A Randomized Isoflavone Intervention among Premenopausal Women

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Abstract

Isoflavones, phytoestrogens contained in soy foods, may play a role in breast cancer prevention. This randomized double-blinded trial with 34 premenopausal women investigated whether 100 mg of isoflavones per day versus placebo affects the ovulatory cycle during 1 year. Compliance with the study regimen was confirmed by the increase of urinary isoflavone excretion among the intervention group. Blood samples were taken 5 days after ovulation as determined by an ovulation kit, at baseline, and at months 1, 3, 6, and 12. Serum levels of estrone, estradiol, estrone sulfate, progesterone, sex hormone-binding globulin, follicle-stimulating hormone, and luteinizing hormone were quantified by immunoassay; free estradiol was calculated. We applied the method of least squares to fit general linear models to test for an intervention effect while taking into account the repeated measurement design. Except for a small difference in age, the two groups were comparable at baseline. Menstrual cycle length did not change significantly during the intervention [F(1,32) = 0.69; P = 0.44]. During 1 year, we did not observe any significant changes in hormone levels by treatment group. The difference in change between intervention and control group was −13.0 pg/ml (95% confidence interval, −57.5 to 31.5) for estradiol and 6.9 pg/ml (95% confidence interval, −17.8 to 31.5) for estrone. Exclusion of 22 non-ovulatory cycles, noncompliant women, or non-Asian women did not affect the results. These findings do not support the hypothesis that isoflavones affect the ovulatory cycles of premenopausal women over a 1-year period. However, isoflavones alone may have different effects on the reproductive cycle than isoflavones present in soy foods.

Introduction

International variations in breast cancer incidence (1) and the fact that breast cancer risk in Asian migrants to the United States approaches the risk among United States whites after a few generations (2) suggest that environmental factors and, in particular diet, may be important determinants of breast cancer risk. As shown in case-control studies, estrogens appear to play an important role in the development of breast cancer (3, 4). The fact that populations with low breast cancer risk have lower levels of endogenous estrogens than women in high-risk populations (5) also supports this hypothesis. Soy-containing diets have long been associated with countries and ethnic groups who experience low breast cancer risk. Some case-control studies have offered support for this hypothesis (6–8), but others (9, 10) including a cohort study from Japan (11) found no effect.

Isoflavones occurring in high amounts in soy (0.2–0.3%) are classified as phytoestrogens because of their estrogen-like structure and of their estrogenic properties (12, 13). Depending on dose and target site, isoflavones may exert an antiestrogenic effect (14) and protect epithelial tissue from the stimulatory effect of endogenous estrogens (5). Several mechanisms for an estrogen-lowering effect of isoflavonoids have been proposed: stimulation or up-regulation of SHBG2 in the liver (15), which will bind free E2; down-regulation of enzymes involved in estrogen biosynthesis, such as aromatase (CYP 19), which converts androgens into estrogens (16); inhibition of 17β-hydroxysteroid dehydrogenase type 1 that converts E1 to the more potent E2 (17); suppression of the gonadotropins FSH and LH, resulting in lower circulating E1 and E2 levels; effects on intestinal flora (18) may influence the hydrolysis of biliary conjugates that affect reabsorption of E2 and lower circulating estrogen levels. However, if the antiestrogenic effects of soy were a result of competitive binding to estrogen receptors, no change in circulating estrogen levels would be expected.

A number of short-term intervention studies, the majority without a control group, using a variety of soy foods with different isoflavone levels have investigated the effect of soy on hormone levels and produced conflicting results (19–25). The purpose of this pilot trial was to determine whether an isoflavone mixture (100 mg) compared with a placebo affects the ovulatory cycle during a 1-year intervention among premenopausal women. Specifically, we wanted to examine the effects of this preparation on the levels of E1, E2, free E2, E1S, progesterone, SHBG, FSH, and LH and on the length of the menstrual cycle.

