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Review

Do phytoestrogens reduce the risk of breast cancer and breast cancer recurrence? What clinicians need to know

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ABSTRACT

Oestrogen is an important determinant of breast cancer risk. Oestrogen-mimicking plant compounds called phytoestrogens can bind to oestrogen receptors and exert weak oestrogenic effects. Despite this activity, epidemiological studies suggest that the incidence of breast cancer is lower in countries where the intake of phytoestrogens is high, implying that these compounds may reduce breast cancer risk, and possibly have an impact on survival. Isoflavones and lignans are the most common phytoestrogens in the diet.

In this article, we present findings from human observational and intervention studies related to both isoflavone and lignan exposure and breast cancer risk and survival. In addition, the clinical implications of these findings are examined in the light of a growing dietary supplement market. An increasing number of breast cancer patients seek to take supplements together with their standard treatment in the hope that these will either prevent recurrence or treat their menopausal symptoms. Observational studies suggest a protective effect of isoflavones on breast cancer risk and the case may be similar for increasing lignan consumption although evidence so far is inconsistent. In contrast, short-term intervention studies suggest a possible stimulatory effect on breast tissue raising concerns of possible adverse effects in breast cancer patients. However, owing to the dearth of human studies investigating effects on breast cancer recurrence and survival the role of phytoestrogens remains unclear. So far, not enough clear evidence exists on which to base guidelines for clinical use, although raising patient awareness of the uncertain effect of phytoestrogens is recommended.

1. Introduction

In addition to the known risk factors for breast cancer, such as inheritance of susceptibility genes, environmental factors are thought to influence the risk and progression of breast cancer. Epidemiological data have demonstrated that breast cancer, in the descendants of women who have migrated from countries of low breast cancer incidence, reaches the

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higher incidence rate of the host country as women adopt new dietary and lifestyle patterns.[1] Consumption of a diet rich in soy-containing foods, known to be rich in phytoestrogens, is proposed to be one of the chemoprotective factors against breast cancer in Asian populations and intake is much lower in countries with higher rates of breast cancer.

Phytoestrogens are polyphenolic plant chemicals that share common structural features with the mammalian oestrogen 17-oestradiol, enabling them to bind to the oestrogen receptor. There is also evidence that phytoestrogens have hormone-independent activities which are listed in Table 1.

2. Sources and metabolism

The two most studied families of phytoestrogens related to diet are isoflavones and lignans. Isoflavones are found in legumes particularly soya beans, traditional soya derived foods like tofu and analogues of Western type foods such as soya milk. Red clover and other herbs rich in isoflavones are usually consumed in the form of a supplement. Lignans, the other main phytoestrogen family, are found in the woody portions of fruit and vegetable, in seed coats and in grain bran of fibre-rich cereals.[2] The main source of phytoestrogens in the Asian diet is isoflavones whereas the Western diet is richer in lignans. The chemical structure of these compounds in comparison with oestradiol is shown in Fig. 1.

Phytoestrogens are derived from parent compounds after complex enzymatic processes that occur in the liver, intestine and colon. These processes are important for their metabolism but may also be important for their biological activity as more potent (oestrogenic and anti-oestrogenic) chemicals

Table 1 – Proposed isoflavone and lignan anti-carcinogenic mechanisms of action independent of oestrogen receptor binding

Mechanisms of action of phytoestrogens		
Mechanism of Action	Isoflavones	Lignans
Mechanisms with direct hormonal effect		
5-α-reductase inhibition	√	√
17-β-hydroxysteroid dehydrogenase inhibition	√	
Aromatase inhibition	√	√
Alteration in SHBG levels	√	√
Alteration in oestrogen metabolite ratios	√	√
Sulphatase and sulphotransferase inhibition	√	
Mechanisms of no hormonal effect		
Anti-oxidant	√	√
Cell adhesion effects	√	√
DNA topoisomerase inhibition	√	
Enhancement of immune system function	√	
Inhibitory effect on cell invasion	√[63,64]	
Inhibition of angiogenesis	√	√
Tyrosine kinase inhibition	√	
Inhibition of tumour metastasis		√[65,66]

