PHYTOESTROGENS

Phytoestrogens are paradoxical. Because of their structural similarity to the physiological oestrogens, they have been assumed to increase the risk of breast cancer. However, nations where the largest amounts of phytoestrogens are consumed in the diet have the lowest incidence of and rate of death from breast cancer. Although these epidemiological observations do not prove that phytoestrogens have anti-cancer properties, many preclinical experiments support this concept. Some indicate that early life exposure to phytoestrogens may be critical for breast cancer prevention.

The issues surrounding phytoestrogens are relevant to us as practitioners of Chinese medicine because some Chinese herbs contain phytoestrogens. This newsletter will attempt to explain what phytoestrogens are, the role they may play in relation to breast cancer and to summarize the clinical studies that have been done so far.

What are phytoestrogens?
The name "phytoestrogens" is rather misleading as it implies a plant source of oestrogens. Phytoestrogens are not oestrogens: they have a chemical structure which is similar to but not the same as that of oestrogens and their effect on the body is not the same as that of oestrogens. The term phytoestrogen actually describes a property that has been identified in some foods, plants and herbs. There is not, as yet, a definitive list of substances that contain phytoestrogens. However, they have been found in the following classes of substances:

- lignans
- isoflavones
- coumestans

GLOSSARY

Phytoestrogen compounds found in plants and herbs
Oestrogen a generic term for estrus-producing compounds; the female sex hormones
Oestradiol a type of oestrogen
Progesterone a steroid hormone
Oestrogen-antagonistic works against oestrogen
Oestrogen-agonistic works with oestrogen
Tamoxifen a drug used in the treatment of breast cancer which has weak oestrogenic effects
Goserelin an oestrogen-inhibiting drug used in the treatment of breast cancer
Lignans, isoflavones, coumestans classes of plant substances in which phytoestrogens are found
Hormone receptor a part of a cell into which a hormone locks in order to exert its effect on the body

Isoflavones is the group in which there is most interest and which is present in soya products. Lignans and coumestans are currently rather understudied. Structural similarity of oestrogens and phytoestrogens

What is hormone-sensitive breast cancer?
The growth of many normal tissues, including breast tissue, is under hormonal regulation and the cancers which arise in them often retain sensitivity to changes in the hormone environment. Therefore, hormone therapy is an essential part of management of any

hormone-sensitive cancer.

To determine whether or not a cancer is hormone-dependant, a woman with breast cancer will always be given what is known as a hormone receptor assay, i.e. a test that measures the presence of oestrogen and progesterone receptors in the tumour cells. If these receptors are present, the tumour is said to be oestrogen-receptor positive or progesterone-receptor positive and is thus hormonal. The role of oestrogen and phytoestrogens is not relevant to non-hormonal cancers.

Every cell contains "hormone-receptors". It is when hormones, such as oestrogen, lock on to these receptors that they exert their effects: if they cannot lock on, then they have no effect. So, therefore, it is only when oestrogen locks on to a hormone receptor that, in terms of breast cancer, it becomes "dangerous", as oestrogen has a proliferative effect on breast cancer cells. Phytoestrogens are also able to lock onto hormone receptors and they therefore block the oestrogen from being able to do the same. It is in this way that it is thought that phytoestrogens help protect against breast cancer.

Although phytoestrogens are often compared to oestrogens, the effect that they have on oestrogen levels in the body is not clearly defined. However, the vast majority of the clinical studies done so far point towards the fact that phytoestrogens have do not have the same effect as oestrogens and that, to the contrary, they help to prevent the proliferation of cancerous cells in the breast.

Oestrogen in the "right" quantity has a purely beneficial effect on women's health. It is an excess of oestrogen that has been linked with the rise in breast cancer. In fact, it is has been proved that women on HRT have an increased risk of breast cancer. A Swedish study of 23, 000 hormone users reported that the incidence of breast cancer compared with that in non-users was increased after six years' use. One of the most recent British studies of 5000 women taking HRT showed that breast cancer mortality in these women compared with the general population rose from 0.55 per 1000 in the earlier period of follow-up to 1984, to 1 per 1000 between 1984 and 1988. Whenever a woman menstruates, oestrogen is produced by the ovaries; it therefore follows that, over a lifetime, the more periods a woman has the more oestrogenic-stimulation occurs. It has been proven that there is a direct, inverse correlation between the age of menarche in women and the number of children they have with the incidence of breast cancer, i.e. the earlier menarche is and the fewer children they have, the higher the chances of developing breast cancer.

Food sources of phytoestrogens:

- Oilseeds, especially flaxseed
- Cereals (e.g. rye, wheat, oats)
- Vegetables (e.g. garlic, squash, asparagus, cabbage, spinach)
- Legumes (e.g chickpeas, kidney beans, lentils)
- Fruits (e.g. pears, plums)
- Soy protein
- Seaweed
- Beansprouts
- Hops

Soya beans contain the most concentrated source of isoflavones and other soya products such as tofu, tempeh and soya milk also contain appreciable quantities of these materials. Lignans, however, another subgroup in which phytoestrogens are found, are associated more with diets high in plant fibre.

