxyprogesterone acetate.[4–6] These drugs have been shown to decrease hot flash frequency and severity by about 85% in placebo-controlled clinical trials—an efficacy similar to what is seen with estrogen use. Nonetheless, many patients and physicians alike have concerns about the use of any hormone. Therefore, nonhormonal treatment options have been sought.

Effective nonhormonal therapies for hot flashes include the newer antidepressants (eg, venlafaxine, paroxetine) and gabapentin.[7–13] These options have been shown to decrease hot flash frequency and severity by about 50 to 70% in placebo-controlled clinical trials. Unfortunately, not all women benefit from these agents, and toxicities may limit their use in some women. Ongoing evaluations of more effective and well-tolerated agents are thus needed in the management of hot flashes.

Sandhya Pruthi: *Division of General Internal Medicine;* Susan L. Thompson, Debra L. Barton, Lisa A. Kottschade, *and* Angelina D. Tan: *Cancer Center;* Paul J. Novotny *and* Jeff A. Sloan: *Cancer Center Statistics Unit; and* Charles L. Loprinzi: *Division of Medical Oncology, Mayo Clinic, Rochester, MN.*

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Reprint requests: Sandhya Pruthi, MD, *Division of General Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; e-mail: pruthi.sandhya@mayo.edu.*

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To date, clinical trials evaluating herbal or dietary supplements and complementary therapies, including vitamin E, black cohosh, soy, and acupuncture, have been unable to convincingly show that these agents, although very popular, result in clinically significant reductions in hot flash severity and frequency to a greater extent than that expected with placebo.[14] Flaxseed, also known as linseed, is another popular dietary supplement that has not been well studied for management of hot flashes. Considered a phytoestrogen, it is a rich source of lignans and omega-3 fatty acids. Lignans are naturally occurring diphenolic compounds found in whole grains and legumes; they have antioxidant properties and are thought to have estrogen agonist and antagonist properties, such as those found in selective estrogen receptor modulators (eg, tamoxifen citrate, raloxifene hydrochloride).

Flaxseed is an annual plant that flowers in the morning and is cultivated in temperate and tropical areas. The plant's components and products that are considered to have medicinal properties include the stem, oil from the seeds, the dry, ripe seeds, linseed cakes, and fresh flowers.[15] Flaxseed is commonly used for management of constipation because of its bulk-forming fibrous properties, which are thought to stimulate intestinal peristalsis. It has also been studied as a cholesterol-lowering agent, with the mechanism of action most likely due to its bulk-forming properties. Flaxseed has been reported to be as effective as an oral estrogen-progesterone preparation in improving mild menopausal symptoms and in lowering glucose and insulin levels.[16]

Research findings suggest that dietary lignans have some cancer-protective effects. Studies have reported reductions in both tumor biologic markers (ie, reductions in the Ki-67 labeling index and c-erb-B2 expression and an increase in apoptosis) and urinary lignan excretion, resulting in a reduction in tumor growth in patients with breast cancer.[17,18] Therefore, flaxseed is an interesting agent to study for vasomotor symptom management and potentially for reduction in breast cancer risk.

On the basis of these reported data, the current phase 2 pilot study was developed to evaluate flaxseed's efficacy in management of hot flashes, as well as its tolerability and toxicity. The purpose of this pilot study was to determine whether a large placebo-controlled double-blind trial should be considered.

Materials and Methods

Eligibility criteria for this trial included being a woman older than 18 years who did not wish to take estrogen on the basis of a perceived increased risk of breast cancer. Participants had to have reported bothersome hot flashes that occurred with a minimum frequency of 14 times per week for more than 1 month before study entry and to have a life expectancy greater than 6 months. Participants were permitted the use of tamoxifen, raloxifene, or aromatase inhibitors if they had been taking a constant dose of the medication for more than 4 weeks and did not plan to stop taking it during the study period.