Modified from Piersen.[62]

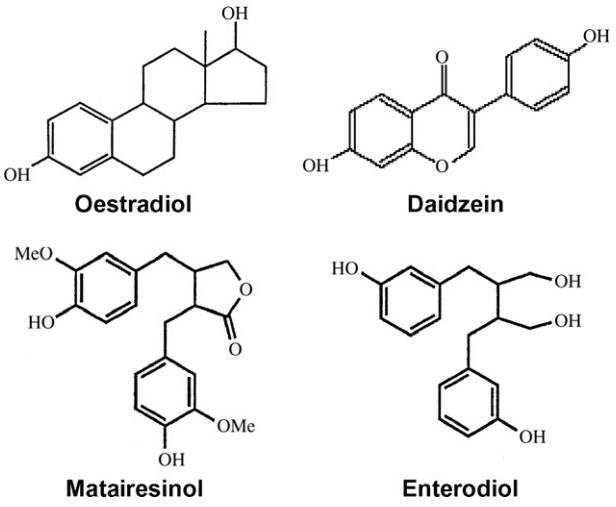

Fig. 1 – Chemical structures of oestradiol, the isoflavone daidzein, the plant lignan matairesinol and the mammalian lignan enterodiol.

are produced; for example, the isoflavone daidzein is converted to the more oestrogenic compound equol.[3]

Metabolism of phytoestrogens can vary greatly between individuals even when exact amounts of phytoestrogen-containing food have been ingested.[4] This could be due to factors affecting the chemical composition of the natural food. For example, the location, climatic conditions and genetics of the plant have been shown to influence the concentration of isoflavones in the raw soya bean.[2] The microbial composition of the intestinal flora may also play a role in inter-individual variation and antibiotic use in humans has been shown to reduce excretion of isoflavone metabolites.[5] Duration and time of exposure to antibiotics during one's lifetime, gender, age and background diet may also contribute to inter-individual variation.[4]

3. Isoflavones and breast cancer risk

Epidemiological studies have investigated the association between isoflavones and breast cancer risk by measuring dietary isoflavone intake, or levels of these in plasma/serum or urine, while some studies have looked at soy and breast cancer risk measuring exposure to soy-containing foods such as tofu and miso soup. Recently, Wu and colleagues[6] conducted two separate meta-analyses of studies carried out in Asian and Western populations to take into account the great variation in isoflavone intake between these two populations. Results from the meta-analysis of eight studies showed that pre- and post-menopausal Asian women consuming the highest amount ($\geqslant$20 mg/d) of dietary isoflavones had a 29% reduction in breast cancer risk when compared to low-level isoflavone Asian consumers ($\leqslant$5 mg/d). A dose–response relationship was also demonstrated for a moderate isoflavone intake of 10 mg/d which resulted in a 12% decrease in risk. In contrast, the meta-analysis of 11 studies carried out in women with Western diets found no association between isoflavone intake and breast cancer risk (median of highest intake was 0.8 mg/d and of lowest intake was 0.15 mg/d).

Two earlier meta-analyses[7,8] also showed a protective effect of isoflavone consumption with an overall odds ratio of 0.86 [95% confidence interval (CI) 0.75–0.99], and a relative risk of 0.75 (CI 0.59–0.95), respectively. Unlike Wu and colleagues,[6] these meta-analyses included studies which had incomplete measurement of total isoflavone intake as only certain soy foods were assessed from the diet. Furthermore, Trock and colleagues[7] included studies where exposure to isoflavones was also estimated by urinary measurement rather than dietary questionnaires alone and calculated the estimated dietary intake from urinary excretion.

