Phytoestrogens and Estrogen-Sensitive Cancers: Review of the Evidence

Eric Yarnell, ND, RH (AHG)

Abstract

Concern has been raised about the effects of phytoestrogenic plants and plant extracts on estrogen-sensitive cancers, largely based on in vitro and animal research. Soy (*Glycine max*) and other legumes and their isoflavones, notably genistein and daidzein, are the plants and constituents most studied, including the potential importance of metabolism of these isoflavones by gut flora to equol and its cogeners. Flax (*Linum usitatissimum*) and its lignans, notably secoisolariciresinol, is also discussed. Essentially, all existing epidemiologic and clinical trial research shows either benefit or absence of harm from these compounds, with some subtleties about dose and equol or enterolactone formation potentially being important. This paper will review the human research and discuss why it is at odds with in vitro research.

Keywords: phytoestrogen, isoflavone, breast cancer, prostate cancer, soy

Introduction

Phytoestrogens are plant compounds that do not look like estrogen, but which do activate estrogen receptors. The best studied among several groups of phytoestrogenic compounds are the isoflavones (see Fig. 1) found throughout the Fabaceae (legume) family.[1] Unlike other flavonoids, the phenolic B ring is attached at carbon 2 of the C ring instead of carbon 3. This small but crucial change makes isoflavones as a class phytoestrogens, while other flavonoids do not have this effect. However, prenylated isoflavones, coumestans, and lignans have also been demonstrated to act as phytoestrogens.

Though fears are continually raised suggesting that phytoestrogen-rich plants and isolated phytoestrogens may cause or aggravate estrogen-sensitive cancers, particularly breast, ovarian, uterine, and prostate cancers, these are generally based on studies showing stimulation of cell lines in vitro or in animal models involving exposure to isolated phytoestrogenic constituents.[2,3] Phytoestrogenic constituents with different effects at various concentrations are extrapolated from in vitro studies, but this has proven to be inaccurate, as the constituents are metabolized, including by gut flora, when ingested (sometimes to far more potent phytoestrogens).[4] There are many reasons that these results should not be extrapolated to humans, as summarized in Table 1 and as will be discussed in depth below. Instead, there is ample evidence supporting that phytoestrogen-rich plants and their constituents are beneficial for both preventing and treating estrogen-sensitive cancers in many people or, at worst, have no effect.

Isoflavones as PhytoSERMs and Beyond

Isoflavones are weak estrogen receptor beta (ERβ) agonists and vastly weaker estrogen receptor alpha (ERα) agonists. If the potency for activation of these receptors is set at 1 for estradiol, then genistein has about a 0.33 potency at ERβ and 0.001 potency at ERα.[5] Put another way, it takes three times the dose of genistein to have the same effect as estradiol on activating ERβ and 1000 times the dose of genistein as estradiol to have the same effect on activating ERα. Functionally, this means that isoflavones do not significantly activate ERα in the body because levels of the constituents and their metabolites cannot generally achieve levels high enough to activate them and also because ERβ appears to act primarily as a negative regulator of ERα.[6,7] This is important because ERα receptors tend to mediate the harmful effects of estrogens because they are found much more broadly throughout the body compared with ERβ, with distribution limited to the reproductive organs, bones, brain, and blood vessels. Genistein also has mixed agonist/antagonist effects on androgen receptors in mice, and ERβ agonism exerts anti-androgen effects in prostate cancer cells.[8,9] Because of the estrogen receptor selectivity of most phytoestrogens, another term coined for these constituents is phytoSERMs (selective estrogen receptor modulators).[10] As stated by Böttner et al., "It is not the ligand, it is the multiplicity of receptors which determines the plethora of estrogen actions."[6]

Phytoestrogenic compounds have antineoplastic effects unrelated to their effects on estrogen receptors. A sampling of the wide array of reported anticancer effects of isoflavones and their metabolites is summarized in Table 2. Many, many more could be listed for a large number of constituents. This sample serves to illustrate that reducing phytoestrogens' effects solely to their impact on estrogen receptors misses a much bigger anticancer picture.