Women were ineligible for the trial if they had received any of the following therapies within the 4 weeks preceding enrolment: antineoplastic chemotherapy, androgens, hormonal agents, or other herbal supplements, including soy. Other contraindications included (1) a history of allergic or other adverse reactions to flaxseed; (2) a history of diabetes; (3) a history of chronic diarrhea; (4) bowel obstruction or esophageal stricture; (5) pregnancy or breast-feeding; (6) current use of anticoagulants, including aspirin, clopidogrel bisulfate, ticlopidine hydrochloride, and warfarin; and (7) a history of a bleeding disorder or von Willebrand disease. The trial was approved by the Mayo Clinic Institutional Review Board according to federal regulations, and all participants signed a consent form.

The first week of the trial served as the baseline week during which no supplement was ingested but hot flashes were recorded in a daily diary. During this week, patients completed questionnaires about baseline toxicities and health-related quality of life.

Therapy with flaxseed, supplied in the form of crushed seed, was initiated the next week at a dose of 40 g per day. Participants were instructed to sprinkle 2 tablespoons of the flaxseed on cereal, in juice, in yogurt, or on fruit twice daily for 6 weeks. Each tablespoon provided 10 g of flaxseed. For every 10 g of flaxseed, an intake of a minimum of 150 mL of liquid was advised.

Flaxseed was provided in a fine granulated powder (Pizzey's Milling, Angusville, MB). The chemical analysis (performed by Medallion Laboratories, Minneapolis, MN, and Eurofins Scientific Inc, Petaluma, CA) described a product containing 26% dietary fiber; 40% triglycerides, mostly in the form of palmitic, stearic, oleic, linoleic, and linolenic acids; and 1% secoisolariciresinol diglucoside (a lignan antioxidant). The product was made from flaxseed hulls and met nutritional grade specifications, providing a high percentage of lignans.

During all of the study weeks, participants completed their hot flash daily diary entries and, once per week, completed a self-report symptom experience questionnaire, which evaluated the following items: nausea,

excessive sweating, joint or muscle pain, chills, headache, nervousness, and negative mood swings. The hot flash diary had been validated previously and used in multiple studies.[19] At the end of the study, participants completed a health-related quality-of-life questionnaire, called the Self-Assessment Scale, which is a numeric analogue scale that corresponds to the subscales of the Profile of Mood States depression scale (ie, fatigue, anxiety, confusion, energy, and anger).[20] During each of the treatment weeks, a study nurse contacted each participant by telephone to assess product tolerability and document compliance, encourage completion of the questionnaire, and address problems.

The primary end point, hot flash score, is a measure of hot flash frequency and severity. Individual hot flash severity is assigned a value from 1 (corresponding to mild) to 4 (corresponding to very severe). The hot flash score is then determined by multiplying the daily frequency by the average hot flash severity. Secondary end points included hot flash frequency, toxicities, and health-related quality of life. Since this was a pilot trial, the primary end point was analyzed as a descriptive reduction in the hot flash score to determine whether it was beyond that expected with placebo. For each patient who completed the study, the values at completion were compared with the baseline values. Paired *t*-tests were used to evaluate changes from baseline. All health-related quality-of-life end point data were converted to a scale from 0 to 100 points, with 100 being the most favorable.

Like previous pilot trials,[7,19,21–25] the current study was developed for 25 participants on the basis of data that showed that this sample size would provide 80% power to detect a reduction in hot flash scores of 50% from baseline using a paired *t*-test. This benchmark has been used in previous trials to account for expected placebo effects of 25 to 30%. If an agent in a phase 2 trial provides at least a 50% reduction in hot flash activity, then it is predicted that there is a reasonable chance that in a larger, adequately powered, placebo-controlled trial, it will yield statistically significant improvement compared with placebo.[19]

Results

Thirty participants were enrolled in this clinical study between June 17 and November 8, 2005. Figure 1 illustrates the participant flow. The characteristics of the 28 participants who provided hot flash information are listed in Table 1.

