Effects of Soya Consumption for One Month on Steroid Hormones in Premenopausal Women: Implications for Breast Cancer Risk Reduction

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Abstract

Soybean consumption is associated with reduced rates of breast, prostate, and colon cancer, which is possibly related to the presence of isoflavones that are weakly estrogenic and anticarcinogenic. We examined the effects of soya consumption on circulating steroid hormones in six healthy females 22–29 years of age. Starting within 6 days after the onset of menses, the subjects ingested a 12-oz portion of soymilk with each of three meals daily for 1 month on a metabolic unit. Daily isoflavone intakes were ~100 mg of daidzein (mostly as daidzin) and ~100 mg of genistein (mostly as genistin). Serum 17β-estradiol levels on cycle days 5–7, 12–14, and 20–22 decreased by 31% (P = 0.09), 81% (P = 0.03), and 49% (P = 0.02), respectively, during soya feeding. Decreases persisted for two to three menstrual cycles after withdrawal from soya feeding. The luteal phase progesterone levels decreased two to three menstrual cycles after withdrawal from soya feeding. The luteal phase progesterone levels decreased two to three menstrual cycles after withdrawal from soya feeding. The luteal phase progesterone levels decreased two to three menstrual cycles after withdrawal from soya feeding. The luteal phase progesterone levels decreased two to three menstrual cycles after withdrawal from soya feeding. The luteal phase progesterone levels decreased two to three menstrual cycles after withdrawal from soya feeding.

Introduction

Ovarian hormones and other reproductive factors (e.g., ages of menarche, menopause, and parity) have important influences on breast cancer development (1). Increased levels of estrogens in blood and urine are markers for high risk for breast cancer (2–5). For example, in a large prospective, case-control study, Toniolo et al. (5) reported a significant relationship between serum estrogen levels and the risk for breast cancer in women in New York. Goldin et al. (6) reported 44% lower blood levels of estrogens and androgens in oriental women who emigrated to the United States from areas of low breast cancer risk, when compared to Caucasian Americans, who have a higher risk for breast cancer. Women in rural China have a low risk for breast cancer and 36% lower plasma estrogen levels when compared to women in Britain where breast cancer is more common (7). Similarly, postmenopausal women in Japan have lower blood estrogen levels and a lower risk for breast cancer than do white women in the United States (8). Earlier studies (9) are in agreement with these recent observations.

Dietary factors, such as legumes, may account at least in part for these differences in hormone levels and breast cancer risk. Consumption of legumes is greater in countries such as China, Japan, and Thailand, where breast and prostate cancers are less common than in Western countries (10–13). Legumes are the major source of protein for vegetarians, another group that is at low risk for many cancers (14, 15). A cross-sectional study in Australia found that legume consumption was associated with lower risk for colon cancer (15). Consumption of rice and tofu (a soy product) was inversely related to prostate cancer risk among men of Japanese ancestry in Hawaii (10). Among premenopausal women in Singapore, breast cancer risk was inversely related to soy protein intake (16, 17). These epidemiological observations are supported by results of animal studies in which soya feeding was protective against experimentally induced mammary and other organ cancers (13, 18).

Possible mechanisms for the cancer protective effects of soya in humans are not established. However, soya contains significant amounts of the isoflavones daidzein and genistein (19). These isoflavones are weak estrogens with uterotropic potencies about 1 × 10⁻⁵ that of diethylstilbestrol and binding affinities for mammalian estrogen receptors, including those from MCF-7 cells (20), about 0.1–2 × 10⁻² that of 17β-estradiol (21). These isoflavones may act as anti-estrogens by competing with endogenous estrogens for receptor binding, and this may reduce estrogen-induced stimulation of breast cell proliferation (20) and breast tumor formation. Alternatively, they may reduce breast cancer risk by decreasing endogenous ovarian steroid levels. For example, genistein stimulates progesterone synthesis by isolated bovine granulosa cells at a concentration <0.2 μM but inhibits progesterone synthesis at a concentration >2 μM (22) and antagonizes TGF-α-induced...
estrogen biosynthesis in granulosa and theca cells (23). Genistein inhibits the enzyme activity of estrogen-specific 17β-hydroxysteroid oxidoreductase type I, an enzyme that converts estrone to 17β-estradiol (24). Unlike some other flavonoids, isoflavones are in general weak inhibitors for aromatase (25) and inefficient inducers of monooxygenase and transferase activities (26). Soya isoflavones may also decrease cancer incidence by mechanisms that do not involve alteration of steroid levels. For example, genistein is a specific inhibitor of tyrosine kinase (Ref. 27; an important enzyme in transmembrane signal transduction) induces cell differentiation (28), inhibits the activity of topoisomerase II (29), and inhibits angiogenesis (30).

