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Christine Duffy, Kimberly Perez, and Ann Partridge
Implications of Phytoestrogen Intake for Breast Cancer
CA Cancer J Clin 2007; 57: 260-277
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  Mathias Schmidt (2 April 2008)

Status of Estrogen Receptors During Administration of Phytoestrogen

20 May 2009

Jun Yu,
Medical Scientist
Center of Teaching Experiment, School of Basic Medical Science, Fourth Military Medical University,
Libing Liu, Wei Wang, Jingguo Wei, and Baoying Chen

Send letter to journal:
Re: Status of Estrogen Receptors During Administration of Phytoestrogen

Email Jun Yu, et al.

Dear Editor,

As reviewed by Dr. Duffy and colleagues, there is conflict about the preventive role of phytoestrogen against breast cancer, due to differences in dietary measurement, lack of standardization of supplemental sources, differences in metabolism amongst individuals, and the retrospective nature of much of the research in this area [1]. In our opinion, the aforementioned problems are with phytoestrogen itself. However, the estrogen receptors (ER), which are equally as important as the ligands, are somewhat neglected.

Estrogen and ER are partners interacting with each other. Various examples in the literature provide evidence that phytoestrogen treatment regulates the expression levels of its receptor, ER, in cell lines [2,3], animals [4-7], and premenopausal patients with breast cancers [8]. Also, phytoestrogen could alter the ER intracellular distributions [9], as well as ER beta/alpha ratio [10]. In addition, there are polymorphisms of ER in the estrogen receptor gene [11]. In a trial of 138 Japanese women, ESR2 gene RsaI polymorphism appeared to modify the effects of phytoestrogen to reduce the risk of endometriosis [12].

Therefore, during administration of phytoestrogen, gene polymorphism and phytoestrogen-induced alteration of ER status might ultimately affect the exact role of phytoestrogen we want to clarify. This is worthy of investigation in the future.

Kind Regards,

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References

[1] Duffy C, Perez K, Partridge A. Implications of phytoestrogen intake for breast cancer. CA Cancer J Clin. 2007;57(5):260-277.

[2] Stettner M, Kaulfuss S, Burfeind P, et al. The relevance of estrogen receptor-beta expression to the antiproliferative effects observed with histone deacetylase inhibitors and phytoestrogens in prostate cancer treatment. Mol Cancer Ther. 2007;6(10):2626-2633.

[3] Cappelletti V, Miodini P, Di Fronzo G, et al. Modulation of estrogen receptor-beta isoforms by phytoestrogens in breast cancer cells. Int J Oncol. 2006;28(5):1185-1191.

[4] Wu Y, Niwa K, Onogi K, et al. Effects of selective estrogen receptor modulators and genistein on the expression of ERalpha/beta and COX-1/2 in ovarectomized mouse uteri. Eur J Gynaecol Oncol. 2007;28(2):89- 94.

[5] Padilla-Banks E, Jefferson WN, Newbold RR. Neonatal exposure to the phytoestrogen genistein alters mammary gland growth and developmental programming of hormone receptor levels. Endocrinology. 2006;147(10):4871-4882.

[6] Shibayama T, Fukata H, Sakurai K, et al. Neonatal exposure to genistein reduces expression of estrogen receptor alpha and androgen receptor in testes of adult mice. Endocr J. 2001;48(6):655-663.

[7] Laurenzana EM, Weis CC, Bryant CW, et al. Effect of dietary administration of genistein, nonylphenol or ethinyl estradiol on hepatic testosterone metabolism, cytochrome P-450 enzymes, and estrogen receptor alpha expression. Food Chem Toxicol. 2002;40(1):53-63.

[8] Touillaud MS, Pillow PC, Jakovljevic J, et al. Effect of dietary intake of phytoestrogens on estrogen receptor status in premenopausal women with breast cancer. Nutr Cancer. 2005;51(2):162-169.

[9] Zhao QW, Huang X, Lou YJ, et al. Effects of ethanol extracts from Adzuki bean (Phaseolus angularis Wight.) and Lima bean (Phaseolus lunatus L.) on estrogen and progesterone receptor phenotypes of MCF-7/BOS cells. Phytother Res. 2007;21(7):648-652.

