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A randomised double-blind controlled trial of oral soy supplements *versus* placebo for treatment of menopausal symptoms in patients with early breast cancer

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Abstract

Menopausal symptoms are a major survivorship issue for patients treated for breast cancer. There are increasing concerns over the use of hormone replacement therapy (HRT) in this setting and a growing consumer interest in ''natural'' therapies. It had been suggested that soy phyto-oestrogens might be beneficial in the treatment of menopausal symptoms. Seventy-two patients with a histologically confirmed pre-existing diagnosis of breast cancer who were having menopausal symptoms were randomised between 12 weeks of treatment with soy capsules or placebo. Quality of life and menopausal symptom scores were assessed at baseline, 4, 8 and 12 weeks. There was no statistical difference in menopausal symptom scores or quality of life between the two arms of the study.

Keywords: Isoflavones; Soybeans; Hot flashes; Randomised controlled trial; Breast neoplasms

1. Introduction

Menopausal symptoms are a major survivorship issue for patients previously treated for breast cancer – both as a result of adjuvant therapies and for those patients who naturally progress through the menopause [1]. The use of hormone replacement therapy (HRT) in this setting had been widespread, but increasing concerns over the safety of HRT both for women without a previous diagnosis of breast cancer [2] and breast cancer survivors [3] have led to a search for alternatives. The pathophysiology of hot flushes (or flashes) is poorly understood, but may be caused by dysfunction of central thermoregulatory centres in the hypothalamus triggered by changes in oestrogen levels [4]. It is postulated that increases in the level of oestrogen or serotonin may improve symptoms.

There has been considerable interest in the use of phyto-oestrogens, both in the lay and the medical press. Phyto-oestrogens are plant-derived substances which mimic or modulate the action of endogenous oestrogens usually by binding to oestrogen receptors. Soy is a rich source of phyto-oestrogens called isoflavones which have a chemical structure very similar to oestradiol.

Epidemiological data from Japan suggest that the incidence of hot flushes is inversely related to the dietary soy intake [5]. Observational studies have suggested that soy supplementation may result in an improvement in menopausal symptoms, particularly vasomotor

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symptoms such as flushing, in patients with no history of breast cancer [6]. A randomised double-blind trial of soy and wheat flour supplementation showed no difference between the two groups [7], but another trial showed that soy protein was superior to casein placebo [8].

It has been suggested that a diet rich in soy products may be a causative factor in the much lower incidence of breast cancer seen in Asian populations [9–11], but the epidemiological evidence is inconclusive.

Genistein (4′,5,7-trihydroxyflavone) is the most abundant isoflavone in soy products, with smaller quantities of daizein and glycitein also being found. Genistein primarily functions as an oestrogen agonist but also has some mixed agonist/antagonist properties [12]. Isoflavones inhibit aromatase (although the concentrations needed for this are quite high) and the enzymes that convert oestrone to the more potent oestradiol [13]. Genistein is known to be a protein tyrosine kinase inhibitor [14] and may inhibit angiogenesis.

In vitro, genistein inhibits the growth of a number of cancer cells lines, including hormone-dependent and hormone-independent breast cancer cell lines [12,15,16]. The interaction of genistein and tamoxifen is not entirely clear. *In vitro* data has shown both inhibition of the effects of tamoxifen and an apparent synergy [12]. However, two animal studies have suggested that the combination of tamoxifen and soy had an inhibitory effect on tumour growth [17,18].

Overall, the evidence suggests that phyto-oestrogens are unlikely to be detrimental to women who are being treated for breast cancer, or have had breast cancer in the past.

We therefore designed a randomised trial of soy isoflavines for the treatment of menopausal symptoms in patients previously treated for breast cancer. Since this trial was initiated, two others have reported on a similar group of patients [19,20] and one in patients without cancer [21]. However, the trial reported here differs from these studies in the methods of assessment, the soy product used, "Phytosoya"™, that is widely available as an over-the-counter medication in Europe, and has a different duration of therapy.

