Soy foods, isoflavones, and the health of postmenopausal women[1–3]

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ABSTRACT

Over the past 2 decades, soy foods have been the subject of a vast amount of research, primarily because they are uniquely rich sources of isoflavones. Isoflavones are classified as both phytoestrogens and selective estrogen receptor modulators. The phytoestrogenic effects of isoflavones have led some to view soy foods and isoflavone supplements as alternatives to conventional hormone therapy. However, clinical research shows that isoflavones and estrogen exert differing effects on a variety of health outcomes. Nevertheless, there is substantial evidence that soy foods have the potential to address several conditions and diseases associated with the menopausal transition. For example, data suggest that soy foods can potentially reduce ischemic heart disease through multiple mechanisms. Soy protein directly lowers blood low-density lipoprotein-cholesterol concentrations, and the soybean is low in saturated fat and a source of both essential fatty acids, the omega-6 fatty acid linoleic acid and the omega-3 fatty acid alpha-linolenic acid. In addition, soflavones improve endothelial function and possibly slow the progression of subclinical atherosclerosis. Isoflavone supplements also consistently alleviate menopausal hot flashes provided they contain sufficient amounts of the predominant soybean isoflavone genistein. In contrast, the evidence that isoflavones reduce bone loss in postmenopausal women is unimpressive. Whether adult soy food intake reduces breast cancer risk is unclear. Considerable evidence suggests that for soy to reduce risk, consumption during childhood and/or adolescence is required. Although concerns have been raised that soy food consumption may be harmful to breast cancer patients, an analysis in 9514 breast cancer survivors who were followed for 7.4 y found that higher postdiagnosis soy intake was associated with a significant 25% reduction in tumor recurrence. In summary, the clinical and epidemiologic data indicate that adding soy foods to the diet can contribute to the health of postmenopausal women. *Am J Clin Nutr* 2014;100(suppl):423S–30S.

INTRODUCTION

Soy foods have been consumed by Asian populations for centuries. Only much more recently have foods made from soybeans made their way into Western cuisine. Initially, they appealed primarily to vegetarians because they are versatile sources of high-quality protein (1). Many soy foods are also sources of the essential omega-3 (n–3) fatty acid α-linolenic acid (2). However, over the past 2 decades, there has been rigorous investigation of the potential for soy foods to exert health benefits independent of their nutrient content. Most of this research can be attributed to the phytochemical content of soy, especially its uniquely rich isoflavone content (3).

Isoflavones bind to estrogen receptors (ERs)[4] and exert estrogenic-like effects under certain experimental conditions (4). However, isoflavones also appear to be tissue selective, likely because of their preferential binding to and activation of ERβ in comparison to ERα. Consequently, in addition to being classified as phytoestrogens, isoflavones are considered to be selective ER modulators, a classification to which tamoxifen and raloxifene belong (4).

Estrogenic and antiestrogenic effects of isoflavones were shown in rodents nearly 50 y ago (5, 6), but only within the past 25 y (7) has research focused on the possibility that isoflavone-rich soy foods can be especially helpful to women transitioning through menopause. This area of investigation gained increased attention when greater numbers of women, because of the disappointing results of the Women's Health Initiative trial, began seeking natural alternatives to conventional hormone therapy (8). This review first provides background information on isoflavones and then briefly summarizes the effects of isoflavones and soy foods on the health of menopausal women in 4 areas: *1*) cardiovascular disease, *2*) osteoporosis, *3*) menopausal symptom relief, and *4*) breast cancer.

ISOFLAVONE INTAKE

Among commonly consumed foods, only soybean-derived products provide physiologically relevant amounts of isoflavones. The soybean contains 12 different isoflavone isomers: the 3 aglycones genistein (4',5,7-trihydroxyisoflavone), daidzein (4',7-dihydroxyisoflavone), and glycitein (7,4'-dihydroxy-6-methoxyisoflavone); their respective β-glycosides genistin, daidzin, and glycitin; and 3 β-glucosides each esterified with either malonic or acetic acid (9). (Isoflavone amounts used in this text refer to the aglycone equivalent weights.) When all forms of the individual isoflavones are considered, genistein, daidzein, and glycitein account for ~50%, 40%, and 10%, respectively, of the total soybean isoflavone content (9).