In the last week of flaxseed therapy, the mean decrease in hot flash scores was 57% and the median decrease was 62%. The mean number of hot flashes reported by the participants at baseline was 7.3 per day, which, at the completion of 6 weeks of flaxseed therapy, had decreased

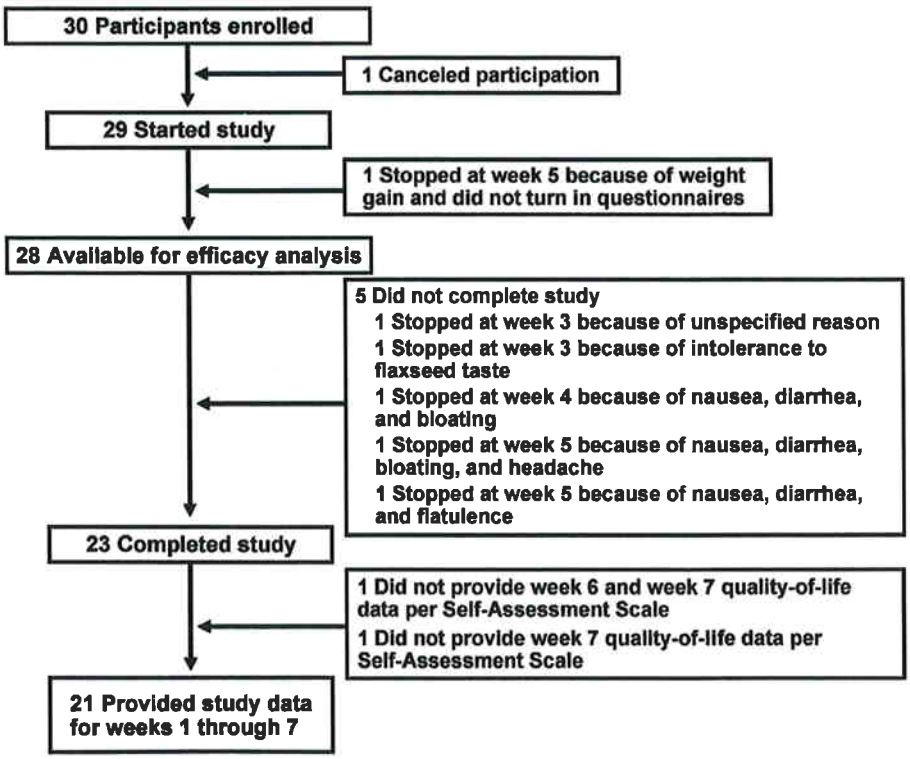

Figure 1. Flow of participants through the study.

Table 1. Characteristics of Study Participants (n = 28)

Characteristic	*Value**
Median age (range), yr	55.5 (47–71)
Age of group, yr	
18–49	5 (18)
≥ 50	23 (82)
Race, white	28 (100)
ECOG performance score	
0	27 (96)
1	1 (4)
Current aromatase inhibitor use	
Yes	1 (4)
No	26 (93)
Unknown (on blinded study)†	1 (4)
Current raloxifene use	
No	24 (86)
Unknown (on blinded study)†	4 (14)
Current tamoxifen use	
Yes	5 (18)
No	18 (64)
Unknown (on blinded study)†	5 (18)
Current antidepressant treatment	
Yes	11 (39)
No	17 (61)
History of breast cancer	
Yes	10 (36)
No	18 (64)
No. of hot flashes per day	
2–3	4 (14)
4–9	9 (32)
≥ 10	15 (54)
History of frequent hot flashes,‡ mo	
< 9	5 (18)
≥ 9	23 (82)

ECOG = Eastern Cooperative Oncology Group.
*Values are given as number of participants and percentage unless otherwise specified.
†Use was unknown because of participation in a blinded study of the agent.
‡Of at least 14 hot flashes per week for at least 1 month.

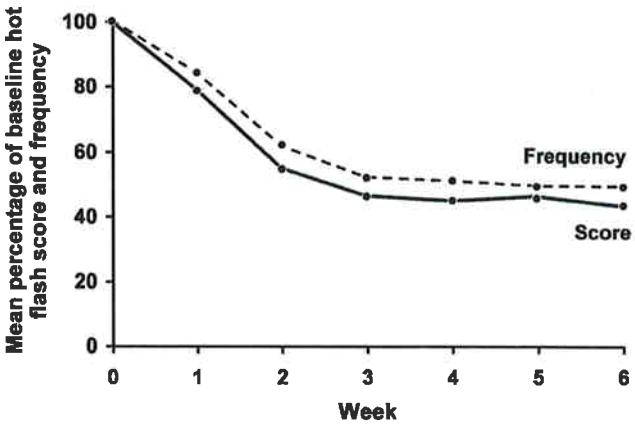

Figure 2. Mean percentages of baseline hot flash score (*solid line*) and frequency (*dashed line*) during 6 weeks of flaxseed therapy.

