

# The Role of Soy Foods in the Treatment of Menopausal Symptoms<sup>1–3</sup>

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## Abstract

The findings of the Women's Health Initiative resulted in a sharp decline in the use of estrogen therapy. Increasingly, menopausal women have been interested in soy foods as an alternative to estrogen therapy for the treatment of menopausal symptoms. This article provides an overview of the limited number of studies that assess the effectiveness of soy foods to alleviate vasomotor and urogenital symptoms. The evidence of the efficacy of soy foods in improving menopausal symptoms is limited due to the small number of trials reporting conflicting results. *J. Nutr.* 140: 2318S–2321S, 2010.

## Introduction

Low estrogen levels in menopause often result in vasomotor symptoms, atrophy of the vaginal epithelium, and bone loss. Most menopausal symptoms are relieved or disappear with estrogen therapy; thus, until recently, symptoms had been primarily managed with hormone therapy (1). The findings of increased risk of breast cancer and cardiovascular complications by the Women's Health Initiative Study (WHI)<sup>7</sup> resulted in the early termination of its estrogen/progestin arm (2) and a sharp

decrease in the number of menopausal women receiving hormone therapy (3–5). Consequently, many have increased the use of foods or herbal products containing phytoestrogens, believing that “natural” estrogens would provide all of the benefits but none of the risks of prescription hormones (6,7). Soy foods are particularly popular because of their isoflavone content, probably based on the fact that Chinese and Japanese women, who traditionally consume a soy-rich diet, have a lower risk of breast cancer, heart disease, and experience less vasomotor symptoms than American women (8,9). This article reviews studies that have assessed the efficacy of soy foods in ameliorating menopausal symptoms. Trials that used tablets or foods enriched with soy isoflavones isolated from soy protein are not included.

## Menopausal symptoms

The initial years of menopause are often accompanied by vasomotor symptoms such as hot flashes and night sweats, somatic symptoms such as fatigue, body aches, and vaginal dryness, and psychological symptoms such as irritability, anxiety, depression, decreased libido, and difficulty sleeping. The frequency, severity, and duration of vasomotor symptoms vary according to the population (10). Hot flashes are the most common menopausal symptom in North America and Europe; up to ~70% of women are affected. Symptoms can begin during the menopausal transition up to 2 y before the cessation of menses. The average duration of hot flashes is 6 mo to 5 y, although 20% of women continue with symptoms into their 70s and 80s. Night sweats can interfere with sleep and lead to chronic sleep deprivation, chronic fatigue, and mood changes. Estrogens are effective in decreasing the frequency and severity of these symptoms and are commonly used as a positive control in clinical trials. However, the management of menopause has changed considerably since the publication of the WHI results in 2002 (11). Menopausal women now account for one of the largest segments of alternative medicine users; 80% of women aged 45–60 y report using nonprescription therapies for the management

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<sup>7</sup> Abbreviations used: WHI, Women's Health Initiative; KI, karyopycnotic index; MV, maturation value; MI, maturation index.

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of menopausal symptoms (12). Soy food sales in the US have increased from \$300 million in 1992 to \$4.5 billion in 2009 (13). The greatest growth was seen in soy-based meat alternatives followed by soymilk and tofu.

### Assessment of vasomotor symptoms

Studies of soy foods have assessed vasomotor symptoms by self report, whether in the form of a diary or questionnaires, such as the Menopause-Specific Quality of Life Questionnaire. None of these studies has utilized objective measures.

### Assessment of vaginal cytology

The epithelium lining the vaginal wall is markedly sensitive to estrogens. The presence of vaginal superficial cells is indicative of estrogen stimulation and has been utilized to evaluate the degree of estrogenization and the effectiveness of estrogen therapy, whether systemic or topical.

