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A Phase III, Randomized, Placebo-Controlled, Double-Blind Trial of Flaxseed for the Treatment of Hot Flashes¹:NCCTG N08C7

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Abstract

Objective—Preliminary data suggest that flaxseed, a rich source of dietary lignans, may be a potentially effective treatment for hot flashes. A phase III randomized, placebo controlled trial was conducted to evaluate the efficacy of flaxseed in reducing hot flashes.

Methods—Postmenopausal women with or without breast cancer were randomly assigned to a flaxseed bar (providing 410 mg of lignans) for 6 weeks vs. a placebo bar. Participants completed daily, prospective, hot flash diaries during the baseline week, and then ate one study bar/day for 6 weeks while recording their daily hot flashes. The intra-patient difference in hot flash activity between baseline and the last treatment week was the primary endpoint. Side effects were evaluated through self report and CTC assessment.

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Based on promising pilot data, a phase III randomized placebo controlled trial was conducted to evaluate the efficacy of flaxseed in reducing hot flashes. This original research report describes results and side effects for 188 postmenopausal women.

Results—188 women were enrolled onto this trial. Mean hot flash score was reduced 4.9 in the flaxseed group and 3.5 in the placebo group ($p=.29$). In both groups, a little over a third of the women received a 50% reduction in their hot flash score. Only one side effect was significantly different between groups, grade 1 pruritis, which was more common in the placebo group (8% versus 1%). Both groups reported abdominal distension, flatulence, diarrhea and nausea. Adherence and ability to detect treatment assignment did not differ between groups.

Conclusions—The results of this trial do not support the use of 410 mg of lignans for the reduction of hot flashes. The bars were fairly well tolerated, with both groups reporting gastrointestinal effects, likely due to the fiber content.

Keywords

flaxseed; dietary supplement; hot flashes; menopause; clinical trial

Introduction

Hot flashes are experienced by up to 75% of women as they travel through the menopause transition^{1,2}. For most women, hot flashes persist for up to 2 years and then subside, but, for others, hot flashes can persist much longer². For women receiving treatment for breast cancer, the need to take endocrine therapy, such as tamoxifen or an aromatase inhibitor, can be associated with bothersome hot flashes. As these medications are taken for five to ten years, this subset of women may experience a prolonged, symptomatic menopause.

Hot flashes are not just a physiologic phenomenon but are accompanied by, and associated with, psychological experiences. The hormonal transitions of menopause can be a time of negative mood, increased stress and anxiety, feelings of loss, and concerns about aging^{3–5}. As such, hot flashes can be a potent trigger for negative psychosocial sequelae.

Estrogens and progestational agents are the most effective agents known to date for reducing hot flashes, with reductions of about 80%^{1,6}. Nonetheless, there is concern about giving these hormonal agents to women who have had breast cancer. Currently, the sentiment is that estrogen therapy should not be prescribed for breast cancer survivors. Information from the Women's Health Initiative citing the increased risk of cancer with an estrogen/progesterone combination as opposed to estrogen alone makes progestational agents also less attractive⁷. In addition, progestational agents are associated with weight gain and negative mood in the literature and are not popularly thought of to positively impact the menopausal experience, despite a lack of such evidence in trials utilizing progestones for hot flashes^{8–9}.

Since 2000, several selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants have been studied and been found to decrease hot flash scores by 50–65%^{10–12}. However, there are some limitations regarding the use of antidepressants for hot flashes. The first is that many women do not like the idea of being on an antidepressant. The second is that there is a fear of sexual side effects with serotonin reuptake inhibitors which makes their long term use unpopular in a population (breast cancer survivors) who already are experiencing negative changes in their sexual health as a result of their cancer treatment¹³. Finally, some effective antidepressants inhibit CYP2D6, an important enzyme for converting tamoxifen to an effective metabolite^{14–16}. Therefore, other options are needed.

