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Soy Food Intake and Biomarkers of Breast Cancer Risk: Possible Difference in Asian Women?

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Abstract

Soy foods may protect against breast cancer in Asian but not in Western populations. We examined if the levels of various markers of breast cancer risk and inflammation, as well as the effects of soy food consumption on these markers, differ between Asian and non-Asian premenopausal women in two soy intervention trials. One study randomized 220 women to a 2-year intervention and the other one randomized 96 women in a cross-over design to examine the effects of consumption of 2 daily soy servings on nipple aspirate fluid (NAF) volume, estrogens in serum, NAF, and urine, insulin-like growth factor-1 (IGF-1), IGF binding protein 3, and inflammatory markers in serum, and mammographic densities. Mixed linear models were applied to assess ethnic differences in biomarkers and response to the soy diet. Serum C-reactive protein, serum leptin, NAF volume, and NAF estrone-sulfate were lower, while urinary isoflavones were higher in Asian than in non-Asian women. A significant interaction ($p_{interaction}$=0.05) between ethnicity and soy diet was observed for IGF-1 but not for other biomarkers. The current findings suggest possible ethnic differences in levels of biomarkers for breast cancer risk but little evidence that Asian women respond differently to soy foods than non-Asian women.

Keywords

Soy foods; dietary intervention; Asian ethnicity; biomarkers; breast cancer risk

INTRODUCTION

Based on observational studies, it appears that soy food consumption provides protection against breast cancer primarily in Asian but not in Western populations (1). This raises the question whether the biologic effects of soy foods vary by ethnicity due to genetic variation in metabolic enzymes, timing of exposure, or intestinal metabolism by microbiota. Consequently, such ethnic variations may be responsible for differences in biomarkers and other indicators of breast cancer risk. Only a limited number of comparative studies and even fewer nutritional interventions have examined effects of soy consumption and addressed differences in biomarker levels between Asian and Western populations (2).

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Investigations that looked at serum estrogens as endpoints observed reductions of more than 20% among Japanese women who consumed soy milk (3), but similar effects were not seen in w (4). While possible ethnic differences may exist, the low rate of nipple aspirate fluid (NAF) production and a lack of breast tissue studies make it challenging to evaluate the effects of soy consumption directly in the breast tissues of Asian vs. non-Asian women (5).

Using existing data from two dietary intervention studies conducted among premenopausal women in Hawaii (6, 7), we compared the effects of two daily servings of soy foods on several biomarkers of breast cancer risk by ethnic background, i.e., Asian vs non-Asian (Caucasian, Native Hawaiian, and other). The measured outcomes included sex steroids in serum, NAF, and urine, i.e., estrone (E_1), estradiol (E_2), estrone sulfate (E_1S), sex hormone-binding globulin (SHBG), progesterone, C-reactive protein (CRP), interleukin-6 (IL-6), adiponectin, and leptin as markers of inflammation, NAF volume, mammographic density, and urinary isoflavones. Based on the hypotheses that women of Asian ancestry have lower levels of biomarkers associated with breast cancer risk and stronger responses to soy foods than non-Asian women, our aims were to determine whether several known biomarkers for breast cancer risk differ by ethnicity and in response to a high soy diet during two separate dietary trials.

MATERIALS AND METHODS

Study population

The first Breast, Estrogens, And Nutrition study (BEAN1) was designed as a 2-year randomized clinical trial to examine the effects of consumption of 2 daily soy servings on sex hormones and mammographic density among premenopausal participants (6, 8). Women were excluded from the study due to pregnancy or breast-feeding, use of estrogen-containing oral contraceptives or dietary supplements containing isoflavones, history of cancer diagnosis, breast implants, or hysterectomy, lack of a regular menstrual period, or intake of >5 soy servings per week. A total of 220 eligible women were randomized to the intervention (high soy diet) or control (low soy diet) group and 189 participants completed 2 years of intervention. The number of dropouts did not differ by group ($p=0.53$).

The second trial (BEAN2) was a 13-month randomized, crossover study consisting of a 6-month intervention and a 6-month control phase, separated by a 1-month washout period (7). The exclusion criteria were the same as in BEAN1 except for the mammogram requirement. In addition, participants had to be able to produce at least 10 μL of NAF. Of the 96 randomized women, 82 completed the study and provided blood, urine, and NAF samples at baseline and months 6 and 13.

