The Human Mammary Gland as a Target for Isoflavones: How Does the Relation Vary in Individuals with Different Ethnicity?

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Abstract
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Based on observational studies, it appears that soy food consumption provides protection against breast cancer primarily in Asian but not in Western populations. Given the problems in examining the effects of isoflavones directly in the human mammary gland, this review describes epidemiologic studies that investigated the association with biomarkers reflecting hormonal activity of isoflavones, in particular sex steroid levels, mammographic densities, nipple aspirate fluid, and tissue specimens from biopsies or surgeries. Three possible mechanisms that may be responsible for ethnic-specific health effects from these compounds are discussed: genetic variation in metabolic enzymes, timing of exposure, and intestinal metabolism by microbiota. Only a limited number of comparative studies and even fewer nutritional interventions have examined effects and addressed differences in biomarkers between Asian and Western populations. Investigations that looked at estrogens and mammographic densities as endpoints observed some associations in Asian women that were not seen in Caucasians. On the other hand, the low rate of nipple aspirate fluid production and a lack of breast tissue studies make it impossible to evaluate effects of isoflavones on these biomarkers in Asian women. Based on the current evidence, it appears likely that the timing of exposure is the most important determinant of beneficial health effects from soy foods. This may be the result of gut microbiota, which colonize the intestine during childhood and facilitates the hydrolysis of glycosides and the formation of equol from dadzein, a pathway that may result in beneficial health effects. The current evidence is insufficient to answer the question whether women of diverse ethnic groups experience distinct effects from soy isoflavones in breast tissue, but as knowledge about the role of early life nutrition and the development of gut microbiota increases, the potential for diverse metabolic pathways of isoflavones in individuals with different ethnic backgrounds and dietary exposures may be clarified.

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Introduction
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Soy foods have been part of traditional Asian diets for many centuries but were introduced in Western countries only a few decades ago [1]. Migrants from Asia maintained their dietary habits to a certain degree when they moved to Western countries, but they also adopted local foods [2]. Research into the protective effects of soy foods was inspired by the low incidence of breast cancer among Asian women – respective 2008 rates of 76, 42.7, and 21.6 per 100 000 women in the US, Japan, and China were reported [3] – and by Japanese migrant studies showing an increase in breast cancer risk over 2–3 generations [4]. Due to the estrogen-like structure of isoflavones found in soy beans and the known role of estrogens in breast carcinogenesis [5], most soy research has focused on the hormonal activity of these compounds despite the many other hypothesized biologic mechanisms of action that may contribute to chemoprevention and possibly cancer therapy [6–9].

As demonstrated in several meta-analyses [10–14], support for a breast cancer protective effect of soy is much stronger among women of Asian, primarily Japanese and Chinese, ancestry than for Western populations. The respective risk estimates in two meta-analyses were 0.71 (95% CI: 0.60–0.85) and 0.76 (95% CI: 0.65–0.86) for Asian populations, while no association was seen in Western women [13,14]. This discrepancy could be due to the low soy intake in Western women and the fact that Asians typically eat whole soy

foods, whereas soy products in Western countries tend to be highly processed or consumed as single soy components [15]. A recent case-control analysis nested within the Multiethnic Cohort in Hawaii and Los Angeles found similar results in an examination of urinary isoflavone excretion as a biomarker of soy intake among 251 cases and 462 controls [16]. The risk associated with breast cancer was 0.69 (95% CI: 0.51–0.92) among Japanese Americans and 0.98 (95% CI: 0.61–1.55) among Caucasians [16]. Thus, it appears that not all populations derive the same benefit from exposure to isoflavones and possibly other components of soy foods. Instead, there is reason to believe that these bioactive compounds exert differential actions across individuals depending on their ancestry.

In order to understand the role of soy isoflavones in breast cancer etiology, investigations to explore the action on breast tissue have been conducted in experimental settings. They have shown the ability of isoflavones to bind competitively to estrogen receptors (ER) α and β, but other biologic actions of mechanisms have also been described [8,9]. The binding to ERs may result in stimulation or reduction of estrogenic activity depending on the hormonal milieu [17–19]. Given the challenge of examining breast tissue from healthy women, a variety of markers suspected to be associated with breast cancer have been analyzed as surrogate endpoints.

