

# Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease

## Hormonal Effects of Soy in Premenopausal Women and Men<sup>1</sup>

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**ABSTRACT** Over the past few years, there has been increasing interest in the possible hormonal effects of soy and soy isoflavone consumption in both women and men. Soy consumption has been suggested to exert potentially cancer-preventive effects in premenopausal women, such as increased menstrual cycle length and sex hormone-binding globulin levels and decreased estrogen levels. There has been some concern that consumption of phytoestrogens might exert adverse effects on men's fertility, such as lowered testosterone levels and semen quality. The studies in women have provided modest support for beneficial effects. One cross-sectional study showed serum estrogens to be inversely associated with soy intake. Seven soy intervention studies controlled for phase of menstrual cycle. These studies provided 32–200 mg/d of isoflavones and generally showed decreased midcycle plasma gonadotropins and trends toward increased menstrual cycle length and decreased blood concentrations of estradiol, progesterone and sex hormone-binding globulin. A few studies also showed decreased urinary estrogens and increased ratios of urinary 2-(OH) to 16 $\alpha$ -(OH) and 2-(OH) to 4-(OH) estrogens. Soy and isoflavone consumption does not seem to affect the endometrium in premenopausal women, although there have been weak estrogenic effects reported in the breast. Thus, studies in women have mostly been consistent with beneficial effects, although the magnitude of the effects is quite small and of uncertain significance. Only three intervention studies reported hormonal effects of soy isoflavones in men. These recent studies in men consuming soyfoods or supplements containing 40–70 mg/d of soy isoflavones showed few effects on plasma hormones or semen quality. These data do not support concerns about effects on reproductive hormones and semen quality. *J. Nutr.* 132: 570S–573S, 2002.

**KEY WORDS:** • phytoestrogen • isoflavone • menstrual cycle • estrogen • testosterone

There has recently been a great deal of interest in the hormonal effects of soy in both men and women. Studies in humans have focused on potential beneficial as well as adverse effects. Most studies have been performed in women, and only a few studies performed in men have been reported. The purpose of this article is to review and summarize the findings from intervention studies that have evaluated the hormonal effects of soy and isoflavone consumption in premenopausal women and men. The premenopausal studies will be restricted to those that controlled for phase of menstrual cycle.

### *Hormonal effects of soy in premenopausal women*

The interest in hormonal effects of soy in premenopausal women has centered mainly on the potential benefits of an-

tiestrogenic effects on estrogen-dependent cancers such as breast cancer. The hormonal endpoints studied include blood concentrations of reproductive hormones and menstrual cycle and phase lengths. A pattern consistent with lowered risk of breast cancer would include a longer menstrual cycle (1), reduced estrogens and increased sex hormone-binding globulin (SHBG)<sup>3</sup> (2), and increased urinary excretion ratio of 2- to 16 $\alpha$ -hydroxy estrogens (3). At the same time, there has been some concern that estrogenic effects in the endometrium and breast might stimulate cancer growth.

Seven studies have been reported that have controlled for menstrual cycle phase in premenopausal women (Table 1). Only three of the seven intervention studies (4–6) fulfilled the ideal design criteria of a randomized crossover or parallel arm study of at least two menstrual cycles in length, with a true control period or group. Additionally, three studies were inpatient studies performed in metabolic wards with excellent dietary control, but the menstrual cycle results may have been confounded by cycle synchronization (7–9).

In none of the intervention studies were there statistically significant alterations of menstrual cycle length, although cycle length increased nonsignificantly in six of seven of the studies by an average of 1.1 d (4–8,10) (Table 1). This

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<sup>3</sup> Abbreviations used: 4-(OH)E<sub>2</sub>, 4-hydroxyestradiol; 4-(OH)E<sub>1</sub>, 4-hydroxyestrone; 16 $\alpha$ -(OH)E<sub>1</sub>, 16 $\alpha$ -hydroxyestrone; SHBG, sex hormone-binding globulin.

