

Report on the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment^{1,2}

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Abstract

The international soy symposium held in Tokyo, November 9–12, 2008, was the eighth in a series that began in 1994. This most recent meeting is noteworthy for several reasons. First, it was held in the country most identified with the foods that are the focus of the meeting. Soyfoods were first consumed in China more than a millennium ago, but it is the low incidence of breast and prostate cancer, heart disease, and hot flashes in Japan, despite the high socioeconomic status of this country, that helped fuel interest in the early 1990s in the possible chronic disease-preventive properties of soy and certain soybean constituents. Second, it was the first time an entire session was devoted to equol, a bacterially derived product of the soybean isoflavone daidzein, which is produced by only ~30% of Westerners and has been proposed to be an especially beneficial compound, i.e., the equol hypothesis. And third, there was greater emphasis during this meeting than at past ones on addressing some of the more hotly debated health effects linked with soy intake. The conference was attended by >250 scientists from 20 countries; there were 33 oral and 40 poster presentations during the 4-d event. The majority of presentations at the Tokyo symposium focused on isoflavones. In this article, the major findings presented at the symposium are highlighted, and commentary about those findings and related background is provided. J. Nutr. 139: 796S–802S, 2009.

INTRODUCTION

The international soy symposium held in Tokyo, November 9–12, 2008, was the eighth in a series that began in 1994. The first meeting took place in Tempe and was followed by gatherings in Brussels (1996), Washington, DC (1999), San Diego (2001), Orlando (2003), Chicago (2005), and Bangkok (2007). Above and beyond the findings presented, which are discussed in this article, this most recent meeting is noteworthy for several rea-

sons. First, it was held in the country most identified with the foods that are the focus of the meeting. Soyfoods were first consumed in China more than a millennium ago, but it is the low incidence of breast and prostate cancer, heart disease, and hot flashes in Japan, despite the high socioeconomic status of this country, that helped fuel interest in the early 1990s in the possible chronic disease-preventive properties of soy and certain soybean constituents. Second, it was the first time an entire session was devoted to equol, a bacterially derived product of the soybean isoflavone daidzein, which is produced by only ~30% of Westerners and has been proposed to be an especially beneficial compound, i.e., the equol hypothesis (1). And third, there was greater emphasis during this meeting than at past ones on addressing some of the more hotly debated health effects linked with soy intake. The conference was attended by >250 scientists from 20 countries; there were 33 oral and 40 poster presentations during the 4-d event.

Since 1994, nearly 10,000 soy-related articles have been published in the peer-reviewed literature. Most of these have focused on isoflavones, so it is not surprising that the majority of presentations at the Tokyo symposium also involved these diphenolic compounds. Isoflavones have a very limited distribution in nature and, among commonly consumed foods, are found in nutritionally relevant amounts essentially only in the soybean

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(2). Not unexpectedly, therefore, per capita isoflavone intake in the United States (3) and Europe (4) is very low, <3 mg/d, whereas in Japan among older adults, it ranges from ~30 to 50 mg/d (5). Each gram of soy protein in unprocessed or traditional soyfoods is associated with ~3.5 mg isoflavones (isoflavone amounts in this text are expressed as aglycone units) (5). In regard to each of the isomeric forms, ~50, 40, and 10% of total isoflavone content in the soybean is comprised of genistein, daidzein, and glycitein, respectively (6).

Isoflavones have attracted the attention they have primarily because of their ability to bind to estrogen receptors (ER) (7), although they also have nonhormonal properties that may contribute to their proposed physiological effects (8). More importantly, in addition to being phytoestrogens, isoflavones have been classified by various groups and researchers as both endocrine disruptors (9,10) and selective ER modulators (7,11,12). It is this dual classification that explains why isoflavones have been studied so extensively and often evoke such heated discussion. In the text below, the major findings presented at the Tokyo symposium are highlighted, and commentary about those findings and related background is provided.