The protocols of the two studies were approved by the University of Hawaii Committee on Human Studies and by the Institutional Review Boards of the participating hospitals. All women signed an informed consent form before entry into the trial and gave written permission to use frozen samples for future analyses. A Data Safety Monitoring Committee reviewed the progress of the studies, reasons for dropouts, and any reported symptoms annually. In both studies, all subjects completed a baseline questionnaire asking for demographic, anthropometric, reproductive, and dietary information.

In the intervention group of BEAN1 or during the high soy diet of BEAN2, women consumed 2 daily servings of various soy foods (tofu, soy milk, roasted soy nuts, soy bars, and soy protein powder) containing approximately 25 mg aglycone equivalents of isoflavones per serving. Dietitians provided dietary counseling on how to replace common dishes with soy foods. In the control group in BEAN1 and during the low soy diet in BEAN2, women were instructed to maintain their regular diet and to consume <3 soy food servings per week. Adherence to the study protocol as assessed by unannounced 24-hour dietary recalls and urinary isoflavone excretion was high in both studies (6, 7).

Sample Collection

If possible, blood and urine samples were collected 5 days after ovulation, determined by ovulation kits at baseline and in month 24 in BEAN1 (9), while, in BEAN2, self-reported information was used to confirm ovulation by the onset of the next period at baseline and in months 6 and 13. Due to scheduling problems, approximately 20% of specimens were obtained outside the luteal phase. All serum specimens were collected in the morning and aliquots of 0.5 mL were stored at −80°C. In both studies, overnight urine samples covering approximately 8–10 hours were collected in containers with added ascorbic and boric acid to control bacterial growth (9). A trained staff member demonstrated the NAF collection technique using a FirstCyte© Aspirator, a device similar to a manual breast pump consisting of a 10 or 20 cc syringe attached to a small suction cup (10). The NAF was collected with microcapillary tubes (10, 20, and 50 μL), and the total amount was recorded, pooled in phosphate-buffered saline (PBS) in a dilution of 1:11, mixed well, aliquoted, and stored at −80°C.

Serum Assays

The serum analysis for E_1, E_2, E_1S, progesterone and SHBG was performed by immunoassays in the Reproductive Endocrine Research Laboratory at the University of Southern California (6). E_1, E_2, and progesterone were purified (organic solvent extraction/Celite column partition chromatography) prior to radioimmunoassay (RIA). E_1S was quantified by direct RIA (Diagnostic Systems Laboratories, Webster, Texas). SHBG was measured on the Immulite analyzer by a solid-phase, two-site chemiluminescent immunometric assay. Serum IGF-1, IGFBP-3, CRP, IL-6, adiponectin, and leptin were assessed in BEAN1 only (11, 12). Double-antibody enzyme-linked-immunosorbent-assay (ELISA) assays (Diagnostic Systems Laboratories, Webster, Texas) were used to measure IGF-1 and IGFBP-3, and the IGF-1/IGFBP-3 molar ratio was calculated (11). The CRP assay was based on a latex particle enhanced immunoturbidimetric method using a Cobas MiraPlus clinical autoanalyser and a kit from Pointe Scientific, Inc, Lincoln Park, MI with a detection limit of 0.1 mg/L (12). IL-6 was assessed as part of a Luminex panel, which was measured using a modification of an Invitrogen (Carlsbad, CA) magnetic high sensitivity 10-plex assay kit (LHC0001) and a Luminex 200 plate reader. Leptin and adiponectin were quantified using double-antibody ELISA assay (R&D Systems, Minneapolis, MN, U.S.A.)

NAF Assays

For each BEAN2 participant, four diluted NAF specimens equivalent to 4×10 μL NAF (baseline, month 3 or 6, month 7, and month 10 or 13) were sent to the Reproductive

Endocrine Research Laboratory, at which E_2 and E_1S were assessed using RIAs as described previously (13).

Urinary Assays

For BEAN1, two urine samples (baseline and month 24) and for BEAN2, 3 urine samples (baseline, month 6 and 13) were analyzed for the 9 predominant steroidal urinary estrogen metabolites (14), E_1, E_2, 2-hydroxyestrone (2–OH E_1), 2-hydroxyestradiol (2–OH E_2), 2-methylestrone (2–MeO E_1), 4-hydroxyestrone (4–OH E_1), estriol (E_3), 16-ketoestradiol (16–keto E_2), and 16α-hydroxyestrone (16α-OH E_1) using orbitrap liquid chromatography-mass spectrometry (LC/MS) (model Exactive, Thermo Fisher Scientific, Waltham, MA) following enzymatic hydrolysis of the conjugated estrogens, using 5 isotopically labeled internal standards as described previously (15). As a result, each estrogen measured represents the combined sulfated and glucuronidated forms of the estrogen. Urinary isoflavones were analyzed by high-pressure liquid chromatography (HPLC) with photo-diode array detection in BEAN1 (6) and by LC/MS in BEAN2 (7). Equol was assessed using LC/MS in both studies (9). To adjust for urine volume, all urinary measurements were expressed as nmol/mg creatinine; creatinine was measured using a Roche-Cobas MiraPlus clinical chemistry autoanalyzer (Roche Diagnostics, Switzerland) (16).