TABLE 1

*Intervention studies of the hormonal effects of soy in premenopausal women<sup>1</sup>*

Reference	Study design	n	Diet	Isoflavone intake (mg/d)	Treatment length (# cycles)	Change in cycle length (d)
Cassidy et al. (7)	Crossover	6	TVP <sup>2</sup>	45	1	+1.5
Lu et al. (8)	T vs. pre/post <sup>3</sup>	6	Soymilk	200	1	+3.5
Nagata et al. (4)	Parallel arm	60	Soymilk	68	2	+0.8
Duncan (5)	Randomized, crossover	14	ISP <sup>4</sup>	10, 64, 128	3	+0.6
Martini et al. (6)	Randomized, crossover	16	ISP	38	2	+0.1
Wu et al. (10)	T vs. pre/post	20	Soyfoods	32	3	+0.1
Lu et al. (9)	T vs. pre/post	10	Soymilk	154	1	-0.6

<sup>1</sup> Selected studies were limited to those that controlled for phase of menstrual cycle.

<sup>2</sup> TVP = textured vegetable protein.

<sup>3</sup> T vs. pre/post = treatment data were compared with data collected before or after the intervention.

<sup>4</sup> ISP = isolated soy protein.

tendency toward increased cycle length is consistent with a recent cross-sectional study of 200 Singapore Chinese women that reported an association ( $P = 0.03$ ) between soy intake and menstrual cycle length (11). In this study, there was an increased cycle length of 1.2 d between the lower and upper quartiles of soy protein intake, which the authors speculate would, over a lifetime, result in 2 fewer years of menstruation (a well-known breast cancer risk factor).

Effects on plasma estrogen concentrations have been inconsistent among the reported studies, although there may be a tendency toward decreased concentrations with soy consumption. A cross-sectional study of 50 premenopausal Japanese women showed an inverse association between soy intake and blood estradiol concentrations (12). Of the seven intervention studies reporting follicular phase blood estradiol concentrations, one study showed significant decreases (9), four studies showed nonsignificant decreases (4,6,8,10), and two studies showed nonsignificant increases (5,7). Of the five studies reporting luteal phase estradiol concentrations, three reported significant decreases (8–10), one reported a nonsignificant decrease (5), and one reported a nonsignificant increase (6). Interestingly, in the study by Wu et al. (10), the significant decrease in luteal phase estradiol was seen only in Asian and not in non-Asian subjects.

The relationship between the main urinary estrogens (estradiol, estrone and estrinol) and breast cancer risk has not been studied as extensively as the relationship between plasma estrogens and breast cancer risk. Although observational data show only modest associations between these urinary estrogens and breast cancer risk factors (13), premenopausal Chinese women living in Asia show a risk of breast cancer approximately one-ninth and levels of urinary estradiol and estrone ~35% lower than presumably assimilated Chinese women living in Boston (14). The possibility that soy consumption

may be responsible for this lowering of urinary estrogens is suggested by data of Xu et al. (15), who reported a significant lowering of urinary estrogens (including estradiol, estrone and estrinol) by soy isoflavone consumption, despite the fact that they did not show statistically significant effects on blood estrogen concentrations.

In addition to the main circulating estrogens, specific estrogen metabolites are considered to be genotoxic and potentially carcinogenic. 16 $\alpha$ -Hydroxyestrone [16 $\alpha$ -(OH)E<sub>1</sub>] exhibits genotoxicity by inducing unscheduled DNA synthesis (16), and 4-hydroxyestradiol [4-(OH)E<sub>2</sub>] and 4-hydroxyestrone [4-(OH)E<sub>1</sub>] form electrophilic quinone products that react with DNA to form depurinating adducts known to generate mutations that initiate cancer (17). The ratios of these metabolites to the relatively inactive 2-(OH) estrogens are believed to reflect the degree of metabolism down the competing pathways. Thus, higher ratios of 2- to 16 $\alpha$ -(OH) or 2- to 4-(OH) estrogens would reflect less formation of genotoxic metabolites.