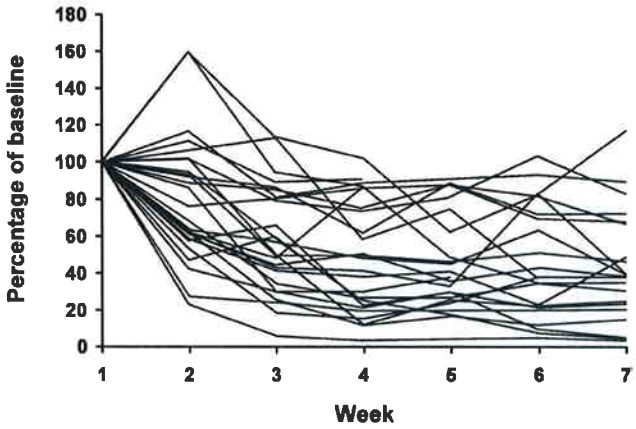

Figure 3. Change in hot flash scores from baseline (100%) in individual patients.

to 3.6 per day. This decrease represents a mean reduction of 50% and a median reduction of 50% ($p < .001$). The reductions in baseline hot flash scores and frequencies are shown in Figure 2. In this study, 13 of the 28 participants (46%) reported a reduction in hot flash frequency of 50% or more. The hot flash score changes in individual participants of this study are illustrated in Figure 3.

Study personnel graded side effects by using the Common Toxicity Criteria of the National Cancer Institute for abdominal distention, bloating, diarrhea, flatulence, pain (headache), and hypersensitivity. This analysis revealed that 14 of the participants (50%) experienced abdominal distention or bloating at some time during the trial. Of these 14 women, 12 experienced mild distention and 2 experienced moderate distention. Another 8 women experienced mild diarrhea, 1 experienced moderate flatulence, 2 had moderate headache, and 1 had a mild hypersensitivity reaction. In total, 6 women (21%) did not complete all 6 weeks of the flaxseed therapy—3 because of abdominal toxicities, 1 because of weight gain, 1 because of taste intolerance, and 1 for unspecified reasons.

Of the participant-reported outcomes, all items queried in the questionnaire except energy indicated a numeric improvement from baseline. Statistically significant improvements were observed for mood, joint or muscle pain, chills, and sweating. The participants' report of the effect of hot flashes on overall quality of life while receiving flaxseed therapy also showed statistically significant

improvement ($p < .001$). Participants reported less anger, anxiety, and fatigue on the Self-Assessment Scale at the end of the trial than at the baseline week. These self-reported data are shown in Table 2.

Discussion

This study provides preliminary data suggesting that 40 g of crushed flaxseed per day may be beneficial in managing bothersome hot flashes. These results need to be evaluated in a larger, adequately powered, placebo-controlled trial. The weak estrogenic properties identified in flaxseed seem to account for the most likely mechanism of its effectiveness in reducing hot flash activity. This finding is supported by the results of the Women's Healthy Eating and Living Study, designed to assess the effect of dietary intervention with a high-fiber, reduced-fat diet on breast cancer recurrence and survival after recurrence.[26] A decrease in vasomotor symptom severity was reported after the participants achieved high dietary fiber intakes.

Pilot trials have shown differing responses in hot flash reduction for various complementary therapies. Interestingly, black cohosh was evaluated initially in a pilot study in a manner similar to that of the current trial.[24] This pilot experience reported a reduction in hot flash score (frequency and severity) that exceeded 50%. A large randomized placebo-controlled study was subsequently initiated, using a crossover technique to assess efficacy and toxicity; however, this trial failed to provide evidence that black cohosh reduced hot flashes more than placebo.[27] These findings support the position that placebo-controlled trials are essential to follow up promising pilot data before declaring that a new agent clearly decreases hot flash frequency and severity.