[10] Konduri S, Schwarz RE. Estrogen receptor beta/alpha ratio predicts response of pancreatic cancer cells to estrogens and phytoestrogens. J Surg Res. 2007;140(1):55-66.

[11] Jiang M, Huhtaniemi I. Polymorphisms in androgen and estrogen receptor genes: effects on male aging. Exp Gerontol. 2004;39(11-12):1603-1611.

[12] Tsuchiya M, Miura T, Hanaoka T, et al. Effect of soy isoflavones on endometriosis: interaction with estrogen receptor 2 gene polymorphism. Epidemiology. 2007;18 (3):402-408.

Reply to Schmidt

2 April 2008

Christine Duffy, MD, MPH,
Assistant Professor of Medicine
Brown University Medical School,
Kim Perez, MD; Ann Partridge, MD, MPH

Send letter to journal:
Re: Reply to Schmidt

Email Christine Duffy, MD, MPH, et al.

We appreciate the thoughtful comments regarding our review of phytoestrogens in breast cancer by Dr Schmidt. Many breast cancer survivors are already altering their intake of soy (and this includes both women who have increased their intake, as well as women who have decreased their intake) as a result of their breast cancer diagnosis. We felt strongly that a review, which focused on the available clinical evidence, would be helpful to providers and their patients. Recommending phytoestrogens to prevent breast cancer, prevent its recurrence, or as a treatment for hot flashes requires high quality, clear, and consistent clinical evidence to support its use. Unfortunately, as indicated by our review, evidence suggesting either a clear protective or a clear deleterious effect is still lacking.

Dr. Schmidt担 comments regarding differences in ER-α and ER-β affinity for phytoestrogens are well taken. As we indicated in our review, the mechanisms that underlie phytoestrogens actions are complex and difficult to fully appreciate from animal or cell models. Our discussion of Petrakis et al [1] and McMichael-Phillips et al [2] was to point out that some studies have suggested a stimulatory effect on breast epithelium. The findings of Hargreaves et al [3] appear to refute those initial findings. However, Hargreaves et al stated that in fact they had difficulty in recruitment and compliance of the patients in the soy arm of the trial, and

many patients found it difficult to consume the required amount of soy on a regular basis. They went on to state, 揂lthough we have been unable to determine any significant effect of short term soy supplementation on the breast, the safety of longer term soy supplementation with potentially estrogenic effects should be determined?and further 揳sudden dietary intervention in adult women with high doses of phytoestrogens may promote increases in breast proliferation, which could pose a risk in the aging breast or in women with premalignant (already initiated) breast lesions.?Until randomized controlled trials are completed that specifically examine this issue, the safety is still not confirmed. National Cancer Institute-sponsored trials are currently underway which will help answer questions regarding any protective (or deleterious) effect of phytoestrogens on markers of breast cancer risk such as mammographic density and breast cell epithelium. Regarding Dr. Schmidt担 assertion about a lack of effect on breast density and endometrial proliferation, we point out that endometrial safety is outside the scope of our review. Secondly, if the primary outcome is not breast density in a particular study, then evidence cannot really be considered conclusive. Dr Schmidt references an article by Palacios et al [4], which addressed the endometrial safety of a soy supplement, without reference to breast safety. Clearly, additional research is needed to clarify the impact of phytoestrogens on breast tissue.

Our discussion of Allred et al [5] was to point out that processing of phytoestrogens might impact their physiologic effects. Data are insufficient to definitely say that supplements are more or less beneficial, but the results of Allred et al [5] suggest that the effects of more processed soy products might be different from those consumed most typically in Asian countries such as soy flour and tofu. Setchell et al [6] have pointed out that 揟here is a paucity of data to confirm that isoflavone-rich supplements are as nutritionally effective as isoflavone-rich foods?and that 揟here should be less concern regarding natural food sources of isoflavones because there is a long history of isoflavone consumption from foods? Although not specifically addressed in our review, another important issue with the use of supplements is that there is often a discrepancy between actual and reported isoflavone content in products [6-8]. Dietary supplements are not subject to rigorous regulatory oversight. While Trock et al [9] found a small, statistically significant reduction in breast cancer risk with soy intake, they acknowledged that this data should be interpreted cautiously, specifically stating that recommendations for high-dose isoflavone supplementation to prevent breast cancer or its recurrences were premature. We appreciate the careful review of phytoestrogens for menopausal symptoms. Tamoxifen is widely used in the treatment of postmenopausal women with ER+ tumors, and is the only adjuvant hormonal treatment available for premenopausal women. Thus, we included studies of tamoxifen-treated individuals with menopausal symptoms. While it is true that Nelson et al [10] did find a small effect of soy on reducing menopausal symptoms after eliminating the women using tamoxifen, even in menopausal non-cancer patients the data quality is poor and results for soy isoflavone