This review will focus on epidemiologic studies that investigated the association between soy foods and biomarkers reflecting the effects of isoflavones in the breast, in particular hormone levels, mammographic densities, nipple aspirate fluid (NAF), and tissue specimens from biopsies or surgeries. The question to be addressed is whether populations with different ethnicity deal with these plant-based compounds in ways that lead to variations in function and disparate health effects. Three possible underlying mechanisms that may be responsible for ethnic differences will be discussed: genetic variation in metabolic enzymes, timing of exposure, and intestinal metabolism by microbiota.

Soy Isoflavones and Biomarkers for Breast Cancer
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Sex steroid hormones
Studies of circulating estrogens and androgens [20] and urinary estrogen metabolites [21–23] have been conducted to elucidate the effect of soy isoflavones on hormonal metabolism. In a single arm intervention, a reduction in luteal phase estradiol (E_2) was observed only among Asian (−17.4%) but not among non-Asian (−1.2%) participants [24]. In a trial with soy milk among Japanese women [25], estrone (E_1) and E_2 decreased in the intervention group. However, a recent cross-sectional study among more than 400 Japanese women reported no association between soy intake and various sex steroids [26]. Also, a meta-analysis of 47 randomized or carefully controlled intervention studies found no effect of soy or isoflavones on circulating E_1 or E_2 levels in pre- or postmenopausal women [20]. Although 4 studies examined estrogens in Asian women, their findings were not analyzed separately. Of these, two studies from Japan and one from Taiwan detected nonsignificant decreases in serum estrogen levels [25,27, 28], while another Japanese investigation reported no effect on E_2 [29].

As to urinary estrogen metabolite patterns, a cross-sectional study among 430 Asian American women found no association of soy intake with 15 estrogen metabolites assessed by liquid chromatography mass spectrometry (LCMS) but detected a high-er 2/16α-hydroxy (OH) E_1 ratio, a possible marker for lower breast cancer risk, among women with high soy intake [30]. Interventions among premenopausal women reported discrepant findings. An investigation with a soy beverage [31] and with an isoflavone supplement [32] detected no change in urinary estrogen metabolites and the 2/16α-OH ratio. The small number of Asian Americans (11 out 34) was not analyzed separately. A gas chromatography mass spectrometry (GCMS)-based crossover trial in 12 women consuming 10, 65, and 129 mg of isoflavones from soy protein powder for 3 months each described significantly lower 16α-OHE$_1$, 4-OHE$_1$, and 4-OHE$_2$ and a higher 2/16α-OHE$_1$ ratio after supplement intake [33]. In a similar investigation with 8 women, soy milk with a high isoflavone content (113–202 mg/day) was associated with a higher urinary excretion of 2-OHE$_1$ and a higher 2/16α-OHE$_1$ ratio [22]. An analysis in Hawaii using GCSM also reported a higher 2/16α-OHE$_1$ ratio at the end of the high-soy diet (p = 0.05), but the individual metabolites did not differ significantly by dietary assignment [23]. An interaction term between soy diet and ethnicity was not significant indicating that the 27% of women of Asian ancestry did not differ from the rest of the study participants. In trials among postmenopausal women, a decrease in the ratio of genotoxic to total estrogens [21] and a higher urinary 2/16α-OHE$_1$ ratio [34] were observed, while no change was seen in other interventions [35]. None of the studies included Asian women.

Mammographic density
Mammographic density refers to the appearance of the human breast in radiologic images and is one of the strongest predictors of breast cancer risk [36]. Women with more than 50% breast density experience a 4- to 6-fold higher risk of breast cancer than those with less than 10% density [36]. Since women of Asian ancestry tend to have higher mammographic densities than Caucasians due to the small size of their breasts [37], appropriate adjustments are necessary. Two cross-sectional investigations, one in Hawaii [38] and two reports from the same study among Chinese women in Singapore using different measures of mammographic density [39,40] suggest slightly lower breast densities among women of Asian descent with regular soy intake, but two larger studies with Japanese and Chinese women did not report any conclusive evidence [41,42]. With great consistency, the randomized trials conducted so far indicate that soy or isoflavones do not modify mammographic densities among adult pre- and postmenopausal Caucasian women [43,44]. A meta-analysis of 8 randomized trials suggested no overall effect in all women combined with a mean difference of less than 1% [44]. So far, no intervention studies with breast density as an outcome were performed among Asian women only and stratification of the Hawaii studies did not suggest any ethnic differences [45,46]. The relatively short duration, the small sample sizes, and the age of the study participants are limitations that may have been responsible for a lack of an effect on breast density in the trials presented here as opposed to the weak associations observed in cross-sectional studies [38–40].