17β-Estradiol stimulates breast cell proliferation and may promote breast tumor growth (31). Progesterone antagonizes the proliferative effect of 17β-estradiol on the endometrium but its role in 17β-estradiol-induced breast cell proliferation is not clear. Human breast epithelial cells proliferate two to three times more rapidly during the luteal phase when progesterone levels are also high (32). This suggests that proliferation of breast cells induced by 17β-estradiol may be further enhanced by high levels of progesterone (31). DHEA3 is an adrenal androgen, an intermediate in the biosynthesis of 17β-estradiol (33) and has a biphasic dose effect on breast cell proliferation in vitro (34). The role of DHEA as an influence on human breast cancer development is still controversial (35). However, a DHEA sulfate-supplemented diet reduced the incidence of mammary tumors in mice (36). Therefore, 17β-estradiol, progesterone, and DHEA sulfate may be useful biomarkers for breast cancer risk. The purpose of the present study was to determine if consumption of soya containing isoflavones can alter these three circulating steroid levels in premenopausal women and, thereby, protect them from developing breast cancer.

Materials and Methods

Study Design. Six healthy, nonvegetarian women with regular menstrual cycles (26–31 days) were admitted for 33 days to the General Clinical Research Center at The University of Texas Medical Branch. Four subjects were Caucasian, 1 African-American, and 1 Hispanic. Their age range was 22–29 years, height 1.6–1.7 m, weight 53.8–70.5 kg, and body mass index 18.9–26.2 kg/m². Five subjects had never taken birth control pills and one had taken an oral contraceptive until 2 months earlier. The collection of samples from all six subjects was completed. Statistical Analysis. To determine if the duration of soymilk feeding in all subjects. We were able to follow four of the six subjects as outpatients for up to 10 months by frequent phone contacts; the lengths of their menstrual cycles were recorded, and blood samples were obtained for hormone analysis.

Hormone Analysis. 17β-Estradiol and progesterone concentrations in the serum were measured by specific RIA after fractionation by microcelite column chromatography as described previously (39, 40). Briefly, 1 ml of serum was extracted twice with 3 volumes of ether after adding 3H tracers of 17β-estradiol and progesterone for assessment of recovery. The extracts were dried under nitrogen and chromatographed on microcelite columns with ethylene and propylene glycol as the stationary phase. This chromatographic separation is effective in removing steroids that can interfere with the assay because of cross-reactivity. The fractions containing progesterone and 17β-estradiol were collected and dried, and the residue was dissolved in the assay buffer. Two aliquots of different volumes of this solution were used in the assay, and 0.1 ml was used for recovery calculations. Blank and control sera were run with each assay. The antibody used in 17β-estradiol assay was highly specific with <0.1% cross-reactivity with estrone and estradiol. Levels of DHEA sulfate were measured by direct RIA (41). The intra-assay coefficient of variation was 4–8% and the interassay variation was 5–9%. Steroid assays began only after the LH surge (to <100 pg/ml), peak again during days 20–24 (100–200 pg/ml), and then decrease to earlier follicular levels before the onset of menses. Progesterone levels are all <0.1 ng/ml during the follicular phase, began to rise after the LH surge (near day 14), and peak during the midluteal phase (5–12 ng/ml; days 20–24; Ref. 38). Therefore, blood samples were obtained from our subjects on days 5–7, 12–14, and 20–22 of each menstrual cycle. This was accomplished for one cycle before soya feeding in three subjects (only on day 5 for one subject), and for the month of soya feeding and for at least 3 cycles within the first 6 months after termination of soya feeding in all subjects. We were able to follow four of the six subjects as outpatients for up to 10 months by frequent phone contacts; the lengths of their menstrual cycles were recorded, and blood samples were obtained for hormone analysis.