Materials and Methods

Experimental Design. We conducted a randomized double-blinded clinical trial with 34 premenopausal women on either a

1 The abbreviated used are: SHBG, sex hormone-binding globulin; E2, estradiol; E1, estrone; E1S, estrone sulfate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HPLC, high-performance liquid chromatography; CV, coefficient of variation; FFQ, food frequency questionnaire.
regimen of 100 mg of a soy isoflavone mixture taken as two 50-mg tablets daily or a placebo. The dose was chosen to achieve an isoflavone intake in the high nutritional, but not in the pharmacologic, range. Whereas the mean consumption of soy in Asian countries provide <50 mg of isoflavones/day (6, 8), a small number of individuals report soy consumption of three or more servings per day. The Committee on Human Studies at the University of Hawaii approved the study protocol. Written informed consent was obtained from each subject before the beginning of the study. HPLC with diode array detection was used to analyze the isoflavone preparation (26). The isoflavone compounds in the 50-mg study tablets provided by the manufacturer, Pharmavite Corporation (San Fernando, CA), were found to be equivalent to 38 mg of aglycone equivalents. The consistency of isoflavone content was tested in triplicate using 10 study tablets. The isoflavone pattern was very similar to that in soy foods, with 51% daidzein, 44% genistein, and 5% glycitein. Only 1% of the isoflavones in the tablets were in the form of aglycones; 91% were glucosides, 5% were malonylglucosides, and 3% were acetylglucosides. The placebo tablet consisted primarily of maltodextrin and other inert substances.

**Subjects and Recruitment.** The premenopausal women were recruited from all ethnic groups in Hawaii who had participated in a previous observational study or who responded to community flyers and newspaper articles. Eligibility criteria in a previous observational study or who responded to community flyers and newspaper articles. Eligibility criteria included age 35–46 years, regular dietary consumption of soy foods <7 servings/week based on a detailed soy food frequency questionnaire (27), a normal mammogram during the last 6 months, no previous history of cancer (except basal cell skin carcinoma), not on oral contraceptives or any hormone preparations now and within the past 3 months, no intention of becoming pregnant within the next year, intact uterus and ovaries, regular menstrual periods, and no serious medical conditions. We also required the successful completion of a 2-week run-in period. During this time, subjects took daily placebo tablets and reported problems with adhering to the study regimen. At the end of the run-in period, we counted tablets to assess compliance and eligibility.

Of the 127 initial contacts, 61 (48%) were ineligible for the following reasons: lack of interest, on hormone medication, hysterectomy, residents of island outside Oahu, age, high soy diet, pregnancy desired, menopausal symptoms, and breast biopsy. We conducted screening visits with 58 women, but 23 women lost interest, decided on hormone medication or pregnancy, did not detect an ovulation, underwent a breast biopsy or uterine procedure, or reported a reaction to the placebo during the run-in period. The remaining 35 women were randomized using a random number scheme. To ensure that hormone differences attributable to ethnicity would not affect our ability to compare the treatment arms, a stratified randomization method with two separate randomization schedules for Caucasian and Hawaiian women in one group and Japanese, Chinese, and Filipino women in the other group was applied. One woman dropped out of the study after randomization, before the start of the intervention, because she desired pregnancy. The resulting study group consisted of 34 women, 17 on isoflavone supplement tablets and 17 on placebo tablets. During periodic phone calls and study visits, we collected follow-up information on health problems. Four women left the study before the end of the year. One was counseled by her doctor to discontinue the intervention; he attributed her increasing acne development to the study regimen; he attributed her increasing acne development to the intervention; he attributed her increasing acne development to the intervention. Also, 1 subject had only four blood draws; she missed the 6-month blood draw, although she remained in the study until the end of the year.

**Nutritional Assessment.** Before entry into the study, all subjects completed a validated FFQ (28), especially designed for a multi-ethnic population and to capture at least 85% of nutrients. The FFQ was self-administered and processed by optical scanning. The analyses were conducted in batches, all samples from baseline; months 1 and 3 were measured at one time, and all 6- and 12-month samples were measured together at a later time. The CVs for interassay variation were 5.6, 5.1, 2.9% for daidzein, genistein, and glycitein, respectively. 

**Sample Collection.** Subjects were asked to donate five urine and blood samples, one at baseline and one after 1, 3, 6, and 12 months of the intervention. All urine and blood samples were collected 5 days after ovulation or approximately on day 19 in a 28-day cycle. Subjects used menstrual calendars and ovulation kits (Ovuquick test kits from Quidel, La Jolla, CA) to determine the time of ovulation. This kit detects the mid-cycle rise of LH using morning urine with a sensitivity of 35 mIU/ml of LH. Blood samples were drawn in the morning after overnight fasting at a commercial laboratory. Serum samples were kept frozen at −80°C after separation and aliquoting. Urine collection containers, with 0.3 g of boric acid and 0.2 g of ascorbic acid to control bacterial contamination, were provided and returned to the Cancer Research Center of Hawaii, where they were also aliquoted and frozen.