Nipple aspirate fluid (NAF)
Little research on the presence and the effect of isoflavonoids directly in the breast has been undertaken, but the presence of isoflavonoids in breast milk with concentrations of 5–110 nmol/L has been documented [47]. In non-lactating women, nipple aspiration is a noninvasive method to obtain breast fluid and epithelial cells using a device similar to a manual breast pump [48]. Giv-

Table 1 Nutritional trials exploring the effect of isoflavones/phytoestrogens on nipple aspirate fluid (NAF).

Author Year	N	Intervention	NAF outcomes	Other outcomes
Petrakis et al. 1996 [53]	14 pre 10 post	Soy protein supplement	*Premenopausal* Volume: increase; p = 0.001 GCDFP-15: increase; p = 0.04 *Postmenopausal* Volume: no significant change GCDFP-15: no significant change Hyperplastic cells: before 1/24-after 7/24; p = 0.02	Plasma E2: no change Plasma progesterone: no change Plasma SHBG: no change Plasma prolactin: no change
Ruhlen et al. 2007 [58]	61	Black cohosh extract	NAF pS2: ▸ Baseline 3.57 ± 1.91 ▸ 12 weeks 1.60 ± 0.68 ▸ 24 weeks 1.01 ± 0.31; ns = nonsignificant decrease NAF cytology: no change	Serum E_2: nonsignificant decrease Serum LH: no change Serum FSH: no change Serum pS2: nonsignificant decrease Menopausal symptoms: significant decrease
Maskarinec et al. 2008 [55]	11	Soy milk	Volume: Baseline 58 μL 1 month 105 μL; p = 0.47 Isoflavonoids: ▸ baseline 66 nmol/L ▸ 1 month 180 nmol/L; p = 0.12	Urinary isoflavonoids: significant increase; p = 0.04
Maskarinec et al. 2011 [48, 59]	82	Soy foods	Volume: ▸ low-soy 28 ± 34 μL ▸ high-soy 33 ± 35 μL; p = 0.52 E_2: ▸ low-soy 313 ± 131 pg/mL ▸ high-soy 113 ± 123 pg/mL; p = 0.07 E_1S: ▸ low-soy 68 ± 115 ng/mL ▸ high-soy 46 ± 69 ng/mL; p = 0.07	Serum E_2, E_1, E_1S: no change Urinary isoflavonoids: significant increase Urinary estrogen metabolites: no change 2/16α-OHE1 ratio: increase; p = 0.05
Khan et al. 2012 [57]	98	Soy isoflavone supplement	Genistein: ▸ treated 8 μL ▸ placebo 11.5 μL; p = 0.63 E_2: ▸ treated 354 pg/mL ▸ placebo 91 pg/mL; p = 0.64 IGF-I: ▸ treated 11.4 ng/mL ▸ placebo 23.4 ng/mL; p = 0.83	Plasma genistein: increase; p < 0.0001 Plasma E_2: no difference; p = 0.77 SHBG: no difference; p = 0.43 FSH: no difference; p = 0.45 Ki-67 in epithelial cells: no difference; p = 0.24 Atypical cytology: no difference; p = 0.83 Gene expression: no difference

en its close contact with breast cells, NAF is thought to provide a more relevant marker of hormonal influence on breast tissue than serum; correlations between hormone levels in NAF and serum are weak [49]. Women who produce NAF appear to be at a higher risk to develop breast cancer [50, 51], but the higher risk is primarily present in women with cellular NAF and atypical cells [52].

The first study to investigate the effects of soy on NAF (○ **Table 1**) was a single-arm intervention among 24 pre- and postmenopausal Caucasian women with 38 g soy protein isolate [53]. Each woman served as her own control and donated NAF monthly for 6 months of soy supplementation and 3 months preceding and following the active intervention. A minimal increase or no response was found in postmenopausal women. In the 14 premenopausal women, the volume of NAF increased 2- to 6-fold after soy intake as compared to baseline. Whereas hyperplastic cells in NAF were found only in one woman at baseline, they were present in 7 women during soy protein intake. Although the implications of finding hyperplastic cells are not well understood, this study raised concern that NAF secretors may be sensitive to soy and react with increased secretion and cell proliferation [54]. However, this suggestion was not confirmed in later studies (○ **Table 1**).