1The abbreviations used are: DHEA, dehydroepiandrosterone; LH, luteinizing hormone.

hormone levels, multiple comparisons of the various treatments were made using paired $t$ tests on the unranked data. Subjects with missing data at a particular time point were not included in the post hoc analysis by paired $t$ tests for only that specific time point, but their data from other time points were included in the ANOVA and the calculation of the means shown in the figures.

Results

Fig. 1 shows the effect of 1-month soymilk ingestion on individual and mean menstrual cycle lengths. The mean ($\pm$ SD) cycle length for this group of six women was $28.3 (\pm 1.9)$ days before soymilk feeding; it increased slightly to $31.8 (\pm 5.1)$ days during the month of soymilk feeding ($P = 0.06$, paired $t$ test) and to $32.7 (\pm 8.4)$ days one cycle after termination of soymilk feeding ($P = 0.11$). Five women experienced increase in cycle length of 1–12 days during soymilk feeding, whereas one woman had a 2-day decrease. The subject who was taking an oral contraceptive 2 months before the study had a 3-day increase in cycle length, which was similar to other subjects.

All women returned to their pre-soymilk cycle lengths five cycles after termination of soymilk feeding (results not shown); this included a subject who had a cycle length of 42 days during soymilk feeding and 49 days during the first cycle after soymilk feeding. This subject consumed soymilk for 4 extra days and also provided one blood sample after the last soymilk dose for hormone measurements.

With only one exception, our subjects had baseline hormone levels within expected normal ranges (see "Materials and Methods:" Ref. 38). Hormone levels from one cycle before and for five to ten cycles after termination of soymilk feeding from our study subjects were similar and, therefore, were averaged and regarded as baseline values for each subject. The results of the second and third cycle after soymilk feeding were combined because there were no detectable differences in hormone levels between these two cycles.

Fig. 2 shows the effect and persistence of 1 month of soymilk feeding on individual and mean $17\beta$-estradiol levels, when these were averaged over a cycle (Fig. 2A) and analyzed separately on specific cycle days (Fig. 2, B–D). One month of soya feeding reduced $17\beta$-estradiol levels either when all measurements were averaged during a cycle (Fig. 2A; $P = 0.0015$, Friedman’s test) or when they were analyzed on cycle days 5–7 (Fig. 2B; $P = 0.16$), 12–14 (Fig. 2C; $P = 0.0001$), and 20–22 (Fig. 2D; $P = 0.08$). Fig. 2A shows that compared to the baseline, the mean cycle levels of $17\beta$-estradiol decreased by 62% during soymilk feeding ($P = 0.03$, paired $t$ test), by 58% during the first post-soymilk cycle ($P = 0.05$), and by 46% during the second to the third cycles after soya ($P = 0.11$). Fig. 2B shows that $17\beta$-estradiol levels in the early follicular phase (days 5–7) decreased by 31% during chronic soymilk feeding compared to control periods ($P = 0.09$). Fig. 2C shows that compared to the baseline, $17\beta$-estradiol levels during the late follicular phases (days 12–14) decreased by 81% during soymilk feeding ($n = 5; P = 0.03$), by 72% during the first cycle post-soya ($n = 5; P = 0.056$), and by 68% during the second to third cycles after soya feeding ($n = 5; P = 0.045$). The late follicular phase $17\beta$-estradiol levels during soya feeding were also 41% lower than those during the second to third cycles after soymilk feeding ($P = 0.003$). Fig. 2D shows that compared to the baseline, $17\beta$-estradiol levels during the luteal phases (days 20–22) decreased by 49% during soya feeding ($n = 5; P = 0.02$), by 68% during the first cycle post-soya ($n = 4; P = 0.04$), and by 29% during the second and third cycles post-soya ($n = 4; P = 0.24$). Thus, chronic soya ingestion decreased $17\beta$-estradiol levels that persisted for two cycles after soya ingestion. During the soymilk feeding, only one woman (who was previously on an oral contraceptive) had a small $17\beta$-estradiol peak (57 pg/ml) on day 14. During the month of soymilk feeding, higher levels of $17\beta$-estradiol in all six subjects were detected on cycle days 22–37 (range, 60–135 pg/ml) compared with those on cycle days 12–14 (range, 22–57 pg/ml), and this was in contrast to the profiles observed during baseline periods. If the highest levels (e.g., independent of
Fig. 2. The effect of 1 month (Mon) of soymilk ingestion on individual and mean serum levels of 17β-estradiol in six women. Comparisons are for average levels of a cycle (A) and for cycle days 5–7 (B), days 12–14 (C), and days 20–22 (D). Baseline values are averages from one menstrual cycle before and/or five to six menstrual cycles after termination of soymilk ingestion. P values (paired t test) refer to comparisons with baseline values.