The metabolism of phytoestrogenic compounds appears to play an important role in their effects in humans. The best

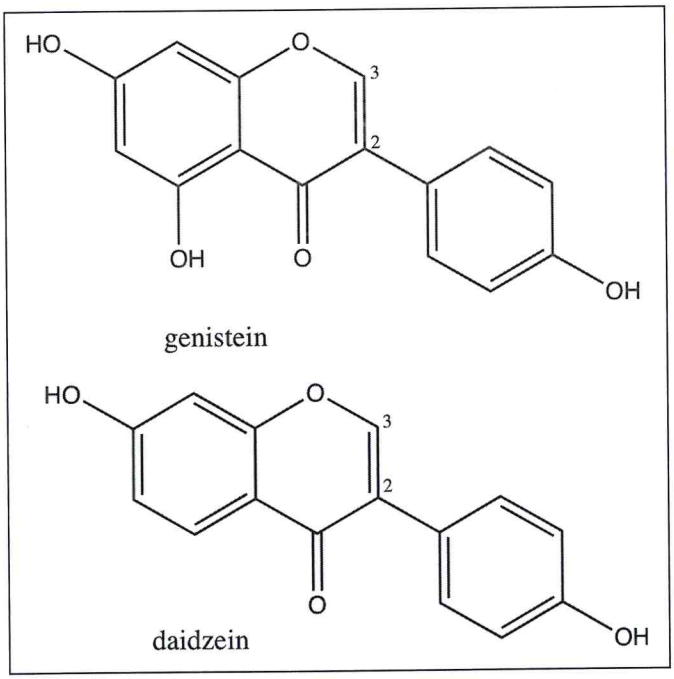

Figure 1. The key isoflavones genistein and daidzein.

studied is the metabolism of daidzein to *S*-equol and genistein to 5-hydroxyequol by gut flora.[11] *Slackia isoflavoniconvertens*, *S. equolifaciens*, and *Adlercreutzia equolifaciens* are three anaerobic gut flora known to be responsible for these conversions.[12–14] Some of these are also responsible for the metabolism of catechins in coffee, green tea, and chocolate.[15] Equol-producing premenopausal women were shown to have lower serum estrone, testosterone, cortisol, and DHEA levels but higher sex hormone-binding globulin (SHBG) and midluteal progesterone levels than non-equol producers were.[16] This profile is much more associated with a low risk of breast cancer. Equol producers also had higher 2-hydroestrone compared to 16αhydroestrogen levels in their urine, a pattern that is associated with a reduced risk of breast cancer.[17] Equol production was not related to breast cancer risk in a cross-sectional study in Alabama (including both white and black women), but intake of phytoestrogens was extremely low in this cohort.[18] Only 18% of this group were equol producers, also a very low number, which could have skewed the results further. This study also found that no equol producers had ER-negative breast cancer, a finding noted in other studies discussed below.

Non-equol producers were more likely to have aggressive disease in a Japanese cohort of prostate cancer patients.[19] Surprisingly, equol producers in this study were more prolific among prostate cancer patients than they were among healthy controls in this cohort. Equol formation was significantly less common among Japanese and Korean men with prostate cancer compared with healthy controls in an observation trial.[20] Equol formation was very low in Americans with prostate cancer and healthy controls (17% and 14%, respectively, compared to >30% in all Asian men), and there was no significant difference between the groups as a result.

Lignans as Phytoestrogens

The other most studied constituents that act as phytoestrogens are various lignans, particularly secoisolariciresinol from *Linum usitatissimum* (flax) and other nuts and seeds. Lignans have a strong parallel to isoflavones in that they are clearly metabolized by gut flora to metabolites (particularly enterolactone and enterodiol) that appear to be what are mainly absorbed and active in the body in patients with the appropriate bacterial species.[21] Enterolactone, as well as secoisolariciresinol, have both been shown to activate and upregulate the third ER, known as the G protein-coupled ER1, an effect that interferes with the pathogenesis of benign prostatic hyperplasia experimentally.[22] There are also many studies confirming these lignans have antineoplastic effects unrelated to any impact on ERs.[23] In animal models, secoisolariciresinol clearly intereferes with breast cancer and has no stimulating effect on ovarian tissue.[24]

Phytoestrogens and Cancer Prevention

Quite a few epidemiologic studies have reviewed the impact of regular consumption of phytoestrogen-rich foods on rates of

Table 1. Reasons Why Phytoestrogens Are Helpful in Estrogen-Responsive Cancers

1. Phytoestrogens are selective estrogen receptor modulators, most often because they are weak agonists of ERβ (which mostly results in inhibition of estrogenic activity) and vastly weaker agonists of ERα.
2. There are other antineoplastic constituents besides phytoestrogens in herbs that contain phytoestrogens.
3. Phytoestrogens have anticancer activities that are independent of their effects on estrogen receptors.
4. Phytoestrogen-rich plants and isolated phytoestrogenic constituents have proven helpful in clinical trials for patients with estrogen-responsive cancers.
5. Differences in gut flora metabolism of phytoestrogenic constituents play a significant role in whether or not people who consume plants containing these compounds have a beneficial or no result.
6. The hormonal and general milieu of the human body affect the activity of phytoestrogens, and thus in vitro models produce results that do not reflect what happens clinically.