extracts are contradictory among the largest and highest quality trials. In addition, even the highest quality trials were rated as only 撼air? A Cochrane review by Lethaby et al [11] of phytoestrogens for vasomotor menopausal symptoms, which includes only rigorously conducted studies, reported no evidence of effectiveness in the alleviation of menopausal symptoms with the use of phytoestrogen treatments. The Cochrane review excluded women with a history of breast cancer, yet still failed to find any effect. The Williamson-Hughes [12] (2006) article which Dr Schmidt references only suggests that previous analyses have failed to find an effect because they have included supplements with low doses (<15mg) of genistein. The Cochrane review recommended further study to help clarify whether supplements with >15 mg of genistein were more beneficial than those with <15 mg. However they also advised, as do we, that at the present time, the use of phytoestrogen supplements is not based on good quality of evidence for benefit.

There are several trials cited in the letter by Dr. Schmidt which have been published since our review was conducted which support a benefit of isoflavone for menopausal symptoms. Both Cheng et al [13] and D扮nna et al [14] conducted randomized controlled trials in which study participants were blinded and showed statistically significant reductions in hot flush scores. It is difficult to know how these two studies, were they incorporated into previous meta-analysis and reviews, might alter the conclusions of the meta-analysis previously conducted [9,10]. Notably, Cheng et al also examined breast epithelium in their study and found no adverse effect after one year of genistein supplements. Replication in breast cancer survivors would be reassuring.

Dr. Schmidt also cites the cohort study of Boyapati et al [15] asserting that soy has no negative effect on breast cancer survival. Our review cites this report as well, which showed no relationship between soy intake and risk of recurrence in breast cancer survivors, but noted that it was neither designed nor powered to detect differences in survival. The study was done in a population of Chinese women and whether the effects would be the same in women born in the United States consuming typical US diets is not known. Several other additional studies were not available at the time of our review, but do offer important insight into soy safety in breast cancer survivors on tamoxifen. Wu et al [16] found that among an Asian American population of breast cancer survivors living in Los Angeles, soy intake (as measured by isoflavone levels, previous intake before breast cancer diagnosis, and previous 2-3 days of intake) was not related to circulating levels of tamoxifen. This study is reassuring, as is that by Hodges-Gallagher et al [17], who found that when MCF7-ERβ cells were treated with increasing amounts of tamoxifen, the presence of ERβ increased both the efficacy and potency of tamoxifen. We respectfully disagree with Dr. Schmidt担 concluding statement regarding proven benefit of soy for menopausal symptoms. While soy may in fact ultimately prove to be beneficial for menopausal complaints in breast cancer survivors, the data are not conclusive for either efficacy or for safety. Recent research has been somewhat reassuring, and

phytoestrogens may some day be recommended for breast cancer survivors. However, at the present time, recommendations to increase soy or, conversely, to eliminate it from the diet, are premature.

Christine Duffy, MD, MPH
Kim Perez, MD
Ann Partridge, MD, MPH

References

1. Petrakis NL, Barnes S, King EB, et al. Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. Cancer Epidemiol Biomarkers Prev 1996;5(10):785-794.

2. McMichael-Phillips DF, Harding C, Morton M, et al. Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. Am J Clin Nutr 1998;68(6 Suppl):1431S-1435S.

3. Hargreaves DF, Potten CS, Harding C, et al. Twoweek dietary soy supplementation has an estrogenic effect on normal premenopausal breast. J Clin Endocrinol Metab 1999;84(11):4017-4024).

4. Palacios S, Pornel B, Bereron C, et al. Endometrial safety assessment of a specific and standardized soy extract according to international guidelines. Menopause 2007;14 (6):1006-1011.

5. Allred CD, Allred KF, Ju YH, et al. Soy processing influences growth of estrogen-dependent breast cancer tumors. Carcinogenesis 2004;25(9):1649-1657.