One dietary treatment, flaxseed, has shown promise in at least one pilot trial and deserves more definitive study as a potentially effective option to relieve hot flashes. Flaxseed is an annual plant that is cultivated in temperate and tropical areas. The seeds, as well as the oil

from the seed, are the main components of the plant that are considered to have physiologic properties¹⁷. Flaxseed is the richest source of lignans, which is one of three major classes of phytoestrogens. The lignans associated with flaxseed are primarily secoisolariciresinol (SDG), the essential fatty acid alpha-linolenic acid, (which is a biologic precursor to omega 3 fatty acids), as well as fiber. Lignans are thought to have estrogen agonist and antagonist effects as well as antioxidant properties. Flaxseed and its lignans may have potent anti-estrogenic effects on estrogen receptor-positive breast cancer and may have benefits in breast cancer prevention efforts^{18,19}. Lignans are converted by colonic bacteria to enterodiol and enterolactone which are metabolites believed to have important physiologic properties such as decreased cell proliferation and inhibition of aromatase, 5 alpha reductase and 17 beta hydroxysteroid activity.

Based on mixed pilot data suggesting flaxseed may reduce hot flashes^{20–21,22} we conducted a phase II, open label trial with one week of baseline and 6 weeks of treatment with flaxseed involving 30 evaluable women to evaluate its impact on hot flash reduction²³. Participants received 40 grams of flaxseed (1 % secoisolariciresinol diglucoside (SDG)) which represents 400 mg of lignans. Crushed flaxseed was administered at 20 grams twice daily and was sprinkled on cereal, yogurt or mixed in a beverage. The pilot data demonstrated a mean decrease in hot flash scores of 57% and mean reduction in daily hot flash frequency of 50%, from 7.3 to 3.6 hot flashes per day. Participants reported mild to moderate abdominal distension (50%) and mild diarrhea and flatulence, with six women withdrawing from the study due to toxicities. This was the first pilot study to evaluate dietary flaxseed therapy with respect to hot flash activity as a primary endpoint. The reduction in hot flash score and frequency was greater than what would be expected with a placebo²⁴. Subsequently, the current phase III trial was developed and implemented to evaluate flaxseed versus placebo for hot flash reduction.

Methods

This study was a randomized, placebo controlled trial, whose primary aim was to evaluate the efficacy of flaxseed in reducing hot flash activity in women. Secondary aims included the evaluation of the side effect profile for flaxseed and to evaluate its effects on secondary endpoints, namely activity interference from hot flashes, mood and other menopausal symptoms. Women eligible for this trial included those who were > 18 years, postmenopausal, with or without a history of breast cancer (currently without malignant disease and having completed chemotherapy/radiation), who wished to avoid estrogen based treatment. The women had to have experienced hot flashes for > 1 month and hot flashes had to occur ≥ 28 times per week. Women with a history of allergies to flaxseed, current or planned use of other agents for treating hot flashes (i.e.: gabapentin, clonidine, antidepressants, hormonal treatments), were excluded. Women could not be receiving anticoagulants, anti-hypertensives or have co-morbid gastrointestinal disorders or uncontrolled diabetes. Tamoxifen, raloxifene, or aromatase inhibitors were allowed if the participant had been on a consistent dose for ≥4 weeks and were not planning to stop the medication during the study period.

Eligible participants were randomly assigned by computer using dynamic allocation to either flaxseed or placebo, stratified by age (18–49 vs. ≥50), current use of tamoxifen/selective estrogen receptor modulator (SERM)/aromatase inhibitor (AI), duration of hot flashes (≤9 months vs. > 9 months), and number of daily hot flashes (4 to 9 vs. ≥10).

The study agent was administered as a bar, containing 7.5 grams of flaxseed (5% lignans) providing 410 mg of lignans, 6 grams of protein and 20% fiber. It contained 190 calories. The matching placebo contained 2 grams of protein, 20% fiber and 200 calories and did not

have any flaxseed, lignans or soy products. Both active and placebo bars were provided by Glanbia Nutritionals, who also arranged product quality testing and content verification by an independent company. Good manufacturing processes were used.