It is also worth noting three case–control studies which have researched the effects of isoflavone intake during adolescence on breast cancer risk later on in life. A Canadian study[9] and two others conducted in Asian women[10,11] have shown a decrease in breast cancer risk with high intake of isoflavones during adolescence. Although the specific time period during which diet can affect breast cancer risk in humans has not been identified, breast tissue during adolescence has been shown to be more susceptible to carcinogens than in adults. In animal studies, early exposure to genistein reduces the number of terminal end buds which have many undifferentiated epithelial cells and increases the number of lobules which have more differentiated cells and are therefore less susceptible to carcinogens.[12]

4. Breast cancer risk and plant/mammalian lignans

Unlike studies of the effects of isoflavones, the majority of studies on lignans have taken place in non-Asian populations mainly owing to the higher consumption of lignan-containing foods in Western diets. Lignans found in food are called plant lignans whereas their metabolic products in humans and animals are called mammalian lignans. The most studied of these compounds in relation to breast cancer have been the mammalian lignans enterolactone and enterodiol. Exposure has been investigated by blood and urine analysis as well as dietary intake assessment.

4.1. *Dietary intake of lignans and breast cancer risk*

Seven retrospective case–control studies have investigated dietary intake of lignans and breast cancer risk.[9,13–18] Of these, one study has investigated the effect of dietary intake during adolescence[9] reporting a protective effect in adulthood for high plant lignan intake early in life. A US study[18] of non-Asian Americans has shown no association between plant lignan levels and breast cancer risk. All other case–control studies have shown a protective role.[13–17] Of three prospective studies carried out, an American study[19] has shown no effect for plant lignan matairesinol and a non-significant increased risk associated with high intake of the plant lignan secoisolariciresinol. However, adjustment for wine intake, a rich source of this plant lignan, attenuated this increase in risk. A Dutch study[20] showed a non-significant inverse association between breast cancer risk and mammalian lignan intake while a more recent study[21] using a French postmenopausal cohort showed a significant protective effect of lignan intake which was limited to oestrogen receptor (ER) and progesterone receptor (PR) positive tumours. This finding would support the idea that lignans have some mechanism of action at the level of the hormone receptor.

4.2. *Blood concentrations of lignans and breast cancer risk*

Assessment of intake using dietary questionnaires and food databases can be very time consuming and sometimes inaccurate. Serum or plasma levels of phytoestrogens have been shown to significantly correlate with dietary intake[22,23] and their measurement can therefore be used as an alternative, more objective method for estimating exposure.

There have been nine epidemiological studies looking at blood levels of lignans and breast cancer risk. Four have shown no association,[22–26] one study has shown a positive association[27] while four others have shown a protective effect.[28–31] It is interesting to note that a Swedish study[27] found an increased risk of breast cancer with both very low and very high enterolactone levels but not with medium levels, indicating a U-shaped relationship. Many studies look for a linear trend statistically making it possible for U-shaped relationships to be overlooked. It is also worth noting that the protective effect of plasma enterolactone on breast cancer risk demonstrated by the Danish study[29] was restricted to ERα negative tumours only. This finding is supported by another study[32] reporting a protective effect for ER negative tumours with increased plant lignan intake but opposite to the findings by Touillaud and colleagues[21] discussed above.

4.3. *Urinary concentrations of lignans and breast cancer risk*

Aside from using blood, urine can also be used to investigate exposure. Phytoestrogen levels in both 24 h urine collections and spot urine samples have been shown to correlate well with dietary intake.[22,23]

Six separate studies have examined the effect of urinary excretion of lignans on breast cancer risk. The results are again inconsistent; one study reported no association,[23] one reported a non-significant increase in risk with increasing lignan concentrations[33] whereas four have shown a protective effect.[34–37]