6. Setchell KD, Brown NM, Desai P, et al. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. J Nutr 2001;131(suppl):1362S-1375S.

7. Nurmi T, Mazur W, Heinonen S, et al. Isoflavone content of the soy based supplements. J Pharm Biomed Anal 2002;28:1-11.

8. Thompson LU, Boucher BA, Cotterchio M, et al. Dietary phytoestrogens, including isoflavones, lignans, and coumestrol, in nonvitamin, nonmineral supplements commonly consumed by women in Canada. Nutr Cancer 2007;59:176-184.

9. Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-analysis of soy intake and breast cancer risk. J Natl Cancer Inst 2006;98 (7):459-471.

10. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006;295(17):2057-2071.

11. Lethaby AE, Brown J, Marjoribanks J, et al. Phytoestrogens

for vasomotor menopausal symptoms. Cochrane Database Syst Rev 2007; Oct 17(4):CD001395.

12. Williamson-Hughes PS, Flickinger BD, Messina MJ, Empie MW. Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies. Menopause 2006;13(5) 831-839.

13. Cheng G, Wilczek B, Warner M, et al. Isoflavone treatment for acute menopausal symptoms. Menopause 2007;14(3 Pt 1):468-473.

14. D扔nna R, Cannata ML, Atteritano M, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause 2007;14(4):648-655.

15. Boyapati SM, Shu XO, Ruan ZX, et al. Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study. Breast Cancer Res Treat. 2005;92(1):11-17.

16. Wu AH, Pike MC, Williams LD, et al. Tamoxifen, soy, and lifestyle factors in Asian American women with breast cancer. J Clin Oncol 2007;25(21):3024-3030.

17. Hodges-Gallagher L, Valentine CD, Bader SE, Kushner PJ. Estrogen receptor beta increases the efficacy of anti-estrogens by effects on apoptosis and cell cycling in breast cancer cells. Breast Cancer Res Treat 2007 Jul 19; [Epub ahead of print].

Implications of Phytoestrogen Intake for Breast Cancer: a Comment

2 April 2008

Mathias Schmidt,
Scientific consultant
Herbresearch Germany

Send letter to journal:
Re: Implications of Phytoestrogen Intake for Breast Cancer: a Comment

Email Mathias Schmidt

Dear Editor,

The potential protective effects of phytoestrogens, and explicitly of soy isoflavones, in the development of breast cancer is a matter of public interest, as demonstrated by the isoflavone and cancer studies currently conducted in the United States. Whether soy isoflavones have a benefit for the prevention of cancer remains to be confirmed--it may seem encouraging that 12 out of 16 case control studies listed by Duffy et al. (2007) showed an inverse correlation between cancer risk and soy isoflavone intake, whereas the others show either no effect, or a trend. The only examination casting a doubt on the safety of soy was a nested case-control study showing increased urinary and serum isoflavone levels associated with increased risk of breast cancer [1]. However, Duffy at al. themselves point to the very low intake of <1 mg of isoflavones per day--a quantity that would qualify as unusually low. But did the study really show a correlation between isoflavone intake and cancer risk? In fact the significance obtained for urinary and serum genistein and daidzein concentrations was lost when estradiol levels were taken into account [1]--a fact not mentioned in the abstract of the study. Thus, none of the case-control studies in the table of Duffy et al. confirms a potential cancer risk.

Whether a protective effect of soy against breast cancer exists or not, one would have to differentiate between the lack of a protective effect and a cancer-promoting effect. Apparently, the conclusion of Duffy et al. that processed soy products may have detrimental effects compared with soy flour and tofu is derived from one single animal study [2]. This study, however, used ovariectomized athymic nude mice transplanted with MCF-7 breast cancer cells, a highly sensitive system to detect even small agonistic effects at the estrogen receptor ER-alpha. It is well known that soy isoflavones predominantly act through an agonistic activity at ER-beta [3], whereas it is doubtful that a relevant activation of ER-alpha could be reached in the human organism. Binding affinity of genistein to ER-alpha was only 4% of that of estradiol, whereas binding affinity to ER-beta was 87% compared to estradiol [4]. In addition, activation of ER-beta by genistein counteracts ER-alpha-mediated effects on the transcriptional level [4]. The protective biological potency of genistein at ER-beta is further increased in the presence of estrogen--a situation found in the human organism, but not in the model experiments focusing on pure ER-alpha-effects of isoflavones [5]. Given these complex interactions, it seems unlikely that relevant concentrations for an activation of ER-alpha by isoflavones will be reached in the human organism, even with highly dosed supplements [5].