There are currently three main views as to the role phytoestrogens may play in preventing and treating breast cancer.

1. ANTIESTROGENIC EFFECT

The most widely held view is that phytoestrogens help to prevent the spread of cancerous cells in the breast, i.e. that they are oestrogen antagonistic. Their effect could be compared to that of the commonly-prescribed drug tamoxifen. Both appear to exert most of their effect by binding to the oestrogen receptor, thereby preventing the activity of circulating estradiol (a type of oestrogen). Obviously, the great advantage of phytoestrogens compared to tamoxifen is that they do not have any side effects and they continue working indefinitely, whereas, according to some, tamoxifen usually stops working after approximately a year.

It has long been known that breast cancer, as well as other cancers such as colon, prostatic, endometrial and ovarian, all have lower incidences in Asia and eastern Europe than in western countries. Japan has consistently been reported to have the lowest risk of hormone-dependent cancers. Moreover, migrants to western countries from Asia who maintain their traditional diet do not increase their risk of these diseases, whereas an increased risk for these diseases accompanies a change toward a westernized diet. Women who do suffer from breast cancer in Japan have a better prognosis that those with breast cancer in the US or Britain. These differences apply to postmenopausal women and are apparently independent of stage of disease at diagnosis. A review of breast cancers in Japanese and white women in Hawaii showed that Japanese women had a higher number of in situ tumours, fever lymph node metastases, and those with metastases were less likely to have three or more nodes involved. Stage for stage, women of Japanese origin in Hawaii have longer survival times after breast cancer resection than white women. These facts point towards the fact that women who have a diet high in phytoestrogens, e.g, a diet containing a lot of soya products, have a lower risk of contracting breast cancer.

2. OESTROGEN-AGONISTIC EFFECT

The opposing view, which is much less commonly held, is that phytoestrogens (specifically genistein, daidzein and equol) actually exhibit agonistic actions on oestrogen-dependent gene expression in breast cancer cells. Proponents of this view agree that, although the significance of phytoestrogens as estrogenic effectors in humans have been suggested to be insignificant, the potential combinatorial actions of these compounds would suggest that the collective effects of multiple phytoestrogens may result in an overall increase in estrogenic potency and possibly clinical significance.

3. BALANCING EFFECT

Another view, which is as yet not supported by any clinical studies, is that phytoestrogens have a balancing or levelling effect on oestrogen levels. Therefore, when production of oestrogen is low, the phytoestrogens can boost oestrogen activity and when production of oestrogen is excessive, phytoestrogens appear to antagonise oestrogen's activity by locking onto the hormone receptors.

CONCLUSION

The overwhelming evidence is that phytoestrogens do not stimulate the growth of cancerous cells in the breast. The most likely way that they achieve their oestrogen-antagonistic effect is through a competitive mechanism whereby the phytoestrogens occupy the receptor sites of tumour cells without enhancing their growth but keeping the body's oestrogens from contacting the receptor and simulating cell proliferation.

Assuming that this is the case, let us look at six possible scenarios of women who are all taking Chinese herbs which contain phytoestrogens in order to illustrate their safety:

a) a healthy woman without breast cancer:
phytoestrogens prevent the proliferation of hormone-sensitive breast cancer cells and improve health in many other ways (see below).

b) a woman with asymptomatic hormone-sensitive breast cancer:
phytoestrogens compete with oestrogens over the oestrogen receptors on the surface of the cancer cells and therefore they would be beneficial.

c) a woman with non-hormonal breast cancer:
the cancerous cells would not be affected one way or the other by phytoestrogens.

d) a woman with hormone sensitive cancer taking tamoxifen:
phytoestrogens would not be harmful because tamoxifen firmly blocks off the estrogen receptors of the cancerous cells.

e) a woman with hormone-sensitive breast cancer taking goserelin (Zoladex):
goserelin does not block receptors but it does reduce the level of estrogen in the body. As in scenario one, the phytoestrogens would lock onto the cell receptors and help prevent the proliferation of cancer cells.

f) a woman with hormone-sensitive breast cancer who is not taking either tamoxifen or goserelin:
this is a very unlikely case but, as in scenario e), the phytoestrogens would block the hormone cell receptors.

Therefore, we can see that, going on the current evidence about the effect of phytoestrogens, it is not only safe, but also beneficial for women with hormone-sensitive or non-hormonal breast cancer to take herbs which contain phytoestrogens. We should also remember that it is impossible to avoid phytoestrogens altogether anyway, as they naturally occur in many everyday foods.

OTHER BENEFICIAL EFFECTS OF PHYTOESTROGENS

The following benefits of phytoestrogens on our health have all been proved:

- they have a positive effect on the lipoprotein profile
- they improve many of the symptoms associated with menopause
- they reduce the risk of cardiovascular disease
- they reduce cholesterol levels
- they have a beneficial effect on osteoporosis by increasing bone density
- they have an anti-viral effect
- they are bacteriocidal
- they have anti-fungal properties
- they have anti-oxidant properties
- they are anti-mutagenic
- they are anti-hypertensive
- they are anti-inflammatory
- they have anti-proliferative properties

CLINICAL STUDIES

1. A Review of the clinical effects of phytoestrogens

In vitro studies using human breast cancer cell lines have confirmed the antiproliferative effects of phytoestrogens. Enterolactone, enterodiol, and synthetic mammalian lignan derivatives were shown to inhibit growth by 18-20% in vitro. The effects of synthetic and naturally occurring flavonoids were tested on the same breast cancer cell line. In all cases, antiproliferative effects were noted. These effects were not purely cytostatic, as cell death was found to increase dosedependently.

