Research Article

Estrogen Levels in Nipple Aspirate Fluid and Serum during a Randomized Soy Trial

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Abstract

Background: On the basis of hypothesized protective effect, we examined the effect of soy foods on estrogens in nipple aspirate fluid (NAF) and serum, possible indicators of breast cancer risk.

Methods: In a crossover design, we randomized 96 women who produced 10 μL or more NAF to a high- or low-soy diet for 6 months. During the high-soy diet, participants consumed 2 soy servings of soy milk, tofu, or soy nuts (~50 mg of isoflavones per day); during the low-soy diet, they maintained their usual diet. Six NAF samples were obtained using a FirstCyte aspirator. Estradiol (E₂) and estrone sulfate (E₁S) were assessed in NAF and estrone (E₁) in serum only, using highly sensitive radioimmunoassays. Mixed-effects regression models accounting for repeated measures and left-censoring limits were applied.

Results: Mean E₂ and E₁S were lower during the high-soy than the low-soy diet (113 vs. 313 pg/mL and 46 vs. 68 ng/mL, respectively) without reaching significance (P = 0.07); the interaction between group and diet was not significant. There was no effect of the soy treatment on serum levels of E₂ (P = 0.76), E₁ (P = 0.86), or E₁S (P = 0.56). Within individuals, NAF and serum levels of E₂ (rₛ = 0.37; P < 0.001) but not of E₁S (rₛ = 0.004; P = 0.97) were correlated. E₂ and E₁S in NAF and serum were strongly associated (rₛ = 0.78 and rₛ = 0.48; P < 0.001).

Conclusion: Soy foods in amounts consumed by Asians did not significantly modify estrogen levels in NAF and serum.

Impact: The trend toward lower estrogen levels in NAF during the high-soy diet counters concerns about adverse effects of soy foods on breast cancer risk. Cancer Epidemiol Biomarkers Prev; 20(9); 1–8. ©2011 AACR.

Introduction

Regular soy consumption has been associated with reduced breast cancer risk (1); however, its protective mechanism, if it exists, is not fully understood. One postulated mechanism involves the estrogenic potential of soy isoflavones, although a recent meta-analysis suggested no effect of soy or isoflavones on circulating sex hormones in premenopausal and postmenopausal women (2). These findings, however, have not invalidated the entire hormonal hypothesis for soy and isoflavones because estrogen levels in breast tissues seem to be quite different from circulating estrogen levels measured in serum (3–7). It has been shown repeatedly that mammary tissue contains enzymes for local estrone (E₁) and estradiol (E₂) production via the aromatase and sulfatase pathways converting androgenic (androstenedione and testosterone) and estrogenic [estrone sulfate (E₁S) and estradiol sulfate] precursors, respectively (7–9). Thus, the possible effects of bioactive steroids within the breast are perhaps not fully captured by measuring circulating hormone levels (10, 11) whereas soy or isoflavones may act directly in the breast by modifying local estrogen levels or breast cell growth. Measurements in nipple aspirate fluid (NAF) may be a more appropriate indicator to detect changes in the breast associated with soy intake. The NAF method offers a noninvasive approach to assess information on cellular and noncellular markers of breast cancer risk. The fluid is in constant contact with the ductal epithelium, the site of development of most breast cancer. In the current analysis, we examine the effects of 2 daily servings of soy foods on E₂ and E₁S levels in NAF and corresponding serum levels among premenopausal women who participated in a 6-month trial.

Materials and Methods

Study design and procedures

We conducted a randomized, crossover soy intervention study with two 6-month diet periods (high-soy and...
short recruitment interval and the maximum of 3 attempts per breast were made. The NAF was collected with microcapillary tubes (10, 20, and 50 µL), and the total amount was recorded. The first 20 µL NAF were pooled in PBS at a dilution of 1:11, well mixed, aliquoted, and stored at −80°C. The next 5 to 20 µL were used to preserve breast cells stored for cytologic analysis. If more NAF was obtained, it was diluted in PBS again. For the 15% of women who were able to produce more than 90 µL NAF, the collection was usually terminated at 120 µL.