Research highlights

Breast cancer. The possibility that isoflavones reduce breast cancer risk, which led the U.S. National Cancer Institute to fund isoflavone research nearly 20 y ago, first brought widespread attention to soy as a functional food (13). During the interim, no clear consensus has emerged about the chemopreventive effects of isoflavones (14), although one school of thought is that to derive protection against breast cancer, consuming soy during adolescence rather than adulthood is required (15,16). Somewhat ironically, during the past 10 y, concern has arisen, despite the historically low Japanese breast cancer incidence rates (17) and better survival (in comparison to the West) of Japanese breast cancer patients (18), that postmenopausal exposure to isoflavones might pose a risk to estrogen-sensitive breast cancer patients and women at high risk of developing breast cancer (19,20).

At the symposium, two oral presentations dealt most directly with this important issue. One was a Chinese prospective study conducted by researchers from Vanderbilt University and the Shanghai Center for Disease Control and Prevention and presented by Xiao Ou Shu from Vanderbilt. To investigate the effect of soy intake after diagnosis on breast cancer prognosis, data from a population-based cohort study of breast cancer survivors, the Shanghai Breast Cancer Survival Study, were analyzed. During the median follow-up period of 26.4 mo, 290 deaths and 410 relapses or breast cancer deaths were documented among the 5046 breast cancer patients who were identified between 2002 and 2007 through the Shanghai Cancer Registry.

Women were enrolled into the study ~6 mo after cancer diagnosis. Information on cancer diagnosis and treatment, lifestyle exposures after cancer diagnosis, and disease progression was collected via in-person interview at study recruitment and during follow-up surveys at 18, 36, and 60 mo. Results showed that soy intake was associated with a more favorable outcome, with a hazard ratio associated with the highest quartile intake being 0.67 ($P < 0.01$; 95% CI 0.50–0.88) for disease-specific mortality or relapse compared with the lowest quartile of intake. Further, the benefit of soyfood intake on survival was more pronounced among women with ER/progesterone receptor-positive breast cancer. Also, there was no interaction between soy intake and tamoxifen use, although women who had used tamoxifen and had the highest soy food intake had the lowest risk of cancer-related death or cancer recurrence (hazard ratio = 0.42,

95% CI 0.20–0.85). These findings offer some measure of comfort about the safety of soyfoods and are consistent with the position of the American Cancer Society about the use of soyfoods by breast cancer patients (21). This having been said, despite the large number of events, the results of this study should be viewed very cautiously because of the relatively short-term follow-up period. The patients in this study are continuing to be monitored, so additional data will likely be forthcoming.

The second study was conducted by researchers from several institutions including the Memorial Sloan-Kettering Cancer Center and the Emory Winship Cancer Institute, Emory University School of Medicine. In this pilot study, which was presented by Omer Kucuk, 64 women with newly diagnosed ductal carcinoma in situ or invasive ductal cancer were randomly assigned to receive either a placebo or 100 mg/d isoflavones for 3 wk before lumpectomy or mastectomy. The expression of bcl-2, Cyclin B1, Bax, Cx43, p21, and pFAK were analyzed by Western blot, and those of epidermal growth factor receptor-related protein, Cx43, p-AKT, p-FAK, p21, caspase-3, and Ki-67 were analyzed by immunohistochemistry. Compared with the placebo group, there were significant decreases in Cx43 and p21 expression in both benign and tumor tissues in the isoflavone group as well as significantly lower bcl-2, cyclin B1, and Bax concentrations in normal, but not tumor, tissues. On the other hand, although there was a trend toward an increase in epidermal growth factor receptor-related protein and Cx43 in malignant and benign parts of the tissue specimens, there were no changes caused by isoflavone exposure in p-AKT, p-FAK, p21, caspase-3, and Ki-67. The down-regulation of the expression of proteins such as Cx43 and p21 suggest restraints on cell proliferation were inhibited; conversely, however, the Ki-67 protein, which is present during all active phases of the cell cycle and is routinely used to measure cell proliferation, was unaffected. In any event, in part because of the difficulty of obtaining sufficient tissue, in most cases the number of samples for each of the markers was quite small—usually less than 10. Only appropriately sized studies and probably only those involving either high-risk women or breast cancer patients, in which breast biopsies are taken before and after isoflavone exposure, have the potential to definitely resolve the soy-breast cancer controversy.