2. Patients and methods

2.1. Patient population

Participants in the trial were women over 18 years of age with a histologically confirmed pre-existing diagnosis of breast cancer who were having menopausal symptoms, defined as menopausal score of >1 (scoring system described in Fig. 1). Patients were excluded if they had advanced or metastatic disease, were already taking soy products, were currently taking other therapy for menopausal symptoms, had a severe concurrent non-malignant illness or were unable to give informed consent. Any concomitant or preceding adjuvant therapy for the current diagnosis of breast cancer was allowed. Participants were recruited from those attending specialist breast oncology clinics at the Beatson Oncology Centre, Western Infirmary, Glasgow, Scotland.

The menopausal symptom score is based on four questions:-

1. Did you have night sweats?
2. If you had night sweats, did they disturb your sleep?
3. Did you have sweats or flushes during the day?
4. Ifyou had sweats or flushes during the day, did the sweats/flushes interfere with your ability to function normally in your everyday life?

These questions are scored as follows:
1= Not at all
2= A little
3= Quite a lot
4=Very much

If the response to questions 1 or 3 is "Not at all" questions 2 and 4 are correspondingly scored "1". The overall menopausal symptom score is the average over questions 1 – 4.

Fig. 1. Menopausal symptom score.

2.2. Study design

Patients were randomised to receive either two soy capsules or two identical placebo capsules twice daily for 12 weeks in a double-blind fashion. The soy capsules each contained 235 mg of soy extract with 17.5 mg of isoflavines – the total dose of isoflavines was 70 mg/day. Identical active and placebo capsules were supplied by Arkopharma (UK) Ltd. There was an option to continue treatment beyond the 12-week period at the patient's request. Any concomitant medications for pre-existing disease were allowed.

Quality of life and response to treatment was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life-Care30 (EORTC QLQ-C30) questionnaire plus Breast Cancer Module BR23, and a menopausal scale developed for the purpose of the study (Fig. 1). Data were collected at baseline, and at 4 weekly intervals during the study. Toxicity was also assessed, and graded using Common Toxicity Criteria scores. Written informed consent was obtained from all patients and local ethics committee approval was gained prior to study commencement.

2.3. Statistical considerations

The primary endpoints were: (i) quality of life, as measured by the EORTC QLQ-C30 at week 12 and (ii) control of menopausal symptoms, as measured by combined estimates of severity of sweats (day or night) and flushes obtained from the menopausal questionnaire at week 12. A secondary endpoint was an assessment of the toxicity of the intervention.

Patients were allocated treatment using a minimisation procedure. The study was stratified for initial sweating/flushing score (<2, ⩾2); age at randomisation (<50 years, >50 years); currently having adjuvant Tamoxifen or after ovarian suppression (yes, no). Patients were analysed on an intention-to-treat basis. The primary end-points were compared between the study arms using analysis of variance techniques including the stratification factors as covariates. The scores derived for the EORTC QLQ-C30 were analysed in a similar way with the addition that the initial QLQ-C30 scores were also used as covariates. A corresponding analysis at 4 weeks was performed to explore the time-course of any treatment effect. The worst toxicities over the time period were tabulated and compared between the arms using the Mann–Whitney *U* test.

To be considered a worthwhile treatment strategy, soy extract would need to benefit around half of the patients treated. A small pilot study indicated that the mean of the average score for patients over the four questions relating to sweating and flushing on the menopausal symptom questionnaire was 2.2 with a standard deviation of 0.7 (questions are scored 1–4). To detect a change of 0.5 in this average score with 80% power would require 32 evaluable patients per arm to be recruited. A recruitment target of 70 patients was set.

3. Results

A total of 72 participants were randomised between 1999 and 2002. A trial flow diagram is show in Fig. 2. The baseline patient characteristics are shown in Tables 1 and 2 illustrating the two study arms were well balanced other than for time since definitive surgery ($P = 0.029$). There was a trend towards duration of menopausal symptoms being longer in the Soy arm, but this was non-significant ($P = 0.96$). In particular, the baseline vasomotor symptom score was well balanced. Reasons for stopping treatment are shown in Table 3.