Various indices are used to measure the estrogenization of the vaginal epithelium. The Vaginal Health Index scores, on a scale of 1 (poorest) to 5 (best), vaginal moisture, vaginal fluid volume, vaginal elasticity, vaginal mucosa, and vaginal pH (14). The karyopycnotic index (KI) and the maturation value (MV) are also used and characterize the hormonal action on the vaginal epithelium in a different way. The KI is expressed as the percentage of superficial cells (the percentage of cells with pycnotic nuclei) within the total population of squamous cells and is more sensitive for evaluating the superficial cells (15). The MV is another quantitative analysis reflecting hormonal action on the vaginal epithelium. The score considers parabasal, intermediate, and superficial cells, to which the values of 0 for parabasal, 0.5 for intermediate, and 1.0 for superficial are assigned. The score can vary from 0 when only parabasal cells are present, as in the case of atrophic specimens, to 100 for specimens that contain only superficial cells, reflecting a mature specimen (16). The vaginal maturation index (MI) is the calculated number of superficial, intermediate, and parabasal cells out of 100.

### Cross-sectional studies

A cross-sectional study in China investigated factors associated with hot flashes in perimenopausal ( $n = 817$ ) and postmenopausal ( $n = 582$ ) women 40–60 y old (17). Among postmenopausal women, an omnivorous diet decreased the prevalence of hot flashes (OR = 0.38; 95% CI = 0.17–0.85).

### Prospective population-based studies

A cohort study in 1106 premenopausal Japanese women aged 35–54 y assessed dietary intake at baseline and hot flashes 6 y later (9). Hot flashes were significantly inversely associated with consumption of soy products and isoflavone intake.

### Prospective clinical trials

Ten prospective clinical trials have assessed the effectiveness of soy foods in ameliorating vasomotor symptoms and/or changes in the vaginal epithelium (Table 1).

A 6-wk trial conducted in Australia enrolled 25 postmenopausal women who received a diet supplemented with soy flour, red clover sprouts, or linseed, each for 2 wk in turn (18). Vaginal MV increased after the 2-wk soy-rich diet ( $P < 0.05$ ) but not after red clover or linseed.

In a U.S. study, 19 postmenopausal women 45–65 y old were randomized to soy foods, substituting one-third of their caloric intake, or usual diet for 4 wk (19). One main dish made from whole soybeans or texturized vegetable soy protein was supplied by the study to provide a daily intake of 165 mg of conjugated isoflavones. Compliance with the soy diet was 73%. In 68% of

the women consuming soy foods, the percentage of superficial cells, an indication of estrogenicity, did not change; it increased in 19% and decreased in 13%. Among the women in the control group, 71% showed no change, 8% had an increase, and 21% had a decrease. These differences were not significant.

In a study from Australia, 58 postmenopausal women ages 30–70 y were randomized to receive soy flour or wheat flour over 12 wk (20). The flour was mixed in a drink or cereal or cooked in a muffin. Participants recorded their vasomotor symptoms and had assessments of their vaginal cytology at baseline and at 6 and 12 wk. Vasomotor symptoms decreased in both groups by 12 wk, with no significant difference between groups. The vaginal MI did not change over time in either group.

A study conducted in Israel recruited 145 women ages 43–65 y to receive a soy-rich diet or usual diet in a 2:1 ratio (21) for 12 wk. The dietary intervention consisted of daily consumption of foods known to contain high concentrations of soy isoflavones and included tofu, soy drink, and miso plus flaxseed, substituting one-fourth of their caloric intake. Participants were evaluated with the Menopause Symptom Questionnaire, which includes questions on vasomotor and genitourinary symptoms. Although 82% of the women reported eating all or part of their assigned foods, the study does not report the actual amount consumed. Hot flashes and vaginal dryness scores were significantly reduced in both groups.

In another study from Australia, 52 postmenopausal were assigned to 1 of 3 dietary regimens (soy, wheat, or linseed) for 12 wk and after a 4-wk washout period, they crossed over to another diet (22). The soy group ingested 4 slices of bread daily containing 45 g of soy grits ( $52.6 \pm 8.7$  mg of isoflavones). Participants consuming the soy diet had an increase of 103% in vaginal cytology MI from baseline ( $P < 0.03$ ), but the rate of hot flashes did not change.