Two other studies presented at the symposium are relevant to the impact of soy intake on breast cancer risk, although not necessarily to the survival of breast cancer patients. In one, presented by Gertraud Maskarinec from the Cancer Research Center of Hawaii, mammograms from 358 postmenopausal women were taken before and after exposure to a placebo or 80 or 120 mg/d isoflavones for 2 y. Subjects were participants of the multisite, randomized, double-blind, and placebo-controlled Osteoporosis Prevention Using Soy trial. An analysis with all mammograms did not show a significant treatment effect; however, time was significant ($P < 0.001$); breast density decreased by 1.6% per year across all groups. The second study was a systematic review and meta-analysis of the effects of soy protein and isoflavone supplements on reproductive hormones in pre- and postmenopausal women presented by Aedin Cassidy from the University of East Anglia. A total of 47 studies were included in the analysis; 11 involved premenopausal women ($n = 579$), 35 postmenopausal women ($n = 1165$), and 1 perimenopausal women ($n = 69$). In younger women, isoflavone exposure had no effect on total estradiol, estrone, or sex-hormone-binding-globulin levels but significantly although modestly reduced follicle-stimulating hormone and luteinizing hormone levels (using standardized mean differences, $P = 0.01$ and 0.05, respectively) and increased menstrual cycle length [1.05 d; 95% CI 0.13–1.97

(10 studies)]. In postmenopausal women, a trend toward an increase in total estradiol was observed following isoflavone intake [standardized mean differences, $P = 0.07$ (21 studies)], but there were no effects on any other hormones.

These latter 2 studies offer no evidence that soy intake during adulthood reduces breast cancer risk; if it does, the mechanisms by which protection occurs must be independent of breast tissue density and changes in serum hormones. As noted previously, emerging evidence suggests that for soy to provide protection against breast cancer, it must be consumed early in life.

Reproductive and hormonal effects in men

Although most isoflavone-related clinical research has focused on postmenopausal women, in recent years, questions have been raised about the possible feminizing effects of soy in men. In fact, a recently published epidemiologic study from the Harvard School of Public Health, which received worldwide media attention, raised the possibility that soy intake lowers sperm concentration (22). However, this was a pilot study that assessed few lifestyle factors other than soy intake that may have been responsible for the reported association, and much of the decreased sperm concentration was actually a result of an increase in ejaculate volume.

At the symposium, 2 studies directly assessed the impact of soy intake on both sperm and semen parameters. In one, a crossover study conducted by researchers from the University of Guelph and the Fred Hutchinson Cancer Research Center in Seattle presented by Alison Duncan, 32 healthy young men consumed diets in random order that were supplemented with milk protein isolate, low-isoflavone isolated soy protein (~1.6 mg/d isoflavones), or high-isoflavone isolated soy protein (~62 mg/d isoflavones) for 57 d each, separated by 28-d washout periods. Analysis of semen samples collected on d 1 and 57 of each treatment period revealed no significant effects of diet on semen parameters including semen volume, sperm concentration, sperm count, total motile sperm count, sperm motility, and sperm morphology. In the second study, presented by Audrey Serafini from the Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele, 20 volunteers were randomized into 3 different groups; groups A, B, and C received 160, 320, or 480 mg/d isoflavones, respectively, for 3 mo. When compared with baseline, there were no significant differences in ejaculate volume, sperm concentration, sperm count, and motility of spermatozoa in men given isoflavones.