Three blood samples were collected on the same day as NAF, 1 at baseline and 1 at the end of each diet period. After allowing the serum to clot for 30 minutes and centrifuging at 3,000 rpm for 15 minutes, it was aliquoted into 1-mL cryovials and frozen at −80°C.

**Estrogen assays in NAF and serum**

For each subject, 4 diluted NAF specimen equivalent to 4 × 10 µL NAF (baseline, month 3 or 6, month 7, and month 10 or 13) and three 1-mL serum samples (baseline, month 6, and month 13) were sent to the Reproductive Endocrine Research Laboratory at the University of Southern California. Using radioimmunoassays (RIA), E2, E1, and E1S were measured in 0.5 mL serum, but because of the small volume, NAF samples were analyzed for E2 and E1S only (18).

For the E2 assay, aliquots (0.1 mL) of previously diluted (1:11) NAF samples were transferred to RIA tubes (12 × 75-mm tubes). Similarly, aliquots of quality control (QC) serum samples were transferred to RIA tubes for monitoring the reliability of the E2 RIA. To monitor procedural losses, approximately 200 cpm of 3H-E2 were added to the QC samples and to 3 counting vials used to determine the total amount of 3H-E2 added. E2 was then extracted by adding 2.5 mL of ethyl acetate/hexane (3:2) to each tube and vortexing the tubes for 1 minute. The organic layer in each tube was transferred to a second set of RIA tubes and the solvents were evaporated under nitrogen at 37°C. The extraction procedure was repeated 1 more time. The residue was then redissolved in 0.2 mL assay buffer (0.1 mol/L phosphate buffer, pH 7.4). An iodinated E2 derivative and rabbit anti-E2 serum were added to all sample and QC tubes, as well as duplicate tubes containing various concentrations of E2 used for generating the standard curve. The contents were then
mixed by brief vortexing. After an overnight incubation period, a second antibody (goat anti-rabbit) was added to all RIA tubes. Following centrifugation, the supernatant was removed and discarded, and the remaining pellet was counted; the counts were used to calculate the E₂ concentration in each NAF sample. The sensitivity of the E₂ RIA is 2 pg/mL. An aliquot from each of the 3 QC tubes was taken for counting, and on the basis of the amount of radioactivity in these tubes and the total ³H-E₂ counts added, the procedural loss was calculated and used to correct the E₂ values obtained by RIA. The QC results in serum based on standards indicated coefficient of variations (CV) of 0.10 to 0.18 for E₁ and E₂ and 0.16 to 0.17 for NAF, whereas those for 14 blinded serum and 16 blinded NAF samples were 0.15 and 0.20.

For the E₁S assay, the water phase left from the NAF E₂ assay after ethyl acetate/hexane extraction was evaporated under nitrogen, and the residue was redissolved in 0.1 mL assay buffer to measure E₁S direct RIA with a commercial kit (Beckman Coulter) that provides assay reagents that measure serum E₁S with high accuracy. Values obtained with this assay are similar to corresponding values obtained by gas chromatography/tandem mass spectrometry. In the RIA, the iodinated E₁S radioligand and antibody against E₁S were added to the RIA tubes containing the redissolved extracts, as well as to tubes containing different concentrations of E₁S and QC samples. After an incubation period of 3 hours at room temperature, a second antibody was added. Following a 15-minute incubation period, the tubes were centrifuged, the supernatant discarded, the pellets counted, and the E₁S values were determined. The E₁S RIA sensitivity is 0.01 ng/mL. The CVs for the standards were 0.07 in serum and 0.06 to 0.08 in NAF, whereas the respective CVs for 14 blinded serum and 16 blinded NAF samples were 0.07 and 0.21.