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[4] Abbreviations used: AHA, American Heart Association; BMD, bone mineral density; CHD, coronary heart disease; CIMT, carotid intima media thickness; ER, estrogen receptor.

First published online June 4, 2014; doi: 10.3945/ajcn.113.071464.

There are ~3.5 mg isoflavones (expressed in aglycone equivalent weight) per gram of protein in traditional soy foods (10). One serving of a traditional soy food provides ~8 g protein and 25 mg isoflavones. In contrast, >70% of the isoflavone content of whole soybeans can be lost in the making of processed soy products, such as isolated soy protein (11). Isoflavone intake varies among Asian populations but ranges from ~10 to 15 mg/d in Hong Kong to 30–40 mg/d in Japan and Shanghai (10). National intake estimates for China tend to obscure the markedly different isoflavone intake that exists among provinces (12).

Among Asian countries with Chinese populations, the vast majority of soy is consumed in the form of unfermented foods such as soy milk, tofu, and tofu products (13, 14), whereas in Japan approximately half of the soy comes from fermented (natto and miso) and half from unfermented (tofu) foods (15, 16). The concentration of isoflavones in soy foods is not changed as a result of fermentation, although in fermented products more of the isoflavones occur in aglycone form due to bacterial hydrolysis of the sugar from the glycoside, the form of isoflavones occurring in soybeans and unfermented foods (11, 17). There are conflicting data as to whether isoflavone form (glycoside compared with aglycone) affects total isoflavone absorption, but if it does, it is likely to be relatively modest (18–23).

The half-life of isoflavones is between 4 and 8 h; consequently, 24 h after isoflavone exposure, nearly all of the absorbed isoflavones are excreted (24). Serum isoflavone concentrations increase in a dose-dependent fashion in response to isoflavone ingestion, but at higher intakes there is a curvilinear relation (25, 26). Therefore, the highest sustained serum isoflavone concentrations are likely achieved by dividing daily isoflavone intake into several doses, which reflects the pattern of isoflavone intake from soy foods in Asia. There is a large interindividual variation in isoflavone metabolism such that in response to the ingestion of similar amounts of isoflavones, circulating concentrations of isoflavone metabolites and parent isoflavones can vary hundredsfold (27, 28). It is noteworthy that only ~25% of non-Asians and ~50% of Asians host the intestinal bacteria that convert the isoflavone daidzein into the isoflavonoid equol (29). Equol has been proposed as an especially beneficial isoflavonoid (30).

Finally, it is important to recognize that 2 primary types of isoflavone supplements available on the market, and that have been used in clinical trials, differ markedly in genistein content. One is made from whole soybeans so it is high in genistein and low in glycitein, whereas the other, which is made from the germ or hypocotyledon portion of the bean, is low in genistein and high in glycitein (31).

CARDIOVASCULAR DISEASE

In 1999, the US Food and Drug Administration approved a health claim for soy foods and coronary heart disease (CHD) on the basis of the cholesterol-lowering effects of soy protein (25 g/d was established as the threshold intake for cholesterol reduction) (32). Nevertheless, the hypocholesterolemic effects of soy protein are not without controversy. In 2006, the American Heart Association (AHA) concluded that the health claim was not justified because, in their estimation, soy protein lowered LDL cholesterol only by 3% (33). (The AHA did conclude, however, that soy foods can help reduce CHD risk via their fiber and high PUFA content.) However, when Jenkins et al (34) conducted a statistical meta-analysis of the same studies identified by the AHA, they found that soy protein lowered LDL cholesterol by 4.3%, an estimate in line with the 4–6% reduction reported by 4 other meta-analyses published since 2005 (35–38). The decrease in LDL cholesterol in response to soy protein is similar to the effect of soluble fiber, which also has a Food and Drug Administration health claim (39).

Isoflavones may not contribute to the cholesterol-lowering effect of soy protein, but research suggests that they may exert coronary benefits by improving endothelial function, as assessed by changes in brachial arm flow-mediated dilation, notwithstanding that studies evaluating this variable have produced inconsistent results. A 2010 meta-analysis by Li et al (40) that included 9 clinical trials involving postmenopausal women found that isoflavones markedly improved flow-mediated dilation but only in women with impaired endothelial function, which may explain previously inconsistent findings. In this meta-analysis, most trials used between 50 and 100 mg isoflavones/d (the amounts provided by ~2–4 servings of traditional soy foods). Very limited observational data indicate that isoflavones may also improve endothelial function by increasing the number of circulating endothelial progenitor cells, which replace damaged endothelial cells (41).