ERβ, estrogen receptor beta.

Table 2. Select Non-Estrogenic Antineoplastic Effects of Phytoestrogenic Isoflavones

Constituent or metabolite	Antineoplastic effect	Reference
Genistein	Polo-like kinase 1 inhibitor	Shin et al. 2016[a]
	Epidermal growth factor receptor inhibitor	Yan et al. 2010[b]
	Inhibition of cancer stem cells	Sekar et al. 2016[c]
	Induces apoptosis involving phosphorylation of 226 proteins	Fang et al. 2016[d]
	Downregulates pro-cancer microRNA miR-155	de la Parra et al. 2016[e]
	Targets multiple signaling pathways crucial to cancer including caspases, Bcl-2, ERK1/2, NF-κB, MAPK, Wnt, and PI3K/Akt	Spagnuolo et al. 2015[f]
	Induces BRCA2 tumor suppressor	Vissac-Sabatier et al. 2003[g]
Daidzein	HER2/neu (erbB-2) suppression	Choi and Kim 2013[h]
	Induces apoptosis via Bcl-2 downregulation and caspase upregulation	Park et al. 2013[i]
	Anticancer epigenetic effects involving DNA methylation, histone modification, and microRNA expression	Rietjens et al. 2013[j]
	Downregulates fibroblast growth factor receptor 3	He et al. 2016[k]
Equol	p53 induction	Choi and Kim 2011[l]
	Induces apoptosis by inducing ERK1/2	Yang et al. 2016[m]
	Induces cell cycle arrest and apoptosis via modulation of Akt pathway	Yang et al. 2015[n]

[a]Shin SB, Woo SU, Chin YW, et al. Sensitivity of TP53-mutated cancer cells to the phytoestrogen genistein is associated with direct inhibition of Plk1 activity. J Cell Physiol 2016 Nov 9 [Epub ahead of print].
[b]Yan GR, Xiao CL, He GW, et al. Global phosphoproteomic effects of natural tyrosine kinase inhibitor, genistein, on signaling pathways. Proteomics 2010;10:976–986.
[c]Sekar V, Anandasadagopan SK, Ganapasam S. Genistein regulates tumor microenvironment and exhibits anticancer effect in dimethyl hydrazine-induced experimental colon carcinogenesis. Biofactors 2016 Jun 3 [Epub ahead of print].
[d]Fang Y, Zhang Q, Wang X, et al. Quantitative phosphoproteomics reveals genistein as a modulator of cell cycle and DNA damage response pathways in triple-negative breast cancer cells. Int J Oncol 2016;48:1016–1028.
[e]de la Parra C, Castillo-Pichardo L, Cruz-Collazo A, et al. Soy isoflavone genistein-mediated downregulation of miR-155 contributes to the anticancer effects of genistein. Nutr Cancer 2016;68:154–164.
[f]Spagnuolo C, Russo GL, Orhan IE, et al. Genistein and cancer: Current status, challenges, and future directions. Adv Nutr 2015;6:408–419.
[g]Vissac-Sabatier C, Bignon YJ, Bernard-Gallon DJ. Effects of the phytoestrogens genistein and daidzein on BRCA2 tumor suppressor gene expression in breast cell lines. Nutr Cancer 2003;45:247–255.
[h]Choi EJ, Kim GH. Antiproliferative activity of daidzein and genistein may be related to ERα/c-erbB-2 expression in human breast cancer cells. Mol Med Rep 2013;7:781–784.
[i]Park HJ, Jeon YK, You DH, Nam MJ. Daidzein causes cytochrome c-mediated apoptosis via the Bcl-2 family in human hepatic cancer cells. Food Chem Toxicol 2013;60:542–549.
[j]Rietjens IM, Sotoca AM, Vervoort J, Louisse J. Mechanisms underlying the dualistic mode of action of major soy isoflavones in relation to cell proliferation and cancer risks. Mol Nutr Food Res 2013;57:100–113.
[k]He Y, Wu X, Cao Y, et al. Daidzein exerts anti-tumor activity against bladder cancer cells via inhibition of FGFR3 pathway. Neoplasma. 2016;63:523–531.
[l]Choi EJ, Kim GH. Anticancer mechanism of equol in 7,12-dimethylbenz(a)anthracene-treated animals. Int J Oncol 2011;39:747–754.
[m]Yang Z, Zhao Y, Yao Y, et al. Equol induces mitochondria-dependent apoptosis in human gastric cancer cells via the sustained activation of ERK1/2 pathway. Mol Cells 2016;39:742–749.
[n]Yang ZP, Zhao Y, Huang F, et al. Equol inhibits proliferation of human gastric carcinoma cells via modulating Akt pathway. World J Gastroenterol 2015;21:10385–10399.