The results were analysed on an intention-to-treat basis and all patients were included in the analysis, including those who stopped early for any reason.

There was no significant difference in menopausal symptoms between the placebo and soy capsule arms of the study. The menopausal symptom scores over the course of the study are shown in Fig. 3: these were analysed using ANOVA techniques including the following as factors – treatment arm, whether on tamoxifen at baseline and whether had had ovarian suppression. Covariates were baseline menopausal score and week of last assessment. We also analysed as covariates the duration of menopausal symptoms and time since definitive surgery, as there was a baseline imbalance between the arms with regards to these criteria. The last recorded menopausal score for each patient was used as the primary endpoint. The estimated treatment difference from the ANOVA (treatment placebo-soya) = 0.04 (standard error (S.E.) = 0.15, $P = 0.806$). The 95% Confidence Interval for the difference runs from −0.27 to 0.35. The study was set up to detect up a difference of 0.5 which on the basis of these results is clearly excluded.

There was also no significant difference in the global quality of life score. The EORTC global quality of life score runs from 0 to 100 – with higher scores indicating better global quality of life. Fig. 4 shows the global quality of life scores over the course of the study. The last recorded global quality of life score was analysed using ANOVA with the same factors and covariates and estimated treatment difference from the ANOVA (treatment placebo-soya) = 3.0 (S.E. = 3.6, $P = 0.844$). The 95% Confidence Interval for the difference runs from −4.2 to 10.2. The study rules out the possibility of even small global quality of life differences in favour of soy.

Toxicity was mild and primarily gastrointestinal. There was no significant difference in toxicity between the arms (Table 4).

4. Discussion

This trial differs from previous reports in two or more of the three following aspects: the soy preparation used, the duration of therapy and the methods of assessment. The results of this randomised, double-blind controlled trial do not support the use of soy supplements for the treatment of menopausal symptoms in this population. There have been three other similar trials reported since the inception of our trial and the results of both of these are consistent with our findings. Quella et al. [19] carried out a trial in 177 patients with a history of breast cancer with a crossover design. Patients received four weeks of treatment prior to crossover to the placebo arm. No difference was seen between the two arms, but experience from conventional HRT suggests that this length of treatment time may have been too short to see any meaningful effect from the soy supplement, and study durations of less than 3 months have been excluded from overviews of the effects of HRT [20]. Van Patten and colleagues studied 123 patients who had been previously treated for breast cancer, randomising them to a soy beverage or placebo rice beverage for twelve weeks of treatment. Both groups experienced a significant decrease in the number of hot flashes, but no difference was seen between the arms suggesting this was a placebo effect. In this trial, hot flashes were quantified by use of a self-reported patient menopause diary. Serum genistein levels were measured and were appropriately higher in the arm that received the soy beverage [21].

The above trials are further corroborated by a randomised, double-blind clinical trial published recently