Statistical analysis

The statistical analysis was carried out using the SAS software package version 9.2. (SAS Institute, Inc.). To assess differences in baseline characteristics between the 2 randomization groups, Student’s t tests were conducted for continuous variables and χ² tests for categorical variables; an α level of 0.05 was considered significant. Because of nonnormal distributions, log-transformed values were used for serum estrogens and Wilcoxon rank-sum tests for NAF estrogens. Within-subject correlations between NAF and serum estrogen concentrations at baseline were assessed using the Spearman rank correlation coefficient. Mixed-effects regression models as described later examined the association across the entire study period and adjusted for menstrual phase, group, and dietary treatment.

Log-transformed values of serum estrogen levels were used in mixed-effects regression (PROC MIXED) models incorporating a random intercept term to examine the effect of soy. For estrogen levels in NAF, mixed-effects regression models accounting for repeated measures and left-censoring limits as described by Thiebaut and Jacqmin-Gadda (19) were implemented using the SAS procedure PROC NLMIXED. Log-transformed values for NAF E₂ and NAF E₁S were modeled by a normal distribution that incorporated the correlation from repeated measures by using a random-intercept term and the left censoring of values below the detection level for NAF E₂ and E₁S, respectively. The model included variables indicating group membership and the diet sequence to test for differences in randomization and for a possible carryover effect. Additional models included an interaction term between diet and group as well as age and menstrual phase at the time of NAF collection to examine the possible influence of imbalance between randomized groups. Furthermore, we excluded women with Asian ancestry, nulliparous women, and women who did not adhere to the study protocol (<40 mg of isoflavones per day during the high-soy diet and >10 mg per day during the low-soy diet based on the 24-hour recalls).

Results

Of the 82 women who completed the study, 40 were in group A and 42 were in group B. At baseline, the 2 randomization groups did not differ by ethnicity, body mass index (BMI), reproductive characteristics, drop-out rate, and NAF concentrations of E₂ and E₁S (Table 1). However, women in group A were 4 years older than women in group B (P < 0.01), excreted more isoflavonoids in urine (P = 0.03), and had lower concentrations of serum E₂ (P = 0.02), E₁ (P = 0.03), and E₁S (P = 0.02) before treatment started. Because of scheduling problems, only 58% of the NAF samples were collected during the midluteal phase. This proportion was nonsignificantly lower for group A than for group B (53% vs. 62%; P = 0.39). After adjustment for menstrual phase, the significant differences in serum estrogen levels persisted.

E₂ and E₁S levels were below the minimum detection limit in 116 (37%) and 82 (26%) NAF samples, respectively; of these, 71 samples had both nondetectable E₂ and E₁S levels. The proportion of nondetectable values was similar by study period but higher during the follicular phase and for women with more than 28-day cycles than for midcycle and luteal samples. The 45 women with at least 1 nondetectable E₂ were more likely to be of Asian or other ethnicity (P = 0.07), reported a higher isoflavone intake before the start of the trial (P = 0.09), were younger by 2.7 years (P = 0.05), and had a lower BMI by 2.1 m/kg² (P = 0.10) than the 37 participants with 4 detectable values.

On the basis of baseline samples, the within-woman correlation between NAF and serum was modest for E₂ (rₚ = 0.37; P < 0.001) and nonexistent for E₁S (rₑ = 0.004; P = 0.97; Fig. 1A and B). The stronger association between NAF and serum for E₂ was confirmed in models incorporating all samples and adjusted for menstrual cycle and group and diet effects (β = 0.94, P < 0.001 for E₂ and β = 0.25, P = 0.60 for E₁S). E₂ and E₁S levels were highly