In a small study with 11 women who consumed 2 daily servings of soy milk for 30 days, isoflavonoid levels in NAF increased substantially [55]; median levels were 66 nM at baseline and 180 nM at the end (median increase of 58 nM; p = 0.12). As a result of a soy challenge in one woman, isoflavonoid levels changed to a similar degree in NAF as in plasma and in urine with correlations > 0.8 but were 10-fold lower in NAF (12–94 nmol/L) than in plasma (46–1141 nmol/L) and comparable to concentrations in breast milk [56].

Three additional phytoestrogen trials (○ **Table 1**) with NAF measures as endpoints were conducted, one with soy foods [48], one with an isoflavone supplement [57], and one with black cohosh, a phytoestrogen-containing plant [58]. A randomized cross-over study in Hawaii administered a high-soy diet and a low-soy diet for 6 months each [48]. The nutritional intervention of 2 daily servings of soy foods did not significantly increase breast tissue activity as assessed by NAF volume [48] or modify estrogen levels in NAF and serum although a trend of lower E_2 and E_1S in NAF after the high-soy diet was observed [59]. The analysis of baseline measurements showed a nonsignificant inverse association of soy intake with NAF volume (p = 0.08) but not with estrogen levels in NAF [60].

In a clinical trial of soy isoflavone supplements described in more detail below [57], NAF hormone and protein levels were mea-

sured, but no treatment effects on NAF parameters were observed. No effect of a black cohosh preparation on pS2, a marker of estrogenic activity, or cellular morphology in NAF was seen during a 12-week trial with 45 women [58].

With the exception of the studies in Hawaii [48,55,59], none of the NAF studies included women of Asian ancestry, but even in the Hawaii studies the numbers were too small for separate analysis. As reported previously, NAF production rates tend to be low in women of Japanese and Chinese ancestry [48,61], an observation that was confirmed in the soy intervention described above; only 26% of Asian candidates screened for participation produced a ≥ 10 µL amount of NAF, whereas 47% of Caucasian women were able to do so [48].

Breast tissue analyses

Studies in primates provide evidence that dietary exposure to isoflavones alone is not a significant estrogen agonist for breast tissue [62]. Soy treatment did not induce proliferation in mammary tissue but mammary gland proliferation induced by E_2 as assessed by increased epithelial staining of the proliferation marker Ki-67 was antagonized by soy in surgically postmenopausal female macaques. In humans, four approaches have been applied to assess the effects of isoflavones directly in breast tissue: specimens from breast reduction surgery, fine needle biopsies, samples obtained during breast cancer surgery, and formalin-embedded pathologic specimens.

Two reports examined isoflavonoids in breast tissue from reduction surgery after 5 days of soy supplementation [63,64]. In trials with 28 and 31 Caucasian women, isoflavonoid concentrations were considerably lower in hydrolyzed breast tissue than in the corresponding serum samples [63,64], but the high proportion of fat cells does not allow firm conclusions about epithelial breast tissue.

In a well-designed clinical trial [57], 126 high-risk women underwent a random fine-needle aspiration; those with 4000 or more epithelial cells were randomized to a double-blind 6-month intervention of soy isoflavones or placebo, followed by another fine-needle aspiration. The median Ki-67 labeling index was 1.18 at entry and 1.12 post-intervention in the 49 treated women, while it was 0.97 and 0.92 in 49 placebo subjects (p = 0.32). Menopausal stratification yielded similar results between groups, but within premenopausal soy-treated women, the Ki-67 labeling index increased more than in postmenopausal women. No treatment effects on cytologic atypia or NAF parameters were observed. Although increases in the expression of 14 of 28 genes related to proliferation, apoptosis, and estrogenic effect were observed within the soy group, the difference between groups was not significant.

Several studies were performed among women scheduled to receive a breast biopsy or to undergo surgery [65,66]. Among 48 women who consumed a 60-g soy supplement for 14 days before a breast biopsy [66], progesterone expression and the proliferation rate of breast lobular epithelium increased. The same investigators reported higher pS2 levels in the breast fluid of 84 premenopausal women in response to soy indicating an estrogenic stimulus [65]. A pilot clinical trial examined the interaction between 2 weeks of an isoflavone supplement and breast cancer growth among 17 patients [67]. The surgical breast cancer tissues and blood obtained prior to and after isoflavone supplement treatment were compared to 26 historical controls with similar characteristics. The apoptosis/mitosis ratios in isoflavone-treated cancer specimens were not significantly different from those of control untreated cancer specimens.