Mammographic Breast Density Assessment

In BEAN1, cranio-caudal views of screening mammograms at baseline and after 2 years were digitized and assessed using a computer-assisted method (17). Percent breast density was calculated as the ratio of the dense to the total area of the breast multiplied by 100. Intraclass correlation coefficients for a random sample of repeated readings were greater than 0.95 for all mammographic parameters.

Statistical analysis

For all analyses, the SAS statistical software package version 9.3 (SAS Institute Inc., Cary, NC) was used and the intent-to-treat principle was applied. Biomarkers and percent mammographic density were log transformed to meet assumptions of normality. We applied mixed-effects regression (PROC MIXED), which allows for missing values, to examine the effect of the soy intervention in each trial separately while taking into account the covariance structure of the repeated measurements. Based on the assumption that the covariance structure is the same at all points in time (18), the “compound symmetry” option was selected in all models. To test the first hypothesis, a fixed ethnicity effect in the mixed models evaluated possible differences in biomarker levels between Asian and non-Asian women. To examine potential effect modification by ethnic group during the soy intervention (hypothesis 2), we included an interaction term between ethnicity and the dietary assignment, i.e., low vs. high soy, and stratified the models by ethnicity. In addition, all BEAN2 models were tested for possible order effects resulting from the cross-over design; only the model for NAF volume showed a significant effect (p=0.03).

RESULTS

The two soy interventions included 220 (109 Intervention and 111 control) women in BEAN1 and 96 women in BEAN2, but the number of participants with measured values varied by biomarker (Table 1). The ethnic composition of the study participants differed between the studies. Whereas 39% of BEAN1 participant were Asian, BEAN2 had a higher proportion of Caucasians and Native Hawaiians with 27% Asians only. The age distribution was comparable across studies; BEAN1 had a mean age of 43.0 ± 2.8 years and BEAN2 39.1 ± 6.4 years.

In BEAN1 (Table 2), the soy diet had a significant intervention effect on IGF-I (p_{diet}=0.03) and IGFBP-3 (p_{diet}=0.02) but not on sex hormones, inflammatory markers, and breast density. Mean CRP ($p_{ethnicity}$=0.003) and leptin ($p_{ethnicity}$=0.001) differed significantly by ethnic background with lower levels in Asian than non-Asian women, whereas estrogen concentrations and the remaining biomarkers were similar in Asian and non-Asian women. The effect of the high soy diet on biomarkers only varied by ethnicity for IGF-1 ($p_{interaction}$=0.05). Asian women of the control and intervention group showed changes of −8 and 5 ng/mL, respectively, while the corresponding values for non-Asian women were 2 and 7 ng/mL. No additional interactions were noted.

In BEAN2 (Table 3), a significant intervention effect of the soy diet was observed for E_1S concentrations in NAF (p_{diet}=0.04) with respective changes of 12 and −12 ng/mL during the low and high soy diet. NAF volume and serum estrogens were not modified by the soy diet. NAF volume and NAF E_1S levels in Asian women were significantly lower than in non-Asian women ($p_{ethnicity}$=0.01 and 0.02) by 15 μL and 12 ng/mL, respectively. When the models for NAF volume were stratified by group to account for the significant order effect in the crossover trial (p=0.03), a larger difference by ethnicity was observed in group B (p=0.05) than group A (p=0.12) but the interaction effects remained non-significant (data not shown). NAF E_2 levels were also lower throughout the trial, but this difference was not statistically significant ($p_{ethnicity}$=0.19). For serum estrogen levels, no ethnic differences and no interactions between the soy diet and ethnicity were detected.

Urinary isoflavones (Table 4) rose in Asian and non-Asian women who participated in both studies as a result of the soy diet (p_{diet}<0.0001 for both), whereas urinary equol increased only among BEAN2 participants during the high soy diet (p_{diet}<0.0001). The increases in urinary isoflavones were >50 nmol/mg creatinine in both studies. The only ethnic difference in urinary analytes was detected for isoflavones in BEAN2 ($p_{ethnicity}$=0.003) with higher values for Asians than non-Asians throughout the study. In BEAN2 but not BEAN1, possible differential responses by ethnicity were suggested for isoflavones ($p_{interaction}$=0.07) and equol ($p_{interaction}$=0.09). Urinary estrogen concentrations were not modified by the soy diet and showed no ethnic differences.