Only recently, the implications of ER-beta-agonists for the inhibition of MCF-7 breast cancer cells were demonstrated [6,7]. Selective ER-beta agonists are currently developed from genistein as new anti-cancer agents [8]. Phenomena as observed in the model of Allred et al. (2004) and many other similarly designed studies must necessarily be expected as a consequence of the small residual effect of isoflavones at ER-alpha in the absence of estrogen and of ER-beta. Thus, answers to the question of cancer risk cannot be derived from selective ER-alpha models (in vitro and in vivo) [9,10]--they would necessarily have to come from clinical or epidemiological evidence.

Duffy et al. (2007) give such evidence: they cite an increase of breast tissue density observed by Petrakis et al. (1996) and by McMichael-Phillips et al. (1998) [11,12]. But do these studies really give a cause for concern? The study of Petrakis was conducted as a non-controlled pilot trial in an inhomogeneous study population, where at least one of the participants used an oral contraceptive, and another obtained hormonal replacement therapy. No inclusion criteria were defined. Fifteen women terminated the study regularly (the abstract mentions 24, which is, however, not consistent with the reported details). In seven participants an epithelial hyperplasia was found, which strangely enough resolved after discontinuation of isoflavone intake (38 mg/day over 6 months), although some of the patients received hormonal replacement. Petrakis et al. themselves called for a closer examination in a more systematic study--which was in fact conducted by McMichael-Phillips et al., a study seemingly confirming the risk of increased breast tissue proliferation under the impact of soy isoflavones. However, this trial was an intermediate analysis of the complete set of data published by Hargreaves et al. (1999) shortly afterwards [13]. In the full analysis, the authors could

explicitly not confirm an effect of soy isoflavones on cell proliferation and differentiation, or on biomarkers of apoptosis, while confirming the existence of certain estrogen-like effects. This systematic trial not only devalidated the intermediate publication of McMichael-Phillips et al. (1998), but also gives an answer to the question raised by Petrakis et al. (1996). Breast density and endometrial proliferation has since then been examined as a safety parameter in many clinical efficacy and safety trials, with no hint to increased proliferation in any of these studies (e.g., [14]).

Finally, Duffy et al. state that there is 搉o compelling evidence that phytoestrogens help in menopausal symptoms? In fact, the results of the four studies analyzed by the authors will necessarily lead to this conclusion. However, we find the selection of studies rather unfortunate: All four studies were performed in tamoxifen-treated patients, partly showing hot flushes not of menopausal origin, but as an adverse effect of tamoxifen treatment. A more suitable answer may be expected by analyzing the studies where soy preparations have been used in menopausal non-cancer patients, as recently and independently published [15,16]. Williamson-Hughes et al. (2006) come to the conclusion that 搃eports concluding that isoflavone supplements do not significantly reduce hot flash symptoms may be incorrect?[15]. The meta-analysis of Nelson et al. (2006) is especially interesting: Despite the negative overall conclusion of Nelson et al. from all analyzed studies including those of an inadequate design and those in women treated with tamoxifen, the analysis of the menopause trials in non-cancer patients gave a statistically clear and positive outcome in favor of soy [16]! Yet both analyses did not even include the most recent double-blind trials [17-19]. An additional benefit of soy preparations has been demonstrated for bone turnover [20].

Even the conclusion of a specific risk of soy for tamoxifen-treated patients in the sense of counteracting the effects of the cancer treatment is not confirmed through the clinical experience cited in the review of Duffy et al. (2007). Additional studies are worth mentioning in this context: According to the cohort study of Boyapati et al. (2005), soy intake had no negative effect on breast cancer survival in 1,459 women [21], whereas Wu et al. (2007) excluded an effect of soy on tamoxifen serum levels [22]. Latest research rather points towards the possibility of an improved effect of tamoxifen when combined with an ER-beta agonist [6,7]--which (if clinically relevant and if applicable to genistein, both remain to be confirmed) would contradict the hypothesis of an inhibition of tamoxifen effects through isoflavones, and may in the long run potentially even lead to a recommendation of soy intake in women treated for breast cancer.