estrogen-sensitive cancers such as that of the breast and prostate. A meta-analysis of studies in Korea found a higher intake of soy foods correlated to a significantly lower risk of developing breast cancer.[25] Similar findings were reported in another meta-analysis of studies looking at Chinese women.[26] Caution is warranted though, as one meta-analysis in Chinese women found that only case-control studies support a protective role for soy foods against breast cancer, while more powerful cohort studies do not; other meta-analyses have not found this difference though.[27,28] Protection is much more marginal in studies in Western populations, though this may simply reflect the vastly lower intake of phytoestrogen-rich foods.[29] Similar results in another meta-analysis suggest there is a clear difference between Asian and Western women when it comes to soy foods and breast cancer risk, and likely this is a combination of low intake of such foods in the West and a correspondingly low level of equol formation.[30] This meta-analysis also reported a reduced risk of breast cancer recurrence in Asian women with high soy diets prior to and after diagnosis with breast cancer. Asian women with high soy intake have about a 20% reduction in breast cancer risk overall based on many epidemiologic studies. Though more limited, epidemiologic research overall suggests higher levels of soy consumption helps to prevent endometrial, cervical, and ovarian cancers.[31]

Similarly, numerous epidemiologic studies have found a protective effect against prostate cancer from high dietary ingestion of phytoestrogen-rich foods, particularly legumes and soy foods. A meta-analysis of 29 studies found that higher intake of such foods reduced risk of developing prostate cancer for men of Asian

and European but not African descent.[32] Other meta-analyses concur with these findings, and particularly note that tofu is protective, and that men of Asian descent benefit the most.[33,34] A meta-analysis of two randomized trials of supplementing soy isoflavones or soy foods found that they reduced risk of prostate cancer in men at risk of developing the disease.[35] A meta-analysis of 23 epidemiologic studies involving >150,000 men found that higher serum levels of daidzein, genistein, and the isoflavone glycitein were protective against prostate cancer, but total isoflavones or equol, total lignans, secoisolariciresinol, and other specific lignan phyeostrogens were not.[36] However, it is not clear that the populations studied ate very high levels of some of these compounds, and so the highest levels of intake still led to subtherapeutic concentrations of the compounds and/or their metabolites to have clinical effects.

There is ample evidence that soy intake also correlates with less severe breast cancer when it does happen. Low intake of legume isoflavones was associated with a signficant increase in risk of developing ER-negative (more severe) breast cancer than ER-positive in a case-control study of 124 premenopausal breast cancer patients.[37] A similar benefit was seen in the California Teachers Study, a large cohort trial ($n = 91,779$).[38] Results from the Shanghai Women's Health Study from 1996 to 2000 confirm that high soy intake was associated with lower rates of ER-negative breast cancer, though this effect was only found in premenopausal patients, while ER-positive breast cancer was less common in postmenopausal patients.[39] A study in Guangdong province, China, found that higher soy intake reduced incidence of all types of breast cancer, regardless of ER status.[40] Long-term soy consumption by women with triple-negative breast cancer revealed that their tumors had significantly higher levels of tumor suppressors and lower levels of oncogene expression, associated with less severe disease.[41] A small sample suggested soy did not increase overall recurrence of breast cancer, but did increase recurrence in HER2-positive patients.[42] However, this analysis was based on just 25 cases, calling its conclusions into doubt.