Premenopausal studies of soy effects on estrogen metabolism are summarized in Table 2. Xu et al. (15) reported that isolated soy protein containing 65 or 129 mg/d of isoflavones increased the ratio of 2- to 16 $\alpha$ -(OH)E<sub>1</sub> by 67% and the ratio of 2- to 4-(OH)E<sub>1</sub> by 33% compared with isolated soy protein containing 10 mg/d of isoflavones. This is consistent with data published by Lu et al. (18), who showed that consumption of soymilk containing 158 mg isoflavones increased the ratio of 2- to 16 $\alpha$ -(OH)E<sub>1</sub> by 27% compared with soymilk containing < 4.5 mg/d. In contrast, Martini et al. (6) showed no statistically significant effects of consumption of isolated soy protein containing 38 mg/d of isoflavones, although there was a nonsignificant 7% increase in the ratio of 2- to 16 $\alpha$ -(OH)E<sub>1</sub> in the 16 women who did not use oral contraceptives.

Several studies evaluated the effects of soy consumption on blood concentrations of SHBG, progesterone and gonadotro-

TABLE 2

*Studies of soy effects on estrogen metabolism in premenopausal women*

Reference	Study design	n	Diet	Isoflavone intake (mg/d)	Treatment length (# cycles)
Xu et al. (15)	Randomized, crossover	14	ISP <sup>1</sup>	10, 64, 128	3
Martini et al. (6)	Randomized, crossover	36	ISP	38	2
Lu et al. (18)	Crossover	8	Soymilk	< 4.5, 158	1

<sup>1</sup> ISP = isolated soy protein.

pins. No studies reported statistically significant effects on SHBG concentrations, although all of the studies that evaluated SHBG levels showed nonsignificant decreases averaging 2% (4,7,10). Of the six studies that reported luteal phase progesterone values, two showed statistically significant decreases of 35–45% (8,9), whereas the others showed nonsignificant decreases in the order of 10–20% (5–7,10). Both studies that reported levels of midcycle gonadotropins showed significant reductions of 20–70% in concentrations of luteinizing hormone and follicle-stimulating hormone (5,7).

Thus, consumption of soy containing 32–200 mg/d of isoflavones seems to increase menstrual cycle length and the ratios of 2- to 16 $\alpha$ -(OH) and 2- to 4-(OH) estrogens and to decrease plasma concentrations of estradiol, progesterone, midcycle gonadotropins and SHBG as well as urinary estrogens. Some but not all of these effects go in the direction of cancer prevention. Studies suggest that both the isoflavones (5,19) and soy protein (20) may be responsible for these effects. At the same time, isoflavones do not seem to affect the endometrium (5), although there is some evidence for mild stimulation of breast cells by soy (21,22).

Of recent interest is the association between phytoestrogen metabolism and plasma hormone concentrations. Equol is a phytoestrogen metabolite excreted by only 30–40% of the population (23). Premenopausal women who excrete equol have been reported to have lower estrogen and androgen concentrations and higher SHBG and progesterone concentrations, a pattern consistent with lower risk of breast cancer (23). Consistent with one previous report (7), women who excrete equol also tended to have longer menstrual cycles (23).

### Hormonal effects of soy in men

The few studies of hormonal effects of soy consumption in men have addressed potential adverse as well as beneficial effects (Table 3). There has been some concern that the recently observed decline in sperm quality may be related to exposure to environmental estrogens (24), and at the same time there has been speculation that these estrogenic compounds may exert inhibitory effects against prostate cancer.

Theoretically, exposure to high levels of dietary estrogens could alter the hypothalamic-pituitary-gonadal axis in men in a similar manner to that of diethylstilbestrol (25). Neonatal injections of very high doses of genistein in rodents altered the pituitary response to gonadotropin-releasing hormone (26) and induced structural changes similar to those induced by diethylstilbestrol (27). In adult mice, subcutaneous exposure to very high levels of genistein resulted in decreased serum and testicular testosterone and pituitary luteinizing hormone concentrations, and decreased prostate weight (27). In contrast, dietary studies performed in rats for the most part have not shown these same hormonal effects. Rats consuming genistein

neonatally did not show altered testosterone levels, sperm count or gonad histopathology (28), and prenatal plus neonatal exposure did not show consistent effects on testosterone, luteinizing hormone or sperm count (29).

Only one study directly evaluated semen and testicular endpoints in men consuming soy phytoestrogens. Mitchell et al. (30) reported a study of 14 young men (18–35 y old) who consumed 40 mg/d of soy isoflavones (in a tablet form) for 2 mo. The subjects were followed for 2 mo before and 3 mo after taking the supplement. The isoflavone supplement had no effects on testicular or ejaculate volume or sperm concentration, count or motility. These results suggest that soy isoflavones do not affect sperm quality when consumed at a dose of 40 mg/d by young adult men. The authors point out that these results do not exclude the possibility of adverse effects from exposure during development or consumption of a higher dose or for a longer period of time.