A third study, which was presented by Jill Hamilton-Reeves from the College of St. Catherine in Minneapolis, represents the first systematic review of the effects of soy and isoflavones on blood levels of testosterone and other reproductive hormones in men. The 36 treatment groups considered eligible for analysis involved a total of 608 participants. Regardless of the statistical model and comparison employed (treatment change vs. control change, ending values of treatment vs. control ending values, and change over time in treatment arms), there were no significant effects of exposure on reproductive hormones, although most studies were relatively short term and small in size and included hormone measurements as secondary endpoints. On the other hand, soy exposure in many studies was much higher than typical Japanese intake.

Bone health

The estrogen-like effects of isoflavones have, not surprisingly, led to considerable interest in the effects of soy on bone mineral density (BMD) in menopausal women (23–25). The results of >25 trials, most of which used soy extracts, i.e., isoflavone

supplements, rather than soyfoods, have been published, and although several show pronounced skeletal benefits, overall the data are quite mixed. The findings of an Italian study presented at the symposium by Francesco Squadrito from the University of Messina, represent the first 3-y data. This trial was formally designed as a 2-y study (26), but about half of the participants agreed to continue for a third year. Among the 71 postmenopausal osteopenic women assigned to receive 54 mg/d genistein, spinal and hip BMD increased by ~8 and 9%, respectively, whereas among the 67 women in the placebo group, BMD decreased at those sites by ~12 and 8%, respectively. These results, because they are by far the most impressive to date, beg the question of which experimental design elements might account for the especially robust findings. In addition to the rapid rate of bone loss experienced by the Italian women in the placebo group, the intervention product was isolated genistein; essentially all other trials involving supplements have used mixed isoflavones, usually in glycoside form.

In support of these clinical results are those from the Singapore Chinese Health Study, a prospective cohort of 63,257 middle-aged and elderly subjects. According to Woon-Puay Koh, National University of Singapore, at recruitment between 1993 and 1998, each subject was administered a validated semiquantitative food frequency questionnaire covering 165 food and beverage items as well as questions on medical history and lifestyle factors. As of the end of 2006, 969 incident hip fracture cases were identified via linkage with hospital discharge databases and verified with medical records. The mean age at fracture was 71.4 y among the 276 male cases, and 72.8 y among the 693 female cases. No relation was noted between isoflavone intake and hip fracture risk among men, but among women, risk was reduced significantly in a dose-dependent manner (P -trend = 0.0004); the relative risk for the highest vs. lowest quartile was 0.72 (95% CI = 0.57–0.90).

In agreement with these results are those from the Shanghai Women's Health Study, another large previously published prospective study, which also found higher soy and isoflavone intake to be associated with an approximate one-third reduction in the risk of fracture (27). Interestingly, in both studies, much of the risk reduction was apparent in the second quartile. In the Singaporean and Chinese studies, the isoflavone intake cutoffs for the second quartiles were ≤ 14 mg/d and ≤ 32.39 mg/d, respectively. These values are far lower than the doses typically thought to be required for efficacy based on the results of intervention studies (25). Although 1 explanation may be that the epidemiologic studies reflect lifelong exposure, there is no evidence from intervention studies that premenopausal isoflavone exposure favorably affects BMD.

Finally, in the previously referred to Osteogenesis Prevention Using Soy trial, at the end of 2 years, as presented by Francene M. Steinberg of the University of California at Davis, there was a significant reduction ($P < 0.05$) in the amount of whole-body bone loss in women in the high-isoflavone (120 mg/d) group compared with the 80 mg/d group and placebo, although this was not the case for any individual bone sites. Note that this study used a soygerm supplement, which has an isoflavone profile that is very low in genistein/genistin (14%) and high in glycitin/glycitein (42%). Finally, equol-producer status did not affect the results, although it is likely the study was underpowered to be a true test of the equol hypothesis.

