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Soyfoods and soybean phyto-oestrogens (isoflavones) as possible alternatives to hormone replacement therapy (HRT)

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Soya is now widely investigated for its role in chronic disease prevention. Early interest in this field was fueled by the lower rates of coronary heart disease (CHD) and breast and prostate cancer in Asia. Numerous *in vitro*, animal, and clinical studies now provide a solid basis for continued investigation. In addition to cancer and CHD, there are data suggesting soya may reduce the risk of osteoporosis and help to alleviate menopausal symptoms. Consequently, soya is viewed as a possible alternative to hormone replacement therapy (HRT).

Focus on soya is due largely to the high concentrations of isoflavones in soybeans. Isoflavones are diphenolic compounds and are a subclass of the more ubiquitous flavonoids. The primary isoflavones in soybeans are genistein and daidzein. Isoflavone content varies among soybean varieties but is approximately 1–4 mg/g. Average daily isoflavone intake in Asia is approximately 10–40 mg. In subjects consuming approximately 100 mg of isoflavones from soyfoods, serum isoflavone levels as high as 6 umol have been achieved [1].

Isoflavones are weakly oestrogenic. Depending upon the assay employed isoflavones possess between 1×10^{-4} and 1×10^{-2} the activity of 17β-oestradiol on a molar basis. However, genistein binds with 5 to 20 times more affinity to the oestrogen receptor (ER)β than ERα [2]. The greater binding affinity of isoflavones to ERβ than ERα suggests that isoflavones may be tissue selective in their effects. Furthermore, some data suggest isoflavones can function as anti-oestrogens in some situations. Consequently, some researchers consider isoflavones to be natural selective oestrogen receptor modulators (SERMs).

Although isoflavones are phyto-oestrogens, the physiological effects of isoflavones, especially genistein, are likely only partially related to direct interaction with or binding to ERs. This is evidenced by the finding that genistein inhibits the growth of a wide range of both hormone dependent and independent cancer cells *in vitro* — a result thought to be due to the ability of genistein to influence signal transduction pathways.

1. Coronary heart disease

The US Food and Drug Administration (FDA) recently approved a health claim for the cholesterol-lowering properties of soya protein. In response to 25 g of soya protein/day one can expect a reduction in serum low-density lipoprotein (LDL)-cholesterol of approximately 10%. The means by which soya protein lowers cholesterol has not been identified. However, recent research suggests that isoflavone-rich soya protein is considerably more effective than soya protein low in isoflavones although this finding is controversial [3]. It is clear though that isoflavones may reduce CHD risk through multiple mechanisms. For example, studies have shown that isolated isoflavones enhance systemic arterial compliance [4] and that isoflavone-rich soya protein inhibits LDL oxidation, although not all studies concur on this point. Thus far, no controlled studies have examined whether soya or isolated isoflavones reduce cardiac events.

2. Osteoporosis

Initial speculation that soya might promote bone health was based on the weak oestrogenic properties of isoflavones and the similarity in structure between soybean isoflavones and the osteoporosis drug, ipriflavone, which is a synthetic isoflavone. In ovariectomised rodents, isolated isoflavones retard bone loss almost as effectively as oestrogen. In contrast, two studies in ovariectomised monkeys indicate soya protein is without effect. Only a few clinical studies have been conducted and these studies have involved small numbers of subjects and have been of short duration. Although findings are somewhat inconsistent, overall, they suggest

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that isoflavone-rich soy products favourably affect bone turnover and reduce bone loss at the lumbar spine [5]. Thus far, no studies have reported effects at the hip and no controlled studies examining the relationship between soya intake and fracture risk have been conducted. Animal and human data indicate isoflavones may both stimulate bone formation and inhibit bone resorption. In addition to a direct effect of isoflavones, substituting soy protein for animal protein substantially reduces calcium excretion [6]. These effects likely stem from the lower sulphur amino acid content of soya protein.

3. Menopausal symptoms

Surveys suggest the incidence of hot flushes in Asian women is markedly lower than in Western women. There is speculation that the weak oestrogenic effects of isoflavones soyfoods may contribute to this lower incidence. More than 10 studies using either isolated isoflavones or isoflavone-rich soya protein have been conducted. Findings from these studies are mixed but suggest that if soya does have an effect it is a relatively modest one [7]. A possible, but untested, explanation for the rather unimpressive findings is that to be effective, soya needs to be consumed prior to the onset of menopause.

4. Cancer

The low breast cancer mortality rates in Asia prompted speculation that soya consumption might reduce breast cancer risk. *In vitro*, genistein inhibits the growth of both ER+ and ER− breast cancer cells, although relatively high concentrations are required. Most animal studies indicate soya reduces the development of chemically-induced mammary tumours. However, case–control and prospective studies do not show that soya consumption is associated with a reduced risk of postmenopausal breast cancer. Some work suggests that to be protective, soya must be consumed early in life. Concerns have been expressed about possible oestrogenic effects of soya on breast tissue and, therefore, whether women with ER+ breast tumours should consume soya. There is evidence on both sides of this issue [8]. Particularly noteworthy though are recent findings indicating that short-term soya consumption does not increase breast cell proliferation in premenopausal women [9]. This finding contrasts with the initially published analysis of that study that included only half of the study subjects. Interestingly, human data indicate that soya does not increase endometrial cell proliferation and in animals, soya consumption has been shown to inhibit the stimulatory effect of oestrogen on breast and endometrial cell proliferation.

5. Conclusions

There are not sufficient data to recommend that soya and/or isoflavones be used in place of HRT. However, recommendations for women not on HRT to incorporate soyfoods into their diet can be made. Given the apparent safety and the relatively easy accessibility of soy products there would appear to be no disadvantage to this recommendation. Of course, other appropriate lifestyle changes should be made in addition to soya consumption.

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