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Table 1. Characteristics of the study participants by randomization group at baseline

| Characteristic                        | All     | Group A (high-to low-soy) | Group B (low- to high-soy) | P
|---------------------------------------|---------|---------------------------|-----------------------------|---
| n                                     | 82      | 40                        | 42                          |   
| Race/ethnicity                        |         |                           |                             |   
| White, n (%)                          | 42 (51) | 20 (50)                   | 22 (52)                     | 0.98
| Asian, n (%)                          | 22 (27) | 11 (23)                   | 11 (22)                     |   
| Other, n (%)                          | 18 (22) | 9 (27)                    | 9 (26)                      |   
| Age at screening, y                   | 39.2 ± 6.1 | 41.3 ± 5.6 | 37.3 ± 6.0 | <0.01
| BMI, mean ± SD, kg/m²                 | 25.8 ± 5.6 | 25.8 ± 5.2 | 25.9 ± 6.0 | 0.91
| Age at menarche, mean ± SD, y         | 12.4 ± 1.4 | 12.4 ± 1.2 | 12.4 ± 1.5 | 0.99
| Number of children, mean ± SD         | 1.5 ± 1.3 | 1.6 ± 1.1 | 1.4 ± 1.5 | 0.40
| Age at first live birth, mean ± SD    | 27.8 ± 6.7 | 27.7 ± 7.1 | 28.0 ± 6.4 | 0.87
| Equol producer status,n (%)           | 43 (52) | 23 (58) | 20 (48) | 0.37
| Isoflavone intake, mean ± SD, mg/d    | 21.2 ± 39.7 | 16.3 ± 38.8 | 25.8 ± 40.5 | 0.28
| Urinary isoflavones, mean ± SD, nmol/mg creatinine | 4.99 ± 9.25 | 7.28 ± 11.33 | 2.81 ± 6.07 | 0.03
| Midluteal menstrual phase at NAF collection, n (%) | 47 (57) | 21 (53) | 26 (62) | 0.39
| NAF E₂, mean ± SD,a pg/mL             | 130 ± 140 | 130 ± 132 | 129 ± 148 | 0.84
| Below detection limit, n (%)          | 27 (34) | 14 (36) | 13 (33) | 0.75
| NAF E₃,S, mean ± SD,b ng/mL           | 56 ± 110 | 68 ± 142 | 46 ± 68 | 0.32
| Below detection limit, n (%)          | 19 (24) | 6 (15) | 13 (32) | 0.09
| Serum E₂, mean ± SD, bg/mL            | 152 ± 90 | 124 ± 55 | 178 ± 107 | 0.02
| Serum E₃, mean ± SD, bg/mL            | 106 ± 52 | 91 ± 34 | 119 ± 62 | 0.03
| Serum E₃,S, mean ± SD, bg/mL          | 2.22 ± 1.28 | 1.89 ± 0.79 | 2.54 ± 1.55 | 0.02

*aP values are from the t test for continuous variables and the χ² test for categorical variables; log-transformed values were used for serum estrogens; the Wilcoxon rank-sum test was used for NAF estrogens.

*bN = 59 for parous women: 31 in group A and 28 in group B.

*cEquol producer status is based on detecting urinary daidzein excretion of 2 nmol/mg or more and urinary equol to daidzein ratio of 0.018 or more in at least 1 of the 8 urine samples collected throughout the study.

*dN = 79 for NAF E₂ and serum E₂ and E₃; N = 80 for NAF E₃,S; N = 78 for serum E₃,S.

correlated within individuals (0.78 for NAF and 0.48 for serum; P < 0.001 for both; Fig. 1C and D). The mean E₂ concentration was lower in NAF than in serum (128 vs. 160 pg/mL, P = 0.01), whereas E₃,S was 30-fold higher in NAF than in serum (60.6 vs. 2.2 ng/mL, P < 0.001). Estrogen concentrations varied across the menstrual cycle for both NAF and serum (Fig. 2). Significantly higher values at the midcycle and midluteal phase than at the follicular phase were observed for NAF E₂, serum E₂, and serum E₃,S (P < 0.05 for all in models adjusted for group and diet effects).