The results of 4 meta-analyses concluded that a variety of soy products, including both isolated isoflavones and soy protein, lower systolic blood pressure and diastolic blood pressure by ~2.5 and 1.5 mm Hg, respectively (42–45), which, although modest, can still meaningfully affect morbidity and mortality. However, in most of the studies included in the meta-analyses, blood pressure was a secondary outcome; therefore, although suggestive, the results do not allow definitive conclusions to be made.

Finally, the results of a 3-y clinical trial arguably provide the most intriguing data to date in support of the coronary benefits of isoflavones (46). In research conducted by Hodis et al (46), isoflavone-rich soy protein was found to reduce the progression of subclinical atherosclerosis as measured by carotid intima media thickness (CIMT). Women were randomly assigned to receive either 25 g milk protein/d or 25 g soy protein/d that provided 99 mg isoflavones. CIMT increased in both groups over the study period but by 16% less in the soy group. Although this difference was not significant ($P = 0.35$), because the difference between groups increased steadily with time, it is reasonable to speculate that a longer exposure period would have led to a larger and significant difference. Furthermore, subanalysis found that among young postmenopausal women (<5 y postmenopausal) CIMT progression was reduced by 68% ($P = 0.05$). Not only was this difference significant, but this finding is consistent with the estrogen-timing hypothesis, which maintains that exposure to estrogenic molecules soon, but not late, after menopause produces pronounced coronary and cognitive benefits (47).

Finally, no intervention studies have evaluated the effect of soy products on myocardial infarction or stroke, although, as discussed above, intermediary markers of these diseases are favorably affected. Therefore, there is justification for conducting long-term trials that include myocardial infarction and stroke as health outcomes.

OSTEOPOROSIS

The well-established skeletal benefits of estrogen therapy (48) combined with the estrogen-like effects of isoflavones (4)

provided a sound basis for initial speculation that soy foods promote bone health. However, isoflavones and estrogen often exert very different effects, and their impact on bone mineral density (BMD) appears to be one case in which this is true, notwithstanding prospective epidemiologic data showing that soy food consumption is protective against fracture.

With regard to the latter point, a study from Shanghai in 24,403 postmenopausal women found that higher soy protein intake (>10 g/d) was associated with an approximate one-third reduction in fracture risk (49). After adjustment for age, major osteoporosis risk factors, socioeconomic status, and other dietary factors, the RRs (95% CI) for fracture were 1.00, 0.72 (0.62, 0.83), 0.69 (0.59, 0.80), 0.64 (0.55, 0.76), and 0.63 (0.53, 0.76) across quintiles of soy protein intake (P-trend < 0.001). During the 4.5-y follow-up period, there were 1170 fractures of all types, although hip (3.3%) and spinal (14.9%) factures accounted for <20% of the total. In agreement are the results of a Singaporean study that included 63,257 Chinese participants between the ages of 45 and 72 y that found that soy intake was unrelated to hip fracture risk in men, whereas in postmenopausal women (n = 35,241) soy protein intake was associated with an approximate 25% reduction in risk (50). Compared with women in the lowest quartile of intakes for tofu equivalents (<49.4 g/d), soy protein (<2.7 g/d), and isoflavones ($<5.8 \text{ mg} \cdot 1000 \text{ kcal}^{-1} \cdot \text{d}^{-1}$), those in the second–fourth quartiles exhibited a 21–36% reduction in risk (all $P < 0.036$). Among the women in this cohort, there were a total of 692 hip fractures during the 7.1-y follow-up period.

One caveat about both of these observational studies is that most of the observed decrease in risk occurred when comparing women in the second soy protein intake quintile or quartile with those in the first. The low intake in this second-intake group raises questions about the biological plausibility of the findings.

In any event, a third prospective study that included 337 postmenopausal white Seventh-day Adventist women also provides support for a bone-protective effect of soy foods. After a 2-y follow-up period, in comparison to not drinking soy milk, consuming soy milk at least once per day was associated with a 56% (OR: 0.44; 95% CI: 0.20, 0.98; P-trend = 0.04) decreased risk of osteoporosis based on calcaneal broadband ultrasound attenuation. In this study, soy milk consumption was almost as protective as estrogen use. However, because dairy intake was protective to a similar degree, the results suggest that the benefits of soy milk may have been attributable to its high calcium content, rather than its isoflavone content.

