

## RESEARCH ARTICLE

# Clinical and Ultrasonographic Changes of the Breast after Use of Soy Isoflavones

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### Abstract

**Background:** Phytoestrogens may be an alternative therapy in control of menopausal symptoms but their definite effects on breast tissue must be determined. Our study aimed to define the clinical and ultrasonographic changes of the breast after use of soy isoflavones in menopausal women. **Materials and Methods:** Menopausal women with hot flashes were randomly grouped as cases and controls and cases received soy isoflavones for 12 weeks. Breast examination (BE) and ultrasonography (US) were done at 0, 6 and 12 weeks. Tenderness and nodularity on BE were graded 1-4 by breast surgeons. **Results:** There were 30 women in the case and 26 in the control group. The mean age was 51.3 years and the mean age of menopause was 49.2 years. There was no change in the BE and US at 6 weeks in controls. In the case group, 10% had grade 1 tenderness and 13.3% grade 2 tenderness and grade 1 nodularity in BE accompanied with diffuse small cysts in US. At 12 weeks, there was no change in BE and US in the 2 groups. **Conclusions:** There was no statistically significant difference in the BE of the 2 groups at 6 and 12 weeks (p value=0.36 and 0.41 for nodularity and tenderness respectively) and in the US results. Although the literature contains many facts concerning PEs and the breast, further prospective studies are needed to identify structural breast changes produced by PEs in order to identify the appropriate dosage and indications of use.

**Keywords:** Breast examination - breast neoplasm - ultrasonography - phytoestrogens - soy isoflavones

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### Introduction

Very often, menopausal symptoms necessitate treatment because of the distress caused for the woman. Hormone replacement therapy with synthetic estrogens has proved useful in modifying many of the menopausal problems, but the various adverse effects of these compounds restrict their regular use. Accordingly, alternative approaches such as the consumption of phytoestrogens have been taken into account. The efficacy of phytoestrogens in controlling the disorder alongside their undesirable effects on body organs has been investigated; a major unsolved question is the consequences for the breast.

The aim of our study was to determine the clinical and ultrasonographic changes induced in the breasts after the consumption of soy isoflavones in menopausal women.

### Materials and Methods

Women under 65 years of age who attended the Gynecology clinic of Arash Women's Hospital and were studied for the treatment of menopausal hot flashes in a parallel study were considered for our purpose. Exclusion criteria consisted of the history of cancer,

diabetes mellitus or renal, hepatic, and heart failure or undiagnosed abnormal uterine bleeding, hormone therapy during the last three months, probable sensitivity to soy products, consumption of drugs interacting with intestinal absorption, a known history of breast disease or the detection of breast mass or nodules in breast examination.

Demographic data of the patients, anthropometric characteristics including weight and height, medical and drug histories, and known or suspected previous allergy to any food or drug was recorded.

The patients were divided accidentally into 2 groups: The case group received soy extracts as 50 mg isoflavones (*soy menopause tablets – nature made*) and the control group received 1 mg acid folic tablets (*Jalinus, Iran*) for 12 weeks. All the patients underwent mammography to rule out breast pathology before entering the study. They went under breast examination (BE) and breast ultrasonography (US) at the first visit and then at 6 and 12 weeks intervals.

Prior to the study, breast tenderness and nodularity in BE were scored each from 1-4 based on a scale defined by two board-certified surgeons experienced in breast diseases and matched on patients with no relation to this study in the breast clinic of the hospital. The hot flushes were assessed by a chief resident of gynecology and BE

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was performed by the two surgeons. A board certified radiologist performed the ultrasonographic scans and reported the mammographies. The physicians were blind to the treatments groups. The ethics institutional review board of Tehran University of Medical Sciences approved the study and informed consent was obtained from all participants.

## Results

The study was undertaken between March and November 2011. The total number of patients was 56 women; thirty in the case group and 26 in the control group. The mean age of the patients was 51.3 years (39-65 years) and the mean age of menopause was 49.2 years (39-55 years). The figures for age and age of menopause were respectively  $51.5 \pm 5$  and  $48.9 \pm 3$  in the intervention group and  $51 \pm 4$  and  $49.4 \pm 2.6$  in the controls, which shows no significant difference ( $p$  value=0.68 and 0.47). Three of the patients in the case group had the history of hormone replacement therapy for a few months several years previous to the study, none of the women in the case group had received any postmenopausal hormonal therapy in the past.

The mean body mass index (BMI) of the patients was  $27.3 \pm 3$  in the case and  $27.9 \pm 2.5$  in the control group, not different statistically ( $p$  value=0.83).

At the first visit before intervention, the BE was normal in all the patients except for a mild bilateral breast tenderness detected in one patients (3.8%) of the placebo group and a soft focal nodularity palpated in one patient in the same group (3.8%), which showed to be a simple cyst in the US. At 6 weeks, in the placebo group, there was no change in either the BE or US. In the case group, three patients (10%) had grade 1 bilateral breast tenderness with otherwise normal BE and 4 patients (13.3%) had got grade 2 bilateral tenderness and grade 1 nodularity in BE accompanied with diffuse small cysts (between 2-3 millimeters simple cysts) in US. The study continued with no change in the intervention and without adding any treatment except for reassurance. At 12 weeks, there was no change in the BE and US in the 2 groups, showing the same changes detected in the case group at 6 weeks.