There is much less research on other phytoestrogen-rich herbs or foods for preventing cancer. However, the Ontario Women's Diet and Health Study compared 2999 Canadian women with breast cancer and 3370 matched health controls, and higher flax seed or flax bread consumption was found to be significantly associated with reduced risk of breast cancer.[43] High enterolactone and equol production were protective against breast cancer in an Australian case-control study.[44] Two case-control studies (one American and one German) found that higher serum enterolactone and enterodiol levels, as markers of dietary lignan intake, were protective against breast cancer risk, though this was mostly only seen in women with CYP17 TC or CC genotypes.[45,46] CYP17 codes the enzyme that is the rate-limiting step for estradiol synthesis; these genotypes have previously been associated with a weak increase in breast cancer risk in some research. However, a review of four case-control and seven prospective epidemiologic studies found no evidence that serum enterolactone levels are protective against prostate cancer.[47]

Results of Clinical Trials

It is well-known that clinical trials are the most definitive way to prove if something is effective or harmful in humans. If phytoestrogens were harmful in patients with estrogen-sensitive cancers, then the ultimate proof of this would come from clinical trials. Multiple clinical trials have been conducted in patients with these cancers, and they uniformly either show a benefit or sometimes no effect, but hardly a wave of dangerous outcomes. This is ultimately the final proof that regardless of any preclinical research, phytoestrogens and the plants they come from are not only safe, but also helpful in patients with estrogen-sensitive cancers.

A pilot clinical trial has investigated the effects of 200 mg of isoflavone supplements from soy in 17 American women recently diagnosed with invasive breast cancer.[48] A group of 26 historical controls matched based on multiple clinical features was used for comparison. After 2 weeks, the 17 volunteers underwent lumpectomy or mastectomy, and their tumors were examined. There was no sign of stimulation of the breast tumors, but instead there was a nonsignificant trend toward higher apoptosis/mitosis ratios in the treated women compared with historical controls, suggesting an antiproliferative effect for isoflavones.

At least three double-blind, placebo-controlled clinical trials have investigated the efficacy of isoflavones from soy on reducing hot flashes or other menopausal symptoms in women with breast cancer. In one, 62 postmenopausal Finnish women with a history of breast cancer were randomized to take 114 mg of total isoflavones per day (containing 58% glycitein, 36% daidzein, and 6% genistein, a rather different mixture than most studies have used) or placebo for 3 months.[49] None were taking tamoxifen or raloxifene. There was no difference between treatments on menopausal symptoms, though equol formation status was not assessed. There was no evidence of any promotion of recurrent breast cancer.

Another trial involved 123 postmenopauseal Canadian women undergoing treatment for breast cancer with exacerbated hot flashes who were randomized to a soy beverage containing 90 mg of total isoflavones daily or a placebo beverage lacking isoflavones for 12 weeks.[50] Both treatments led to very significant reductions in hot flashes compared with baseline, but there was no statistically significant difference between the groups. Tamoxifen use was relatively low in this cohort as well, so it did not explain the differences. Again, there was no evidence of any exacerbation of breast cancer by the soy beverage. There was high interindividual variability in isoflavone levels in the soy group, though equol formation was not assessed.

A third trial randomized 177 American women who were breast cancer survivors with severe hot flashes to 50 mg of isoflavones (40% genistein, 40% daidzein, 20% glycitein) or placebo three times daily for 9 weeks.[51] Most of the women were taking tamoxifen, and some were taking raloxifene. There was no difference between the groups in hot flash frequency or severity. There was also no difference in breast cancer recurrence or any other sign of activation or aggravation of breast cancer. It is possible that the doses and duration of all of these

trials have been insufficient to be effective, or that soy isoflavones simply are not useful for hot flashes. And again, none of the trials assessed equol production, which might be a key factor in efficacy of these products, but very low levels of equol formation in Western populations might explain low efficacy.

These and five other clinical trials using soy isoflavones have reported no incidence of endometrial hyperplasia, further supporting that phytoestrogens do not act like estrogens in postmenopausal women at reasonable doses.[52] One study found that just 4/298 women developed endometrial hyperplasia after taking 150 mg of of isoflavones per day for 5 years, though this was statistically significant compared with placebo.[53] A meta-analysis of 40 randomized trials of soy and *Trifolium* spp. (clover), another source of isoflavones, found no evidence of causation, stimulation, or aggravation of breast cancer in any setting.[54]

Though flax has been little studied in women with breast cancer, existing non-randomized trials have only shown evidence that it is beneficial at inhibiting cancer proliferation.[55] Observational studies suggest higher flax intake is correlated with reduced mortality from breast cancer.[55] One study found that the aromatase inhibitor anastrozole, commonly used in women with breast cancer, interfered with enterolactone formation in women with breast cancer taking flax.[56]