Concluding, the benefit of soy against menopausal complaints has meanwhile been confirmed, whereas the risk remains theoretical and contradicting the general clinical and epidemiological experience.

References

1. Grace PB, Taylor JI, Low YL, et al. Phytoestrogen concentrations in serum and spot urine as biomarkers for dietary phytoestrogen intake and their relation to breast cancer risk in European Prospective Investigation of Cancer and Nutrition-Norfolk. Cancer Epidemiol Biomarkers Prev 2004;13(5):698-708.

2. Allred CD, Allred KF, Ju YH, et al. Soy processing influences growth of estrogen-dependent breast cancer tumors. Carcinogenesis 2004;25(9):1649-1657.

3. Heldring N, Pike A, Andersson S, et al. Estrogen receptors: how do they signal and what are their targets. Physiol Rev 2007;87(3):905-931.

4. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med 2002;346 (5):340-352.

5. Harris DM, Besselink E, Henning SM, et al. Phytoestrogens induce differential estrogen receptor alpha- or Beta-mediated responses in transfected breast cancer cells. Exp Biol Med (Maywood) 2005;230(8):558-568.

6. Behrens D, Gill JH, Fichtner I. Loss of tumourigenicity of stably ERbeta-transfected MCF-7 breast cancer cells. Mol Cell Endocrinol 2007;274(1-2):19-29.

7. Hodges-Gallagher L, Valentine CD, Bader SE, Kushner PJ. Estrogen receptor beta increases the efficacy of antiestrogens by effects on apoptosis and cell cycling in breast cancer cells. Breast Cancer Res Treat 2007; Publication ahead of print, DOI 10.1007/s10549-007-9640-6.

8. Sarkar FH, Adsule S, Padhye S, et al. The role of genistein and synthetic derivatives of isoflavone in cancer prevention and therapy. Mini Rev Med Chem 2006;6(4):401-407.

9. Messina M, McCaskill-Stevens W, Lampe JW. Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. J Natl Cancer Inst 2006;98(18):1275-1284.

10. Cheng G, Warner M, Gustafsson JA, Landgren BM. Letter to the Editor. Menopause 2007;14(5):958-959.

11. Petrakis NL, Barnes S, King EB, et al. Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. Cancer Epidemiol Biomarkers Prev 1996;5(10):785-794.

12. McMichael-Phillips DF, Harding C, Morton M, et al. Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. Am J Clin Nutr 1998;68(6 Suppl):1431S-1435S.

13. Hargreaves DF, Potten CS, Harding C, et al. Two-week

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14. Palacios S, Pornel B, Bergeron C, et al. Endometrial safety assessment of a specific and standardized soy extract according to international guidelines. Menopause 2007:14 (6):1006-1011.

15. Williamson-Hughes PS, Flickinger BD, Messina MJ, Empie MW. Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies. Menopause 2006;13(5):831-839.

16. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 2006;295(17):2057-2071.

17. Kaari C, Haidar MA, Junior JM, et al. Randomized clinical trial comparing conjugated equine estrogens and isoflavones in postmenopausal women: a pilot study. Maturitas 2006;53 (1):49-58.

18. Cheng G, Wilczek B, Warner M, et al. Isoflavone treatment for acute menopausal symptoms. Menopause 2007;14(3 Pt 1):468-473.

19. D'Anna R, Cannata ML, Atteritano M, et al. Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study. Menopause 2007;14(4):648-655.

20. Ma DF, Qin LQ, Wang PY, Katoh R. Soy isoflavone intake inhibits bone resorption and stimulates bone formation in menopausal women: meta-analysis of randomized controlled trials. Eur J Clin Nutr 2007; Publication ahead of print, DOI: 10.1038/sj.ejcn.1602748.

21. Boyapati SM, Shu XO, Ruan ZX, et al. Soyfood intake and breast cancer survival: a followup of the Shanghai Breast Cancer Study. Breast Cancer Res Treat 2005;92(1):11-17.

22. Wu AH, Pike MC, Williams LD, et al. Tamoxifen, soy, and lifestyle factors in Asian American women with breast cancer. J Clin Oncol 2007;25(21):3024-3030.