cycle day) were compared, those during soymilk feeding (84.7 ± 21.6 pg/ml; range, 60–135 pg/ml) were also lower than during baseline study periods (186.9 ± 99.3 pg/ml; range, 50–402.5 pg/ml; P = 0.04). The subject who was on an oral contraceptive previously had a similar but smaller decrease in 17β-estradiol levels compared with other subjects.

Follicular phase progesterone levels before, during, and after soymilk feeding were all <0.1 ng/ml, as expected (results not shown). Luteal phase progesterone levels during baseline periods in five subjects were 4–18 ng/ml on cycle days 20–22, which is within the expected range of women with a 28–30 day cycle (31). Luteal phase samples could not be obtained in the sixth subject during baseline periods. During soymilk feeding, four subjects had higher progesterone levels on cycle days 20–24 than on other cycle days as for baseline periods. Two subjects who experienced 5- and 12-day increases in cycle length had progesterone levels <0.1 ng/ml on cycle days 20–24, and these levels were lower than those on cycle days 27 and 37 (9 and 3 ng/ml, respectively). The highest progesterone levels detected for all subjects during soymilk feeding (7.1 ± 3.0 ng/ml; range, 3.2–12.5 ng/ml) were all lower than their respective maximal values during baseline periods (9.5 ± 2.9 ng/ml; range, 4–17.5 ng/ml; P = 0.06). Fig. 3 shows the effect of 1 month of soymilk feeding on individual and mean progesterone levels measured on cycle days 20–22. The progesterone levels during the soymilk ingestion cycle were 35% lower than baseline (P = 0.002) and 28–38% lower than the first three cycles after termination of soya feeding (0.10 < P < 0.03). The subject who used birth control pills before entering the study did not provide a blood sample on cycle days 20–22 during the baseline period; therefore, her data was not included in the post hoc analysis by paired t test.

DHEA sulfate levels were measured at least three times/cycle. Because DHEA sulfate levels do not undergo cyclic changes, all measurements in a cycle were averaged for each subject. Thus, the values during the soymilk feeding represented means from varying lengths of soymilk ingestion. Baseline intra-individual variability in DHEA sulfate levels within a cycle were ~15%, and inter-individual variability was ~40%. One month of soymilk feeding reduced DHEA sulfate levels
averaged over a cycle (\( P = 0.0006 \), Friedman’s test; Fig. 4A), and this change increased with the duration soya ingestion (\( P = 0.06 \); Fig. 4B). Levels of DHEA sulfate averaged over the cycle were lowest during soya feeding and were 23\% lower than before soya (\( P = 0.03 \); Fig. 4A), 20\% lower than during the first cycle after soya (\( P = 0.01 \)), and 27\% lower than during the second to third cycles after soya feeding (\( P = 0.006 \)). DHEA sulfate levels at two to three cycles post-soya were slightly greater than pre-soya levels (\( P = 0.08 \)). Fig. 4B shows that during soymilk ingestion, DHEA sulfate levels decreased progressively as the number of days of soymilk ingestion increased. Compared with baseline, the decrease was significant after \( >8 \) days (\( P \) values are shown in Fig. 4B).

**Discussion**

Steroid hormones such as 17\( \beta \)-estradiol, progesterone, and DHEA sulfate can modulate the proliferative rates of mammary epithelial cells. A change in menstrual cycle length alters the relative duration of mammary epithelial cells in the luteal phase of a cycle during which time the breast cells are more proliferative. Thus, levels of these steroid hormones and menstrual cycle length are recognized risk factors for breast cancer (reviewed in Refs. 31, 35). In this study, the effects of consuming a soya diet rich in isoflavones (~200 mg/day) on these risk factors were studied in six healthy, premenopausal women. We found that 1 month of soymilk ingestion effectively reduced levels of 17\( \beta \)-estradiol, progesterone, and DHEA sulfate and increased menstrual cycle length.