**Compliance.** Compliance to the study regimen was determined by urinary isoflavone analysis and tablet counts. At every visit, study subjects returned the medication bottles with the remaining tablets. Higher levels of daidzein, genistein, glycitein, and equol during intervention, as compared with baseline, indicated that women in the intervention group had taken the study tablets.

**Urinary Analysis.** Urine samples were analyzed for daidzein, genistein, glycitein, O-desmethylandolensin, and equol by the Analytical Laboratory of Cancer Research Center of Hawaii using HPLC (26, 29, 30). After centrifuging, 2 ml of the clear urine sample were incubated with β-glucuronidase and arylsulfatase in phosphate buffer for 1 h at 37°C. After isolating the hydrolyzed analytes by partitioning into ethyl ether, drying of the organic phases, and redissolving in methanol and an acetate buffer, injection into the HPLC system was performed. The detection limit (1.0 nmol/l) of the HPLC system far exceeded the isoflavone levels found in human urine after soy intervention. The CVs for interassay variation were 5.6, 5.1, 2.9% for daidzein, glycitein, and genistein, respectively.

**Serum Analysis.** Hormone assays were conducted at the Department of Obstetrics and Gynecology, University of Southern California in the Reproductive Endocrine Research Laboratory. The analyses were conducted in batches, all samples from baseline; months 1 and 3 were measured at one time, and all 6- and 12-month samples were measured together at a later time. Blood samples were assayed for E2, E1, E1, E2, SHBG, progesterone, FSH, and LH. E1, E2, progesterone, and SHBG were quantified in serum by specific and sensitive RIAs (31, 32). Before RIA, E1 and E2 were first extracted with ethyl acetate: hexane (2:3) and then purified by Celite column partition chromatography, using ethylene glycol as stationary phase. E2 and E1 were eluted off the column with 15% and 40% toluene in isoctane, respectively. [3H]E1 and [3H]E2 were used as internal standards to follow procedural losses. When the first batch was analyzed, the interassay CVs were 13.0, 8.0, and 7.0% at 82, 158, and 354 pg/ml and 9.0, 7.0, and 9.0% at 53, 114, and 202 pg/ml for the E1 and E2 RIAs, respectively. The CVs for the second batch were 7.8 and 7.5% at 105 and 262 pg/ml for E1 and 9.4 and 9.9% at 38 and 77 pg/ml for E2, E1, and SHBG were measured by direct RIAs using kits obtained from Diagnostic Systems Laboratories (Webster, TX).
The interassay CVs for the E_1 S RIA were 10.9 and 11.6% at 1.0 and 8.8 ng/ml, respectively; for the progesterone RIA, 7.0 and 8.0% at 4.0 and 12.0 ng/ml, respectively; and <0.5% at 74 nM for the SHBG RIA. Free E_2 (non-SHBG or albumin-bound E_2) was determined by calculation using a computerized algorithm described previously (33). FSH and LH levels in serum were determined by calculation using a computerized algorithm (36). Analyses for all serum levels were repeated with data restrictions or adjustments for presumed anovulatory status, compliance, ethnicity, and group mean age differences. With an alpha level of 0.05, we had a power of 90% to detect a difference in E_1 of 27.6 pg/ml or 26.6% of the overall mean of 103.7 pg/ml for both groups. The respective values for the minimum detectable differences for the raw E_2 levels and the logged score of E_2 were 42.2 pg/ml (mean, 133.3 pg/ml) and 0.32 (mean, 4.83).

**Results**

Mean age was the only variable that differed significantly between groups at baseline (Table 1). We detected no significant differences in ethnic distribution, body weight, or dietary intake of energy, fat, fruits, and vegetables. Mean soy intake did not differ between groups at baseline (>1 tofu serving/week for both groups). Nutritional assessments completed as subjects exited the study showed that both groups maintained their regular diet and did not increase their soy intake significantly. Analysis of urinary isoflavone excretion (Table 2) indicated very high compliance with the study regimen. Isoflavone excretion was equally low in both groups at baseline. The excretion rate in the intervention group increased by a factor of ~15 after baseline and remained much higher than in the control group. Although the mean urinary isoflavone excretion continued to be at least five times lower in the control group than in the intervention group, there was a small increase in the control group relative to baseline. This agrees with the data on dietary intake assessment (Table 1). Taking 412 nmol/h of total isoflavones (twice the overall mean at baseline) as threshold for compliance, 80.8% of the intervention group and 79.4% of the control group were compliant. These values were very similar at all specimen collection times. There were no significant differences in tablets taken at the consecutive visits, although the number of tablets returned was slightly higher for the intervention group after 1 month of intervention (Table 2).

