

Benefits and Risks of Isoflavones in Menopausal Women



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Introduction

Many health benefits have been attributed to soy consumption, and especially to the fraction of isoflavones. Among other effects, soy isoflavones are known to alleviate vasomotor menopausal complaints.

With isoflavones classified as "phytoestrogens" their benefits and safety is often directly compared with the effects of estrogen. As the hormone has been linked to an increase of breast cancer in menopausal women [1], isoflavones are likewise under scrutiny regarding potential proliferation-enhancing effects in estrogen-sensitive tissues of breast and endometrium [2,3].

The safety and benefits of soy isoflavones applied to improve menopausal vasomotor symptoms shall be discussed in this contribution.

Benefits of Soy Isoflavones

The efficacy of soy isoflavone preparations has been tested in randomized, placebo-controlled trials, and was confirmed in meta-analyses and reviews [4]. In an own study we observed a statistically significant improvement of the number and severity of vasomotor menopausal symptoms in 192 women after 12 weeks of double-blind, placebo-controlled supplementation with 100 mg of soy isoflavones/day (corresponding to 60 mg of aglycones), followed by 12 weeks of open supplementation [5].

Recent metaanalyses have pointed to the heterogeneity in the design of clinical trials with soy preparations [6]. A common database for analysis is therefore difficult to achieve. We identified and analyzed clinical placebo-controlled double-blind trials with a minimum duration of 12 weeks, from which the daily frequency of hot flushes and their standard deviation could be derived. Eight studies were included into this analysis. Frequency and standard deviations of daily hot flushes before and after placebo-controlled intake of a soy preparation was entered into MedCalc and submitted to a metaanalysis. Difference between groups was found statistically significant ($p < 0.0001$).

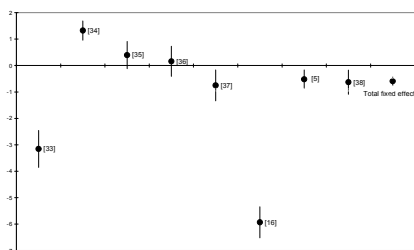


Figure 1: Metaanalysis of effect of soy isoflavones on daily hot flushes

This analysis clearly confirms the overall positive conclusion drawn in a most recent review [4]. The benefit of soy isoflavones in the treatment of vasomotor menopausal complaints must be considered positive.

Safety of Soy Isoflavones

The transfer of proliferation-enhancing properties of estrogens to "phytoestrogens" is mainly based on the observation of increased proliferation of estrogen-dependent cancer cells *in vitro* and in xenotransplanted ovariectomized (and mostly athymic) rodents. Both models are based on the induction of proliferation mediated by the estrogen-receptor alpha (ER- α). At this receptor genistein and daidzein display a relative affinity of 4% and 0.1% of that of 17 β -estradiol, respectively, whereas the relative affinity to ER- β is 87% and 0.5%, respectively [7]. This small, but measurable affinity to ER- α will necessarily be detected in sensitive models of estrogenic effects at ER- α , especially in the absence of estrogen and a working immune system [8]. The absence of ER- β must be considered another important contributor to the observation of proliferation-enhancing effects under experimental conditions, which is in contrast to cancer-protective effects attributed to dietary soy isoflavone consumption.

The proliferation-enhancing effect of isoflavones directly applied to MCF-7 cells *in vitro* is reflected in an activation of corresponding gene patterns. When serum samples of women supplemented with soy extract are tested, the enhancement of proliferation is much weaker than that of estradiol supplementation (samples adjusted to 20 pM as present in postmenopausal women), and the gene activation pattern is changed towards a suppression of proliferation. A clear reversal of proliferation enhancing effects of estradiol was observed when the hormone was supplemented in combination with isoflavones [9] (Fig. 2).

The models of MCF-7 cell cultures and ovariectomized athymic mice are important models to examine effects at estrogen receptors, but cannot be used for the extrapolation of a carcinogenic risks to postmenopausal women.

Safety of soy isoflavones has been amply tested, among others in state of the art toxicological studies with a focus on genotoxicity [10-15]. The lack of a carcinogenic potential and the high degree of clinical safety has been confirmed in supplementation studies with doses up to 900 mg of isoflavones and durations of supplementation of up to three years [16-19].

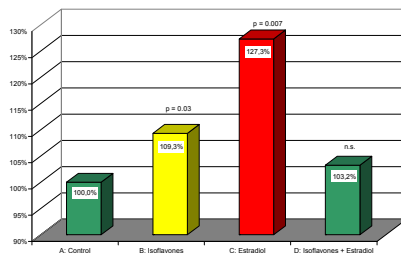


Figure 2: Relative proliferation of MCF-7 cells after supplementation of postmenopausal women with either isoflavones, estradiol, or a combination of both (data from [9]).

Clinically, the hints on potentially cancer-promoting effects are rare and scientifically highly debatable:

- The observation of hyperplasia in the verum group, but not in the placebo group after five years of supplementation with 150 mg of isoflavones [20] has been doubted [21-23]. In contrast, soy intake has been linked to a decreased risk of endometrial cancer [24,25].
- The observation of a potential increase of breast tissue proliferation after soy isoflavone intake by pre- and postmenopausal women, as observed in a pilot study [26] and a preliminary evaluation of a supplementation study [27], was not confirmed when the full set of data was analyzed [28]. Most recent analyses of the available data do not confirm enhancement of breast tissue proliferation under the influence of soy isoflavone supplementation [8,29].
- The recent publication of three case reports of endometrial pathology including leiomyoma related to the consumption of soy food [30] has been challenged for apparent inconsistencies, among other the reported intake of 40 g of isoflavones/day (corresponding to 400 litres of soy milk), a gross overestimation of the isoflavone content in supplements as compared with soy food, and the lack of corresponding adverse event observations in studies with the systematic assessment of safety parameters relevant for breast and endometrial health [31].

In epidemiologic studies a dose-dependent protective effect of isoflavone ingestion has been demonstrated, expressed by a 16% reduction of breast cancer risk for each 10 mg of isoflavones [32].

The overall risk profile of soy extracts and isoflavones derived from all available clinical data is clearly positive.

Conclusions

The benefits of soy isoflavones for menopausal women are clearly demonstrated, whereas the hypothesis of carcinogenicity was not confirmed by clinical observations. Women with menopausal vasomotor symptoms may profit from the supplementation, either with soy preparations alone or in combination with hormones.

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8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment
Tokyo, November 9-12, 2008