One month of soya feeding increased menstrual cycle length in five of the six subjects. The increase was most pronounced in the two subjects who during soymilk feeding had very low levels (<0.1 ng/ml) of progesterone on cycle days 20–24 (Fig. 3), suggesting that there were delays in ovulation. In general, when cycle length increases, the length of follicular phase increases more than the luteal phase (42). Because breast cells proliferate two to three times more rapidly during the luteal phase than during the follicular phase (32), an increase in cycle length, as observed in our subjects with soya feeding, may shorten the duration of exposure of breast tissues to progesterone in the luteal phase. If this occurs repeatedly over a long period of time of soya ingestion, the relative amount of time during which breast tissue is stimulated to proliferate may decrease accordingly, and this may decrease the overall risk of breast cancer development. Indeed, Henderson et al. (43) suggested that menstrual cycle length may modulate breast cancer risk. Differences in cycle lengths between breast cancer cases and controls (44) and between populations of women in countries with different breast cancer risks are consistent with this suggestion (45).

During baseline cycles, our subjects had plasma levels of 17\( \beta \)-estradiol and progesterone that were similar to those reported by others in normal women (38). Their levels of 17\( \beta \)-estradiol were highest on cycle days 12–14, intermediate on cycle days 20–22, and the lowest on cycle days 5–7. 17\( \beta \)-Estradiol levels were considerably lower during soymilk feeding, when averaged over each cycle (Fig. 2A), when compared during certain days of the cycle (Figs. 2, B–D), or when the highest levels detected were compared. Moreover, during soymilk feeding in all women, peak levels of 17\( \beta \)-estradiol were observed only after cycle day 20. Soya feeding reduced 17\( \beta \)-estradiol levels in all six women, including one who had a 2-day decrease in cycle length. These observations suggest that total 17\( \beta \)-estradiol production was decreased during the month of soymilk ingestion. Progesterone production may also be reduced by soya feeding. All six women had lower luteal progesterone levels during soya consumption than during baseline cycles. DHEA sulfate levels, which unlike 17\( \beta \)-estradiol and progesterone do not exhibit cyclicity, were also reduced during soymilk feeding (Fig. 4). DHEA sulfate levels in this study decreased in a time-dependent manner with longer duration of soymilk feeding (Fig. 4B). Thus, the effect of soya feeding on DHEA sulfate levels may result from the inhibition

**Fig. 4.** The effect in six women of 1 month (Mon) of soymilk ingestion on individual and mean serum levels of progesterone on cycle days 20–22. \( P \) value (paired \( t \) test) refers to comparisons with baseline values.
of the synthesis of DHEA, which is an intermediate in the biosynthesis of 17β-estradiol. Reduction of 17β-estradiol, progesterone, and DHEA sulfate levels during soya feeding may reduce the extent of breast cell proliferation (31) and, thus, breast cancer risk.

Reduced 17β-estradiol and progesterone (but not DHEA sulfate) levels during soymilk ingestion may in part result from delayed peak formation and subsequently delayed ovulation because cycle length increased in five of six women during soya ingestion. All six subjects had higher levels of 17β-estradiol during the luteal phase of the cycle when soymilk was ingested in contrast to higher levels on days 12–14 during baseline periods (compare Figs. 2, C and D). Because the two women who experienced >5-day increases in menstrual cycle length had progesterone levels >1 ng/ml and peak 17β-estradiol levels on cycle days 27 and 37, reduced levels of ovarian steroids during soymilk feeding may be at least in part a consequence of delays in peak and ovulation. The delays in ovulation during soya feeding would also account for the increase in menstrual cycle lengths in our subjects. This will decrease the duration of breast cells in the luteal phase and in proliferation and, thus, lower breast cancer risk, as already discussed.