4.4. *Summary*

Overall, there is some epidemiological evidence of increased isoflavone and lignan intake being associated with a reduced risk of breast cancer but it is, inconsistent. Possible reasons for this include differences in populations investigated (Asian and non-Asian), sample size, study designs and adjustment for different confounding factors. Focus on investigating only certain sub-groups of breast cancer patients based on menopausal or receptor status versus the whole population can also add to the complexity. Furthermore, there are inherent problems with each method of measuring exposure such as the use of different and incomplete dietary databases, sensitivity and comparability of sample analysis techniques (e.g. time resolved fluorescence, gas chromatography/mass spectrometry) and methods of intake assessment (e.g. validated

and non-validated questionnaires). Variation in phytoestrogen metabolism owing to differences in intestinal microflora, and possibly the genetic make-up of participants[14] may also need to be considered when comparing data across studies. The timing of exposure to lignans, as well as isoflavones, may be important in elucidating their role in breast cancer risk. Evidence from one retrospective study[9] showing a protection in adulthood when lignans were consumed in adolescence needs to be confirmed.

5. Human intervention studies and breast cancer

There have been relatively few human intervention studies exploring the possible link between phytoestrogens and breast cancer. The effect of supplementation on breast cell proliferation has been investigated in six trials[38–43] (see summary Table 2). Studies were small, varied in the type of intervention used and the type of subjects, having either healthy women, breast cancer patients or a combination of breast cancer patients and women with benign breast disease. Study duration was short in all studies except one[43] where the intervention lasted for 12 months.

Three studies reported oestrogenic stimuli[38–40] following isoflavone supplementation, which may be associated with an increased risk of breast cancer. This was demonstrated by appearance of hyperplastic epithelial cells[38] in nipple aspirate fluid, increased proliferation of lobular breast epithelium cells, up-regulation of progesterone receptor expression[39] and changes in oestrogen-regulated proteins.[40] There are also three trials which have reported no difference in cell proliferation between intervention and control groups[41–43] although one of these has only published preliminary data.[42] Only one study has reported a potentially protective effect;[44] unlike other studies, the intervention used was lignan-rich flaxseed. Comparative examination of tumour tissue from core biopsy and surgery showed a significant reduction in tumour cell proliferation, an increase in apoptosis and a decrease of c-erbB2 (HER2) in the flaxseed-eating group only.

The mammographic density of the breast is considered a predictor of breast cancer risk.[45] Consequently, the effect of phytoestrogen supplementation on breast density has been investigated in several intervention studies. Two double-blind, placebo controlled studies[46,47] found no significant difference in percent density between the control group and the isoflavone-consuming group after 1 year. A longer 2-year study[48] carried out in ethnically diverse Hawaiian subjects also failed to show any significant difference in mammographic outcome between women supplementing their diet with soy foods and those on a regular diet. However, as lifetime soy intake was also assessed, the authors found that women who consumed soy throughout their lifetime had higher percent densities than those who ate no soy but this was only observed in Caucasian and not Asian women. No intervention trial has studied lignan supplemention on mammographic patterns; however, a large cross-sectional study carried out in Norway[49] found that higher levels of enterolactone in the blood were associated with a slight increase in breast density. In another study,[50] a protective effect for high dietary intake of plant lignan secoisolariciresinol was demonstrated but as the sample size was small these results need to be confirmed by larger studies.

6. Phytoestrogens, breast cancer recurrence and survival

The relationship between phytoestrogen intake and breast cancer recurrence and survival has yet to be evaluated. Two studies have explored pre-diagnosis phytoestrogen intake and breast cancer survival. In a study conducted in the US[51] dietary intake of isoflavones was assessed by a food frequency questionnaire in 1210 newly diagnosed pre- and post-menopausal breast cancer patients. The authors reported a 48% lower risk of all-cause mortality for the highest versus lowest quintile of isoflavone intake [hazard ration 0.52, 95%CI (0.33–0.82)]. A similar reduction in risk was found for breast cancer mortality but it was limited to postmenopausal women.

The second study was conducted in an Asian population.[52] Dietary information during a 5-year period prior to diagnosis was collected from 1459 Chinese breast cancer patients (both pre- and post-menopausal) using a validated questionnaire. After a 5-year follow-up period, no overall association was reported between soy intake (either as total soy protein or as total isoflavone) prior to cancer diagnosis and disease-free breast cancer survival [adjusted hazard ratio 0.99 (95% CI 0.73–1.33)] for women in the highest tertile of intake compared with those in the lowest tertile. The association remained the same regardless of ER/PR status, TNM staging, age at diagnosis, body mass index, waist to hip ratio and evaluation for genetic polymorphisms for ERα and ERβ.