2. Regulation of Inducible nitric oxide synthase by dietary phytoestrogen in MCF-7 human mammary cancer cells.
The effects of the phytoestrogen biochanin A on the growth of MCF-7 human breast cancer cell line was examined. The results showed that biochanin A treatment induced dose- and time-dependent inhibition on MCF-7 cell growth at concentrations above 20 microg x ML (-1). An examination of treated MCF-7 cell morphology revealed condensation of the chromosome and dehydration of the cytoplasm, suggesting apoptosis as an important factor in biochanin A-related cell growth inhibition. The results also showed that at a concentration of 40 microg x mL (-1), biochanin A decreased the levels of inducible nitric oxide synthase, thus inhibiting the production of nitric oxide, a known second messenger and inducer of apoptosis, and affecting the overall cell protein pattern. No significant difference in superoxide dismutase protein levels were, however, detected at concentrations of 40 or 100 microg x mL (-1) of biochanin A. The data suggest that the inhibitory effects of biochanin A on human breast cancer cell growth are linked to inducible nitric oxide synthase and the associated production of nitric oxide.

3. Potential tissue selectivity of dietary phytoestrogens and oestrogens
The recent discovery of a second oestrogen receptor subtype, oestrogen receptor-b, may significantly advance our understanding of tissue specific effects of oestrogenic compounds, both natural and synthetic. Although specific effects mediated by oestrogen receptor-b in vivo remain to be elucidate, hypothetically the existence of two oestrogen receptor subtypes (differing in both tissue distribution and biological activity) may help to explain the curious pharmacological behaviour of many oestrogenic compounds, including the naturally occurring dietary phytoestrogens.

4. Effects of phytoestrogens on aromatise, 3beta and 17beta-hydroxy steroid dehydrogenate activities and human breast cancer cells.
This study explored the mechanisms by which phytoestrogens may exert cancer-preventive effects. Phytoestrogens were tested for estimating anti-aromatise, anti-3beta-hydroxy steroid dehydrogenate delta5/delta4 isomerase (3beta-HSD and anti-17beta-hydroxy steroid dehydrogenate (17beta HSD) activities in human placental microsomes. It was found that isoflavonoids and compounds which presented the phenolic B ring in the 3 position on the pyran ring preferentially inhibited 3beta-HSD and/or 17beta-HSD activities than aromatise activity. The interactions with the oestrogen receptor using a stably transfected human breast cancer cell line (MVLN) were also evaluated. Also, phytoestrogens were evaluated for their effects on the proliferation in oestrogen-dependent (MCF-7) and independent (MDA-MB231) human breast cancer cells. A structure-activity relationship was established and determined regions or/and substituents essential for these different activities. However, at high concentrations, it seems that some phytoestrogens exert their protection against breast cancer through other oestrogen-independent mechanisms.

5. Phytoestrogens have agonistic and combinatorial effects on oestrogen-responsive gene expression in MCF-7 human breast cancer cells
This study sought to investigate whether oestrogen-dependent gene expression may be further influenced by the collective treatment of breast cancer cells with multiple phytoestrogens. Accordingly, MCF-7 breast cancer cells were transfected with oestrogen-responsive reporters followed by treatment with one of four phytoestrogens (genistein,

daidzein, formononetin, and equol) or a combination of these in the absence of estradiol. The results demonstrated clear-cut agonistic effects of phytoestrogens on oestrogen-dependent gene expression. Moreover, combinatorial treatment consistently stimulated reporter activity above that observed for individual phytoestrogens. In as much as the phytoestrogens tested are frequently found together in food sources, these combinatorial responses may more accurately reflect the consequences of in vivo exposure.

6. Case-control study of phytoestrogens and breast cancer
Researchers in Perth, Australia, obtained 72-hour urine samples from 144 women with newly diagnosed breast cancer and followed an equal number of age-matched, non-sufferers. The urine sample were monitored for several compounds found naturally in soya-rich foods and vegetable fibre-analogues (isoflavones and lignans), since excretion of these compounds mirrors both dietary intake and bioavailability. After adjustment, high excretion rates of both groups of compounds were associated with a statistically significant reduction in breast cancer risk. Additionally, the larger the urinary output of these molecules the greater the protection.

7. Interaction of Oestrogenic Chemicals and Phytoestrogens with Oestrogen Receptor ß
This study found that, while the estrogenic potency of industrial-derived estrogenic chemicals is very limited, the oestrogenic potency of phytoestrogens is significant, especially for Erß, and they may trigger many of the biological responses that are evoked by the physiological oestrogens.