In a study using paraffin-embedded blocks from 268 breast cancer patients [68], hormonal and proliferation markers were examined in benign and malignant breast tissue using tissue microarrays (TMAs). The TMAs were stained for ERα, ERβ, progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), proliferating cell nuclear antigen (PCNA), and Ki-67. With the exception of lower HER2/neu expression, no significant associations between soy intake and pathologic markers were observed in malignant tissue. In benign tissue, early life soy intake showed higher ER and PR expression, but no difference in proliferation markers. After stratification by ethnicity, slightly divergent results were observed for the association of adult soy intake with PR and Ki-67. Whereas in Caucasians, higher soy intake suggested higher marker expression, the relation was in the opposite direction among Japanese women, but none of the results was statistically significant [68].

Possible Mechanisms for Ethnic Differences
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Two obvious reasons why Asian populations may experience more beneficial health effects from soy foods than Western populations [15] are the high amounts and the types of soy foods commonly consumed in Asian countries. Typical intakes based on dietary surveys indicate that Asian populations consume as much as 25 g of soy protein or 100 mg of isoflavones per day, whereas a Western diet provides less than 1 g of soy protein or 1 mg of isoflavones per day [15]. Secondly, isoflavones from fermented soy foods, such as miso and natto, may be more bioavailable than non-fermented products, e.g., tofu and soy milk, because the glucosides in the latter require hydrolyzation to aglycones by intestinal bacteria before uptake is possible, whereas aglycones in fermented soy foods do not [69,70].

Support for the idea that chronic ingestion and ethnic origin may influence isoflavone pharmacokinetics and bioavailability comes from a report that compared healthy young Asian and Caucasian men [71]. After consuming soya-based cheese with 46 mg isoflavones as part of a Western diet, the 12 Asians exhibited significantly higher maximum plasma concentrations and areas under the plasma concentration-time curve for genistein and daidzein than the 12 Caucasians, in whom both values only increased after chronic intake.

Genetic variation in metabolic enzymes

Not all individuals may benefit from soy food exposure to the same degree due to variations in genes that metabolize isoflavones [72]. The dramatic variability in interindividual response to any type of dietary intervention may be the result of gene-diet interactions, i.e., the modulation of the effect of a dietary component by a genetic variant [72]. For example, genetic polymorphisms in the cytochrome P450 (CYP) or catechol-O-methyltransferase (COMT) enzymes may alter activity or modulate the expression of genes involved in metabolic pathways of estrogens and estrogen-like compounds [73,74]. There is limited research in this area, but a few studies from Asian countries reported interesting findings. A Chinese breast cancer study observed differential effects of *CYP1A1*, *CYP1B1*, and *COMT* polymorphisms after stratification by soy intake [75]. In addition, several Japanese studies describe a genetic influence on the effect of isoflavones. Polymorphisms in gene coding for 17β-hydroxy-

steroid dehydrogenase type I and for sex hormone-binding globulin [76] as well as for ERβ [77] modified the association between isoflavone intake and breast cancer risk. Similarly, specific polymorphic variations appeared to influence the association of soy intake with prostate cancer [78] and testosterone levels [79].

Timing of exposure

As has been shown in animals, the overall effect of soy foods on carcinogenesis may depend on the time of life when isoflavones were administered due to the possibility that isoflavones exert estrogenic or antiestrogenic effects depending on the hormonal environment during different stages of life [17]. Since experimental studies indicate that estrogen exposure in young animals induces protection against cancer development [80,81], the weak estrogenic effects of isoflavones in soy beans, if consumed early in life, may achieve or accelerate differentiation of breast tissue structures similar to an early pregnancy and, thereby, decrease tissue susceptibility to carcinogens and prevent tumor development later in life. A number of case-control studies assessed soy intake during childhood or adolescence and found a stronger protection for early life than adult soy intake [82–85]. Noteworthy is the observation from a California study that Asia-born women experience more protection from soy consumption than US-born women of Japanese and Chinese ancestry [86]. This may explain why breast cancer incidence rates in Asian migrants reached levels of the US population over consecutive generations as early life exposure to soy foods declined [87].