Menopausal symptoms

The first clinical study to examine the ability of an isoflavone-rich product to alleviate hot flashes in postmenopausal women was published in 1995 (28). Since that time, >50 such studies have

been published, but most reviews to date have either failed to conclude that isoflavones alleviate hot flashes (29,30) or have concluded that they do but only very modestly (31). However, nearly all reviews have failed to analyze the data according to the specific soybean extract used in the study. This failure appears to be an important oversight because the 2 primary types of supplements used clinically have markedly different isoflavone profiles (32). To this point, an analysis presented by Patricia Williamson-Hughes, from Archer Daniels Midland found that all 9 of the studies that intervened with a soybean-derived isoflavone supplement that provided at least 15 mg genistein were efficacious, whereas only 1 of the 9 studies in which the supplement provided less than this amount reported significant effects. This having been said, Martin Imhoff from the Humanis Clinicum Korneuburg in Vienna reported that the intake of a supplement of 60 mg/d isoflavones that provided <15 mg genistein modestly alleviated hot flashes in Austrian postmenopausal women. At wk 12, hot flash frequency decreased in the placebo and isoflavone group by ~32 and 43%, respectively ($P = 0.001$). When the analysis was limited to women with ≥ 7 hot flashes/d at baseline, the difference between the groups was more pronounced. The impact of baseline hot flash frequency on the efficacy of isoflavones has been reported by several investigators (31,33).

Cholesterol-lowering effects of soy protein

In 1995, a meta-analysis that included 38 trials found that soy protein lowered LDL cholesterol by 12.9% (34). Four years later, the U.S. FDA approved a health claim for soy protein and coronary heart disease based on the cholesterol-lowering effects of soy protein (35). However, in 2006, the American Heart Association revised their year-2000 position on soy protein (36) by stating that “the direct cardiovascular health benefit of soy protein or isoflavone supplements is minimal at best” (37), and in December 2007, the FDA announced they were reevaluating the evidence in support of the health claim along with 3 others.

Meta-analyses published since 1995 clearly indicate that the hypocholesterolemic effects of soy protein are smaller than initially reported; estimates range from ~3 (37,38) to 5% (39, 40). Those analyses that included only studies that used soy protein (and not isoflavone extracts) produced estimates at the higher end of the range. At the symposium, the most comprehensive systematic review and meta-analysis of the relevant literature, which covered the years 1978 through the present, was presented by Elaine Krul, from Solae. To evaluate the data, the scientific guidelines recommended by the FDA for the evaluation of health claims were used. Of the 152 studies considered, 47 were judged to be of high or moderate quality. Among the 71 soy protein arms included in the descriptive analysis, approximately two-thirds reported a significant reduction in either total cholesterol or LDL cholesterol. The meta-analysis indicated that the net reduction in LDL cholesterol was ~0.18 mmol/L (~5%), which is in line with the meta-analyses published since 2005. Although modest in comparison to statins (41) and even phytosterols (42), the cholesterol-lowering effects of soy protein are similar to those of soluble fiber (43,44) and would certainly appear to be relevant from a public health perspective (45).

Mineral status

The poorer bioavailability of iron and zinc from plant foods and the lower content of the latter in vegetarian diets have raised questions about the impact of substituting soyfoods for animal products on iron and zinc status (46,47). Because relatively little red meat is needed to easily satisfy iron and zinc biological requirements, this issue is probably most germane only to

nonmeat eaters (48). Parenthetically, relatively new research suggests that the iron in soybeans may be much better absorbed than previously thought because it is in the form of ferritin (49,50). To examine the impact of soy on mineral status, a 10-wk randomized clinical trial was conducted by researchers from Iowa State University and presented by Manju Reddy. The design of the study called for young premenopausal women to consume daily either 2 to 3 servings of soyfoods ($n = 31$) or non-soyfoods ($n = 32$) matched for type of food; i.e., soy burgers in place of hamburgers, soy milk in place of dairy milk. Subjects ate their meals 3 d/wk at the research unit and carried out frozen meals (soy or control) to consume at home the other days. Results showed that there were no significant effects of soy on urinary and serum zinc, serum hemoglobin and iron, and transferrin saturation. In the soy group, body iron appeared to be slightly lower, although the difference between groups was not significant.