Subjects were asked about any health problems and symptoms that emerged during the study. In the control group, 6 women reported at least one symptom, and 7 women reported at least one symptom in the intervention group. The most common symptom categories were gastrointestinal (2 versus 3 subjects in the control and intervention groups, respectively) and headaches/dizziness (1 versus 4 subjects in the control and intervention groups, respectively), but there were no significant group differences. One woman in the control group was diagnosed with breast cancer after the end of the study.

We observed neither a significant treatment effect nor a significant treatment-by-time interaction effect on menstrual cycle length [F(1,32) = 0.69, P = 0.44; F(12,351) = 1.06, P = 0.40 for treatment effect and interaction effect, respectively]. At no point in the study was there a significant difference between group mean menstrual cycle length (Table 2). The difference of change between intervention and control group among the 26 women who had data for at least 12 menstrual cycles was ~0.09 (95% confidence interval: -3.25 to 3.07). Serum hormone levels measured at baseline did not differ significantly between groups (Table 3). For all hormonal outcomes, the results offer no support for a treatment effect or an interaction effect between treatment and time. None of the
Isoflavone Intervention

Discussion

In this pilot trial, the administration of an isoflavone supplement to premenopausal women did not lead to an observable effect in their ovulatory cycles. All measured outcomes in the intervention group, E1, E2, free E2, E1S, SHBG, progesterone, FSH, LH, and cycle length, did not differ from the results in the placebo group over a 1-year period. From the two measures of compliance, we are confident that women in both groups adhered to the study regimen. The number of returned tablets in the intervention group was 13% as compared with 7% in the control group. Urinary isoflavone excretion in the intervention group increased significantly for the women in the intervention group and remained high throughout the intervention period, whereas urinary isoflavone excretion in the control group remained low, indicating that the women did not increase their consumption of soy foods significantly. Drop-ins, i.e., control group women increasing isoflavone intake, are unlikely for two reasons: (a) dietary supplements containing isoflavones were just entering the health food market at the time of this study and were not widely available yet; and (b) nutritional information from the FFQ indicates that the women in the control group did not modify their diet significantly during the study period.

Our findings contradict a number of published reports that suggested estrogen-lowering effects of soy foods or supplements (Table 4). In a 1-month intervention study with soy milk (20), serum E2 levels decreased by 31, 81, and 49% on cycle days 5–6, 12–12, and 20–22, respectively. Similarly, in a 2-month Japanese intervention study (22), follicular E1 and E2 levels decreased considerably, but the change was not statistically significant. The estrogen-lowering effect of soy foods was restricted to Asian women in an intervention from a third study (25). All other interventions (Table 4) observed either no change in serum E1 and E2 levels (19, 23, 24) or a slight increase (21). The average cycle length became somewhat longer in only half of the published studies (19, 20, 22) but not in the other studies. Longer intervals between ovulations have been considered protective against breast cancer (5). The dose of isoflavones in this trial was similar to or higher than the estimated intake in the previous studies (Table 4), making it unlikely that the lack of effect was attributable to the amount of isoflavones in the tablets. As observed previously (25), studies using soy milk or other foods appear to have more significant results than studies using soy protein. We have limited the comparison to interventions investigating serum hormone levels among premenopausal women. Additional studies in premenopausal women have suggested weak estrogenic effects of soy supplements with respect to urinary hormone levels (38) and breast proliferation (39).

The fact that we measured serum E1 and E2 levels at different times is a serious limitation of this study. Lab drift resulted in a substantial difference in measurements between the first and second batch. Despite this problem, the results of the randomized comparison clearly support the result of no treatment effect. At no time did we observe a difference between groups; the lab drift was proportional in both groups.

