Commentary

Isoflavones and women’s health
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Abstract
There is evidence that diets which contain high levels of phytoestrogenic isoflavonoids are associated with a low incidence of osteoporosis and menopausal vasomotor symptoms. Plant extracts such as red clover, which contain high levels of isoflavonoids, have been used to reduce menopausal symptoms and have been shown to reduce bone loss in healthy women. A placebo-controlled clinical trial [ISRCTN42940165] of red clover is reported in this issue of Breast Cancer Research and shows that these phytoestrogens do not cause any oestrogenic increase in breast density, which would indicate that they are unlikely to cause an increased risk of breast cancer.

Keywords: isoflavones, red clover, women’s health

Introduction
Vasomotor symptoms such as hotflushes and night sweats, associated with insomnia and cognitive dysfunction, commonly occur in women after the menopause and are caused by a lowering of oestrogen levels in the hypothalamus due to ovarian failure. These symptoms are the main reason for women taking oestrogen (sometimes with a progestin) as hormone replacement therapy (HRT). An added advantage of taking oestrogen is that it also prevents bone loss and osteoporotic fractures. However, HRT has been associated with an increase in breast cancer, uterine cancer, thromboembolism, heart disease and stroke [1].

Because of these problems, there is now a substantial effort to develop drugs with a spectrum of oestrogenic and anti-oestrogenic activity (the Selective Estrogenic Receptor Modulators or SERMs), which give a better profile of activity than oestrogen for women’s health benefits. For example, the SERM raloxifene (Evista, Eli Lilly) has been shown to reduce the risk of breast cancer [2], osteoporotic fractures in the spine [3], and heart disease in women at high risk [4], but it is not effective at reducing vasomotor and cognitive symptoms and, like oestrogen, still causes an increase in thromboembolism. The search therefore continues to find the ideal SERM that has a spectrum of oestrogenic and anti-oestrogenic activity which would reduce vasomotor symptoms, improve cognitive dysfunction, reduce breast cancer, uterine cancer and perhaps ovarian cancer, reduce the risk of osteoporotic fracture, heart disease and stroke, and not cause an increase in thromboembolism. This is theoretically possible.

Natural products and women’s health
For many years plant extracts have been used for controlling the vasomotor symptoms of the menopause, which would indicate that there are naturally occurring phytoestrogenic agents in these plants [5]. A group of candidate agents likely to be oestrogenically active in these plant extracts are the isoflavones. The question is then raised as to whether these extracts, used to control vasomotor symptoms, have adverse effects like HRT, and if they increase breast cancer risk. There is good epidemiological evidence, however, that in Asian populations where the diet is high in isoflavones, from sources such as soya [6] there is a low incidence of breast cancer, osteoporosis, heart disease and stroke with...
Atkinson and colleagues, [7] reports a randomised, double-blind, placebo-controlled trial of Promensil (Novogen), an extract of red clover, given to 205 pre- and postmenopausal healthy women with radiologically dense breasts (an established oestrogenic risk factor for breast cancer). Promensil is an extract of red clover containing very accurately determined amounts of the principal isoflavonoids: biochanin A, formononetin, genistein and daidzein (total isoflavonoid content of 40 mg per tablet) [8]. The trial is well designed with the principal objective of evaluating any adverse oestrogenic effect of red clover, at a dose of 40 mg of isoflavones per day, on breast density as a surrogate marker of increased breast cancer risk.

The study has shown that, at this dose of Promensil, there is no evidence of any increase in radiological breast density in women who already have increased breast density, in spite of the well-documented evidence that HRT will increase breast density and tamoxifen will reduce breast density. There is little other data relating to isoflavones and breast density, with only one small trial involving 30 premenopausal women receiving 100 mg of isoflavones versus placebo for one year showing no significant effect on breast density [9]. Larger trials are needed to evaluate the effect of these higher doses of isoflavones on healthy women particularly those with an increased breast density.

Rather surprisingly, the trial reported by Atkinson and colleagues failed to show any beneficial effect on menopausal symptoms or reduction in follicle-stimulating hormone in post menopausal women, indicating a lack of oestrogenic activity of 40 mg per day of Promensil on the hypothalamus. A recent small but well designed trial reported by van de Weijer showed that 12 weeks of 80 mg per day of Promensil in 30 healthy women with marked vasomotor symptoms caused a 44% reduction in hot flushes for women on Promensil compared to placebo ($P<0.01$) [10]. The negative result in the trial reported by Atkinson and colleagues may be because women in the trial women were not recruited because of moderate or marked hot flushes and the dose of Promensil was only 40 mg per day.

In this same trial, a recent paper reports the results of bone density and bone marker measurements in the 205 women [11]. The results shows that Promensil will significantly reduce the loss of bone mineral density in the lumbar spine compared to placebo ($P<0.05$), with an associated increase in markers of bone formation ($P<0.05$) indicating a beneficial oestrogenic effect of 40 mg per day of isoflavones for one year on the bones.

**Red clover isoflavone trials**

On this basis, and in this issue of the journal, by Atkinson and colleagues, [7] reports a randomised, double-blind, placebo-controlled trial of Promensil (Novogen), an extract of red clover, given to 205 pre- and postmenopausal healthy women with radiologically dense breasts (an established oestrogenic risk factor for breast cancer). Promensil is an extract of red clover containing very accurately determined amounts of the principal isoflavonoids: biochanin A, formononetin, genistein and daidzein (total isoflavonoid content of 40 mg per tablet) [8]. The trial is well designed with the principal objective of evaluating any adverse oestrogenic effect of red clover, at a dose of 40 mg of isoflavones per day, on breast density as a surrogate marker of increased breast cancer risk.

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**Conclusion**

Overall, this trial has shown encouraging evidence of a significant oestrogenic effect of 40 mg of isoflavonoids on bone with no evidence of an adverse oestrogenic effect on breast density. The possible benefit on vasomotor symptoms has not been adequately tested in this trial. Larger trials, involving more women treated for a longer period and perhaps at higher doses, are needed to test for possible overall clinical benefit in healthy women. At this time it is reassuring that there is no evidences that the widespread use of isoflavones to treat hot flushes is likely to be harmful.

**Competing interests**

TP is principle investigator for a clinical trial of red clover in healthy women.
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