A number of in vitro (31,32), animal (33) and epidemiological (34) studies have suggested that soy consumption may reduce prostate cancer risk. Because prostate cancer is believed to depend on reproductive hormones (35,36), it has been suggested that soy consumption may reduce prostate cancer risk in part by altering endogenous hormones concentrations. Only four studies have reported the effects of soy consumption on reproductive hormones in men.

Nagata et al. (37) performed a cross-sectional analysis of the relationship between soy product intake and reproductive hormones in 69 Japanese men with a mean age of 60.5 y. Average isoflavone intake was estimated by dietary questionnaire to be 22 mg/d, although the authors point out that diet records estimated soy intake to be 40% higher. After age, body mass index, smoking status and ethanol intake were controlled for, inverse correlations were seen between soyfood consumption and serum concentrations of estradiol ( $r = -0.32$ ,  $P = 0.009$ ). Borderline significant associations were seen between soyfood consumption and serum concentrations of estrone ( $r = -0.24$ ,  $P = 0.05$ ), total testosterone ( $r = -0.25$ ,  $P = 0.05$ ), and free testosterone ( $r = -0.25$ ,  $P = 0.06$ ).

Three dietary intervention studies have reported the effects of soy or soy phytoestrogen consumption on reproductive hormones in men. Habito et al. (38) performed a randomized crossover study of 42 men with a mean age of 45.7 y who consumed 150 g lean meat or 290 g tofu (containing ~70 mg isoflavones) daily for 4 wk. Blood concentrations of estradiol, testosterone, dihydrotestosterone and androstenediol glucuronide did not differ between the two diets. The mean testosterone-estradiol ratio was 10% lower ( $P = 0.05$ ), SHBG was 9% higher ( $P = 0.01$ ), and the free androgen index (total testosterone/SHBG  $\times$  100) was 7% lower ( $P = 0.06$ ) after tofu consumption. This slight reduction in androgen activity was not confirmed by Nagata et al. (39), who reported a parallel-arm study of 34 men with a mean age of 32.4 y, one-half of

TABLE 3

#### Intervention studies of the hormonal effects of soy in men

Reference	Study design	n	Diet	Isoflavone intake (mg/d)	Treatment length (mo)
Habito et al. (38)	Randomized, crossover	42	Tofu	70	1
Nagata et al. (39)	Parallel arm	34	Soy milk	48	2
Mitchell et al. (30)	T vs. pre/post <sup>1</sup>	14	Soy extract	40	2

<sup>1</sup> T vs. pre/post = treatment data were compared with data collected before or after the intervention.

whom consumed an average of 343 mL soymilk (containing ~48 mg isoflavones) daily for 2 mo. Blood concentrations of estradiol, total and free testosterone, and SHBG did not differ between the two groups, although estrone concentrations tended to decrease in the group consuming soymilk. These results are generally consistent with those of Mitchell et al. (30), who found no changes in serum concentrations of estradiol, testosterone, follicle-stimulating hormone or luteinizing hormone in men consuming a tablet containing 40 mg/d of soy isoflavones.

These four studies performed in adult men suggest that there are no adverse effects of soy isoflavone consumption on sperm quality, although there may be small effects of soy consumption on SHBG and steroid hormones. Note that none of these studies evaluated the prostate itself, and it is possible that soy consumption alters local hormone metabolism and action within the gland.

## CONCLUSION

The reported studies suggest that soy consumption exerts small effects on hormones in both men and premenopausal women. Although these effects are generally in a beneficial direction, their clinical significance is yet to be established. The largest observed effects have been reductions in urinary estrogens and estrogen metabolites in women. Future studies should focus on elucidating the responsible components and the optimal forms and doses as well as the dietary, environmental and genetic factors that influence particular subgroups to respond to soy. These factors may include ethnicity as well as individual phytoestrogen metabolism. Finally, it is of great importance to establish the clinical relevance of these small differences.

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