The effectiveness of soya feeding in reducing circulating ovarian steroid levels in premenopausal women may explain epidemiological observations that legume consumption is protective against breast cancer development (16, 17), and that Chinese and Japanese women from low risk areas have lower

Fig. 4. The effect in six women of 1 month of soymilk ingestion on individual and mean serum levels of DHEA sulfate averaged over each cycle (A) and on the time course of individual and mean serum DHEA sulfate levels during soymilk feeding (B). P values (paired t test) refer to comparisons with baseline values.
plasma estrogen levels than do women from regions with high risk (6–8). Among the many chemopreventive components of soya (reviewed in Refs. 12, 18, 46–49), only the isoflavones and their metabolites have been detected in urine and blood of humans from populations with low breast and prostate cancer risks (37, 50–53). Thus, the soya isoflavones may play an important role in protecting women from developing breast cancer. However, other potentially chemopreventive components of soya, such as Bowman-Birk protease inhibitor, phytoestrogens, saponins, and isonitrosals may also contribute to the effects observed (18, 54).

An anti-estrogenic effect may be one of the mechanisms by which the soya phytoestrogens reduce proliferation of breast epithelial cells and thus breast cancer risk. However, soya phytoestrogens may also modify breast cell proliferation by decreasing circulating ovarian steroid levels. Our observation that the levels of three different steroids, 17β-estradiol, progesterone, and DHEA sulfate, were reduced suggests that the synthesis of these steroids were inhibited during soya diets. Moreover, the effects on 17β-estradiol levels persisted for two cycles after termination of soy milk feeding, during which time soya isoflavones were no longer detected in blood and urine (53). In in vitro assays, genistein inhibits the biosynthesis of progesterone by bovine granulosa cells (22), antagonizes transforming growth factor α-induced synthesis of estrogen in granulosa and theca cells (23) and inhibits the enzyme activity of 17β-hydroxysteroid oxidoreductase type I (24), an enzyme that converts estrone to 17β-estradiol. The effect of genistein on the synthesis of these three steroids may result from its effect on transmembrane signal transduction, a mechanism that may explain the persistence of soya-induced effect on 17β-estradiol levels. Phytoestrogens are weak estrogens but at high doses may have sufficient estrogenic activity to down-regulate the hypothalamus and pituitary and, thereby, reduce the ovarian synthesis of estrogens. However, in vitro studies have shown that some of biological effects of the genistein are independent of estrogen receptor status (55).

Cassidy et al. (56) reported that daily consumption of a soya diet (containing 45 mg of isoflavones) for 1 month suppressed mid-cycle surges of LH and follicle-stimulating hormone in six premenopausal women. We did not measure follicle-stimulating hormone and LH in this study, but we observed increases in menstrual cycle length and delays in progesterone production during soy milk ingestion, suggesting that phytoestrogens may delay ovulation. However, Cassidy et al. (56) reported that soya feeding increased follicular phase 17β-estradiol levels and had no effects on mid-cycle and luteal 17β-estradiol levels, a result different from our observation. Larger amounts of isoflavones (>200 mg) were provided in a soya diet in our study than in the study by Cassidy et al. (56).

Baird et al. (57) studied the effects of 1 month of feeding of soya containing 165 mg of isoflavones daily in free-living postmenopausal women and observed no effect on 17β-estradiol levels. The reason for these differences in results are not known but may relate to differences in doses of isoflavones administered, types of soya products used, and other aspects of study design. The dose responses of genistein in many biological systems are often biphasic. For example, the effects of genistein on progesterone synthesis (22), cell proliferation (24), and pituitary responsiveness to the stimulation of gonadotropin-releasing hormone (58) differ depending on the doses of genistein used.

In summary, we show that consumption of soy milk containing >200 mg of phytoestrogens daily for 1 month can reduce circulating levels of 17β-estradiol, progesterone, and DHEA sulfate and increase cycle length in premenopausal women. These endocrine factors are known to influence breast cell proliferation and breast cancer risk (2–5, 43, 44). Therefore, these effects of soya on ovarian steroid levels may provide a biological basis for epidemiological observations that legume consumption is associated with reduced estrogen levels in blood and urine (6–8) and reduced risk for breast cancer (16, 17). We also showed that the effects of soya feeding on 17β-estradiol levels persisted after termination of soya diets, suggesting that soya consumption may be oncoprotective without daily consumption. However, the persistence of this effect in relationship to endocrine function also requires more studies.

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Effects of soya consumption for one month on steroid hormones in premenopausal women: implications for breast cancer risk reduction.

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