The equol hypothesis examined

A recurring issue raised throughout the symposium was whether the conflicting results from the clinical studies involving soy and isoflavones might be related to “equol-producer status,” that is, the so-called “equol hypothesis,” which was first proposed by Setchell et al. (1) in 2002. Equol [4-hydroxy-3-(4'-hydroxyphenyl)-chroman] is a specific metabolite of daidzein (51) and was first found >30 y ago as an unknown diphenolic compound in human and rat urine. Initially thought to be a new hormone, and originally referred to as Compound 386/192 (52,53), its structure was later elucidated by GC-MS and NMR analyses (54). It was then shown to be exclusively a bacterially derived metabolite of the soy isoflavones daidzin or daidzein (55). The early observation that not all adults who consume soyfoods produce equol (51) and the later finding of differences in the frequency rates of equol producers among different populations have led to the search for factors involved in equol production (1).

Highlighted in this session on equol was the relatively high proportion of equol producers in the Chinese population. A presentation by Keyou Ge from the University of Peking and the Second Military Medical University reported on the frequency of equol producers in 580 adults from Beijing, Shanghai, and Guangzhou. These regions differ in average daily soyfood intake. Adults living in the more southern region of Guangzhou consume lower amounts of soyfoods than those in the more northerly regions, and this was evident from the finding of equol in the urine of only 14.1% of adults from the Guangzhou region compared with 26.4 and 30.8% equol producers for Beijing and Shanghai, respectively. However, when participants in this study were subjected to a 40-mg isoflavone challenge, the frequency of equol producers ranged from 54.4 to 60.4% for all regions. This finding illustrates the importance of the need to perform an isoflavone/soy challenge to tease out the equol producer (56,57) and reinforces the critical requirement of bacteria for equol production (58).

The high frequency of equol producers in China contrasts with data reported at this meeting by Nadine Brown from the Cincinnati Children's Hospital Medical Center. In a study of dietary and developmental factors related to equol production that included 159 American and Australian adults challenged with soy milk for 3 d, the frequency of equol producers in the 2 populations was similar but only about half the rate reported for China. Analysis of 3-d diet records did not confirm earlier reported associations of high carbohydrate/low saturated fat intakes favoring equol production (59) but rather indicated that high polyunsaturated fat intake was significantly correlated with

equol production, as was higher fiber and carotenoid intake. Repeated testing of adults over a 2-y period showed that equol-producer status was stable, although some antibiotic therapies abolish equol production. Brown also presented results from a longitudinal study of 90 infants (breast-fed, cows-milk formula-fed, and soy formula-fed) who were followed from age 6 to 36 mo, showing that the frequency of equol producers, determined after a 3-d soy challenge, increased from 10% at 6 mo of age to 62.5% by 36 mo. The propensity to make equol was greatest in infants who were predominantly breast-fed, rather than bottle-fed, in early infancy. Whether the decline in equol producers between 3 y of age and adulthood can be attributed to antibiotic use is a matter of conjecture, but these findings confirm that the overriding factor related to equol production is the requirement of specific equol-producing bacteria and that dietary factors may facilitate equol formation.

A critical question related to the equol hypothesis is whether a non-equol producer can become an equol producer. If not, a way to circumvent this limitation would be to develop equol as a pharmaceutical or nutraceutical agent. Along these lines, several presentations have focused on the pharmacology and safety of equol. Equol can be produced by patented processes using either a specific equol-producing bacterium (*Lactococcus sp.*) or by chiral chemistry to synthesize the 2 enantiomeric forms, *S*-(−)equol and *R*-(+)equol. Kenneth D. R. Setchell, from the Cincinnati Children's Hospital Medical Center, reported on the use of stable-labeled [¹³C]analogs to compare the pharmacokinetics of *S*-(−)equol, the naturally occurring enantiomer made by intestinal bacteria in humans (58), with *R*-(+)equol in healthy adults. The results confirmed the rapid uptake and high bioavailability (65–83%) of both enantiomers when compared with published data for daidzein (30–40%) or genistein (7–15%) (60). The plasma half-life of elimination was shown to be 6–7 h for both enantiomers, which is consistent with an earlier report for racemic equol (58), although research presented by Shaw Watanabe from the National Institute of Health and Nutrition in Japan, involving Japanese women given a natural *S*-(−)equol-containing supplement (10.9 mg/capsule) made from the incubation of soy germ with *Lactococcus sp.* reported a surprisingly short half-life of only 82.3 min. The reason for this difference is unclear.