There is a pressing need for further work in this area to evaluate the safety and potential interactions of phytoestrogen use with hormonal breast cancer treatments. Animal work has shown that the anti-proliferative action of tamoxifen is negated in the presence of low doses of genistein but retained in high doses.[53] Such interactions have not yet been examined in any human studies.

A prospective cohort study investigating the effects of phytoestrogens (DietCompLyf study) in breast cancer survivors is being conducted by our group at University College London. The study's aim is to assess the relationship between phytoestrogen exposure after diagnosis and survival. Breast cancer patients enter the study 1 year after diagnosis of primary invasive breast cancer. Information is then collected on dietary intake, lifestyle behaviours, use of supplements and complementary therapies both prior to diagnosis and during an additional 4-year follow-up period. Urine and blood samples are also collected for phytoestrogen analysis by UPLC-MS (ultra performance liquid chromatography–mass spectrometry). Recruitment of 3000 patients is anticipated to be completed by 2010.

7. Emerging phytoestrogen supplement market

A number of phytoestrogen-containing supplements have flooded the market in the last decade marketed as safe

Table 2 – Phytoestrogen intervention studies in humans investigating effects on breast cell proliferation

Author, year	PE[a] source and dose	Sample sizes, study details	Study duration	Results	Comments
Petrakis et al., 1996 (38)	38 mg/d of genistein (form: soy protein isolate)	24 healthy women (14 pre- and 10 postmenopausal). Needle aspirate fluid obtained monthly and examined cytologically	12 months of which 6 had intervention (from 4th to 9th month)	7 of the 24 women developed hyperplastic epithelial cells after intervention. Volume of fluid aspirate increased in premenopausal women only during and after soy supplementation	Inter-individual variability minimised owing to crossing over design of study
McMichael-Phillips et al., 1998 (39)	45 mg/d isoflavones(form: soy protein)	48 premenopausal women (9 with breast cancer and the rest with benign breast disease). Randomised design. 19 patients received soy	14 d prior to surgery	increase in breast epithelial cell number and progesterone receptor expression in soy-treated patients	Details of recent antibiotic use collected
Hargreaves et al., 1999 (40)	45 mg/d isoflavones (form: soy protein)	28 women randomised to received intervention and 23 acted as controls. Majority of patients had benign breast disease. Tissue from 33 historical cases added to control group	14 d prior to surgery	No difference in breast epithelial proliferation and apoptosis between groups. Increase of pS2 and apolipoprotein D in soy intervention group only.	Expansion of McMichael-Phillips study. Considerable variation in serum isoflavone levels between soy-patients.
Sartippour et al., 2004 (41)	Isoflavone tablets. Total dose: 200 mg/d	17 breast cancer patients received intervention. 26 historic breast cancer cases acted as controls	23 d (range 13–45) for soy group and 21 d (4–42) for historic controls	No significant difference in apoptosis/mitosis ratio between groups.	No information of habitual diet of historic controls had been recorded
Palomares et al., 2004 (42)	100 mg/d isoflavone tablet	23 postmenopausal cases with either in situ or invasive breast cancer randomised to an isoflavone tablet or placebo. Core biopsies at baseline, 6 months and 12 months time points	12 months	Evaluation of biopsy pairs from baseline and 6 months for 18 subjects showed no significant increase in Ki67 labelling index between intervention and control groups.	Tissue biopsied from contralateral breast. Only preliminary results published. No 12 month follow-up data presented.
Thompson et al., 2005 (44)	25gr of ground flaxseed in muffin	32 postmenopausal breast cancer patients. Double-blind randomised intervention to either flaxseed muffin or normal muffin from time of diagnostic core biopsy till surgery	32 d (mean) for flaxseed group and 39 d (mean) for placebo group	Decrease in Ki67 labelling index, increase in apoptosis and decrease in c-erbB2 in flaxseed group only.	Although flaxseed is rich in lignans it also contains other constituents.
Cheng et al., 2007 (43)	30 mg isoflavones as part of fruit flavoured drink	60 healthy postmenopausal women. Double-blind randomised intervention to either isoflavone drink or placebo drink	12 weeks	No change in Ki67 in breast biopsies obtained by middle needle biopsy before and after intervention.	Compliance measured by urinary analysis of isoflavones