For estrogen concentrations in serum, no effect of the high-soy diet on serum estrogen concentrations was detected in mixed-effect regression models (Table 2). For E₂ and E₃,S in NAF, mean values were lowest during the high-soy diet; however, this difference did not reach statistical significance. The respective parameter estimates in the mixed-effect regression models were −0.63 pg/mL (P = 0.07) and −0.58 ng/mL (P = 0.07). The effect for group in the NAF E₃,S but not in the E₂ model was significant (P = 0.01 vs. 0.07), whereas diet sequence was not significant in either model. An interaction term between diet and group was not significant for both
analytes (P = 0.58 and P = 0.11). Similar results for the intervention effect on NAF levels were obtained when we adjusted for age at screening or menstrual phase to control for the imbalance in randomization; the parameter estimates and P values changed minimally. The exclusion of Asians or nulliparous women made no substantial difference, but the restriction to adherent women strengthened the association for E1S (P = 0.03) but not for E2. After stratification by equol producer status, the dietary treatment was not significant in either group. The respective parameter estimates for the 43 producers and 39 nonproducers were −1.46 and −0.24 pg/mL for E2 and −0.91 and −0.41 ng/mL for E1S, respectively.

Discussion

The current analysis among premenopausal women with various ethnic backgrounds found no significant effect of a 6-month soy diet on NAF or serum concentrations of E2 and E1S, although there was a modest decline in estrogen levels during the high-soy diet that did not reach statistical significance. Equol producer status did not modify the intervention effect. E2 and E1S levels were strongly correlated in both NAF and serum, but their levels in NAF and serum showed only a weak relationship. When the observations were grouped by menstrual cycle phase, serum levels of E2 and E1S and NAF E2 showed similar patterns throughout the cycle, whereas varying patterns were observed for E1S with NAF levels being much higher than serum levels. These findings suggest that, although no significant influence of soy intake on NAF E2 and E1S was detected, estrogens in NAF provide different information than serum levels and additional clues to understanding local estrogen synthesis and its possible effect on breast tissue activity.

The lack of an effect on serum estrogens agrees with our previous report (20) and with a meta-analysis (2) based on 11 studies in premenopausal women including our own results (20) and did not detect any effect of soy and isoflavones on E2 and E1. Given the difficulties of obtaining breast tissue, only 3 studies so far have investigated the effects of soy on breast cells in humans (21–23). The only previous soy intervention that collected NAF did not assess estrogen levels in NAF but noted a moderate increase in volume, gross cystic disease fluid protein concentration, and hyperplastic epithelial cells (21). Two studies among women scheduled to receive a breast biopsy indicated an increase in progesterone expression and proliferation rate of breast lobular epithelium (22) and a decrease in apolipoprotein D levels and an increase in pS2 levels in breast fluid (23).

In comparison with previous reports of estrogens in NAF and serum, the levels in the current study are considerably lower than in early studies that reported

![Figure 2. Mean serum (●) and NAF (○) concentrations of E2 and E1S from subjects retrospectively grouped by phase of the menstrual cycle. Menopausal phases include more than 28 days (NA), follicular (FL), midcycle (MC), midluteal (ML), and late luteal (LL). MC and ML are significantly different from FL adjusting for group and diet effects (P < 0.05).](image)

Table 2. Estrogen concentrations in NAF and serum

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean ± SD</th>
<th>Effect of high-soy dietb</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2, pg/mL</td>
<td>135 ± 152</td>
<td>313 ± 131</td>
</tr>
<tr>
<td>Above minimum detection limit, n (%)</td>
<td>98 (66)</td>
<td>51 (63)</td>
</tr>
<tr>
<td>E1S, ng/mL</td>
<td>64 ± 128</td>
<td>68 ± 115</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2, pg/mL</td>
<td>152 ± 90</td>
<td>175 ± 172</td>
</tr>
<tr>
<td>E1, pg/mL</td>
<td>106 ± 52</td>
<td>116 ± 94</td>
</tr>
<tr>
<td>E1S, ng/mL</td>
<td>2.22 ± 1.28</td>
<td>2.21 ± 1.28</td>
</tr>
</tbody>
</table>

NOTE: Participants were randomized to either a 6-month high-soy (2 servings per day) or low-soy (<3 servings per week) diet and crossed over after a 1-month washout period. Baseline, low-soy, and high-soy estrogen concentrations reflect raw values.