Some assurance about the safety of equol was also given by Watanabe based on acceptable tolerance in a chronic study of postmenopausal Japanese women given the aforementioned supplement. In agreement with the results of preclinical studies, rats and monkeys given oral doses of pure chemically synthesized *S*-(−)equol presented by Richard L. Jackson from Ausio Pharmaceuticals in Cincinnati, equol demonstrated no genotoxicity or uterotrophic effects at physiologically relevant concentrations. The effect of equol on the uterus is an important issue because this compound gained its notoriety as the metabolite of formononetin—which is found in species of clover responsible for causing endometriosis and infertility in sheep, referred to as Clover disease—that devastated the sheep-breeding industry in regions of Southwest Australia over 60 y ago (61).

In this regard, it was of some reassurance that Andreas Constantinou from the University of Cyprus reported results showing that in Sprague-Dawley rats, the endometrial abnormalities typically induced by the breast cancer drug tamoxifen could be significantly inhibited if tamoxifen was given together with daidzein. It was proposed that this inhibition was mediated by the conversion of daidzein to equol. Note that the rat almost exclusively converts daidzein to equol (62). Specifically in this study, the tamoxifen-induced increase in markers of oxidative DNA

damage as assessed by changes in 8-hydroxy-2-deoxyguanosine and cell proliferation as determined by changes in proliferating cell nuclear antigen and the decrease of phosphatase and tensin homolog, a tumor suppressive marker, were all reversed when daidzein was given as an adjunct. Whether these findings can be extrapolated to patients undergoing chemotherapy with tamoxifen is uncertain; furthermore, these findings need to be confirmed with pure equol rather than daidzein.

Finally, a recent focus of the pharmaceutical industry has been to target ER β agonists as potential new agents for the treatment of prostate cancer (63) because, in contrast to the androgen receptor, 1 role for ER β in the prostate is to suppress proliferation and promote differentiation (64). Equol fits the criteria as an ER β agonist (58,65); furthermore, the ability of equol to antagonize the action of dihydrotestosterone (66), a potent hormone that drives prostate growth, means it may potentially be useful in both the prevention and treatment of prostate cancer. In this session, Constantinou showed in a PC3 prostate cancer cell line that equol also inhibits the urokinase activator system, a regulator of tumor metastasis and a predictor of recurrence in patients undergoing radical prostatectomy. Other inhibitors of this system, such as amiloride or *p*-aminobenzamidine, reduce the invasiveness of prostate cancer cells in vitro. Although these multiple targets of equol offer some hope of equol as a therapeutic agent in prostate cancer, future clinical studies are needed to clarify its true potential. It is tempting to speculate that the low rates of prostate cancer in the Japanese might result from the regular consumption of soyfoods and the high frequency of equol producers in this population.

Conclusions

Soyfoods, in part because they are a rich source of isoflavones, continue to attract the attention of the research community. From the number of younger investigators presenting at the symposium in Tokyo, indications are that research in this field will continue at an impressive pace. There is certainly ample basis for continued investigation. At the molecular level, much more insight is needed about the mechanisms by which isoflavones exert their proposed physiological effects. And at the clinical level, there is a pressing need to understand and identify the experimental design elements that contribute to the inconsistent data. Obviously, understanding the role of isoflavone metabolism, and specifically the importance of equol production, will require much more research. Confirmation of the equol hypothesis is possible only through clinical trials using equol as the intervention product, not by subanalysis of data according to subject equol-producer status.