Participants did not eat any study bars during the first study week, but kept daily diaries and completed baseline questionnaires. This baseline week was followed by 6 weeks in which participants were instructed to eat one bar daily, in keeping with the design of the positive pilot trial. This could be eaten all at once or throughout the day. The primary outcome measure was a prospective self report daily diary, in which participants recorded both the frequency and severity of hot flashes during each 24 hour period over the 7 week study period. Secondary endpoint measures included the Hot Flash Related Daily Interference Scale (HFRDIS)²⁵, the Profile of Mood States (POMS)²⁶, the Menopause Quality of Life Scale (MenQOL)^{27,28}, the Global Impression of Benefit²⁹, and a side effect questionnaire. Side effect and menopausal symptom information were collected weekly, while the HFRDIS and POMS were completed at the end of the study. Study personnel called women during weeks 2, 3, 5 and 7 to answer questions, encourage adherence and grade toxicities per the Common Terminology Criteria.

The intra-patient difference in hot flash activity between baseline (study week 1) and the last treatment week was the primary endpoint. Hot flash activity was measured by the weekly average hot flash score²⁴, which is a composite entity of both frequency and severity of hot flashes. The daily hot flash score was computed by multiplying the mean severity grade by the frequency over a 24 hour period. Taking the average of daily hot flash scores over a week produces the weekly average hot flash score. The independent two-sample *t*-test or Wilcoxon rank-sum test was used to examine the change of weekly average hot flash score from baseline to treatment termination between flaxseed and placebo arms. All endpoints for the secondary analysis were assessed for changes from baseline to the last treatment week, except for Global Impression of Benefit which was only evaluated at the end of the study, before the patient was unblinded. Participants who did not provide baseline or week 7 data were excluded from the analysis. Patterns of missing data were evaluated and were found to be similar between groups.

From previous hot flash trials, a mean reduction in hot flash score for placebo was estimated to be 3.5 units, with an additional 3.5 units between the placebo and flaxseed arm considered to be clinically important²⁴. Therefore, using a two sided independent sample *t*-test, an accrual goal of 64 patients per arm to provide 80% power with a 5% type I error rate was desired. An additional 13 patients per arm were accrued to account for missing data.

Results

188 patients were enrolled on this study between 10/09/2009 and 12/18/2009 from 22 sites across the United States. There were 7 cancelled patients and 3 ineligible patients. The CONSORT diagram depicts the flow of data (Figure 1). Data from 146 patients were available for efficacy analysis. Characteristics were equally distributed between arms (Table 1).

There were no significant differences in the reduction of hot flash scores between arms over the study period, with both arms experiencing similar reductions in hot flashes. Mean change from baseline in hot flash score was -4.9 in for the women taking flaxseed and -3.5 for those on placebo ($p=0.29$, 95% CI -0.7,3.5). Percent changes in hot flash score (figure 2) and frequency (figure 3). The reduction in frequency in the placebo arms was 28% versus 29% in the flaxseed arm ($p=.90$). A little over 1/3 of the women in each arm experienced a

50% reduction in their hot flash scores over the course of the study, 25 (36%) in the flaxseed arm and 28 (36%) in the placebo arm.

There was only one toxicity that was significantly different between groups when evaluations were done per the Common Terminology Criteria. The placebo group experienced more pruritus than the flaxseed group, 8% vs 1%, primarily grade 1 ($p=.04$). Although not statistically different, the flaxseed group did report more abdominal distention, flatulence and nausea, while the placebo group reported more diarrhea (Table 2). Self reported side effects revealed a slightly different profile with the women on the flaxseed arm reporting more diarrhea and flatulence and the women on placebo reporting more bloating, although none was significantly different.

None of the subscales or total mood disturbance on the POMS or subscales on the MENQOL were significantly different between arms, with all subscales improving over time in both arms (data not shown). One item on the HFRDIS, leisure interference was significantly better in the flaxseed arm over the placebo arm ($p=.03$) but none of the other items were significantly different (Table 3).

Repeated measures analysis of variance analysis was performed to evaluate the role of important variables in predicting the frequency of hot flashes. Hot flash frequency was not significantly different based on history of breast cancer, time since menopause, age, use of tamoxifen or aromatase inhibitors or treatment arm. Significant variables with respect to hot flash frequency were study week ($p<.001$) and baseline hot flash frequency ($p<.0001$).

Women were asked to rate their impression of change from the study agent. 33% of women on flaxseed indicated a change of moderate to very much better (+2, +3) while 33% of women on placebo indicated this improvement in their hot flashes. 35% of women on placebo and 38% on flaxseed indicated there was no change in their hot flashes.