Despite containing oxalate and phytate, 2 compounds that inhibit calcium absorption, the absorption of this mineral from fortified soy milk is quite good (51). The high bioavailability of calcium from soy milk is supported by the results of a 1-y intervention study in nearly 200 adolescent Chinese girls from Hong Kong aged 14–16 y, which found that supplementation with calcium-fortified soy milk (375 mL/d, 600 mg calcium) improved hip BMD relative to the control group who consumed their usual diet without supplementation (52). In contrast, no benefits were observed in an 18-mo intervention study in postmenopausal Chinese women, but in this case, the soy milk provided only 250 mg calcium/d (53). Also, no information about the bioavailability of the fortificant was provided.

The first clinical trial evaluating the effects of isoflavones on BMD in postmenopausal women was published in 1998 (54). Since then, the more than 25 clinical trials that have been conducted have produced mixed results as evidenced by the conclusions of 3 recently published meta-analyses (55–57). However, most trials were small in size and short in duration. Ideally, conclusions about skeletal benefits should be based on large, long-term studies. Three such studies in postmenopausal women, 2 in the United States (58, 59) and one in Taiwan (60), involving isoflavone supplements have been conducted. They were 2 or 3 y in duration and included between 200 and 400 women. Isoflavone intakes ranged from 80 to 300 mg/d. None of the trials found isoflavones to favorably affect hip or lumbar spine BMD. In addition to these 3 studies, a 2-y study by Vupadhyayula et al (61) in 203 postmenopausal women also failed to find that isoflavone-rich soy protein favorably affected lumbar spine, femoral neck, or total femur. A 2-y study in postmenopausal women (n = 403) also found that isoflavone supplementation was without effect, but because the intervention product was a supplement derived from soy germ, which, as noted has a different isoflavone profile than soy foods, the findings may not be relevant to soy foods (62).

There are several possible explanations for the differing results from the 2 Asian epidemiologic studies noted above and the clinical trials. It may be that the benefits of soy in the epidemiologic studies reflect lifelong intake, which contrasts with the 2- to 3-y intervention period in the clinical trials. It is also possible that components in soybeans other than isoflavones promote bone health, although there is no evidence in support of this possibility.

MENOPAUSAL SYMPTOM RELIEF

On the basis of their estrogenic effects and the low prevalence of hot flashes among native Japanese women (63), Adlercreutz et al (64) proposed in 1992 that isoflavones alleviate hot flashes. Since the first clinical trial was conducted in 1995 (65), at least 60 trials have examined the effects of isoflavone-rich products (eg, soy foods, soy protein, and supplements derived from soybeans and red clover). These trials have produced mixed results as reflected by the conclusions of several recently published analyses (66–69), although a large meta-analysis by Bolaños et al (70) did find that a variety of isoflavone products were efficacious. It is notable that the findings from this analysis have been misinterpreted, because the results, which were expressed as the standardized mean difference (−0.39 to −0.51 for different categories of soy products), were mistaken for the actual reduction in hot flashes, that is, a decrease of ∼0.5 hot flashes/d (71).

One limitation with the previously cited analyses is that none of them subanalyzed the data according to the isoflavone profile of the intervention product. Doing so is important because the isoflavone profile of red clover–derived supplements differs from that of soybean-derived supplements, and soybean-derived supplements can differ markedly in composition. The first to take these differences into consideration was a systematic review and meta-analysis by Taku et al (72), which was published in 2012. This analysis, which involved 13 trials (n = 1196 women) that evaluated frequency and 9 trials that evaluated severity (n = 988 women), included only those studies that intervened with supplements of isoflavones derived from soybeans. In the overall analysis, the net (minus the placebo effect) decrease in frequency and severity in response to isoflavones was 20.62% (P = 0.00001) and 26.19% (P = 0.001), respectively. The combined reduction in frequency and severity was 50.2% and 47.6%,

respectively. Baseline hot flash frequency did not influence efficacy (when expressed as percentage reduction), although trials lasting >12 wk led to larger decreases than did trials that were shorter in duration. Most trials intervened with at least 50 mg total isoflavones/d.