A preliminary study in men with prostate cancer found that 300 or 600 mg of genistein and half as much daidzein daily for up to 84 days caused an increase in breast changes and hot flashes, with prostate specific antigen (PSA) levels climbing slightly less quickly when patients were not taking isoflavones, though the difference was not statistically significant.[57] One open trial administered 100 mg twice daily of an isoflavone to 39 American men with stage 1–3 prostate cancer.[58] Total PSA levels stabilized in 83% of patients with androgen-sensitive cancer and 35% of those with androgen-independent disease; the rate of rise of total PSA slowed significantly compared to baseline for all participants with a median treatment duration of 5.5 months. A meta-analysis of six randomized trials of isoflavone supplements in men with active prostate cancer concluded there was no benefit in terms of changes in PSA levels, but all were of short duration and small sample size.[59] There was clearly no aggravation of prostate cancer found in these trials.

Conclusion

The evidence from human studies is consistent that phytoestrogens, be they isoflavones or lignans, and the foods/herbs they come from do not cause, promote, or aggravate various estrogen-sensitive cancers, including breast, endometrial, ovarian, cervical, and prostate. While more powerful clinical trials would be ideal to confirm these findings, particularly on the cancer preventative effects that consistently show up in epidemiologic studies of high intake of soy foods and flax, there is no clear reason to avoid reasonable amounts of these agents. Extrapolating from single properties of complex substances seen in vitro to humans is very rarely reasonable. Although isolated phytoestrogens stimulate estrogen-sensitive cancer cells in some in vitro models, this does not mean that these findings translate into clinical reality. ■

References

1. Cornwell T, Cohick W, Raskin I. Dietary phytoestrogens and health. Phytochemistry 2004;65:995–1016.

2. Helferich WG, Andrade JE, Hoagland MS. Phytoestrogens and breast cancer: A complex story. Inflammopharmacology 2008;16:219–226.

3. Allred CD, Allred KF, Ju YH, et al. Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose-dependent manner. Cancer Res 2001;61:5045–5050.

4. Magee PJ, Rowland IR. Phyto-oestrogens, their mechanism of action: Current evidence for a role in breast and prostate cancer. Br J Nutr 2004;91:513–531.

5. Kuiper GG, Lemmen JG, Carlsson B, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor b. Endocrinology 1998;139:4252–4263.

6. Böttner M, Thelen P, Jarry H. Estrogen receptor beta: Tissue distribution and the still largely enigmatic physiological function. J Steroid Biochem Mol Biol 2014;139:245–251.

7. Chang EC, Charn TH, Park SH, et al. Estrogen Receptors alpha and beta as determinants of gene expression: Influence of ligand, dose, and chromatin binding. Mol Endocrinol 2008;22:1032–1043.

8. Pihlajamaa P, Zhang FP, Saarinen L, et al.The phytoestrogen genistein is a tissue-specific androgen receptor modulator. Endocrinology 2011;152:4395–4405.

9. Thelen P, Wuttke W, Seidlová-Wuttke D. Phytoestrogens selective for the estrogen receptor beta exert anti-androgenic effects in castration resistant prostate cancer. J Steroid Biochem Molec Biol 2014;139:290–293.

10. Simons R, Gruppen H, Bovee TF, et al. Prenylated isoflavonoids from plants as selective estrogen receptor modulators (phytoSERMs). Food Funct 2012;3:810–827.

11. Setchell KD, Clerici C, Lephart ED, et al. *S*-equol, a potent ligand for estrogen receptor beta, is the exclusive enantiomeric form of the soy isoflavone metabolite produced by human intestinal bacterial flora. Am J Clin Nutr 2005;81:1072–1079.

12. Matthies A, Blaut M, Braune A. Isolation of a human intestinal bacterium capable of daidzein and genistein conversion. Appl Environ Microbiol 2009;75:1740–1744.

13. Jin JS, Kitahara M, Sakamoto M, et al. *Slackia equolifaciens* sp. nov., a human intestinal bacterium capable of producing equol. Int J Syst Evol Microbiol 2010;60:1721–1724.

14. Maruo T, Sakamoto M, Ito C, et al. *Adlercreutzia equolifaciens* gen. nov., sp. nov., an equol-producing bacterium isolated from human faeces, and emended description of the genus Eggerthella. Int J Syst Evol Microbiol 2008;58:1221–1227.

15. Takagaki A, Nanjo F. Biotransformation of (-)-epigallocatechin and (-)-gallocatechin by intestinal bacteria involved in isoflavone metabolism. Biol Pharm Bull 2015;38:325–330.