Table 2 Compliance with study regimen and menstrual cycle length

<table>
<thead>
<tr>
<th>Time of assessment</th>
<th>Control group</th>
<th>Intervention group</th>
<th>P of difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Tablets taken (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>93.9</td>
<td>4.9</td>
<td>83.9</td>
</tr>
<tr>
<td>3 mo</td>
<td>92.6</td>
<td>8.2</td>
<td>85.3</td>
</tr>
<tr>
<td>6 mo</td>
<td>91.2</td>
<td>7.7</td>
<td>92.0</td>
</tr>
<tr>
<td>12 mo</td>
<td>92.6</td>
<td>9.1</td>
<td>87.7</td>
</tr>
<tr>
<td>Total isoflavones (nmol/h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>200</td>
<td>349</td>
<td>213</td>
</tr>
<tr>
<td>1 mo</td>
<td>227</td>
<td>398</td>
<td>3054</td>
</tr>
<tr>
<td>3 mo</td>
<td>565</td>
<td>1826</td>
<td>2876</td>
</tr>
<tr>
<td>6 mo</td>
<td>401</td>
<td>817</td>
<td>3771</td>
</tr>
<tr>
<td>12 mo</td>
<td>367</td>
<td>911</td>
<td>4757</td>
</tr>
<tr>
<td>Menstrual cycle length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean number of days/time period)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>27.4</td>
<td>3.6</td>
<td>29.1</td>
</tr>
<tr>
<td>Month 1</td>
<td>26.9</td>
<td>4.6</td>
<td>28.4</td>
</tr>
<tr>
<td>Months 2–3</td>
<td>28.2</td>
<td>3.1</td>
<td>29.3</td>
</tr>
<tr>
<td>Months 4–6</td>
<td>27.0</td>
<td>4.2</td>
<td>28.7</td>
</tr>
<tr>
<td>Months 6–12</td>
<td>27.5</td>
<td>3.2</td>
<td>27.7</td>
</tr>
</tbody>
</table>

Differences in change between intervention and control group (Table 3) were significant, and the 95% confidence intervals were wide. The means of serum levels showed little variation over time for either group. The drop in E1 and E2 levels from month 3 to month 6 was due to lab drift and was proportional across groups. As described above, the substantial autocorrelation within subjects across repeated measures was modeled and included within the statistical model tested.

Several analyses were conducted to rule out possible confounders. If progesterone levels are <5 ng/ml, we assumed that ovulation had not taken place. Of all 162 serum samples analyzed, 22 (13.6%) had progesterone levels <5 ng/ml. They were distributed equally across groups (13 placebo versus 18 intervention), but 11 anovulatory cycles occurred at the time of last blood draw. No significant group or interaction effects were found under the following conditions: excluding all samples from presumed anovulatory cycles; excluding samples with evident noncompliance (urinary isoflavone excretion <412 nmol/h); excluding non-Asian subjects; or including age in the model.

A finding of lower estrogen levels among equol (a metabolite of daidzein) excretors (37) was not confirmed by our results. At baseline, 1 and 3 months, only 1 woman excreted equol. The number of equol excretors increased to 14 and 9 at 6 and 12 months, respectively. With the exception of two control group women at month 6, all equol excretors belonged to the intervention group. Mean levels of E1 and E2 did not differ at month 6 and 12 by equol excretion status.
high correlation between the first three and the last two serum E₁ and E₂ measurements for individual women supports the validity of our results. Although compliance with the study treatment appears satisfactory, it is always possible that not all women took the tablets regularly. The five urine samples can only assess isoflavone intake during 1–2 days preceding the collection day because the consumption of isoflavones leads to a rapid increase in the soy isoflavones daidzein, genistein, and glycitein in body fluids (29, 40), which return to baseline levels after 36–48 h. Occasional consumption of soy foods may have affected the urinary isoflavone assessment, but intake was minimal according to the FFQ, not more than one or two servings/week. Dietary isoflavone exposure of humans derives predominantly from soy foods (41, 42). Given the strong variation in hormone levels by cycle day, errors in the timing of ovulation may have caused some problems. However, the average time between ovulation and blood draw in the placebo group was 5.4 days, which is very close to the 5.3 days in the intervention group. Despite the limitation that ovulation kits are not always sensitive enough to detect low LH surges, progesterone measurements show that only a small proportion of cycles were anovulatory. Age was probably a problem in some subjects in respect to determining ovulation dates because women >40 years of age start entering perimenopause with its wide fluctuations in hormones and irregular cycle lengths. Given our requirement of a normal screening mammogram, it was not possible to identify a large number of younger women for whom mammography screening is not recommended. As shown by the power calculations above, it was very unlikely to identify a large number of younger women for whom mammography screening is not recommended.
sample size. We considered this research a pilot study and have initiated a larger nutritional intervention since the completion of this trial.