a PE: phytoestrogen.

alternatives to hormone replacement therapy for alleviating menopausal symptoms. At the same time all supplement use has increased. A recently published study[54] conducted in Canada showed an increase in the use of complementary/alternative medicine products from 62% in 1998 to 70.6% in 2005 by breast cancer survivors. Amongst the most commonly used products in 2005 were flaxseed and soy.

These supplements are usually acquired without medical advice and their content is unregulated. In addition, only a

few randomised, double blind, placebo-controlled trials have been carried out administering phytoestrogen-containing food or tablets to breast cancer survivors to evaluate their efficacy in terms of alleviating menopausal symptoms such as hot flushes.[55–58] The duration of supplementation investigated in these studies ranged from 9 to 12 weeks during which no severe side-effects were experienced. There was no statistical difference in menopausal symptoms between the treatment and placebo groups in all four studies. These results are consistent with findings from a recent review of 32 randomised controlled trials in women with no malignant breast disease, of food or supplements containing at least 30 mg/d of isoflavones. The authors concluded that there was no evidence that the use of phytoestrogens treatments was effective in alleviating menopausal symptoms.[59] Trials on breast cancer patients investigating the efficacy of the herb Black Cohosh have not been considered here as more recent work has not detected phytoestrogen chemicals in Black Cohosh.[60]

Isoflavones in soy have been consumed for centuries by Asian populations. In contrast, the western diet is richer in lignans than the Eastern diet but poorer in isoflavones. The introduction of isoflavones in the western diet has only occurred within the last few decades. Moreover, their presence in the diet has predominantly been in forms which are highly processed and depleted from many bioactive components rather than the traditional forms consumed in Far Eastern cultures. Interestingly, a study by Allred and colleagues[61] showed that, unlike soy flour which had no effect, soy extracts and purified isoflavones resulted in growth stimulation of MCF-7 cells transplanted into ovariectomised athymic mice. The authors proposed that processing of soy increases its oestrogenicity. Consequently, breast cancer patients consuming soy extracts, isolated isoflavones or food containing highly processed soy could potentially be increasing their risk of recurrence. The genetic make-up of populations is adapted to dietary habits over long periods of time. It is therefore possible that the introduction of certain phytoestrogens, especially outside their food matrix as in the case of supplements or processed food ingredients, may have unpredictable biochemical and cytological long-term effects.

8. Conclusion

Data collected from human studies to date have not provided clear evidence that could be used to provide guidelines on phytoestrogen use for clinicians. Two meta-analyses of observational studies suggest a protective effect of phytoestrogens on breast cancer risk, with a third more recent one confining this only to Asian populations. However, early short-term intervention studies suggest a possible stimulatory effect of phytoestrogens on breast tissue, and this can only be confirmed by long-term human intervention studies. Questions also still remain regarding the influence of phytoestrogens in women at high risk of breast cancer and those with breast cancer, the interaction of these compounds with hormonal therapies for breast cancer and the use of these compounds as supplements isolated from the food matrix.

Although clear guidelines cannot yet be given to patients by clinicians, it is worth making breast cancer patients aware of the, as yet, undetermined role of phytoestrogens. Such discussions with patients need to take place soon after cancer diagnosis to pre-empt any decisions about dietary changes and supplement use involving phytoestrogens.

Conflict of interest statement

None declared.

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