DISCUSSION

Although urinary isoflavone excretion increased substantially during both soy interventions demonstrating adherence to the study protocol, only two biomarkers, i.e., IGF-1 and

IGFBP-3 measured in BEAN1, were modified significantly. As to the hypothesis of ethnic differences in biomarker levels, serum CRP and leptin were lower in Asian than non-Asian women as were NAF volume and E_1S in NAF, a finding that suggests a possible role of these markers in the differential breast cancer risk across ethnic groups. Little evidence supporting the second hypothesis that soy intake affects biomarkers to a stronger degree in Asian than non-Asian women was detected in the current analyses. Only the interaction term between ethnicity and IGF-I was significant, possibly a chance finding due to multiple testing.

Few dietary interventions have compared the effects of soy in Asian and non-Asian women within one study. An intervention in California (19) found that a significant reduction in luteal phase E_2 was observed only among Asian (−17.4%) and not among non-Asian (−1.2%) participants. At the same time, urinary excretion of isoflavones was higher among Asians than non-Asians (29.2 vs 17.1 μmol; p= 0.16) during the intervention period. In a Japanese investigation with soy milk (3), serum estrogen levels decreased by more than 20%, but a similar effect was not detected in a meta-analysis of trials conducted primarily in Caucasian women (4). It is possible that the response to isoflavones differs in Asian women because of their lifetime exposure to these compounds. Isoflavone intake of older Japanese adults was estimated at 25–50 mg per day, with somewhat lower values in Chinese populations (20), whereas consumption in Western populations tends to be <1 mg per day (1).

A number of reports have indicated that beneficial effects of soy against breast cancer are restricted to Asians. A meta-analysis stratified by ethnicity showed that studies conducted in high soy consuming Asians show a significant lower risk with higher soy food intake with an odds ratio (OR) of 0.71 (95% CI: 0.60–0.85) for the lowest among highest intake, whereas soy intake was unrelated to breast cancer risk in studies conducted in the 11 low soy-consuming Western populations (1). Within the Multiethnic Cohort, the association of urinary isoflavone excretion with breast cancer risk was only significant in Japanese women (OR=0.69; 95% CI: 0.51–0.92) and not in Caucasians (OR= 0.95; 95% CI: 0.70–1.30) (21). Differential associations for soy consumption were also detected for prostate cancer risk (22); stratified analyses showed a combined risk of 0.52 (95% CI: 0.34, 0.81; p=0.01) for studies with Asian populations and 0.99 (95% CI: 0.85, 1.16; p=0.91) from studies with Western populations. However, no ethnic difference was observed for colorectal cancer (23).

As to other biomarkers, a cross-sectional study in Hawaii detected a positive relation between soy food consumption and mammographic density in Caucasian and Native Hawaiian women but a non-significant inverse association in Japanese women (24). For IGF-I, an investigation among 611 Japanese, Japanese Americans, and Caucasians detected 11% lower mean IGF-I levels among women in the highest tofu intake category compared with the lowest, but this difference in IGF-I levels was only significant among women in Japan (25). A comparative pharmacokinetic trial indicated better uptake of isoflavones in Asians. Maximum isoflavone concentrations in plasma were higher and the area under the plasma concentration-time curve for genistein and daidzein were greater for young Asians than Caucasians after intake of soy (2). Equol production has been shown to be higher in Asians than other ethnic groups (26).

Strengths of this study included the relatively long duration of the two BEAN studies among free-living participants. Women prepared their own soy foods, a more accurate representation of traditional soy intake in Asian countries than consuming high doses of soy in the form of supplements. This possibly contributed to the high adherence to the study, as monitored by dietary recalls and urinary isoflavones, and the low drop-out rate. In addition, a relatively large number of women were studied when considering both BEAN studies. Although pooling of data across studies was not possible due to the different study designs, the similar dietary protocols allowed the comparison of results for several common biomarkers. The timing of sample collection from premenopausal women was satisfactory and assured the comparability of sex steroid values. In BEAN1 and BEAN2, 87 and 79%, respectively of women had specimens collected during the luteal phase of the menstrual cycle.