Adherence to the treatment did not differ between arms and during the treatment weeks, 92% of the women reported eating 75% or more of their assigned bar daily. When asked if they were receiving flaxseed or placebo, 52% of each group reported being on placebo and 48% reported being on flaxseed. Hence, there was no difference in the ability to correctly guess the treatment assignment.

Discussion

This study, which used a standardized flaxseed product delivering a large dose (410 mg) of lignans, was not able to provide support for the use of flaxseed in reducing hot flashes more than a placebo. Both the flaxseed and placebo reduced hot flashes equivalent to what placebos have typically been found to provide (25 – 30% reduction). Hot flash reduction in this study was not influenced by the intervention, but rather, greater reductions in hot flashes were seen at weeks 6 and 7 and women with higher numbers of hot flashes at baseline experienced greater reductions. The one item on the HFRDIS, (leisure interference), that was significantly improved, may well be a fluke of multiple comparisons. The participants in this study were quite adherent to the treatment and were blinded appropriately to their treatment assignment.

Although there were not any significantly worse toxicities experienced by the women receiving flaxseed, there were some side effects from both products, namely GI toxicities of bloating, flatulence and diarrhea. This was likely due to the fiber content that was found in both the flaxseed and the placebo bars (20% fiber). It is difficult to know whether the low grade pruritis of 8% in the placebo group is meaningful in any way.

These findings are in contrast to preliminary data evaluating flaxseed for its effects on hot flashes and other menopausal symptoms. A small, randomized clinical trial with 25 women that evaluated diet and flaxseed versus diet and estrogen +/- progesterone therapy for lipid effects, also looked at the impact of the two arms on menopausal symptoms as measured by the Kupperman Index. The investigators used 40 grams per day of flaxseed (21 mg of lignans) versus 0.625 mg of conjugated estrogen and concluded that both arms were equally efficacious in reducing mild menopausal symptoms²¹. Yet another study using flaxseed muffins delivering 50 mg/day of lignans versus soy muffins versus a placebo muffin found a significant decrease in the severity of hot flashes for those on flaxseed but no significant differences in frequency²². However, like the present study, a larger placebo-controlled trial with 179 women evaluating 40 grams of flaxseed (21 mg of lignans) over one year on numerous endpoints, did not find that the flaxseed reduced hot flashes per the MENQOL any more than did the wheat germ placebo²⁰. Our study did not find any benefit for flaxseed in any of our secondary endpoints, including the MENQOL.

Complementary therapies have become increasingly popular remedies used by women to decrease menopausal symptoms, including hot flashes. In one descriptive study, Harris and colleagues found that breast cancer survivors were 7 times more likely to use alternative treatments for hot flashes, such as soy, vitamin E and herbal therapies as women with without breast cancer³⁰.

This is important to note because a minority of these alternative therapies have been studied in rigorous, randomized, controlled trials and there is a known placebo effect in hot flash trials that can be wide ranging. Of those therapies that have been evaluated, none, to date, have been proven effective³¹⁻³³. This supports that caution is in order regarding the use of popular herbs/dietary supplements for hot flashes and general menopause symptoms, that have not been studied utilizing rigorous trial designs.

From a clinical standpoint, women will continue to want to experiment with complementary therapies, particularly given the recent concerns about breast cancer risk and mortality with hormonal therapy. Clinicians need to be prudent in assessing complementary therapy use by their patients and educate women who are seeking alternative therapies about the known risks, benefits and limitations of the evidence to date.