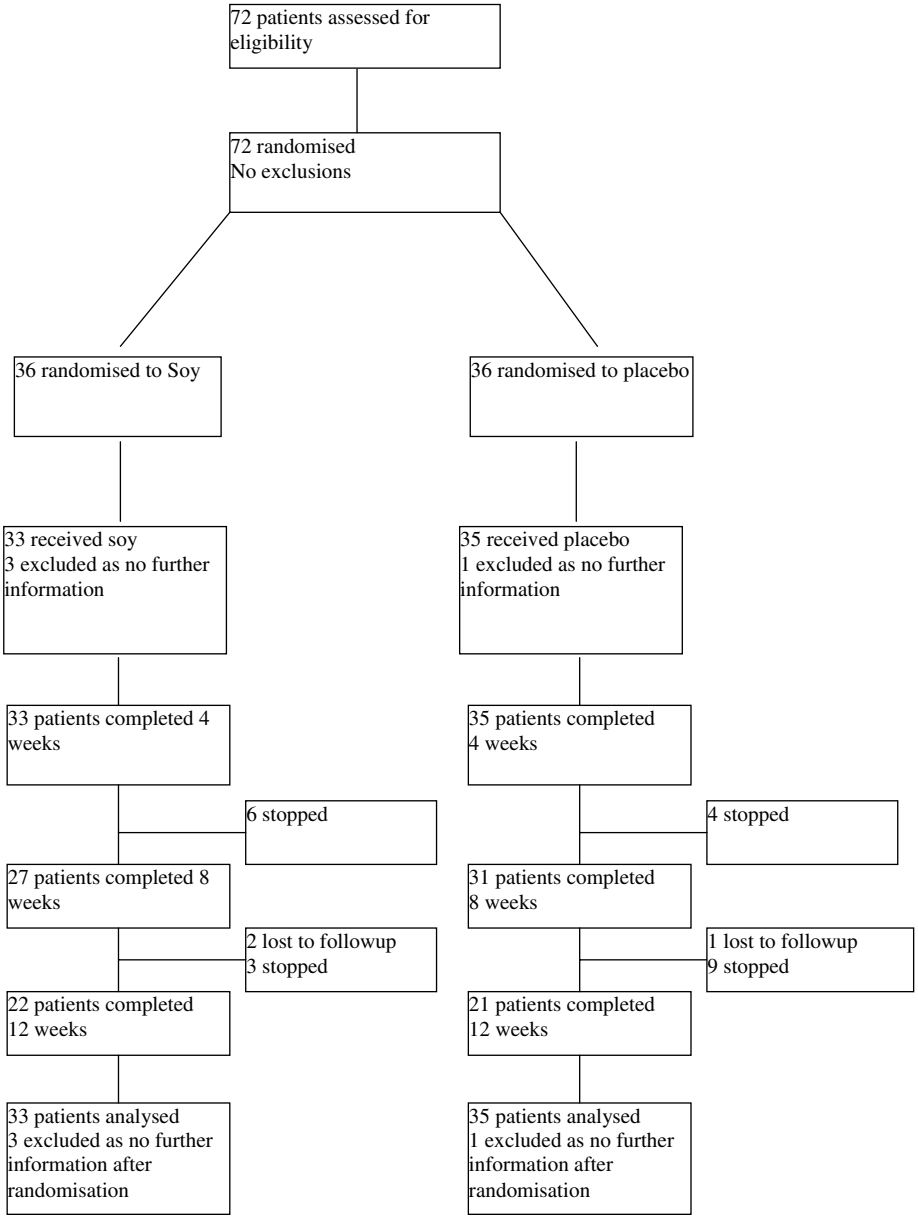

Fig. 2. Trial flow diagram.

including 252 symptomatic menopausal women with no history of cancer that showed two different doses of isoflavone supplements from red clover have no clinically meaningful effect on hot flushes [22].

The study reported here employed the standard EORTC QLQ C-30 quality of life scale as the primary efficacy measure. Climacteric symptoms experienced by these patients are not confined to hot sweats or hot flushes, but also include, for example, fatigue, irritability, vaginal dryness and difficulty coping. Global quality-of-life was therefore deemed a major issue. However, the breast module of this scale only has a single question asking directly about vasomotor symptoms, therefore it was used in conjunction with a four question menopausal score questionnaire of the same format. The results of this study are internally consistent between each of the two measures employed.