On the other hand, the findings are limited because the inflammatory markers, IGFs, and mammographic density were only measured in BEAN1 and NAF only in BEAN2 (Table 1). As the data were not pooled across studies, the sample size and statistical power remained low and made it unlikely to detect significant findings. The exploratory nature of this secondary analysis of a large number of biomarkers resulted in multiple testing and increased the likelihood of false positive results. Of all the biomarkers tested, only four showed ethnic differences and only one responded differentially in Asian vs. non-Asian women, possibly a chance finding. Due to the 10 μL NAF requirement for BEAN2, many interested Asian women had to be excluded, but selection bias was probably also introduced into BEAN1 by recruiting only women who had received a mammogram. The resulting selection bias limits the applicability of findings to a general population of women.

The current evidence offers no substantial support for the hypothesis that women of Asian ethnicity experience distinct effects from soy isoflavones in breast cancer risk as assessed by a wide variety of biomarkers, except for a possible soy diet and ethnicity interaction in serum IGF-1; however, it showed interesting differences in CRP, leptin, and NAF between Asian and non-Asian women that may be related to the lower breast cancer risk in Asian countries (27). As knowledge about the role of early life nutrition and the development of gut microbiota increases, the potential for diverse metabolic pathways of isoflavones in individuals with different ethnic backgrounds and dietary exposures may be clarified. Based on the current evidence, it appears likely that the timing of exposure is the most important determinant of beneficial health effects from soy foods (28).

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REFERENCES

1. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. Br J Cancer. 2008; 98:9–14. [PubMed: 18182974]

2. Vergne S, Sauvant P, Lamothe V, Chantre P, Asselineau J, et al. Influence of ethnic origin (Asian v. Caucasian) and background diet on the bioavailability of dietary isoflavones. Br J Nutr. 2009; 102:1642–1653. [PubMed: 19622188]

3. Nagata C, Takatsuka N, Inaba S, Kawakami N, Shimizu H. Effect of soymilk consumption on serum estrogen concentrations in premenopausal Japanese women. J Natl Cancer Inst. 1998; 90:1830–1835. [PubMed: 9839524]

4. Hooper L, Ryder JJ, Kurzer MS, Lampe JW, Messina MJ, et al. Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis. Hum Reprod Update. 2009; 15:423–440. [PubMed: 19299447]

5. Petrakis NL, Lee MM, Wrensch MR, Ernster VL, Miike R, et al. Birthplace and yield of nipple aspirate fluid in Chinese women. Cancer Epidemiol Biomarkers Prev. 1998; 7:835–839. [PubMed: 9752995]

6. Maskarinec G, Franke AA, Williams AE, Hebshi S, Oshiro C, et al. Effects of a 2-year randomized soy intervention on sex hormone levels in premenopausal women. Cancer Epidemiol Biomarkers Prev. 2004; 13:1736–1744. [PubMed: 15533901]

7. Maskarinec G, Morimoto Y, Conroy SM, Pagano IS, Franke AA. The volume of nipple aspirate fluid is not affected by 6 months of treatment with soy foods in premenopausal women. J Nutr. 2011; 141:626–630. [PubMed: 21325473]

8. Maskarinec G, Takata Y, Franke AA, Williams AE, Murphy SP. A 2-year soy intervention in premenopausal women does not change mammographic densities. J Nutr. 2004; 134:3089–3094. [PubMed: 15514280]

9. Maskarinec G, Morimoto Y, Heak S, Isaki M, Steinbrecher A, et al. Urinary estrogen metabolites in two soy trials with premenopausal women. Eur J Clin Nutr. 2012; 66:1044–1049. [PubMed: 22713773]

10. Petrakis NL. Nipple aspirate fluid in epidemiologic studies of breast disease. Epidemiol Rev. 1993; 15:188–195. [PubMed: 8405203]

11. Maskarinec G, Takata Y, Murphy SP, Franke AA, Kaaks R. Insulin-like growth factor-I in a 2-year soy intervention among premenopausal women. Br J Nutr. 2005; 94:362–367. [PubMed: 16176606]

12. Maskarinec G, Steude JS, Franke AA, Cooney RV. Inflammatory markers in a 2-year soy intervention among premenopausal women. J Inflamm (Lond). 2009; 6:9. [PubMed: 19348684]

13. Maskarinec G, Ollberding NJ, Conroy SM, Morimoto Y, Pagano IS, et al. Estrogen levels in nipple aspirate fluid and serum during a randomized soy trial. Cancer Epidemiol Biomarkers Prev. 2011; 20:1815–1821. [PubMed: 21742946]

14. Eliassen AH, Ziegler RG, Rosner B, Veenstra TD, Roman JM, et al. Reproducibility of fifteen urinary estrogens and estrogen metabolites over a 2- to 3-year period in premenopausal women. Cancer Epidemiol Biomarkers Prev. 2009; 18:2860–2868. [PubMed: 19843676]