There was no evidence of a dose-response relation between total isoflavone content and hot flash alleviation. However, the genistein content of the supplement greatly influenced efficacy. In 2006, Williamson-Hughes et al (73) showed that isoflavone supplements that provide a threshold genistein intake were more efficacious than those supplements low in genistein. In examining this hypothesis, Taku et al (72) found that among studies providing genistein intakes above the median for all studies (18.8 mg/d), the net reduction in hot flash frequency was 29.13% compared with a reduction of only 12.47% for supplements providing ≤18.8 mg/d (difference between groups, $P = 0.03$). Therefore, one can anticipate an approximate 60% reduction in hot flash frequency in response to isoflavone supplements providing at least ~19 mg genistein/d.

Because isoflavone pharmacokinetics in response to the ingestion of soy foods and isoflavone supplements are similar (74), one would expect the former to be as efficacious as supplements for alleviating hot flashes. However, studies evaluating the efficacy of soy foods have produced very mixed results, although relatively few such trials have been conducted (75).

BREAST CANCER PREVENTION

The impact of soy intake and breast cancer risk has been rigorously investigated for >2 decades, ever since the US National Cancer Institute first expressed interest in this area of research (76). At that time, the proposed protective effect of soy, largely because of its isoflavone content, was the focus of attention. However, in the late 1990s, rodent research raised concerns that isoflavone exposure might be harmful to breast cancer patients (77). Much has been learned in recent years about both the proposed protective and alleged harmful effects of soy food consumption.

Epidemiologic data generally show that high soy food intake among Asian women is associated with protection against breast cancer (78–80). However, soy foods have little effect on intermediary markers of breast cancer risk (*see* the following section) (81). In 1995, a hypothesis emerged, based on rodent research, that exposure to isoflavones early in life reduces breast cancer risk (82, 83). A similar benefit has been proposed for early pregnancy (84, 85). Animal studies published in more recent years support this hypothesis (86–89). In addition, all 4 Asian retrospective epidemiologic studies support this hypothesis, although in the largest study, protective effects were evident only in premenopausal women (90). Two of these studies were conducted in Shanghai (90, 91) and 2 in the United States (92, 93), although the US studies involved women of Asian ethnicity. Two Canadian epidemiologic studies (94, 95) also found that early isoflavone intake was protective against breast cancer, but because intake was so low in these studies the reduced risks are not likely to have a causal basis (96).

It is not possible to ascertain from the 4 studies referenced above the precise age at which soy intake may be most protective, but it is interesting to note that in the small study by Korde et al (93), consumption during ages 5–11 y was more protective than during the teenage years. Also, Boucher et al (97) reported that women with a history of breast cancer were less likely to have used soy infant formula during infancy; however, because this finding was based on an extremely small sample size, it should serve primarily as a basis for discussion about future research. Several biological explanations for the breast cancer–protective effects of soy foods have been proposed (85, 87, 88, 98). Although this hypothesis remains speculative, it seems reasonable to encourage young females to consume soy foods because the epidemiologic data suggest as little as one serving per day may be protective. In any event, these observational studies examining the effect of early soy intake suggest that postmenopausal soy intake may not reduce the risk of developing breast cancer.

SOY INTAKE AND THE BREAST CANCER SURVIVOR

In athymic ovariectomized mice implanted with estrogen-sensitive breast cancer cells (Michigan Cancer Foundation-7 cells), dietary isoflavone exposure stimulates the growth of existing mammary tumors (for review, *see* reference 99). This model is widely used by cancer researchers, but recently published data suggest that it may not be suitable for evaluating isoflavones because athymic mice metabolize these soybean constituents very differently than humans (74). Furthermore, not all studies using this model showed that isoflavones stimulate tumor growth (100). More importantly, the human evidence is supportive of the safety and potential benefit of soy food consumption by breast cancer patients.