16. Duncan AM, Merz-Demlow BE, Xu X, et al. Premenopausal equol excretors show plasma hormone profiles associated with lowered risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2000;9:581–586.

17. Atkinson C, Skor HE, Dawn Fitzgibbons E, et al. Urinary equol excretion in relation to 2-hydroxyestrone and 16alpha-hydroxyestrone concentrations: An observational study of young to middle-aged women. J Steroid Biochem Mol Biol 2003;86:71–77.

18. Virk-Baker MK, Barnes S, Krontiras H, Nagy TR. S-(-)equol producing status not associated with breast cancer risk among low isoflavone consuming US postmenopausal women undergoing a physician recommended breast biopsy. Nutr Res 2014;34:116–125.

19. Akaza H, Miyanaga N, Takashima N, et al. Is daidzein non-metabolizer a high risk for prostate cancer? A case-controlled study of serum soybean isoflavone concentration. Jpn J Clin Oncol 2002;32:296–300.

20. Akaza H, Miyanaga N, Takashima N, et al. Comparisons of percent equol producers between prostate cancer patients and controls: Case-controlled studies of isoflavones in Japanese, Korean and American Residents. Jpn J Clin Oncol 2004;34:86–89.

21. Gaya P, Medina M, Sánchez-Jiménez A, Landete JM. Phytoestrogen metabolism by adult human gut microbiota. Molecules 2016;21:E1034.

22. Ren GY, Chen CY, Chen WG, et al. The treatment effects of flaxseed-derived secoisolariciresinol diglycoside and its metabolite enterolactone on benign prostatic hyperplasia involve the G protein-coupled estrogen receptor 1. Appl Physiol Nutr Metab 2016;41:1303–1310.

23. Adolphe JL, Whiting SJ, Juurlink BH, et al. Health effects with consumption of the flax lignan secoisolariciresinol diglucoside. Br J Nutr 2010;103:929–938.

24. Delman DM, Fabian CJ, Kimler BF, et al. Effects of flaxseed lignan secoisolariciresinol diglucosideon preneoplastic biomarkers of cancer progression in a model of simultaneous breast and ovarian cancer development. Nutr Cancer 2015;67:857–864.

25. Woo HD, Park S, Oh K, et al. Diet and cancer risk in the Korean population: A meta-analysis. Asian Pac J Cancer Prev 2014;15:8509–8519.

26. Liu XO, Huang YB, Gao Y, et al. Association between dietary factors and breast cancer risk among Chinese females: Systematic review and meta-analysis. Asian Pac J Cancer Prev 2014;15:1291–1298.

27. Zhong X, Zhang C. Soy food intake and breast cancer risk: A meta-analysis. Wei Sheng Yan Jiu 2012;41:670–676 [in Chinese].

28. Qin LQ, Xu JY, Wang PY, Hoshi K. Soyfood intake in the prevention of breast cancer risk in women: A meta-analysis of observational epidemiological studies. J Nutr Sci Vitaminol (Tokyo) 2006;52:428–436.

29. Chen M, Rao Y, Zheng Y, et al. Association between soy isoflavone intake and breast cancer risk for pre- and post-menopausal women: A meta-analysis of epidemiological studies. PLOS ONE 2014;9:e89288.

30. Dong JY, Qin LQ. Soy isoflavones consumption and risk of breast cancer incidence or recurrence: A meta-analysis of prospective studies. Breast Cancer Res Treat 2011;125:315–323.

31. Andres S, Abraham K, Appel KE, Lampen A. Risks and benefits of dietary isoflavones for cancer. Crit Rev Toxicol 2011;41:463–506.

32. Zhang M, Wang K, Chen L, et al. Is phytoestrogen intake associated with decreased risk of prostate cancer? A systematic review of epidemiological studies based on 17,546 cases. Andrology 2016;4:745–756.

33. Hwang YW, Kim SY, Jee SH, et al. Soy food consumption and risk of prostate cancer: A meta-analysis of observational studies. Nutr Cancer 2009;61:598–606.

34. Yan L, Spitznagel EL. Soy consumption and prostate cancer risk in men: A revisit of a meta-analysis. Am J Clin Nutr 2009;89:1155–1163.

35. van Die MD, Bone KM, Williams SG, Pirotta MV. Soy and soy isoflavones in prostate cancer: A systematic review and meta-analysis of randomized controlled trials. BJU Int 2014;113:E119–E130.