Various other treatments for menopausal symptoms, in particular hot flushes or flashes, have been investigated in breast cancer survivors. In most randomised trials, a significant placebo effect has been seen in the order of approximately 20–30% reduction in symptoms with placebo alone. Although consistant with a 20% effect, only a non-significant placebo effect was seen in our trial (Fig. 3), possibly due to the severity of the initial symptoms in most patients or possibly due to the duration of therapy. However, this lack of meaningful placebo effect is compatible with clinical experience which would

Table 1
Baseline patient characteristics

	Treatment			
	Placebo (n = 36)		Soya (n = 36)	
	%	Number	%	Number
Presently on Tamoxifen?[a]				
Yes	78	28	78	28
No	22	8	22	8
Had ovarian suppression?[a]				
Yes	11	4	14	5
No	89	32	86	31
Adjuvant chemotherapy				
Yes	58	21	64	23
No	42	15	36	13
Previously had HRT				
Yes	36	13	33	12
No	64	23	67	24
Previous therapy for menopausal symptoms since developing breast cancer?				
Yes	58	21	64	23
No	42	15	36	13

[a] Stratification factor. HRT, hormone replacement therapy.

Table 2
Baseline patient demographics

	Treatment	
	Placebo (n = 36)	Soya (n = 36)
Age (years)		
Median	51	51
IQ range	45–56	46–58
Range	33–70	37–69
Baseline vasomotor symptom score[a]		
Median	2.75	2.75
IQ range	2.50–3.25	2.31–3.50
Range	1.50–4.00	2.00–4.00
Duration of menopausal symptoms (weeks)		
Median	47	59
IQ range	17–100	24.5–130
Range	2–312	16–306
Time since definitive breast cancer surgery (months)		
Median	14	24
IQ range	8–28	13–41
Range	2–142	5–100
Time since completing adjuvant chemotherapy (months) (n = 21, placebo; n = 23, soya)		
Median	11	21
IQ range	3–26	6–27
Range	2–74	3–66

IQ, inter-quartile range.
[a] Stratification factor.

suggest that for most breast cancer patients any placebo effect is mild and of short duration.

The progestational agent megestrol acetate was shown to reduce hot flashes in breast cancer survivors and men undergoing androgen deprivation for prostate cancer, with 74% of the treatment group having a reduction of 50% in the frequency of their hot flushes compared with 21% of the placebo group [23]. Selective noradrenaline reuptake inhibitor (SNRI) class antidepressants, such as venlaflaxine [24] and Paroxetine, or fluoxetine, SSRIs [25], have been shown to significantly reduce hot flushes in breast cancer patients by 50–60%. Gabapentin has been recently examined in a placebo-controlled randomised clinical trial followed by a dose escalation open-label phase and was found to significantly reduce hot flashes compared with placebo – an effect that appeared to increase as the dose increased in the open-label section of the trial [26].

The α blocker clonidine has been investigated, but the effects are modest and the side-effects of dry mouth and sleepiness can be problematic [27]. A further crossover study showed a minimal effect from vitamin E supple-

Table 3
Reasons for stopping treatment

Reason for stopping treatment[a]	Treatment	
	Placebo	Soya
Lack of effect	10	7
Toxicity	1[b]	2[c]
Disease progression	0	0
Patient request	3	1
No reason recorded	1	0
Perceived weight gain	2	0

[a] More than one reason may be recorded for each patient.
[b] Mood swing pre-menstrually (grade 3).
[c] Vaginal bleeding (grade 1), pelvic discomfort, shortness of breath (grade 1); nausea/constipation (grade 2) and vomiting (grade 1).

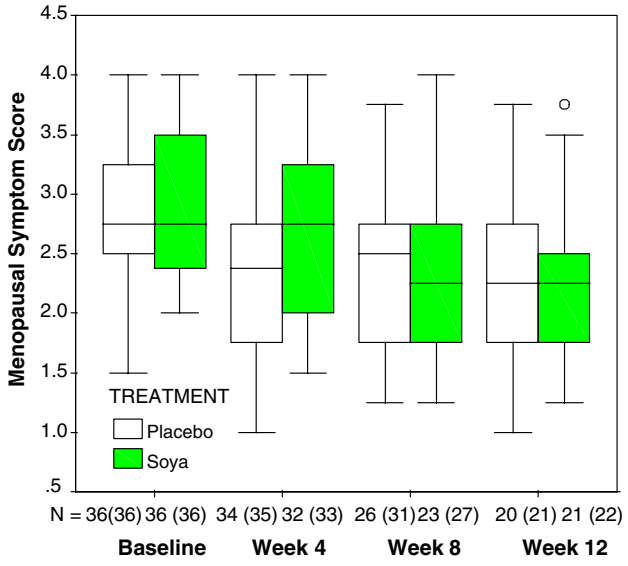

Fig. 3. Menopausal symptom scores over course of study. The figures in brackets are the number of assessments that should have been made; the figures alongside are the number of actual assessments.