Not unexpectedly, no intervention studies have examined the effect of postdiagnosis isoflavone intake on the outcome (ie, recurrence and/or death) of breast cancer patients. However, as noted previously, clinical studies showed that soy does not affect markers of breast cancer risk. For example, a meta-analysis by Hooper et al (101) found that soy intake did not affect mammographic density in postmenopausal women. In another meta-analysis by these authors that evaluated reproductive hormones (102) in postmenopausal women, isoflavone intake had no effects on estradiol, estrone, sex hormone–binding globulin, follicle-stimulating hormone, or luteinizing hormone, although there was a small, nonsignificant increase (~14%) in total estradiol. However, Huber et al (103) noted that the parallel decrease in estrone concentrations observed in this meta-analysis would have theoretically nullified any possible increase in breast cancer risk because of the increase in estradiol.

Five studies have evaluated the effects of soy-derived isoflavones on breast cell proliferation, an intermediary marker of breast cancer risk generally thought to be more reflective of risk than mammographic density and reproductive hormone concentrations. The intervention periods ranged from 14 d (104) to 1 y (105), and the daily isoflavone dose from 36 (106) to 239 (107) mg/d. All but one study used isoflavone supplements (104). Two studies involved postmenopausal women only (105, 106), one mostly postmenopausal women (108), one premenopausal only (104), and one was equally divided between pre- and postmenopausal women (107). None of the studies found an increase in cell proliferation in response to isoflavones relative to the placebo. In contrast to the lack of effect of isoflavones, combined hormone therapy increases breast cell proliferation in postmenopausal women by 4- to 10-fold (109, 110).

Of the 7 prospective epidemiologic studies that have evaluated the impact of postdiagnosis soy intake on the prognosis of breast cancer survivors (111–117), by far the 3 largest and longest are the Shanghai Breast Cancer Survival Study (SBCSS) (111), the Women's Healthy Eating and Living (WHEL) Study (112), and

the Life After Cancer Epidemiology (LACE) study (113). Recently, Nechuta et al (118) pooled results from these 3 studies, which included 9514 breast cancer patients (approximately half of whom were white) who were followed for a mean of 7.4 y. When comparing the highest isoflavone intake group with the lowest (≥10 compared with <4 mg/d), risks of total mortality, breast cancer–specific mortality, and breast cancer recurrence were reduced by 13% (HR: 0.87; 95% CI: 0.70, 1.10), 17% (HR: 0.83; 95% CI: 0.64, 1.07), and 25% (HR: 0.75; 95% CI: 0.61, 0.92), respectively.

In the pooled analysis, soy consumption tended to reduce recurrence to a greater extent in tamoxifen users than in nonusers (HR: 0.63 compared with 0.79), in ER-negative compared with ER-positive patients (HR: 0.64 compared with 0.81), and in postcompared with premenopausal women (HR: 0.64 compared with 0.93), although there were no significant interactions observed between these groups. That there was a suggestion that soy intake was more beneficial in women with a history of tamoxifen use is notable because the opposite would have been predicted on the basis of the results from the ovariectomized athymic mouse model discussed previously (119). That rodent model also found that isoflavones inhibit the efficacy of letrozole, an aromatase inhibitor (120). However, in a small prospective study, not only did Kang et al (115) find that soy intake did not interact with tamoxifen but they also found that it actually enhanced the efficacy of the aromatase inhibitor anastrozole. The results from the studies included in the pooled analysis almost certainly greatly contributed to the recent conclusions by the American Institute for Cancer Research and the American Cancer Society that soy foods are safe for breast cancer patients (121).

Finally, because the epidemiologic data are supportive of benefit but the clinical studies are supportive only of safety, it is possible that soy improves breast cancer prognosis via mechanisms not detected by the breast cancer risk markers discussed previously.

SUMMARY AND CONCLUSIONS

There is intriguing evidence indicating that soy foods can potentially reduce CHD risk through multiple mechanisms. Both the macronutrient (protein and PUFA) and isoflavone content of soy foods likely contribute to the coronary benefits. There are also impressive data indicating that genistein-rich isoflavone supplements alleviate hot flashes. In contrast, the evidence that soy foods, by virtue of their isoflavone content, improve bone health is unimpressive. With regard to breast cancer, although observational studies suggest that postmenopausal soy intake reduces risk, other data indicate that this benefit is a result of soy consumption early in life. Finally, clinical studies evaluating intermediary markers of breast cancer risk indicate that isoflavone exposure does not adversely affect breast tissue, and prospective epidemiologic studies show that soy food intake reduces tumor recurrence in breast cancer patients.

The author regularly consults for companies that manufacture and/or sell soy foods and/or isoflavone supplements.

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