Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis

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CRD summary
The authors concluded that isoflavone-rich soy products decreased follicle stimulating hormone and luteinizing hormone in premenopausal women and may have increased oestradiol in postmenopausal women, but the clinical implications of these changes were unclear. This was a well-conducted and clearly reported review and the authors’ conclusions are likely to be reliable.

Authors' objectives
To evaluate the effects of soy and isoflavones on circulating oestrogen and other hormones in premenopausal and postmenopausal women.

Searching
MEDLINE, EMBASE, The Cochrane Library and meta Register of controlled trials were searched from inception to December 2007. Search terms were reported. Reference lists of large non-systematic reviews were screened and experts contacted for details of any other published and unpublished studies. There were no restrictions on publication status or language.

Study selection
Parallel or cross-over randomised controlled trials (RCTs) and residential cross-over studies were included if they compared an increased intake of soy, soy products or purified soy isoflavones with usual diet with or without placebo in healthy, non-pregnant, non-breastfeeding premenopausal and postmenopausal women aged 16 or over. Studies had to assess a primary outcome (circulating oestradiol, oestrone, sex hormone binding globulin) or a secondary outcome (follicle stimulating hormone, luteinizing hormone, progesterone, circulating oestrone sulphate, circulating free oestradiol, thyroid hormones, urinary oestrogens, metabolites of oestrogen, menstrual cycle length, luteal and follicular phase lengths and insulin-like growth factor I).

Included studies compared the following: isoflavone extract versus control; isoflavone-containing isolated soy protein (ISP) versus isoflavone-depleted ISP; ISP versus another control; and whole soy or soy foods versus control. Some studies contained more than one comparison. All but one study were set in the community. Most studies were set in North America. Intervention durations ranged from four to 104 weeks.

Two reviewers independently selected studies and resolved disagreements by discussion.

Assessment of study quality
Two reviewers independently assessed validity using: blinding of participants and outcome assessors; industry funding or involvement; study duration (at least four weeks for postmenopausal studies and at least three cycles for premenopausal studies); assessment and reporting of compliance; isoflavone content (total isoflavone, genistein and daidzein content reported for each group); dose of isoflavones; isoflavones analysed (intervention dose checked and reported); and drop-outs. Studies were classed as being at low risk of bias if they met criteria for blinding, duration, drop-outs and no reported industry funding; other studies were classed as moderate or high risk of bias.

Data extraction
Isoflavone dose was calculated in aglycone equivalents. Means and standard deviations of changes from baseline were extracted. For cross-over studies, means and variances for each treatment group were calculated (most studies did not provide within-participant differences). For premenopausal studies, data at the point with the highest control group baseline level were extracted for each outcome. Outcome data were extracted at the last time point nearest to 53 weeks. Authors were contacted for additional data if required.
Two reviewers independently extracted data onto a form developed by the review team.

**Methods of synthesis**

Data on premenopausal and postmenopausal women were analysed separately. Standardised mean differences (SMDs) with standard errors (SEs) of primary outcomes were calculated using a random-effects model (SMDs were used since studies measured outcomes using different scales). Pooled mean differences (MDs) with standard errors were calculated for cycle length. Heterogeneity was assessed using the $I^2$ statistic.

A number of sensitivity analyses were conducted. For premenopausal studies, sensitivity analysis was conducted using data from the luteal phase for oestrogens, follicle stimulating hormone, luteinizing hormone with the follicular phase selected for progesterone. Data were reanalysed without using data from cross-over studies where exact t-test or p-values for the relationship between the two treatment periods were not reported. Meta-analyses were repeated using mean differences instead of standardised mean differences. Analyses were repeated for only studies at low risk of bias.

Subgroup analyses were used to examine the effect on primary outcomes of the following: intake of soy protein; isoflavone dose; intervention intensity; and isoflavone source.

The possibility of publication bias was explored using a funnel plot.

**Results of the review**

Forty-seven RCTs were included (n=1,813 analysed): 32 parallel studies and 15 cross-over studies. The studies included 11 studies of premenopausal women (n=579 analysed), 35 studies of postmenopausal women (n=1,165 analysed) and one study of perimenopausal women (n=69 analysed). Sample size ranged from 10 to 304 women analysed. Intervention duration ranged from four to 104 weeks; 29 studies lasted four to 12 weeks and only two studies lasted more than one year.

Study quality varied. All except one were randomised. Thirty-five studies blinded patients, 31 blinded outcome assessors, nine assessed compliance, 20 reported commercial funding, 42 reported an adequate duration of intervention and 25 fully reported drop-outs. Ten studies were classified as being at low risk of bias.

**Primary outcomes for premenopausal women:** There was no significant difference between soy/isoflavone and control in circulating total oestradiol, oestrone or sex hormone binding globulin (based on six to 11 comparisons per analysis). No significant heterogeneity was found. Findings were similar after excluding crossover studies and using only data from the luteal phase.

**Primary outcomes for postmenopausal women:** There was a non-statistically significant increase in circulating total oestradiol associated with soy/isoflavone groups (SMD 0.13, 95% CI -0.01 to 0.27; 21 studies); there was no significant difference when mean differences were used. The funnel plot suggested some evidence of publication bias. There was no significant difference between soy/isoflavone and control in circulating total oestrones (seven studies) or sex hormone binding globulin (17 studies). No significant heterogeneity was found.

**Secondary outcomes for premenopausal women:** Soy/isoflavones were associated with a statistically significant reduction in follicle stimulating hormone (SMD -0.45, SE 0.1735) and luteinizing hormone (SMD -0.34, SE 0.1709) and a significant increase in menstrual cycle length (MD 1.05, SE 0.4694).

**Secondary outcomes for postmenopausal women:** There was no significant difference between soy/isoflavone and control in follicle stimulating hormone or luteinizing hormone.

Results for other secondary outcomes and subgroup analyses were reported.

One author had links with a manufacturer of soy/isoflavone products.

**Authors' conclusions**
Isoflavone-rich soy products decrease follicle stimulating hormone and luteinizing hormone in premenopausal women and may increase oestradiol in post-menopausal women. Clinical implications of these changes are yet to be determined.

CRD commentary
The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched. Some attempts were made to minimise publication and language biases. Methods were used to minimise reviewer errors and bias in the selection of studies, extraction of data and assessment of validity. Only RCTs or well-controlled trials were included, validity was assessed and results were reported. Appropriate methods were used for the meta-analyses. Heterogeneity was assessed. Various predefined subgroup and sensitivity analyses were conducted. This was a well-conducted and clearly reported review and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was required to determine the clinical relevance of the modest changes in hormones found in this review at different stages of a woman’s life cycle.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.