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Figure 1.
CONSORT Diagram

Figure 2.
Percent change from baseline in hot flash score

Figure 3.
Percent change from baseline in hot flash frequency

Table 1

Baseline Patient Characteristics

	Flaxseed (N=88)	Placebo (N=90)	p value
Mean Age			0.6665
< 50	24 (27%)	22 (24%)	
>= 50	64 (73%)	68 (76%)	
Race			0.4622
White	82 (93%)	86 (96%)	
Black or African American	1 (1%)	0 (0%)	
Asian	0 (0%)	1 (1%)	
No. of Hot Flashes per Day			0.7797
4-9	50 (57%)	53 (59%)	
10+	38 (43%)	37 (41%)	
Hot Flashes Duration (Month)			0.8057
< 9	6 (7%)	7 (8%)	
>= 9	82 (93%)	83 (92%)	
Breast Cancer History			0.7668
Yes	44 (50%)	47 (52%)	
Time Since Menopause			0.7266
1 year	8 (9%)	6 (7%)	
2 years	15 (17%)	21 (23%)	
3 years	14 (16%)	15 (17%)	
>3 years	50 (58%)	48 (53%)	
Anti-estrogen Therapy			0.5946
Aromatase Inhibitor	15 (17%)	12 (13%)	
Tamoxifen	19 (22%)	25 (28%)	
Other	2 (2%)	0	
Concurrent Anti-depressive Therapy			0.7807
Yes	19 (22%)	21 (23%)	
Which Anti-depressive Therapy			0.6661
Selective Serotonin Reuptake Inhibitor	13 (68%)	13 (62%)	
other	6 (32%)	8 (38%)	

Table 2

Adverse Events as Measured Using the CTCAE v 4.0

	Flaxseed (N=86)	Placebo (N=90)	Wilcoxon p-value
ABDOMINAL DISTENSION			0.4124
0-None	55 (64%)	62 (69%)	
1-Mild	20 (23%)	21 (23%)	
2-Moderate	11 (13%)	6 (7%)	
3-Severe	0 (0%)	1 (1%)	
ABDOMINAL PAIN			0.9680
0-None	84 (98%)	88 (98%)	
2-Moderate	2 (2%)	2 (2%)	
DIARRHEA			0.4423
0-None	76 (88%)	76 (84%)	
1-Mild	9 (10%)	12 (13%)	
2-Moderate	1 (1%)	2 (2%)	
FLATULENCE			0.1968
0-None	45 (52%)	52 (58%)	
1-Mild	24 (28%)	31 (34%)	
2-Moderate	17 (20%)	7 (8%)	
NAUSEA			
0-None	67 (78%)	78 (87%)	0.0992
1-Mild	14 (16%)	12 (13%)	
2-Moderate	5 (6%)	0 (0%)	
PRURITUS			0.0358
0-None	85 (99%)	83 (92%)	
1-Mild	1 (1%)	6 (7%)	
2-Moderate	0 (0%)	1 (1%)	
RASH MACULO-PAPULAR			0.3420
0-None	83 (97%)	84 (93%)	
1-Mild	3 (3%)	6 (7%)	
VOMITING			0.4656
0-None	84 (98%)	86 (96%)	
1-Mild	0 (0%)	4 (4%)	
2-Moderate	2 (2%)	0 (0%)	

Table 3

Change from baseline to week 7, HFRDIS (Higher numbers are better)

	Flaxseed (N=69)	Placebo (N=77)	p value
Work			0.9428 ¹
Mean (SD)	11.9 (27.07)	11.2 (22.63)	
Social			0.1672 ¹
Mean (SD)	12.8 (24.00)	7.0 (23.42)	
Leisure			0.0342 ¹
Mean (SD)	15.6 (24.55)	6.9 (23.58)	
Sleep			0.4310 ¹
Mean (SD)	18.8 (27.92)	15.4 (26.96)	
Mood			0.1065 ¹
Mean (SD)	19.5 (28.53)	11.2 (26.60)	
Concentration			0.1881 ¹
Mean (SD)	15.7 (24.01)	10.4 (26.34)	
Relationship			0.0775 ¹
Mean (SD)	13.7 (28.47)	4.6 (22.29)	
Sexuality			0.2401 ¹
Mean (SD)	15.6 (24.48)	12.4 (29.73)	
Enjoyment of Life			0.1743 ¹
Mean (SD)	13.0 (24.73)	8.7 (23.56)	
Overall QOL			0.1319 ¹
Mean (SD)	12.0 (22.97)	7.9 (24.41)	
HFRDIS Total			0.0886 ¹
Mean (SD)	13.9 (18.57)	9.8 (19.65)	
Kruskal Wallis ¹			

Abbreviation: QOL – quality of life