Of all participants, 21% did not complete this trial because of abdominal toxicities, taste intolerance, or weight gain. These issues need to be evaluated further in a placebo-controlled manner. It is possible that initiating flaxseed therapy at a lower dose—and titrating the dose upward—may decrease abdominal toxicities.

Is flaxseed a potentially safe dietary supplement to consider in women with a history of breast cancer or other hormone-sensitive tumors? Numerous epidemiologic studies have evaluated the relationship between phytoestrogens and breast cancer risk. This class of compounds consists of nonsteroidal estrogens—natural plant substances that include isoflavones and lignans. Isoflavones are present in soy products, whereas lignans are present in fiber-rich foods such as flaxseed. Plant lignans are metabolized to mammalian lignans by intestinal micro-

Table 2. Mean Self-Reported Symptoms or Toxicities and Health-Related Quality-of-Life Scores ($n = 21$)*

	Score		*Difference between Scores of Weeks 1 and 7*	
Scored Feature	*Week 1*	*Week 7*	*Value*	p
Symptom/toxicity (reported in SED†)				
Negative mood swings	81.00	93.50	12.50	.004
Excessive sweating	59.00	77.00	18.00	.004
Joint/muscle pain	64.00	76.00	12.00	.02
Nervousness	86.50	92.00	5.50	.148
Chills	77.00	91.00	14.00	.01
Headache	89.50	95.00	5.50	.13
Nausea	98.00	99.50	1.50	.25
Health-related quality of life				
Effect of hot flashes on quality of life (reported in SED)	56.00	79.00	23.00	< .001
Fatigue (SAS‡)	41.90	64.76	22.86	.001
Anger (SAS)	83.81	92.86	9.05	.016
Anxiety (SAS)	67.62	80.48	12.86	.063
Confusion (SAS)	86.19	92.38	6.19	.109
Energy (SAS)	56.19	55.24	−0.95	.570
Overall quality of life (reported in SED)	72.00	77.00	5.00	.513

SAS = Self-Assessment Scale; SED = symptom experience diary.
*All quality-of-life scores are from 0 to 100, with higher scores indicating better outcomes.
†Self-reported symptoms graded on a numeric analogue scale.
‡Numeric analogue scale corresponding to subscales of the Profile of Mood States depression scale.

flora. Lignans appear to have two properties: weak estrogenic effects and antiestrogenic effects.[28] The antiestrogenic potential has been evaluated by several studies that, overall, have demonstrated no evidence of flaxseed consumption causing an increased risk of breast cancer.[28] Lignans have also been shown to inhibit the aromatase enzyme in human preadipocytes, suggesting a mechanism by which lignan consumption may contribute to a reduction in estrogen-dependent breast cancer.[29] Further, a small study evaluating the effects of dietary flaxseed on tumor growth in newly diagnosed breast cancer in postmenopausal patients demonstrated a reduction in tumor growth and an increase in urinary lignan excretion.[30]

The chemical structure of lignans appears to be similar to that of estradiol and the selective estrogen receptor modulator tamoxifen. This similarity suggests that flaxseed appears to behave like a selective estrogen receptor modulator, such as tamoxifen and raloxifene. The interaction between flaxseed and tamoxifen is not entirely clear. Of note, Chen and colleagues reported that flaxseed and tamoxifen together had an increased tumor inhibitory effect in estrogen receptor–positive breast cancer.[31] The significance of this effect in patients is not clear at this time.

The potential chemopreventive benefits of flaxseed may also be due to its influence on endogenous sex hormone production and metabolism. Flaxseed consumption studied in both premenopausal and postmenopausal women was found to increase urinary estrogen metabolite excretion, resulting ultimately in a decrease in estrogen availability to cells.[32,33] Thus, flaxseed appears to be a safe, potentially beneficial agent to test in patients with a history of breast cancer.

The only other known published study specifically designed for evaluating dietary flaxseed supplementation in hot flash management is a study that assessed the effect of soy muffins compared with flaxseed muffins and wheat muffins (control) on quality of life and hot flashes.[34] This report, similar to the current report, supports the conclusion that flaxseed may decrease hot flashes. The pilot data from these two trials provide support for pursuing a double-blind, randomized, placebo-controlled study to verify this suggestion and to better determine the toxicity of this treatment approach.

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