Intestinal metabolism by microbiota

Given the need for bacterial action before uptake of glycosides, the bioavailability of isoflavones varies substantially across individuals [71]. In addition, the possible importance of equol production, i.e., the capacity of the intestinal bacteria to metabolize the isoflavone dadzein into the metabolite equol may confer a greater protection against disease than the other isoflavonoids [88,89]. This trait has been proposed as an explanation for the more commonly found positive associations between soy foods and health in Asians because the prevalence of equol production appears to be higher in Asian (50–55%) than Western (20–35%) populations [90–92]. Experimental support for this idea comes from a study showing that isoflavones differentially induce gene expression changes in lymphocytes from women who form equol as compared to nonproducers [93]. However, an analysis of equol levels in repeated samples challenges the widely held belief that equol status remains stable within individuals over time; 16% of premenopausal participants with diverse ethnic backgrounds were inconsistent equol producers in a 1-year period [94] and 14–35% of predominantly Caucasian postmenopausal women changed equol status over 2.5 years [95].

As the increasing importance of gut microbiota in human health is emerging [96], it has become apparent that patterns of intestinal bacteria acquired during gut colonization in early life are related to dietary exposure and geographic location [97]. Thus, infants exposed to isoflavones early in life may become more competent to hydrolyze glycosides allowing uptake of isoflavones and to produce equol later in life as suggested by a comparison between Korean American and Caucasian girls [90]. Given the high levels of isoflavones in breast milk when mothers consume soy foods [98,99], the acquisition of bacteria that are capable of metabolizing isoflavones may begin during infancy [100], but later events continue to modify bacteria composition. At this time, little is known about how early life isoflavone exposure determines equol status later in life [101] and which specific bacteria are able to metabolize isoflavones or produce equol although a few bacteria have been identified [100,102].

Conclusions
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One of the more consistent findings in soy research is the fact that epidemiologic studies report a stronger protective effect of soy foods against breast cancer among women who grew up in Asian countries and in those who consumed soy foods throughout childhood and adolescence [13]. As to other cancer sites, a meta-analysis of prostate cancer studies also supports the idea of ethnic differences. A lower risk associated with soy consumption was observed only among Asian (OR = 0.52; 95% CI: 0.33–0.81) but not Western populations (OR = 0.99; 95% CI: 0.85–1.16) [103]. On the other hand, the Multiethnic Cohort described similar associations between urinary isoflavone excretion and prostate cancer across ethnic groups [104]. Smaller meta-analyses for less studied sites, such as endometrial, ovarian, and colorectal cancer, described only small differences in associations by ethnicity [105,106].

The current body of literature is insufficient to answer the question whether women of diverse ethnic groups experience distinct effects from soy isoflavones in breast tissue; only a limited number of comparative studies address differences in biomarkers between Asian and Western populations, and very few interventions included women of Asian ancestry. Nevertheless, ethnic differences in the prevalence of biomarkers discussed in this review are evident. Asian women have lower levels of sex steroids and higher mammographic densities. Also, they are less likely to produce NAF and more likely to convert isoflavones to equol. However, information that addresses effect modification of the association between soy and breast cancer risk by ethnicity is more limited. Based on the current evidence, soy consumption might have a stronger association with mammographic densities [39,40], and possibly estrogen levels [20] in Asian than Western women. The low rate of NAF production and a lack of breast tissue studies in Asian women challenge our ability to explore soy food intake in relation to breast cell and tissue measures. Comparisons of biomarkers in Asian and Caucasian women have contributed considerably to our knowledge about ethnic differences in breast cancer risk and elucidated biologic mechanisms of action for isoflavones in relation to breast carcinogenesis. Based on the current evidence, it appears likely that the timing of soy exposure is the most important determinant of beneficial health effects. Since reports about cancer-protective effects of soy come primarily from Asian populations who consumed soy foods since childhood, diet in early life may be more important than adult nutrition. This may be due to gut microbiota, which colonize the intestine during infancy and facilitate the hydrolysis of glycosides for improved bioavailability and the formation of equol from dadzein, a pathway that may result in beneficial health effects. As knowledge about the role of early life nutrition and the development of gut microbiota and their functions increases, the potential for diverse metabolic pathways of isoflavones in Asian individuals may be clarified.

Conflict of Interest
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The author declares that there is no conflict of interest.

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