36. Zhang Q, Feng H, Qluwakemi B, et al. Phytoestrogens and risk of prostate cancer: An updated meta-analysis of epidemiologic studies. Int J Food Sci Nutr 2016 Aug 9 [Epub ahead of print].

37. 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;51:162–169.

38. Link LB, Canchola AJ, Bernstein L, et al. Dietary patterns and breast cancer risk in the California Teachers Study cohort. Am J Clin Nutr 2013;98:1524–1532.

39. Baglia ML, Zheng W, Li H, et al. The association of soy food consumption with the risk of subtype of breast cancers defined by hormone receptor and HER2 status. Int J Cancer 2016;139:742–748.

40. Zhang C, Ho SC, Lin F, et al. Soy product and isoflavone intake and breast cancer risk defined by hormone receptor status. Cancer Sci 2010;101:501–507.

41. Guo X, Cai Q, Bao P, et al. Long-term soy consumption and tumor tissue MicroRNA and gene expression in triple-negative breast cancer. Cancer 2016;122:2544–2551.

42. Woo HD, Park KS, Ro J, Kim J. Differential influence of dietary soy intake on the risk of breast cancer recurrence related to HER2 status. Nutr Cancer 2012;64:198–205.

43. Lowcock EC, Cotterchio M, Boucher BA. Consumption of flaxseed, a rich source of lignans, is associated with reduced breast cancer risk. Cancer Causes Control 2013;24:813–816.

44. Ingram D, Sanders K, Kolybaba M, Lopez D. Case-control study of phyto-oestrogens and breast cancer. Lancet 1997;350:990–994.

45. McCann SE, Moysich KB, Freudenheim JL, et al. The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women. J Nutr 2002;132:3036–3041.

46. Piller R, Verla-Tebit E, Wang-Gohrke S, et al. CYP17 genotype modifies the association between lignan supply and premenopausal breast cancer risk in humans. J Nutr 2006;136:1596–1603.

47. Saarinen NM, Tuominen J, Pylkkänen L, Santti R. Assessment of information to substantiate a health claim on the prevention of prostate cancer by lignans. Nutrients 2010;2:99–115.

48. Sartippour MR, Rao JY, Apple S, et al. A pilot clinical study of short-term isoflavone supplements in breast cancer patients. Nutr Cancer 2004;49:59–65.

49. Nikander E, Kilkkinen A, Metsa-Heikkila M, et al. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. Obstet Gynecol 2003;101:1213–1220.

50. Van Patten CL, Olivotto IA, Chambers GK, et al. Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: A randomized, controlled clinical trial. J Clin Oncol 2002;20:1449–1455.

51. Quella SK, Loprinzi CL, Barton DL, et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. J Clin Oncol 2000;18:1068–1074.

52. Mahady GB. Do soy isoflavones cause endometrial hyperplasia? Nutr Rev 2005;63:392–397.

53. Unfer V, Casini ML, Costabile L, et al. Endometrial effects of long-term treatment with phytoestrogens: A randomized, double-blind, placebo-controlled study. Fertil Steril 2004;82:145–148.

54. Fritz H, Seely D, Flower G, et al. Soy, red clover, and isoflavones and breast cancer: A systematic review. PLOS ONE 2013;8:e8196.

55. Flower G, Fritz H, Balneaves LG, et al. Flax and breast cancer: A systematic review. Integr Cancer Ther 2014;13:181–192.

56. McCann SE, Edge SB, Hicks DG, et al. A pilot study comparing the effect of flaxseed, aromatase inhibitor, and the combination on breast tumor biomarkers. Nutr Cancer 2014;66:566–575.

57. Fischer L, Mahoney C, Jeffcoat AR, et al. Clinical characteristics and pharmacokinetics of purified soy isoflavones: Multiple-dose administration to men with prostate neoplasia. Nutr Cancer 2004;48:160–170.

58. Hussain M, Banerjee M, Sarkar FH, et al. Soy isoflavones in the treatment of prostate cancer. Nutr Cancer 2003;47:111–117.

59. van Die MD, Bone KM, Williams SG, Pirotta MV. Soy and soy isoflavones in prostate cancer: A systematic review and meta-analysis of randomized controlled trials. BJU Int 2014;113:E119–E130.

Eric Yarnell, ND, RH (AHG), is chief medical officer of Northwest Naturopathic Urology, in Seattle, Washington, and is a faculty member at Bastyr University in Kenmore, Washington.