15. Franke AA, Custer LJ, Morimoto Y, Nordt FJ, Maskarinec G. Analysis of urinary estrogens, their oxidized metabolites, and other endogenous steroids by benchtop orbitrap LCMS versus traditional quadrupole GCMS. Anal Bioanal Chem. 2011; 401:1319–1330. [PubMed: 21713421]

16. Franke AA, Hebshi SM, Pagano I, Kono N, Mack WJ, et al. Urine accurately reflects circulating isoflavonoids and ascertains compliance during soy intervention. Cancer Epidemiol Biomarkers Prev. 2010; 19:1775–1783. [PubMed: 20615889]

17. Maskarinec G, Takata Y, Franke AA, Williams AE, Murphy SP. A 2-year soy intervention in premenopausal women does not change mammographic densities. J Nutr. 2004; 134:3089–3094. [PubMed: 15514280]

18. Littell RC, Henry PR, Ammerman CB. Statistical analysis of repeated measures data using SAS procedures. J Anim Sci. 1998; 76:1216–1231. [PubMed: 9581947]

19. Wu AH, Stanczyk FZ, Hendrich S, Murphy PA, Zhang C, et al. Effects of soy foods on ovarian function in premenopausal women. Br J Cancer. 2000; 82:1879–1886. [PubMed: 10839307]

20. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006; 55:1–12. [PubMed: 16965235]

21. Goodman MT, Shvetsov YB, Wilkens LR, Franke AA, Le ML, et al. Urinary phytoestrogen excretion and postmenopausal breast cancer risk: the multiethnic cohort study. Cancer Prev Res (Phila). 2009; 2:887–894. [PubMed: 19789300]

22. Yan L, Spitznagel EL. Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis. Am J Clin Nutr. 2009; 89:1155–1163. [PubMed: 19211820]

23. Yan L, Spitznagel EL, Bosland MC. Soy consumption and colorectal cancer risk in humans: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2010; 19:148–158. [PubMed: 20056634]

24. Maskarinec G, Meng L. An investigation of soy intake and mammographic characteristics in Hawaii. Breast Cancer Res. 2001; 3:134–141. [PubMed: 11250760]

25. Takata Y, Maskarinec G, Rinaldi S, Kaaks R, Nagata C. Serum insulin-like growth factor-I levels among women in Hawaii and Japan with different levels of tofu intake. Nutr Cancer. 2006; 56:136–142. [PubMed: 17474858]

26. Setchell KD, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol-a clue to the effectiveness of soy and its isoflavones. J Nutr. 2002; 132:3577–3584. [PubMed: 12468591]

27. Ferlay, J., Soerjomataram, I., Ervik, M., Forman, D., Bray, F. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012. Lyon: International Agency for Cancer Research; 2014. http://globocan.iarc.fr/Default.aspx. 9-3-2014

28. Messina M, Hilakivi-Clarke L. Early intake appears to be the key to the proposed protective effects of soy intake against breast cancer. Nutr Cancer. 2009; 61:792–798. [PubMed: 20155618]

Table 1

Characteristics of 275 premenopausal women from two soy intervention studies[a]

Characteristic	BEAN1		BEAN2
	Intervention	Control	
N	109	111	96
Ethnicity			
Asian	41 (40%)	44 (38%)	26 (27%)
Caucasian	42 (39%)	46 (41%)	48 (50%)
Native Hawaiian	14 (13%)	13 (12%)	16 (17%)
Other	12 (11%)	8 (7%)	6 (6%)
Age, years	43.2 (2.7)	42.8 (2.9)	39.1 (6.4)
Body mass index, kg/m^2	26.2 (5.5)	25.9 (5.9)	25.9 (5.6)
Number of children	1.7 (1.2)	1.7 (1.6)	1.5 (1.3)
Biomarkers measured (Number of women)			
Serum estrogens, progesterone, SHBG	100	105	79
Serum IGF proteins	97	99	
Serum CRP, IL-6, adiponectin, leptin	90	93	
NAF volume			96
NAF estrogens			79
Urinary estrogens	93	95	79
Urinary isoflavones	108	110	82
Mammographic density	108	110	

[a]Data are presented as mean (standard deviation) unless otherwise noted.

Abbreviations: E_1: estrone; E_2: estradiol; SHBG: sex hormone-binding globulin; Prog: progesterone; IGF: insulin-like growth factor; CRP: C-reactive protein; IL-6: interleukin 6; NAF: nipple aspirate fluid.

