Phytoestrogens: emerging multifaceted plant compounds

A phytoestrogen-rich diet may help to protect against some cancers and help ease menopausal symptoms

Why do certain foods seem to help prevent some diseases? It is now clear that the link between our health and the food we eat cannot be adequately explained by nutrient composition alone. Nutrition research is now focusing on phytochemicals, naturally occurring biologically active plant compounds not generally regarded as nutrients, with a particular focus on phytoestrogens.

Phytoestrogens, whose chemical structure is similar to that of the mammalian hormone oestrogen, compete with oestrogen for its cellular receptor, and can act as both oestrogen agonists and antagonists; they also decrease oxidant activity at the tissue level, decrease cell turnover, and decrease new vessel formation. Categorised according to chemical structure as isoflavones, lignans, coumestans and resorcylic acid lactones, phytoestrogens are found in grains, legumes and various other vegetables and fruits. Soy and linseed contain high levels of isoflavones and lignans, and research has focused on these two phytoestrogens as they are the most common in the human diet.

Most research has been directed at the oestrogenic effect of the phytoestrogens — after the menopause in women and in cardiovascular disease and cancers in both women and men. The first study to show the oestrogenic effects of phytoestrogens in humans was published in 1990, and revealed an increase in vaginal-cell maturation index (an indicator of oestrogenicity) in postmenopausal women.[1] Two other studies have also shown significant improvements in vaginal-cell maturation index in women who had a soy-supplemented diet.[2,3] The effect of the phytoestrogens on menopausal hot flushes remains to be resolved, with more studies showing a beneficial effect of these compounds than no effect.[4,5]

Dietary soy supplementation also increased bone mineral content in postmenopausal women,[2] and a soy protein diet protected against bone loss in a postmenopausal animal model.[6]

Phytoestrogens may also exert a cardiovascular protective effect by modulating lipid levels. A recent meta-analysis of 38 clinical studies of the effects of soy-rich diets on lipid levels showed significant reductions in total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides.[7] These reductions were associated with soy intake, and various components of soy, such as fatty- and amino-acid composition and isoflavones, were implicated.[7] Direct effects of phytoestrogens on lipid profiles have been demonstrated in humans. In postmenopausal women taking two different doses of phytoestrogen tablets, 40 mg/day of isoflavones significantly increased HDL cholesterol levels.[5] As a reduced level of HDL cholesterol is a better predictor of cardiovascular disease in women than total cholesterol and LDL cholesterol levels, this increase is of interest.

Phytoestrogens may protect against some types of cancer, as indicated in animal, in-vitro and human epidemiological cancer studies. In a rat breast cancer model, soy and linseed decreased or prevented mammary tumour formation.[8,9] Soy protein isolate decreased the number of aberrant crypt foci, the preneoplastic lesions of colon cancer, in a rat colon cancer model,[10] and linseed had similar inhibitory effects.[11] Results from prostate cancer animal and cell studies are still preliminary, but phytoestrogens inhibited 5α-reductase, the enzyme that converts testosterone to 5α-dihydrotestosterone, the hormone responsible for prostate development and function,[12] and soy was shown recently to inhibit prostatic adenocarcinoma in rats.[13] Population-based studies show a lower incidence of breast, colon and prostate cancer in Asia, where soy intake is high, compared with Western countries, where intake is relatively low.[14] Epidemiological studies show a significant inverse relationship between soy protein intake and breast cancer risk in premenopausal but not postmenopausal women.[15]

In premenopausal women, phytoestrogen-rich diets significantly prolonged the follicular phase of the menstrual cycle, from 15 to 17.5 days.[16] The hypothesis is that, over a lifetime, a woman with longer menstrual cycles will be exposed to less total oestrogen (because the follicular phase of the cycle is prolonged), and therefore there is the potential for a decreased risk of breast cancer.

Further research, including long-term studies of the effects of phytoestrogens on bone and human studies on the relation of phytoestrogen intake to cancers, will help to evaluate other potential beneficial effects, as well as the risks, of these interesting compounds. The safety of soy formulas for infants has recently been questioned, but phytoestrogen exposure in infants fed with these formulas is estimated to be 200- to 300-fold less than doses that affect sexual differentiation in animals.[17]

Once we determine the advantages of phytoestrogens, perhaps we may then increase the intake of these multifaceted compounds in the Australian diet.

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Clopidogrel: a new safe and effective antiplatelet agent. But unanswered questions remain

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Clopidogrel is safe and better than aspirin for reducing the risk of thrombotic events in patients with atherosclerotic vascular disease

Systemic atherosclerosis, manifesting as stroke, heart attack or intermittent claudication, is the major cause of death and disability in developed countries.[1] Strategies to prevent recurrence among survivors include vascular risk-factor control, antiplatelet and anticoagulant therapy, and surgery and angioplasty/stenting of the symptomatic artery in appropriate patients. The "gold standard" antiplatelet agent is aspirin — it is safe and inexpensive, and reduces the rate of subsequent stroke, myocardial infarction (MI) or vascular death by about 25%.[2] Other effective antiplatelet agents include ticlopidine and dipyridamole plus aspirin.[2,3]

A new antiplatelet agent, clopidogrel, is about to enter the arena. A novel thienopyridine derivative chemically related to ticlopidine, its mechanism of action is entirely different from that of aspirin. Clopidogrel irreversibly inhibits the binding of adenosine diphosphate to its receptor on platelets and strongly reduces the activation of the glycoprotein IIb/IIIa complex (the main fibrinogen receptor on platelets), thus protecting against the formation of the platelet plug.

But is it as safe and effective as aspirin? This question has just been addressed in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) international clinical trial.[4] The trial enrolled 19 185 patients with a history of recent ischaemic stroke (atherothrombotic, not cardioembolic), acute MI or symptomatic atherosclerotic peripheral arterial disease (intermittent claudication) who did not have contraindications to antiplatelet therapy. The rationale for including this broad spectrum of patients was that:

- The patients all manifested symptoms of complicated atherosclerosis (e.g., mural thrombus formation causing vessel occlusion or thromboembolism), but in different arterial sites;
- Atherosclerosis involving different arterial sites is likely to be the same disease;
- Platelets play an integral role in atherothrombosis (i.e., atherosclerotic plaques are complicated by intraplaque haemorrhage or necrosis, leading to plaque ulceration and platelet adhesion, activation and aggregation, which, in turn, initiates blood coagulation and mural thrombus formation[5,6]); and
- The treatment effect of antiplatelet agents on symptomatic atherosclerosis involving different arterial sites is likely to be similar. Evidence from the Antiplatelet Trialists Collaboration supports a widespread treatment effect for patients with different clinical manifestations of atherothrombosis.[2]

In the CAPRIE trial, patients were randomised to take aspirin (325 mg) or clopidogrel (75 mg) once daily. The two groups were evenly matched in number and important prognostic variables. All but 42 (0.2%) patients were followed up rigorously for one to three years (mean, 1.9 years).

The actuarial annual rate of subsequent ischaemic stroke, MI or vascular death (the primary outcome event) was 5.83% in the aspirin-treated group and 5.32% in the clopidogrel-treated group. This was a relative-risk reduction (RRR) of 8.7% (95% confidence interval [95% CI], 0.3–16.5; $P=0.043$). The absolute-risk reduction was 0.51%, indicating that for every 200 patients treated with clopidogrel one major outcome event would be avoided each year compared with the results of aspirin treatment.

The trial compared clopidogrel with an active, effective treatment (aspirin), *not a placebo*; the actuarial annual rate of ischaemic stroke, MI or vascular death in a placebo-treated group in the CAPRIE population would be expected