## Discussion

Phytoestrogens (PE) are compounds derived from plants, harboring structural estrogenic characteristics, which could exert some effects on breast tissue via estrogenic or anti-estrogenic features (Bondesson et al., 2010; Liu et al., 2012; Zaineddin et al., 2012). They can be categorized as isoflavones, lignans, stilbenes and coumestans and some like genistein, dadzein and resveratrol have been assessed more widely in researches (Liu et al., 2012).

The major steps of breast development occur after birth under hormonal control. Estrogens are essential for completion of the process and operate via estrogen receptors alpha and beta ( $ER\alpha$ ,  $ER\beta$ ). PEs probably exert their estrogenic or antiestrogenic effects over the breast by binding to these receptors, mainly  $ER\beta$ , which is the

dominant one in normal breast tissue (Pelekianou et al., 2011). Bolca et al estimated the effects of ingested PEs on normal breast tissue by measuring the isoflavone levels in breast biopsies of healthy women undergoing esthetic breast reduction after eating soy and showed that levels were high enough to cause health effects (Bolca et al., 2010).

In our study 56 postmenopausal women attending the gynecology clinic of Arash Women's Hospital were put into case and control groups. The 2 groups were not different statistically in their age, age of menopause and BMI as well as in BE and breast US at the time of entering the study. The mild changes detected in the breast at BE after receiving soy extracts were not bothering to the patient and needed no intervention. There was no statistically significant difference in the BE of the 2 groups at 6 and 12 weeks of the study ( $p$  value=0.36 for nodularity changes at BE at 6 and 12 weeks intervention;  $p$  value=0.41 for tenderness changes at BE at 6 and 12 weeks intervention). The US changes were minimal and no important pathology was detected at 6 or 12 weeks. The changes after drug discontinuation at the end of the study were not followed and are unknown but we know that none of the patients attended the breast or gynecology clinic of the hospital with breast complaints in the next three months.

The abundant research focused on PEs has not yet ascertained the protective or exacerbating role of these compounds on breast disease (Mense et al., 2008). No association between serum PE levels and mammographic density has been detected in areas with low levels of PE consumption (Lowry et al., 2012).

Most studies including phytoestrogen effects on the breast have focused on their role in breast cancer. The review of Bondesson et al. (2010) points out that while epidemiological studies suggest a reduced risk of breast cancer risk and a better prognosis induced by the use of PEs, the results of intervention and animal studies are not definite (Bondesson et al., 2010).

A meta-analysis of randomized clinical trials showed no significant increment in breast cancer with PE consumption (Tempfer et al., 2009), and a prospective cohort of 45,448 women resulting in 1014 invasive breast cancers in 13 years follow up found no association between intake of PEs and breast cancer risk (Hedelin et al., 2008). However, most studies have showed a lowering effect of PEs over breast carcinogenesis. Significantly reduced tumor growth after consumption of genistein and soy extracts in the mouse (Kim et al., 2008), better prognosis in breast cancer patients with higher plasma genistein levels (Iwasaki et al., 2008), higher frequency of ER and PR positivity, resulting probably in better cancer prognosis (Zhang et al., 2010), overall decrease in premenopausal breast cancer (Morimoto et al., 2012) -merely in overweight women (Cotterchio et al., 2008)- or postmenopausal disease (Goodman et al., 2009; Buck et al., 2010; Anderson et al., 2012; Zaineddin et al., 2012) - especially ER+PR+ tumors (Anderson et al., 2012) with more frequent use of PE, have all been detected in different valuable studies.

Nonetheless, data concerning worsening of breast

cancer risk by higher intake of PEs is not scarce. A higher rate of aggressiveness in tumors developed in premalignant breast tissue of rats treated with soy protein (Dave et al., 2010), reduction of the growth inhibitory effect of fadrozole, an aromatase inhibitor, by genistein in the in vitro model of Van Duursen et al (van Duursen et al., 2011), increased tumor growth and rate of metastases of subcutaneously implanted breast tumors in nude mice treated with daidzein or combined soy isoflavones (Martinez-Montemayor et al., 2010), and a probable association between breast cancer and some urinary PE biomarkers in the European Prospective into Cancer-Norfolk cohort study (Ward et al., 2008) all warn against the careless use of PEs.

Although the literature contains many facts concerning PEs and the breast, still further prospective studies need to be carried out to identify the actual effect on this end organ. Concern about PEs is not limited to the malignant disease itself, structural breast changes produced by PEs have to be evaluated and classified in order to identify the appropriate dosage and indications of use.

Our study shows some clinical and ultrasonographic benign non-significant changes of the breast induced by soy extracts. Further prospective study is needed to allow safe use of phytoestrogens in hormone depletion status.

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