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Table 2

Mean Serum Sex Steroid and Inflammatory Marker Levels and Mammographic Breast Density in the BEAN1 Study at Baseline and After 2 years in the Control and Intervention Arms, Stratified by Ethnicity[a]

		Control			Intervention					
		Baseline	Final	Change	Baseline	Final	Change	P_{diet}[b]	$P_{ethnicity}$[c]	$P_{interaction}$[d]
E_1 (pg/mL)	All	97	92	−4	90	88	4	0.84	0.44	0.83
	Asian	98	90	−9	94	92	−6			
	Non-Asian	96	94	−1	87	85	11			
E_2 (pg/mL)	All	150	136	−17	136	138	13	0.46	0.52	0.66
	Asian	153	125	−33	135	141	1			
	Non-Asian	148	143	−6	137	136	20			
SHBG (nmol/L)	All	58	59	0	57	56	−1	0.46	0.20	0.81
	Asian	56	56	−1	51	54	3			
	Non-Asian	60	61	1	60	57	−3			
Prog (ng/mL)	All	12	10	−2	11	10	−1	0.18	0.78	0.38
	Asian	12	10	−2	12	11	−1			
	Non-Asian	11	10	−1	10	10	−1			
IGF-1 (ng/ml)	All	320	315	−2	322	327	6	0.03	0.16	0.05
	Asian	332	321	−8	309	319	5			
	Non-Asian	312	311	2	331	332	7			
IGFBP-3 (ng/ml)	All	4284	4247	−26	4413	4379	0	0.02	0.22	0.16
	Asian	4378	4313	−6	4367	4341	21			
	Non-Asian	4219	4203	−41	4444	4405	−14			
IGF1: IGFBP3	All	0.28	0.28	0	0.27	0.28	0.01	0.38	0.36	0.23
	Asian	0.28	0.28	−0.01	0.27	0.28	0.01			
	Non-Asian	0.27	0.27	0	0.28	0.28	0			
CRP (mg/L)	All	2.3	2.1	−0.2	1.9	2.6	0.6	0.22	0.003	0.40
	Asian	1.3	1.3	0	1.7	1.4	−0.3			
	Non-Asian	3.1	2.7	−0.3	2.1	3.4	1.2			
IL-6 (pg/mL)	All	1.4	1.3	0	1.1	1.2	0.1	0.15	0.18	0.85
	Asian	1.1	1.2	0.1	0.9	1.0	0			

		Control			Intervention					
		Baseline	Final	Change	Baseline	Final	Change	P_{diet} [b]	$P_{ethnicity}$ [c]	$P_{interaction}$ [d]
Adipo (μg/mL)	Non-Asian	1.5	1.4	0	1.1	1.3	0.2			
	All	8.1	8.4	0.1	7.9	7.9	0	0.56	0.55	0.95
	Asian	7.6	8.3	0.6	7.4	7.8	0.5			
Leptin (ng/mL)	Non-Asian	8.5	8.5	−0.2	8.2	8.0	−0.3			
	All	19.1	21.0	2.0	19.4	19.2	0.3	0.32	0.001	0.23
	Asian	12.6	14.7	2.5	17.1	16.6	−0.7			
Breast density (%)	Non-Asian	23.5	25.3	1.6	21.0	20.9	1.0			
	All	48	43	−4	46	41	−3	0.63	0.50	0.93
	Asian	50	45	−5	48	41	−4			
	Non-Asian	47	42	−4	44	40	−2			

[a] Abbreviations: E_1: estrone; E_2: estradiol; SHBG: sex hormone-binding globulin; Prog: progesterone; IGF-1: insulin-like growth factor 1; IGFBP3: insulin-like growth factor binding protein 3; CRP: C-reactive protein; IL-6: interleukin 6; Adipo: adiponectin.

[b] P-values were obtained from mixed general linear models evaluating the difference between the low and high soy diet.

[c] P-values for ethnicity as a fixed effect.

[d] P-values represent interaction terms of ethnicity with dietary assignment, i.e., low soy diet vs. high soy diet.