Given the weak evidence for an estrogen-lowering effect of supplemental soy foods in the literature, our study results add new information to this area of investigation. In contrast to earlier research, this study was randomized, a basic requirement for a valid clinical trial, and lasted longer, 12 months, than most previous studies. Another strength of this study is the fact that it was conducted among free-living individuals for 1 year as opposed to the short-term controlled feeding approach used previously (19–21). Therefore, we consider the present study a more valid test of the hypotheses that isoflavones affect estrogen levels than previous uncontrolled, short-term feeding studies. Our study does not exclude the possibility that whole soy foods or other substances in soy have different effects on the reproductive cycle than isoflavones alone. Moreover, alternate cancer protective mechanisms of isoflavones (13) may lower breast cancer risk in women who consume soy foods regularly. The following cancer protective mechanisms have been hypothesized for isoflavones: antioxidant effects (43), modification of enzyme activities (44), up-regulation of phase II enzymes including glutathione-S-transferase, quinone reductase and UDP-glucosyl transferase to protect against potentially carcinogenic xenobiotics (45), radical scavenging (43), antimutagenic differentiation inducing through inhibition of topoisomerase (46), and inhibition of tyrosine kinase activity and nuclear factor-κB activation (47). The differential binding of isoflavones to the estrogen receptor “β” (48) and the differential tissue distribution of this receptor may also play a role regarding the estrogenic action of isoflavones. Finally, animal evidence suggests that the cancer protective effect of soy foods may be limited to exposure during intrauterine and early life (49, 50). Unfortunately, these long-term effects of soy intake, in particular during developmental years, cannot be addressed in a randomized trial. Because the population at-large is increasing their consumption of isoflavone-containing foods and supplements, some of them in doses far exceeding intake in traditional Asian diets, it is important to elucidate biological mechanisms of actions to explore possible risks and benefits associated with soy consumption and to disseminate results that disagree with marketing claims made by manufacturers that are supported by limited scientific evidence.

Acknowledgments

We are grateful to the women who donated their time and effort to participate in this study. Thanks to Ann Kelminski, Casey Robbins, Lixin Meng, Tammy Brown, and Laurie Custer for work on the project.

References


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**Table 4** Comparison of published soy/isoﬂavone interventions among premenopausal women

| Author            | Daily isoflavone dose | Length of study (mo) | Type (1) | Cycle length (days) | % change (days) | E1 | E2 | P | SHBG | FSH | LH |
|-------------------|-----------------------|----------------------|----------|--------------------|----------------|----------------|---------|---------|---------|-------|-------|-------|
| Cassidy et al. (19) 1994 | 45 mg | 1 | CO | 6 | +2 | NA | 0 | −14 | −5.2 | −66 | −47 |
| Petrakis et al. (21) 1996 | 75 mg | 6 | CO | 14 | NA | +18 | −41 | −36 | NA | NA |
| Lu et al. (20) 1996 | 200 mg Soy milk | 1 | CO | 6 | +4(T) | NA | −49 | −35(T) | NA | NA | NA |
| Nagata et al. (22) 1998 | 109 mg Soy milk | 2 | RI | 31 | 3 | −23 | −27.4 | (F) | NA | 0 | NA | NA |
| Duncan et al. (23) 1999 | 10, 65, 129 mg Soy protein powder | 3 | CO/R | 14 | 0 | −7 | −6.4 | −13 | 0 | 0 | +9 |
| Martini et al. (24)(5) 1999 | 38 mg Soy beverage | 2 | OC | 16 | 0 | −2 | −6.4 | −7.1 | 0 | NA | NA |
| Wu et al. (25) 2000 | 32 mg Tofu, soy milk, soybean | 3 | CO | 20 | 0 | −9.3 | −14 | +2 | NA | NA |

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(1) CO, cross-over; R, randomized; I, intervention; C, control; F, follicular phase; T, total cycle; P, progesterone; H, high dose; NA, not available.

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(2) Only data for the 16 non-users of oral contraceptives are presented here.
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