It is certainly important to recognize that although isoflavones may be the soy component of most interest, there are many other components that are also under investigation, most notably soy protein. Importantly, data suggest that in addition to lowering cholesterol, soy protein is hypotensive (67), and so it is likely future symposia will include presentations on this aspect of soy. Clearly, there needs to be greater understanding of how background diet influences the health effects of soy (68) and how these effects are influenced by the processing of soy protein and soy extracts (69).

Finally, since the third soy symposium, those researchers impacting the field have been formally recognized for their work. This year, the award for "Outstanding contributions to increasing scientific understanding of the health effects of soyfoods and soybean constituents" was given to Mindy Kurzer, PhD (University of Minnesota), Johanna Lampe, PhD, RD (Fred Hutchinson Cancer Research Center), Aedin Cassidy, PhD (University of East Anglia), Shaw Watanabe, PhD, MD (National

Institute of Health and Nutrition, Japan), and Chisato Nagata, PhD (Gifu University). The award for "Outstanding contributions in promoting awareness of the nutritional and health attributes of soyfoods" went to Ms. Boon Yee Yeong (American Soybean Association, Singapore).

Authors and presentation titles

Nadine Brown, Department of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center, "Dietary and developmental factors related to equol production and stability"; Aedín Cassidy, University of East Anglia, "Do soy or isoflavones exert hormonal effects in women? A systematic review and meta-analysis"; Andreas Constantinou, University of Cyprus, "Equol diminishes tamoxifen-induced endometrial abnormalities in Sprague-Dawley rats" and "Equol inhibits prostate cancer cell invasion and metastasis"; Alison M. Duncan, University of Guelph, "Soy protein isolates of varying isoflavone content do not adversely affect semen quality in healthy young men"; Jill Hamilton-Reeves, College of St. Catherine, "Clinical studies show no effects of soy protein or isoflavones on reproductive hormones in men: Results of a meta-analysis"; Martin Imhoff, Humanis Clinicum Korneuburg, "Soy isoflavones improve menopausal symptoms: A clinical study report"; Richard L. Jackson, Ausio Pharmaceuticals, LLC, "Development of S-equol as a pharmaceutical product to provide the health benefits of soy"; Ge Keyou, Chinese Nutrition Society, "Twenty-four-hour urinary equol excretion and equol producing status in China"; Woon-Puay Koh, National University of Singapore, "Gender-specific effects of soy isoflavones on risk of hip fracture in the Singapore Chinese Health Study"; Elaine Krul, Solae, LLC, "Meta-analysis confirms soy protein's cholesterol-lowering efficacy"; Omer Kucuk, Emory University School of Medicine, "Modulation of biomarkers of growth and differentiation in breast cancer by soy isoflavones"; Gertraud Maskarinec, Cancer Research Center of Hawaii, "Soy isoflavone supplementation and mammographic density in postmenopausal women"; Audrey Serafini, Istituto di Ricovero e Cura a Carattere Scientifico, "Effects of soy isoflavones in spermatogenesis"; Manju Reddy, Iowa State University, "Does soy food consumption affect iron and zinc status in women of childbearing age?"; Kenneth D. R. Setchell, Cincinnati Children's Hospital Medical Center, "The pharmacokinetic behavior of enantiomers of equol in healthy adults"; Xiao Ou Shu, Vanderbilt University, "Soyfood consumption and breast cancer survival"; Francesco Squadrito, University of Messina, "Safety and efficacy of genistein"; Francine M. Steinberg, University of California, Davis, "Equol and its relation to Osteoporosis Prevention Using Soy"; Shaw Watanabe, National Institute of Health and Nutrition in Japan, "Isoflavone metabolism: The key to understanding the health effects of soy?"; Patricia Williamson-Hughes, Archer Daniels Midland Co., "Isoflavone supplements containing predominantly genistein reduce hot flashes."

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