Table 3

Mean Estrogen Levels in Serum and Nipple Aspirate Fluid in the BEAN2 Study at Baseline and After 6 months of Low soy or High soy Intervention, Stratified by Ethnicity[a]

	Baseline (BL)	Low soy (LS)	High soy (HS)	Change (BL to LS)	Change (BL to HS)	P_{diet}[b]	$P_{ethnicity}$[c]	$P_{interaction}$[d]
Serum E_1 (ng/mL)								
All	106	116	107	12	4	0.42	0.33	0.53
Asian	103	95	105	−6	5			
Non-Asian	107	124	108	19	4			
Serum E_2 (pg/mL)								
All women	152	175	152	26	4	0.44	0.59	0.61
Asian	148	151	149	4	4			
Non-Asian	154	184	153	33	5			
NAF volume (μL)								
All	33	28	33	−8	−3	0.64	0.01	0.77
Asian	22	26	29	1	4			
Non-Asian	37	29	34	−11	−6			
NAF E_1S (ng/mL)								
All	56	76	49	12	−12	0.04	0.02	0.70
Asian	48	67	45	11	−6			
Non-Asian	60	78	50	12	−14			
NAF E_2 (pg/mL)								
All	130	141	120	−4	−19	0.29	0.19	0.87
Asian	103	128	111	6	6			
Non-Asian	140	145	123	−7	−27			

[a] Abbreviations: E_1 estrone; E_2 estradiol; E_1S: estrone sulfate; NAF: nipple aspirate fluid.

[b] *P*-values were obtained from mixed general linear models evaluating the difference between the low and high soy diet.

[c] P-values for ethnicity as a fixed effect.

[d] *P*-values represent interaction terms of ethnicity with dietary assignment, i.e., low soy diet vs. high soy diet.

Table 4

Urinary Estrogens and Isoflavones in the BEAN1 & BEAN2 Studies at Baseline and End of study[a]

BEAN1[b]	Control			Intervention					
	Baseline	Final	Change	Baseline	Final	Change	P_{diet}[c]	$P_{ethnicity}$[d]	$P_{interaction}$[e]
Total estrogens									
All	219	211	−6	215	355	139	0.98	0.68	0.32
Asian	197	173	−24	156	565	410			
Non-Asian	233	237	6	253	222	−31			
E_1									
All	42	38	−4	42	60	18	0.85	0.74	0.36
Asian	42	32	−10	35	86	51			
Non-Asian	42	42	0	46	44	−3			
E_2									
All	14	13	−1	15	17	2	0.45	0.99	0.66
Asian	16	12	−3	13	22	8			
Non-Asian	14	14	0	17	15	−2			
Isoflavones									
All	5.9	9.9	4.3	9.2	64.1	54.5	<0.0001	0.40	0.50
Asian	6.9	15.2	6.8	12.2	72.3	56.9			
Non-Asian	5.2	6.4	2.7	7.5	59.2	53.1			
Equol									
All	0.2	0.1	−0.2	0.3	0.5	0.4	0.58	0.70	0.33
Asian	0.1	0.1	0.0	0.2	0.9	0.7			
Non-Asian	0.2	0.1	−0.4	0.3	0.3	0.2			

BEAN2[b]	Baseline (BL)	Low soy (LS)	High soy (HS)	Change (BL to LS)	Change (BL to HS)	P_{diet}[c]	$P_{ethnicity}$[d]	$P_{interaction}$[e]
Total estrogens								
All	197	225	234	5	46	1.00	0.08	0.94
Asian	160	153	180	−6	20			
Non-Asian	210	250	267	40	56			

BEAN1[b]	Control			Intervention					
	Baseline	Final	Change	Baseline	Final	Change	P_{diet}[c]	$P_{ethnicity}$[d]	$P_{interaction}$[e]
E_1									
All	42	46	54	5	12		0.62	0.16	0.66
Asian	34	33	43	1	9				
Non-Asian	45	51	58	7	13				
E_2									
All	16	16	19	1	3		0.74	0.33	0.63
Asian	14	12	16	−1	2				
Non-Asian	16	18	20	1	3				
Isoflavones									
All	5.0	5.2	56.9	0	52.0		<0.0001	0.003	0.07
Asian	7.2	12.5	64.9	5.1	57.8				
Non-Asian	4.2	2.7	53.9	−1.5	49.7				
Equol									
All	0.5	0.5	3.9	−3.4	3.4		<0.0001	0.83	0.09
Asian	0.9	1.6	4.0	−2.6	3.1				
Non-Asian	0.4	0.2	3.9	−3.6	3.5				

[a] Abbreviations: Total E molar: total estrogens; E_1 estrone; E_2 estradiol

[b] Units: Total E molar, E_1, and E_2 in pmol/mg creatinine and equol and isoflavones in nmol/mg creatinine.

[c] *P*-values were obtained from mixed general linear models evaluating the difference between the low and high soy diet.

[d] *P*-value for ethnicity as a fixed effect.

[e] *P*-values represent interaction terms of ethnicity with dietary assignment, i.e., control (low soy diet) vs. intervention (high soy diet).