aSamples collected at baseline and after the 1-month washout period prior to crossover.

bReflect the predicted mean difference for the effect of the high-soy diet on log-transformed estrogen concentrations from mixed-effects models.
E₂ levels of 800 pg/mL and more (3–6). However, more recent publications presented levels between 100 and 400 pg/mL (7, 24, 25), which are in the range of our findings. Improved methodology, in particular extraction and higher antibody specificity, may explain the trend toward lower levels. The exception is 1 report with NAF E₂ levels of 800 to 2,000 pg/mL in 40 premenopausal women (10), which were described as unusually high (Dr. R. Chatterton, written personal communication). Given the wide range in published NAF E₂ levels, disagreement persists whether or not NAF levels are equal or higher than serum levels. Although serum and NAF E₂ levels were measured in the same range in the current study and in 1 other report from premenopausal women (24), 5- to 30-fold differences have also been reported (5–7, 10). Over time, NAF E₂ levels seem to be relatively stable; the correlation between 2 measurements, 15 months apart was reported as 0.65 (26). The poor correlation between estrogen levels in NAF and serum observed in our study agrees with others (5, 6, 10, 24, 25); significant associations have only been reported for progesterone (10, 25). The high E₁S levels in NAF as compared with serum and the strong association between E₂ and E₁S concur with previous reports (10, 25), supporting the idea that E₁S in breast tissue provides a reservoir for E₂ production via the sulfatase pathway (7–9). Our findings in relation to the menstrual cycle are in contrast to Chatterton and colleagues (10); we observed higher NAF E₂ concentrations during the midcycle and midluteal phase than during the follicular phase corresponding to serum level changes during the menstrual cycle.

Limitations of the current study include the large number of potential participants who were ineligible because of insufficient NAF production, the fact that randomization did not lead to completely balanced groups (12), the small amounts of NAF fluid collected limiting the number of analytes, the relatively large proportion of nondetectable estrogen values in NAF, and the difficulty to collect samples from premenopausal women at the same time within the menstrual cycle. We cannot exclude the possibility that imbalance in the randomized groups biased the results, although there was no significant interaction between diet and group and adjustment for age and menstrual phase (Table 1) did not explain the differences in serum estrogens or the nonsignificantly lower NAF estrogens after the high-soy diet (Table 2). It is also difficult to explain why E₂ levels in NAF were higher at the end of the low-soy diet than at baseline; a similar trend was apparent for serum levels. One possibility is that the small amounts of soy in the regular diet of participants had a similar effect as the high-soy intervention. From experimental research, it is known that enzymes involved in steroidogenesis may be affected by isoflavones and influence the balance of E₁ and E₂ (27).

Despite these weaknesses, this study had considerable strengths. In comparison with the literature, its sample size was quite large; NAF was obtained repeatedly for 82 women from different ethnic backgrounds. The adherence to the high-soy diet was excellent and the drop-out rate was low (12). The estrogen assay used a purification step, that is, organic solvent extraction prior to the RIA, a method that has been shown to be important for accurate results (28). Because NAF is in constant contact with the ductal epithelium, the site of development of most breast cancer (29), it provides noninvasive insight into breast tissue activity and is more likely to reflect actual estrogen levels in the breast than those measured in serum (10, 11). In particular, the high E₁S concentration in NAF as compared with serum points to local estrogen production.

At this time, it is not known whether estrogen levels in NAF are related to breast cancer, but there is evidence that women who produce NAF, in particular those with cellular NAF, are at higher risk (30, 31). When NAF production was added to the Gail model, the relative risk for women with NAF containing normal cells was 1.5 and the population attributable risk fraction for NAF production was 18% (32). Although this trial detected no significant effect of 6-month daily soy consumption on NAF estrogen levels, the trend points toward lower levels during the high-soy diet, an observation that counters concerns about adverse effects of soy foods and isoflavones on breast cancer risk (33). In addition to estrogen levels, a future analysis will examine breast epithelial cells in those participants who provided sufficient NAF.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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