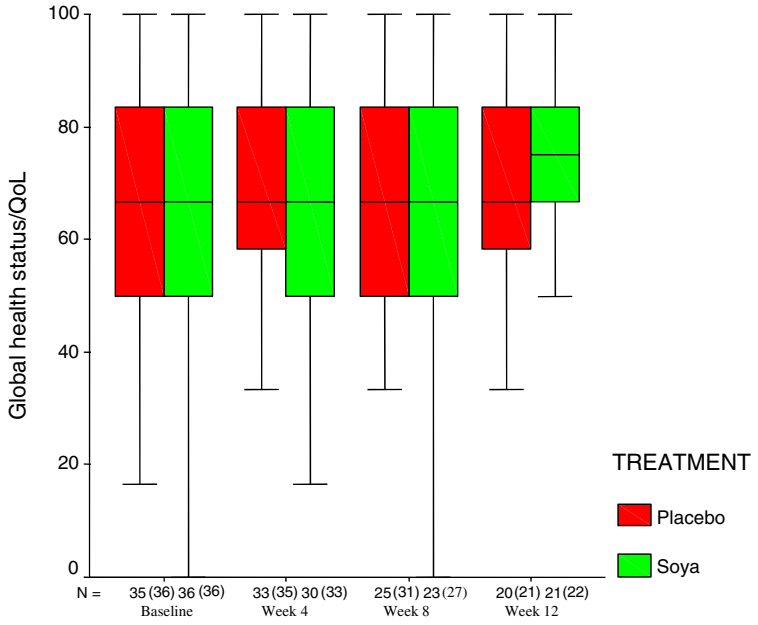

Fig. 4. Global quality of life scores. The figures in brackets are the number of assessments that should have been made, the figures alongside are the number of actual assessments.

Table 4
Toxicity

	Worst grade recorded	Treatment				*P*-value
		Placebo ($n = 35$)		Soya ($n = 33$)		
		%	Number	%	Number	
Constipation	0	94	33	85	28	0.231
	1	3	1	9	3	
	2	3	1	6	2	
Flatulence	0	89	31	97	32	0.357
	1	9	3	0	0	
	2	3	1	3	1	
Nausea	0	94	33	82	27	0.135
	1	3	1	12	4	
	2	3	1	6	2	
Headache	0	94	33	85	28	0.231
	1	3	1	9	3	
	2	3	1	6	2	

Toxicities are tabulated above only where they affect $\geqslant 10\%$ of patients in at least one of the treatment arms.
Toxicities recorded as "not related" to the study treatment are not considered.

mentation which while statistically significant was not clinically significant [28].

Black cohosh (*Cimicifuga racemosa*) has been approved in Germany for the treatment of hot flashes, where several small studies had suggested that it might relieve hot flash symptoms, but a randomised clinical trial from the United States of America (USA) suggests that there is no improvement over placebo [29]. In menopausal patients with no history of breast cancer, randomised controlled trials have shown no benefit from evening primrose oil (*Oenothera biennis*) [30] and ginseng [31] compared with placebo for the relief of vasomotor symptoms.

In summary, our study confirms that there does not appear to be any benefit of soy supplementation over placebo in the treatment of menopausal symptoms experienced by breast cancer survivors. If pharmacological intervention is required then a newer antidepressant or gabapentin should be considered in patients where a hormonal agent is considered undesirable.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias this work.

Active drug and placebo tablets were supplied free of charge by Arkopharma Laboratories, Carros, France.

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