An Italian study evaluated the effects of a 6-mo soy-rich diet on the vaginal epithelium of 187 menopausal women 39–60 y old. Participants were randomized to soy, estrogen therapy, or placebo (23). With the goal of providing 20–30 mg/d of soy isoflavones, an intake comparable to the average consumption in Asian women, participants in the diet group were asked to add 1 soy food serving daily (soymilk, miso, soup, tofu, etc.) and a phytoestrogen-rich food twice per week. The size of the servings was not reported. The trial had a high drop-out in the diet group (42%), probably because soy products are not usual components of the Italian diet. Food diaries kept by the participants indicated a daily isoflavone consumption of 47 mg, mostly from soy milk. Compliance in the participants who remained in the study, assessed from pooled morning urine collected over 14 d, showed significantly higher urinary daidzein concentrations in the soy-rich diet group. The biggest increase in MV and KI was in the estrogen therapy group; these indices had a smaller but significant increase in the diet group and no change in the control group.

The Herbal Alternatives for Menopause Study was conducted in the US and recruited 351 menopausal women between the ages of 45 and 55 y who had  $\geq 2$  vasomotor symptoms/d; 52% were in the menopausal transition and 48% were postmenopausal (24,25). Participants were randomized to 1 of 5 interventions: multibotanical plus soy dietary counseling vs. multibotanical vs. black cohosh vs. estrogen therapy vs. placebo. The women in the soy food intervention group reported an average of 0.6 servings/d of soy at baseline and increased dietary soy by 1.1 servings/d between baseline and 3 mo. A serving was defined as 240 mL of soy milk or 1/4 cup (60 mL) of soy nuts. At 12 mo, the multibotanical plus soy intervention group had

**TABLE 1** Clinical trials testing soy foods

Publication (reference)	Intervention	n	Duration	Age, y	Outcomes	Results	Comments
Wilcox et al., 1990 (18)	Soy flour vs. red clover sprouts vs. linseed	25	2 wk	51–70	Vaginal MV	MV increased	
Baird et al., 1995 (19)	Daily dish made from whole soybeans vs. texturized vegetable soy protein vs. usual diet <sup>1</sup>	19	4 wk	45–65	VMI <sup>2</sup>	Negative findings	
Murkies et al., 1995 (20)	Soy flour vs. wheat flour	58	12 wk	<sup>3</sup>	VMS and VMI <sup>4</sup>	Negative findings	19% dropout
Brzezinski et al., 1997 (21)	Soy foods vs. usual diet	145	12 wk	43–65	VMS and UGS <sup>5</sup>	Significant reduction in symptoms	
Dalais et al., 1998 (22)	Bread made with 45 g soy grits <sup>6</sup> vs. wheat bread vs. linseed bread	52	12 wk	45–65	VMS and VMI	Increase in VMI	20% dropout
Chiechi et al., 2003 (23)	Encouraged 1 soy food serving daily vs. ET <sup>7</sup> vs. placebo	187	6 mo	39–60	MV and KI	Increase in MV and KI	42% dropout in soy food group
Newton et al., 2005 (24,25)	Multibotanical + soy dietary counseling vs. multibotanical vs. black cohosh vs. ET vs. placebo	351	12 mo	45–65	VMS	Increased VMS in the multibotanical + soy group	
Lewis et al., 2006 (26)	Soy flour muffins vs. wheat vs. flaxseed	99	16 wk	45–60	VMS	Negative findings	
Manonai et al., 2006 (27)	Soy-rich foods <sup>8</sup> vs. animal protein	42	12 wk	45–70	VHI <sup>9</sup>	Negative findings	15% dropout
Welty et al., 2007 (28)	Soy nuts	60	8 wk	<sup>10</sup>	VMS and Menopause-Specific QoL <sup>11</sup>	41–45% decrease in VMS	27% dropout

<sup>1</sup> 165 mg isoflavones.

<sup>2</sup> VMI, vaginal MI.

<sup>3</sup> Mean age in group with  $\leq 4.5$  hot flashes/d  $51.9 \pm 5.5$  y and  $54.6 \pm 5.4$  y in group  $> 4.5$  hot flashes/d.

<sup>4</sup> VMS, vasomotor symptoms.

<sup>5</sup> UGS, urogenital symptoms.

<sup>6</sup> 52 mg/d isoflavones.

<sup>7</sup> ET, estrogen therapy.

<sup>8</sup> 50 mg/d isoflavones.

<sup>9</sup> VHI, vaginal health index.

<sup>10</sup> Mean age  $53.8 \pm 1.0$  y in soy group and  $56.0 \pm 0.9$  y in wheat group.

<sup>11</sup> QoL, Quality of Life questionnaire.

higher (worse) symptoms relative to placebo ( $P = 0.016$ ). The study did not detect differences  $< 1.5$  vasomotor symptoms/d between treatment groups.

In Canada, 99 women aged 45–60 y and menopausal for 1–8 y were enrolled in a 16-wk study of quality of life and hot flash frequency and severity (26). They received 1 muffin daily containing soy, wheat, or flaxseed flour. Soy muffins contained 25 g of soy flour, supplying 42 mg of isoflavones daily. Among the 87 women who completed the trial, there was no significant difference in the frequency and severity of hot flashes between treatment groups.

A study in Thailand enrolled 42 women ages 45–70 y with at least 3 mo of amenorrhea and 1 or more symptom of urogenital atrophy (27). The study had a cross-over design of two 12-wk periods and two 4-washout periods, where participants were randomized to a soy-rich diet of 25 g of various soy foods such as soy milk or soft tofu containing  $> 50$  mg daily of isoflavones or an equivalent amount of animal protein. The groups did not differ before or after treatment.

In the US, 82 women with irregular menses or in amenorrhea for at least 12 mo were randomized in a cross-over design between 2 diet sequences: therapeutic lifestyle changes diet with soy or without soy (28). Participants received 1/2 cup of soy nuts (roasted soybeans) containing 25 g of soy protein and 101 mg aglycone isoflavones daily to be eaten throughout the day. The main outcome of this study was changes in blood pressure. Of the 60 women who finished the study, 39 had hot flashes.

Participants recorded the number of hot flashes in calendars and were asked to complete the Menopause-Specific Quality of Life Questionnaire at the end of each 8-wk period. Soy nut ingestion was associated with a 45% decrease in hot flashes in women with  $> 4.5$  hot flashes/d at baseline ( $P < 0.001$ ) and a 41% decrease in those with  $\leq 4.5$  hot flashes/d. The reduction in hot flashes was apparent at 2 wk in both groups, although there was some attenuation in the benefit of soy nuts over time in the low-hot flash group. When hot flashes were assessed by the menopausal symptom quality of life questionnaire, the group consuming soy nuts reported a 19% decrease in vasomotor score ( $P = 0.004$ ).

The limitations of these studies include small sample size, short duration, the use of different soy foods that contain varying amounts of isoflavones, and enrollment of women in a wide age range or who differed in the number and severity of menopausal symptoms. Studies evaluating vasomotor symptoms commonly observe a significant placebo effect, with up to 30% reduction in hot flashes in the placebo group; therefore, trials longer than 12 wk are necessary to evaluate the sustainability of effects.

In conclusion, menopausal symptoms are common, although their incidence varies according to the population that is studied. The findings of the WHI have resulted in a sharp decline in the use of estrogen therapy among menopausal women and an increase in the consumption of soy foods and soy supplements for the management of menopausal symptoms. Studies evaluating the effectiveness of soy foods in ameliorating vasomotor and

vaginal symptoms have been conducted worldwide and have utilized a variety of soy foods containing different amounts of isoflavones. Among the 10 studies published in the last 20 y, 4 have had negative results and 1 reported worsening of symptoms in the group consuming soy food. Of the 4 studies that assessed only vaginal cytology, 3 reported beneficial effects. Only 1 of the 4 studies exclusively assessing vasomotor symptoms reported a reduction in symptoms. Two studies evaluated both outcomes, with opposite findings. In conclusion, considering the conflicting results provided by a small number of studies, the efficacy of soy foods in improving menopausal symptoms remains unclear.

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